The Panel would have liked to see the extent to which posterior parameter distributions are correlated. If rodent parameters were correlated as might be expected, how this correlation was accounted for in human-specific model parameter estimates should be discussed.

Recommendations:

- Present better descriptions and/or details on the choice of prior distributions, the Bayesian fitting methodology and fit of the posterior distribution for each model parameter.
- Provide some information on correlations around posterior medians for species-specific parameters.
- Supply more information on the model ordinary differential equations and on the likelihood function used in the Bayesian estimation.

1c Parameter Calibration

Parameter calibration as described in the draft Document was accomplished via a hierarchical fitting approach that used the posterior results in mice to establish the rat priors and the rat posterior results to set the human priors. The Panel generally endorsed this hierarchical fitting approach.

Recommendation:

- Improve the quality and the description of the assumptions underlying the use of the hierarchical approach to parameter calibration. Help the reader to understand the extent to which these assumptions are used consistently throughout the parameter calibration process.

1d Model Fit Assessment and Dose Metric Projections

There were a very large number of parameters in the PBPK model which made critical review of the whole model and in particular identifying the key issues around model fit a significant challenge.

A review of Figures 3-9, 3-10, A-3 and A-4, suggested that the updated model has adequate fit. Table 3-45 was particularly useful, as were the graphs in the linked documents that provided detailed descriptions of how well the model fit for the individual in vivo studies. When evaluating the quality of each prior, the draft document focused on agreement of the interquartile ranges. In Figure 3.9 (page 3-107), the vertical axes changed from the Hack model fit to the updated model fit. This added a challenge to assessing model fit since the models were predicting two slightly different quantities [N-Ac(1,2-DCVC) excreted (ug) for the Hack model and N-Ac(1,2 or 2,2 -DCVC) excreted (ug) for the updated model].

As a measure of model goodness of fit, the draft document presented the residual error geometric standard deviations (Table 3-41, page 3-98). The Panel was not certain how to use this statistic. For example, what does it say about model fit when the residual error is GSD 2.7 for venous blood TCE? Does this indicate a good fit or poor fit? For people who are not familiar with the design of the PBPK model, it is hard to critically interpret the values in this table.

ED_002435_00003498-00021

The Panel pointed out other issues related to the evaluation of the posterior distributions. Some of the posteriors were flatter than their priors, which was an unexpected result. In addition, in Table 3-36, (section 3.5.6.2), pages 3-88 to 3-89, the Panel observed that prior and posterior distributions of model parameters were almost identical and only in a few cases were the distributions different.

The Panel noted that a large number of studies were available to EPA for this review. Some of the rat studies were not used for parameter calibration and hence were used to assess the validity of the model; that is, to determine whether the fitted model was adequate to predict data from situations not specifically covered in the parameter estimation exercise. The Panel approved of this approach, finding that even a limited validation analysis improved the confidence of users in the final PBPK model and helped point to areas where the model may still be inadequate.

Recommendations:

- Move some graphical presentations from the linked graphics documents into the body of the report or into Appendix A.
- Incorporate more discussion on model fit and in particular indicate areas where the model fits well and areas where it did not fit well. Tie this discussion somehow to Table 3-41.
- Include graphs that show predicted versus observed values for all data points used in the analysis (one graph per endpoint).
- To help readers identify which parameters are better specified than others, provide a table of model parameters listed in reverse order by the width of their posterior variability (width of the IQR or width of 95% CI).
- Identify those parameters with very different prior and posterior distributions and discuss why this might be a reasonable result of the parameter calibration process. An alternative would be to provide a table where parameters are ranked based on the percent change of the posterior from the prior.
- Clarify which parameters are related to variability and which address parameter uncertainty. Separate the discussion of the two types of parameters.

1e Lack of an adequate sensitivity analysis

The charge to the Panel did not specifically address parameter sensitivity but the Panel did discuss the lack of and need for some form of sensitivity analysis. A common feature of PBPK models is that the output is highly sensitive to a few parameters (key parameters) and far less sensitive to the remaining parameters.

Recommendation:

- Perform a local sensitivity analysis, starting from the final fitted PBPK model, to assess how small changes in model parameter estimates impact predictions. Provide graphical presentations of the sensitivity of the model to changes in key model parameters in the final documentation.

ED_002435_00003498-00022

2. Meta-analysis of cancer epidemiology

NRC (2006) recommended that EPA develop updated meta-analyses of the epidemiologic data on TCE exposure and cancer, and provided advice as to how EPA should conduct such analyses. Is EPA's updated meta-analysis of the epidemiologic data on TCE exposure and kidney cancer, lymphoma, and liver cancer clearly and transparently described and technically and scientifically adequate for supporting EPA's hazard characterization and dose-response assessment? Specifically, please address the standards of epidemiologic study design and analysis as they were applied to select studies for inclusion in the meta-analysis; the rationales for study relative risk estimate selections; the meta-analysis methods; and the characterization of the conclusions of the meta-analyses. [Note: The scope of this charge question only includes the meta-analysis methods and results and not the overall weight of evidence for TCE carcinogenicity, which is addressed as part of a subsequent charge question.]

Response

NRC recommended that EPA conduct a new meta-analysis and to (1) pay attention to essential design features; (2) include only studies where exposure is documented; (3) classify studies on objective characteristics; (4) assess study power for each; (5) combine cohort and case-control studies unless it introduces substantial heterogeneity; (6) test for heterogeneity; and (7) perform sensitive analyses.

The Panel agreed that EPA followed these principles in their meta-analyses for lymphoma, and cancers of the kidney and liver. The EPA approach was clearly and transparently described and technically and scientific appropriate for supporting EPA's hazard characterization and dose-response assessment. The Panel found EPA performed a thorough literature review and clearly developed a comprehensive listing of candidate studies for the meta-analyses. The strengths and weaknesses of each study were characterized and clearly presented in the draft document. Procedures for selection of studies for the meta-analyses were clearly described.

Studies selected for inclusion had clear indications of TCE exposure and included exposure assessments for each study participant. Exposure levels differed considerably among and within the studies, which was an advantage. Candidate studies were also evaluated based on study design, endpoints evaluated, TCE exposure assessment, follow-up procedures for cohort studies, interview type (for case-control studies), use of proxy respondents (for case-control studies), sample size, and statistical analysis. Information on these factors was clearly presented for each candidate study. Appropriate criteria for including and excluding studies from the meta-analysis were developed and carefully applied. Reasons for excluding studies were clearly stated. Studies included had cohort or case-control designs, appropriate evaluation of cancer incidence or mortality, adequate selection of study subjects, characterization of individual TCE exposure for each subject, and relative risk estimates for lymphoma or cancers of the kidney or liver adjusted for at least age, sex, and race. For example, studies where individual exposure to TCE could not be reasonably determined were excluded, even though some exposure to individuals in the group was a reasonable assumption. Although excluded studies likely included some individuals who had exposure to TCE, exclusion was appropriate because inclusion would

ED_002435_00003498-00023

likely result in classification of some unexposed individuals as exposed, which would increase exposure misclassification and bias estimates of relative risk downward. The Panel found EPA carefully considered and described overlap between different studies (because of slightly overlapping study populations and extended follow-up of individual cohorts) and made appropriate selection of the results to include in the meta-analyses. The strengths and weaknesses of the meta-analyses were appropriately considered in the evaluation and interpretation of the results in relation to hazard characterization.

The Panel found that EPA discussed possible misclassification of exposure and disease for the studies included in the meta-analyses. EPA appropriately noted that most exposure assessment limitations would diminish relative risks and mute exposure-response gradients.

EPA indicated that in only one study were the interviewers blinded with regard to case/control status. Although it is desirable to attempt blinding for case-control studies, it is usually not possible to fully accomplish this because subject responses during the interview provide clues as to subject status. The Panel thought this was not a serious limitation.

The Panel found that EPA clearly described the statistical techniques used in the meta-analyses. Both random and fixed-effect models were used in the meta-analyses. This was useful to assess the accuracy of the underlying assumptions regarding study variation. The Panel agreed with EPA's reliance upon the random effects models for interpretation. Use of several approaches to evaluate heterogeneity provided a fuller characterization than would be available from any single technique. The potential for publication bias was appropriately evaluated. The robustness of the findings was highlighted based on the tests for heterogeneity and sensitivity. Results from the meta-analyses were fully and clearly presented in tables and figures.

Meta-analyses were performed only for lymphoma, and cancers of the kidney and liver. The text did not make clear why only these three were selected for the meta-analysis approach, although it was assumed this was because prior reviews of the literature had identified these cancers as possibly associated with TCE exposure. The Panel found it might be useful to have information on other cancers to provide evidence regarding possible confounding. For example, kidney cancer was associated with smoking. Most cohort studies lacked information on tobacco use. However, if there was confounding by smoking, there would have to be an excess of lung cancer and other tobacco-related diseases in the cohorts. Absence of an excess of lung cancer was very strong evidence that workers exposed to TCE did not smoke more than the unexposed, or comparison population. Although no studies had excess of lung cancer, a meta- analysis of lung cancer showing no association with TCE would document this conclusion regarding possible confounding. Smoking could not cause excesses of kidney cancer, liver cancer or lymphoma without also causing an excess of lung cancer. The lack of effect of TCE for lung cancer in individual studies provided convincing evidence that confounding by smoking is unlikely.

The Panel agreed that EPA carefully evaluated the data from the studies included in their review and results from the meta-analyses against standard epidemiologic criteria for causality, i.e., consistency, strength of the association, specificity of the association, temporal relationship, exposure-response gradient, biologic plausibility, coherence, experimental evidence, and analogy. The document provided a full discussion of these issues.

ED_002435_00003498-00024

Bias and confounding are concerns in epidemiologic studies. The Panel agreed that the draft document had a strong discussion on potential confounding. Age, gender and race were appropriate potential confounders to include in the meta-analyses and the meta-analyses included effect estimates that were adjusted. The potential for confounding was evaluated in a number of ways. Several of the case-control studies could directly adjust for potential confounding from important risk factors and provide directly adjusted relative risks. EPA also pointed out that many potential confounders, e.g., obesity, diabetes, tobacco, and hypertension in kidney cancer, were unlikely to be associated with the level of TCE exposure and, thus, were unlikely to confound. If these factors did confound, other cancers would be affected. Other occupational exposures were mentioned as possible confounders, e.g., other organic solvents, cutting fluids, and hydrazine. The link between most of these and the cancers of concern relative to TCE was weak or non-existent, so they were not strong candidates for confounding. Biases are also a concern in observational studies. In case-control studies, case-response bias and case or control selection bias are a concern, while in cohort studies biases associated with follow-up and exposure are a concern. No obvious bias that would occur across studies of different designs, in different countries, and with different exposure metrics falsely produced an association with TCE. The Panel did not think confounding or bias were likely explanations for the findings from the epidemiologic studies and meta-analyses.

The Panel agreed that the findings of several community studies although intriguing, were appropriately omitted from the meta-analyses due to large misclassification errors and lack of control for confounding, which would tend to bias estimates from the meta-analysis.

The Panel found that EPA appropriately discussed the changing classification of hematopoietic and lymphatic system tumors and selected lymphoma (predominately non-Hodgkin's lymphoma (NHL) as an outcome for meta-analysis. EPA specifically wanted to select studies with the best outcome definitions, rather than pick at studies where the hematopoietic cancers were grouped. (e.g. myeloid and lymphoid neoplasms together). EPA selected studies representing various groupings of NHLs (with some studies that included chronic lymphocytic leukemia) or focused on specific subtypes of NHL (including one study that focused on hairy cell leukemia), but did not include studies of Hodgkin lymphoma (if any such studies existed). Given that the EPA's intent was to conduct a meta-analysis with NHL as the outcome, the Panel felt that the terminology should be changed to 'non-Hodgkin lymphoma' instead of 'lymphoma', throughout the document. The term 'NHL' more accurately describes the intent of the analysis as well as the overwhelming majority of cases in the analysis, despite changing classification schemes. The focus of the meta-analysis on NHL and any indication in the meta-analysis where cases definition may diverge from classical NHL (as in studies that included chronic lymphocytic leukemia) should be clearly explained in both Appendix C and in the Hazard Characterization section (section 4.6.1.2.2) in the main document.

The Panel agreed that appropriate approaches were used in the meta-analysis. Effect size (the relative risks or odds ratios) included in the meta-analyses were selected appropriately using the most appropriate selection criteria. However the Panel had a few questions of clarification about the meta-analysis for kidney cancer.

ED_002435_00003498-00025

There are a number of technical points that should be mentioned as footnotes to the meta analysis plots. First, the exact confidence intervals given in the original publications have been replaced with approximations. The Panel suggests that the explanation in Appendix C be reiterated in the main document. For reference, Appendix C, Table C-6 (pages C-26 to C-27) shows the actual SE(logRR) used to calculate the weights. In addition, Appendix C, page C-3, lines 14-20 explains the discordant confidence intervals in the figures. A second example is that a 20 year lag was used for the Zhao study while lags were either not given or not used in the other studies. Clarify the rationale for selecting the "20 yr lag" result from Zhao et al. (2005) and not selecting the "20 yr lag" result from Raaschou- Nielsen et al. (2003).

The Panel agreed with EPA's conclusions from the meta-analyses that TCE increased the risk for the three cancers studied. The Panel's agreement with EPA's conclusion was based on the strict and appropriate inclusion criteria, the methods of conducting the meta-analyses, including consideration of bias and confounding, and the robustness of the findings based on the tests for heterogeneity and sensitivity.

Recommendations:

- Provide a rationale for the three cancer sites selected for the meta-analysis. The rationale could be nicely summarized in a table.
- Consider including meta-analysis for lung cancer for confounding purposes or other sites for comparison for which some association with TCE exposure has been reported in epidemiologic studies, such as childhood leukemia and cervical cancer. It might also be possible to provide this information without a formal meta-analysis.
- Provide measures of heterogeneity such as the I^2 statistic for each meta-analysis. Although this information was provided and accurately explained in Appendix C, it was mischaracterized at several points in the primary document. For example, the summary of the kidney cancer meta-analysis on p. 4-167 of the primary document states that "there was no observable heterogeneity across the studies for any of the meta-analyses," but Appendix C indicates "the I^2 value of 38% suggested the extent of the heterogeneity was low-to-moderate." Non-significant heterogeneity is indeed observed heterogeneity.
- Evaluate the likely impact of converting odds ratios to relative risk estimates (i.e., using the method of Greenland (2004) or Zhang and Yu (1998), and decide if necessary to perform these conversions for the meta-analysis.
- Change the terminology regarding the meta-analysis results for 'lymphoma' to 'non-Hodgkin lymphoma' throughout the document.

ED_002435_00003498-00026

3. Non-Cancer Hazard Assessment

Does EPA's hazard assessment of non-cancer human health effects of TCE logically, accurately, clearly, and objectively represent and synthesize the available scientific evidence to support its conclusions that TCE poses a potential human health hazard for non-cancer toxicity to the central nervous system; the kidney; the liver; the immune system; the male reproductive system; and the developing fetus, including the role of TCE in inducing fetal cardiac defects?

Response:

The Panel agreed that the EPA's TCE hazard assessment has clearly, accurately, logically and objectively represented and synthesized the available scientific evidence to support its conclusions that TCE poses a potential human health hazard for non-cancer toxicity. Specifically, the EPA has provided a comprehensive and thorough synthesis of the available evidence regarding the effects of TCE and its major metabolites in each of the tissues addressed in the charge question. This includes human epidemiological studies, animal studies, in vitro studies using renal cell cultures, and in vivo and in vitro metabolism studies.

3a Central Nervous System

TCE-associated auditory impairment was discussed in this section (4.3.2.3.). It is noted that auditory impairment is commonly seen with various autoimmune conditions and inflammation-based diseases and these were among the immune dysfunctions observed with TCE exposure.

3b The Kidney

In regard to the effects of TCE in the kidney, EPA had provided a thorough and clear description of these effects. One issue of concern here was the quantitative aspect of the GSH pathway metabolites. Dr. Wolfgang Dekant, in his public comment, suggested that data obtained using the "Reed method" overestimated the amount of DCVG produced. This HPLC method is characterized by variability and overall decline in retention times over the life of the HPLC column due to derivatization of amine groups on the column (Lash *et al.*, 1999b). Although data are limited, GSH pathway metabolite levels reported by methods that utilize ^{14}C TCE and radiochemical detection followed by mass spectrometry identification of the metabolites (Green et al, 1997a) are lower than those from reports using the "Reed method". In addition, studies using HPLC-MS/MS techniques with stable isotope-labeled DCVG and DCVC standards have also been used to detect GSH pathway metabolite levels (Kim et al, 2009). Based on the in vitro work presented in Table 3-23 (page 3-44 of the draft EPA document) determining DCVG formation by the "Reed method" in human, rat and mouse liver, one would expect mouse serum DCVG levels to be ~4-6 times lower than humans. However, using the HPLC-MS/MS technique of Kim et al., the peak DCVG serum levels are ~1,000 times lower in mouse serum than determined by Lash et al. (1999a) in human serum. Although differences in exposure routes, exposure doses, etc. should be considered, this much larger than expected difference also suggests that the "Reed method" provides an overestimation of DCVG levels in humans. This could occur if the "Reed method" identifies non-specific derivatives as DCVG or other GSH

ED_002435_00003498-00027

pathway metabolites. Thus, interpretation of DCVG levels from the Lash et al. (1999a) paper should be made with caution.

It is noted that the focus on animal data in the EPA report is appropriate because human data on non-cancer kidney effects from TCE are limited by two factors. The first is outcome assessment. Due to the insensitivity of the clinical kidney outcomes such as glomerular filtration rate and end stage disease, human nephrotoxicant work often uses kidney early biological effect markers. Unfortunately, research to accurately determine the prognostic value of these biomarkers is fairly limited and data analysis in many of these studies is quite rudimentary often involving only a comparison of unadjusted mean values between an exposed and a control group. A range of biomarkers are used and results are frequently not entirely consistent as noted in Section 4.4. The second challenge is that human exposure often involves a mixture of solvents making determination of the impact of an individual solvent difficult. For example, the GN-PROGRESS retrospective cohort study in Paris, France, which examined the impact of solvents on risk of end stage renal disease (ESRD) and progression of glomerulonephritis, included patients with a wide range of solvent exposures. Solvent exposure was assessed by industrial hygienists from lifetime occupational histories collected by interview and a list of the 30 most common solvents. These authors noted an elevated risk for progression of glomerulonephritis to ESRD from TCE although numbers were small and did not achieve statistical significance (adjusted hazard ratio [95% CI] 2.5 [0.9 to 6.5]) (Jacob et al, 2007). These authors also did not discuss how they addressed exposure to solvent mixtures as they attempted to focus on specific agents.

3c The Liver

The only criticism noted for this section was the (perhaps unavoidable) repetitive nature of their coverage, as these issues appeared elsewhere in the document. Less repetition and better integration of these sections would improve the readability of the document.

3d The Immune System

It is noted that the children's exposure data and adverse outcomes are consistent with the immunotoxicity reported in the animal developmental models. It is noted that while TCE exposure can produce a range of immune dysfunctions, including immunosuppression, elevated risk of autoimmunity and dysregulation of inflammation, it is possible that the doses of TCE producing each category of adverse immune outcomes may differ. For example, most studies reporting autoimmune dysregulation used higher doses of exposure compared with at least some studies where immunosuppression was observed.

3e The Male Reproductive System

It is noted that male potency/sterility issues can be associated with inflammatory dysfunction in the testes produced by some environmental pollutants (usually associated testicular macrophage dysfunction) (see Pace et al., 2005). Since inflammatory dysfunction is associated with TCE exposure, this is an additional possible mechanism that may be associated with adverse outcome for male potency. For in utero exposure studies in rodents using lower doses of TCE and metabolites, where effects (carcinogenic and non-carcinogenic) can be

ED_002435_00003498-00028

observed transgenerationally, attention should be directed to epigenetic changes as possible MOA for TCE-mediated effects on the reproductive systems.

3f The Developing Fetus, Including the Role of TCE in Inducing Fetal Cardiac Defects

It is noted that the type of cytokine dysregulation seen with TCE exposure (e.g., involving IL-6) can play a role in cardiac dysfunction. The report explains logically why the Johnson et al. (2003) study was used to derive some reference points. Some recent publications confirm and reinforce the results obtained in the Johnson et al. (2003) study and could be cited to make a stronger argument. They are listed as follows:

- TCE effects on the cardiac system were specific for a narrow window of development corresponding to myocardial expansion and endocardial cushion formation, consistent with previous findings from Drake et al,2006a and b; Mishima 2006; Boyer et al. 2000, and consistent with the definition of a teratogen.
- The types of defects and morphological changes (e.g cardiac hypertrophy and hypoplasia) were consistent with a mechanism of action involving disruption of calcium handling and cardiac contractility, observed by Caldwell et al, 2008 in rat cardiomyocytes. Numerous literature data (reviewed in Lehnart et al., 2008; Lebeche et al, 2008; Yano et al., 2008; Gyorke et al., 2008) confirm the notion that alteration of calcium homeostasis is sufficient to induce alteration of contractility and in turn heart defects.
- A non-monotonic dose-response relationship was found that confirms several other studies (Caldwell et al., 2008; Drake et al., 2006) suggesting the presence of more than one MOA due to presence of metabolites, enzymatic sensitivity, etc.

Recommendations

- If additional endpoints of renal dysfunction (e.g. diuresis, increased glucose excretion) were present in the reported studies, they should be included in the report. Often only one or two parameters of renal function and histopathology were presented. A better overall description of renal dysfunction should be presented if available (especially for animal studies).
- There should be a better description of the location of the renal lesion, including nephron segment, if known. For example, TCE and DCVC appeared to affect the proximal tubule at the level of the outer stripe of the medulla (S3 segment of proximal tubule). Is this the site of lesions seen with other TCE metabolites? Explaining the role (or lack of a role) of any other TCE metabolites in TCE nephrotoxicity could be strengthened by comparing the sites of the renal lesion.
- On page 4-338, please clarify the use of the phrase, "subpopulation levels", on lines 31 and 33.

ED_002435_00003498-00029

- A statement should be added that the spectrum of TCE-induced immune dysfunctions (immunosuppression, autoimmunity, inappropriate and/or excessive inflammation) included in this EPA draft report has the potential to produce adverse effects that are seen well beyond lymphoid organs and involving several other physiological tissues and systems. The types of immune-inflammatory dysfunctions described in this report have been observed to affect function and risk of disease in the nervous system (e.g., loss of hearing), the skin, the respiratory system, the liver, the kidney, the reproductive system (e.g., male sterility), and the cardiovascular system (e.g., heart disease, atherosclerosis).

- A statement should be added to emphasize the cell-mediated immune effects of TCE as some of this has been supported by the human epidemiology data and the issue is pertinent to risk of cancer.

ED_002435_00003498-00030

4. Cancer Hazard Assessment

Using the approach outlined in the U.S. EPA Cancer Guidelines (U.S. EPA, 2005a), does EPA's hazard assessment of carcinogenicity logically, accurately, clearly, and objectively represent and synthesize the available scientific evidence to support its conclusions that TCE is carcinogenic to humans by all routes of exposure? Specifically, please address the epidemiologic evidence for associations between TCE and kidney cancer, lymphoma, and liver and biliary tract cancer; the extent to which the results of the meta-analyses contribute to the overall weight of evidence for TCE carcinogenicity; the laboratory animal data for rat kidney tumors, mouse liver tumors, and lymphatic cancers in rats and mice; and the toxicokinetic and other data supporting TCE carcinogenicity by all routes of exposure.

Response:

The Panel agreed that cancer hazard characterization hinges on the synthesis of the accumulated scientific evidence, especially the epidemiologic evidence supporting the carcinogenicity of TCE. Assessment of the causal association and weight of evidence supported the conclusion that TCE is carcinogenic to humans by all routes of exposure as outlined in the US EPA cancer guidelines. Results from animal bioassays and toxico-kinetic data provide further support to the EPA conclusion. The report logically, accurately, clearly, and objectively presented the methodological review of the epidemiologic evidence, highlighted the criteria for study inclusion in meta-analyses and the meta-analysis methods (as noted in charge question 2) and appropriately assessed the weight of the evidence to conclude that TCE is causally related to lymphoma, and kidney and liver cancer.

Epidemiological Data

The report appropriately highlighted the causal criteria in support of the conclusion. The consistency of the findings was notable given the rarity of the cancers, differences in latency and potential for exposure misclassification as described in the study assessments highlighted in the hazard characterization. Multiple explanations would be needed to account for the associations between TCE and several cancers from studies with differing designs, strengths and weaknesses.

The summary risk estimates from the meta-analyses provided a clear indication of a cancer hazard from TCE. The pooled risk estimates from the meta-analyses for kidney cancer and liver cancer, although modest, were robust with no indication of publication bias or heterogeneity. Meta-analyses for both kidney cancer and lymphoma found higher increases in the risk estimates associated with higher TCE exposure than for any TCE exposure and no evidence of strong confounding, which further supported a causal association.

EPA concluded TCE is carcinogenic to humans by all routes of exposure. This conclusion was based on convincing evidence of a causal association between TCE exposure and kidney cancer, compelling evidence for lymphoma, and more limited evidence for liver cancer. The epidemiologic data, in the aggregate, were quite strong. In addition, the epidemiologic data were supported by bioassays and toxicokinetic data. Although issues of concern could be raised

ED_002435_00003498-00031

about individual studies, the overall pattern and the results from the meta-analyses were quite compelling. Potential confounding from established risk factors for these cancers of concern could be directly assessed in some studies and indirectly evaluated by reviewing cancer excesses that did not occur in TCE exposed populations, e.g., the absence of an excess for lung cancer indicates confounding from smoking is not likely.

Some studies had low power to evaluate the TCE-cancer relationship, but the meta-analysis provides a tool to combine underpowered studies and assess the overall effect. Exposure assessment in epidemiologic studies is difficult in the best of circumstances. EPA appropriately focused on studies with the stronger exposure assessment efforts to minimize the effects of exposure misclassification. However, misclassification of exposure undoubtedly occurred. In the cohort studies the effect of exposure misclassification on estimates of relative risk will be largely non-differential because factors used in exposure assessment were recorded before occurrence of the disease. Thus, it will tend to depress estimates of relative risk and mute exposure-response gradients and is not an explanation for any observed excesses. Non-differential exposure misclassification would also occur in case-control studies. Differential misclassification is more of a concern in case-control studies. Differential misclassification can bias relative risks upward or downward, although the upward bias is usually raised in positive studies. However, no evidence is available to suggest that differential exposure bias occurs across all the case-control studies. The summary estimates from the meta-analysis provided a clear indication of a cancer hazard from TCE. EPA concluded the association between TCE and lymphoma and liver cancer were more limited than that for kidney cancer. These conclusions about the epidemiologic data were supported by the statistically significant excesses for these tumors in the meta-analyses, no statistically significant heterogeneity, and consistency of findings after exclusion of individual studies in sensitivity analyses. The consistency of the findings was remarkable given the rarity of the cancers, differences in latency and potential for exposure misclassification, as described in the study assessments highlighted in the hazard characterization.

EPA concluded that the epidemiology data were convincing for a causal association between TCE and kidney cancer, compelling for lymphoma, and positive but more limited for liver cancer. The Panel did not have strong disagreement with this statement, although some felt that the data for liver cancer were as compelling as that for lymphoma. Liver cancer has a much lower incidence than kidney cancer or lymphoma in Western countries (where most of the epidemiologic studies were conducted) and this requires more reliance on the meta-analysis for a summary effect estimate with adequate power. The meta-analysis found that the association of TCE exposure with liver cancer was elevated and statistically significant. Further grouping liver cancer cases by the level of exposure resulted in numbers that were too small to adequately evaluate risks among persons with higher exposures. Nevertheless, we considered these results for liver cancer to be strong because there was no evidence of heterogeneity or publication bias in the meta-analysis, and because the epidemiologic findings were supported by observations of liver cancer in animal models. Although potential confounding by other risk factors for liver cancer is possible, strong risk factors such as hepatitis are very rare in Western countries (where most of these studies were conducted), so this is unlikely to have caused such a degree of confounding. There were no studies to evaluate whether hepatitis might be a confounder in TCE studies, although this seemed unlikely.

ED_002435_00003498-00032

The meta-analysis results were impressive for lymphoma, showing a significantly elevated relative risk for ever-exposure to TCE and an even higher effect estimate for high TCE exposure. However, it is important to note that there was weak evidence of publication bias in the lymphoma meta-analysis results, which means that studies showing no TCE effect or inverse associations may not have been published. In addition, there was significant heterogeneity in the meta-analysis results for lymphoma for ever-exposure to TCE, indicating that there is an unexplained factor causing heterogeneity that indicates it may be inappropriate to combine the estimates in a meta-analysis. This heterogeneity may reflect the complicated and changing definitions for lymphoma across studies and over time. It is also possible that effects from TCE may differ by type of lymphoma. The association with lymphoma was further supported by the larger relative risk in meta-analyses for the higher exposure categories compared to the overall relative risk. This was evidence for an exposure response gradient, even though no individual studies showed much evidence of this.

Animal Data and Toxicokinetics

The Panel agreed that human data, when available, should be preferred over rodent data when estimating unit risk since within species uncertainty is easier to address than between species uncertainty. The Panel believed that the animal and toxicokinetic data were thoroughly reviewed and the biologic plausibility and coherence of the epidemiologic findings were supported by the laboratory animal data and the toxicokinetic data.

Recommendations:

- The immune effects as highlighted in the hazard assessment should be referred to in the conclusion especially in the criteria of biological plausibility and coherence because of the relationship between immune system dysfunction and cancer risk.

- Although the summary evaluation focused on the scientific evidence and meta-analysis for kidney, lymphoma and liver cancers, there is also some suggestive evidence for TCE as a risk factor for cancer at other sites including bladder, esophagus, prostate, cervix, breast and childhood leukemia. This evidence that also supports the conclusion should be mentioned in the summary evaluation (section 4.11.2.1).

- Add a paragraph describing the definition of lymphoma as used in IRIS. Change the terminology regarding the meta-analysis to 'non-Hodgkin lymphoma' instead of 'lymphoma', throughout the document. The term 'NHL' more accurately describes the intent of the analysis as well as the overwhelming majority of cases in the analysis, despite changing classification schemes. The focus of the meta-analysis on NHL and the exact classifications the meta-analysis includes where it may diverge from classical NHL (as in studies that included chronic lymphocytic leukemia) should be clearly explained in both Appendix C and in the Hazard Characterization document (section 4.6.1.2.2).

- To assist the reader, please include references in the summary section (section 4.11.2). For example, "The other 13 high-quality studies [note: besides Hardell and Hansen] reported

ED_002435_00003498-00033

ED_002435_00003498-00034

5. Role of Metabolism on TCE Toxicity

Does EPA's hazard assessment logically, accurately, clearly, and objectively represent and synthesize the available scientific evidence to support its conclusions regarding the role of metabolism in TCE carcinogenicity and non-cancer effects? Specifically, please address EPA's conclusions that the liver effects induced by TCE are predominantly mediated by oxidative metabolism, but not adequately accounted for by the metabolite trichloroacetic acid (TCA) alone and that the kidney effects induced by TCE are predominantly mediated by metabolites formed from the GSH-conjugation pathway.

Response

The Panel agreed that EPA's hazard assessment in the draft document has produced a systematic, thorough, objective and clear summary of information on the role of metabolism in TCE-induced toxicity with regards to both cancer and non-cancer health effects. The Panel also found that EPA has presented a comprehensive review of metabolite formation in animals and humans, and has provided a clear, logical assessment of the role these metabolites play in mediating its carcinogenic and non-cancer effects.

5a Mediation of TCE-Induced Liver Effects by Oxidative Metabolism

The Panel found that EPA's conclusion that oxidative metabolites of TCE are responsible for mediating the liver effects is sound and based on a wealth of supportive studies.

The document was a thorough review of the extensive literature on the role of oxidative metabolism in TCE toxicity to the liver. Direct evidence that oxidative metabolism was required for liver toxicity, such as studies which modulated TCE toxicity by modulating P450 activity, was somewhat limited. One noted exception is the study by Ramdhan et al. (2008), that reported CYP2E1-deficient mice produced considerably less oxidative metabolites and showed reduced hepatoxicity, although due to a small number of animals studied, effects were significant only at the highest TCE dose. Nonetheless, the collective evidence, especially from studies with two major oxidative metabolites of TCE - TCA and DCA, was very strong that in rodents, at doses where metabolism is not saturated, the majority of TCE was metabolized and that metabolites from the oxidative pathway predominated over those of the glutathione conjugation pathway. Mice are the most susceptible species with respect to TCE-induced liver effects and the majority of studies support the conclusion the oxidative metabolites are playing the major role.

5b Contribution of TCA to Adverse effects on the Liver

The Panel found the conclusion that "the adverse effects on the liver of one of the TCE metabolites, trichloroacetic acid, cannot adequately account for the liver effects of TCE" is sound and supported by several lines of experimental evidence.

TCA is the predominant oxidative metabolite of TCE and its effects are well known to be associated with liver toxicity and carcinogenicity. However, oxidative metabolism of TCE generates a number of molecules and the confidence in the ability to identify TCE's oxidative metabolite(s) that may be responsible for hepatotoxicity and/or liver cancer in rodents or humans is much less than that for the overall role of oxidative metabolism. This uncertainty is due in

ED_002435_00003498-00035

part to the problems with quantitative assessment of DCA formation after TCE administration. There is sufficient evidence to implicate DCA in mediating carcinogenic effects of TCE that are not related to those produced by TCA. The EPA correctly stated that DCA was a minor metabolite of TCE in vivo, at least in rodents, and that some of the earlier reports on DCA dosimetry may have been erroneous due to the issues with the analytical methods. There are, however, several studies (Delinsky et al., 2005; Kim et al., 2009) which provide information on the blood levels of DCA after oral exposure to TCE in rats and mice. Such data, together with a large body of literature on TCA formation after treatment with TCE, should be carefully evaluated with regards to the estimation of the internal dose (or relative amounts) of each of these key metabolites.

The Panel found that EPA has taken several approaches to determine whether liver tumors induced by TCE can be accounted for by TCA formation alone. The first approach was to compare dose-response profiles for non-cancer liver toxicity endpoints from TCE and TCA based on TCA dose equivalents, an internal dose metric. In contrast to DCA, the quantitative data available for TCA and TCOH, together with PBPK models relying on their measurements, are among the most consistent and allow for the assessment of the oxidative metabolite flux from TCE. Analysis of liver weight changes (Fig 4-7, 4-8) suggested that while total TCE oxidative metabolism was strongly correlated with liver weight changes ($R^2 = 0.89$), the amount of TCA formed underestimated the degree of liver hypertrophy observed. The dose-response relationships for liver hypertrophy observed between TCE and TCA, based on TCA daily dose equivalents, were strikingly different in both slope of the dose-response and overall magnitude, suggesting that the mechanisms of hypertrophy, and/or the metabolites involved, were different. This analysis was compelling because TCA daily liver dose equivalents were used for comparison. The internal dose metrics, if accurately applied, should account for potential differences due to bioavailability and exposure route issues that have been previously raised for TCE and TCA. The Panel notes that the bioavailability of TCE, DCA and TCA in oral gavage studies was dependent, among many factors, on the type of the vehicle and the magnitude of the administered dose. It has been suggested [Sweeney et al., 2009; NRC review of the IRIS assessment of Tetrachloroethylene (Appendix B)] that the bioavailability of TCA (when administered directly) was highly non-linear with an increasing dose. Thus, the internal dose of each metabolite of interest, either through metabolism from TCE or following direct administration, was key for the comparison of health effects between the parent and its metabolites.

The second approach used in the draft document to support the conclusion that multiple metabolites were involved in liver tumors induced by TCE included comparisons of liver phenotypic markers (glycogen staining, c-jun staining) and tumor-derived genetic markers (incidence of H-ras mutations). This analysis was interesting, yet qualitative in nature. The use of phenotypic markers such as H&E staining, glycogen staining, antibody reactivity, tumor tincture, etc., must be interpreted with caution since the underlying biochemistry/molecular biology of these descriptive attributes is often not well understood and may be highly dependent on the state of progression of the tumors The criteria used in each study for phenotypic classification (i.e., staining intensity, background staining) is not always clearly outlined in the original literature reports. The EPA has included adequate discussion noting the technical limitations for each of the studies, which increased the confidence that such evidence from a

ED_002435_00003498-00036

single study was not overly weighted in drawing conclusions about the role of TCA. While individual studies comparing phenotype/genotype of TCE-, TCA- and DCA- induced tumors have important limitations, the collective group of studies was consistent with the interpretation that TCE tumors displayed phenotypic and genotypic heterogeneity that was different than that of tumors induced by TCA alone. This was in agreement with the EPA conclusion that these data also did not support the hypothesis that TCA was a sole acting liver metabolite of TCE. However, since factors such as interactions among metabolites and tumor progression state may have unknown influences in the phenotype/genotypes observed, this type of qualitative evidence was not sufficient to invoke specific roles for other contributing metabolites, or to discount potential contributing roles of other metabolites.

The draft included little in terms of the comparative quantitative evaluation of the hepatocarcinogenic potency of TCE, TCA and DCA even though extensive information was available, especially in mice. A recent draft of the IRIS assessment of a highly related chemical, tetrachloroethylene (PERC), provided the evaluation of the consistencies between PERC and TCA with regards to the liver cancer endpoint (Appendix 4A of PERC IRIS draft document). TCA is a major metabolite of both TCE and PERC and it is debatable whether TCA toxicity can account for the majority (if not all) of the adverse liver effects of PERC.

Given the controversy of DCA as a contributing metabolite in liver effects induced by TCE and the importance of this issue as it relates to understanding TCA's role, it is somewhat surprising that there was relatively little analysis of the literature related to the use of DCA as a therapeutic agent in humans as an integrated part of this section of the review. Although these studies obviously involved high doses, they are relevant to the potential spectrum of effects observed in humans.

Recommendations:

- The EPA should examine studies that provide quantitative assessment of TCA and DCA formation after TCE exposure *in vivo* and draw conclusions with regards to the relative amount and kinetics of the oxidative metabolites of interest for liver toxicity.
- A careful evaluation of the concentration-time kinetics is needed to achieve certainty in the comparisons of liver effects and the conclusions drawn by the EPA which suggest that TCA-induced adverse liver effects do not explain those observed with TCE. Equally important is to fully consider the bioavailability of TCE itself with regards to the vehicle effects between studies.
- The body of the document could be further strengthened by reporting EPA's evaluation on the strength of the specific criteria used for phenotypic classification described in each study discussed, and noting where specific criteria were not reported. While most of this information was included in the appendix, the EPA may consider constructing a summary table for Section 4.5.6.
- Dose-response modeling, similar to that performed for PERC, may be considered by the EPA to provide science-based information on relative contribution, or lack thereof, of TCA and/or DCA to the apical liver carcinogenesis effect of TCE. While data gaps exist and there are limitations in the comparisons between independent cancer bioassays, the document should clearly state what the limitations are should such analysis be deemed futile.

ED_002435_00003498-00037

- The draft assessment may be strengthened by including information from human use of DCA in clinical practice.

5c Role of GSH-Conjugation Pathway on TCE-Induced Kidney Effects

The Panel concluded that EPA has provided a clear and comprehensive summary of the available evidence that metabolites derived from GSH conjugation of TCE are responsible for mediating kidney effects.

The Panel found the integration of the data from human epidemiological, animal and *in vitro* mechanistic studies produced a clear and transparent weight-of-evidence assessment supportive of TCE GSH conjugation metabolites' role in kidney toxicity and cancer. Whereas sufficient amounts of oxidative metabolites of TCE (i.e., TCOH) may be formed which could contribute to kidney effects, potentially through formic acid, the literature indicated the pathological effects on the kidney induced by oxidative metabolites were not consistent with those observed with TCE. In contrast, the pathological effects on the kidney induced by DCVC/DCVG were similar to TCE. Thus, a reasonable conclusion was that the glutathione conjugation pathway played a more important role in driving these effects. The primary challenge was to determine the true flux through the glutathione conjugation pathway.

Many uncertainties exist in PBPK model estimates for the GSH pathway. This issue is critical, since these uncertainties can result in orders of magnitude differences in flux between rodents and humans. The argument that mercapturates of the glutathione conjugates, as detoxication pathway products, are not quantitative markers of flux through the GSH pathway is rational and supported by in vivo human and rodent data. The level of urinary mercapturates, as deactivation products, is evidence that the pathway operates in humans, but does not necessarily reflect the amount of DCVC formed. Direct data on DCVG/DCVC formation, or its reactive metabolites, are the more appropriate measures of flux for this pathway. This was clearly and adequately discussed in the review.

The quantitative analysis of the species differences in GSH metabolism was somewhat narrow. Specifically, the issue of vast differences in human vs rodent metabolism of TCE to GSH conjugates hinged on the very limited experimental evidence. Only one human *in vivo* study was available that directly quantified DCVG in urine in a few subjects (Lash et al. 1998). The rodent in vivo data (Kim et al. 2009) was limited to only one isogenic (hybrid) mouse strain. Other important differences between these studies were that they utilized different exposure routes, doses, and analytical methods. The uncertainties associated with the potential several orders of magnitude difference in TCE metabolism through GSH pathway between species should be considered more carefully.

In addition, multiple *in vitro* studies have been published in the peer reviewed literature. For example, in vitro GSH conjugation data were used to develop prior distributions for GSH conjugation rates, something which was not done for previous PBPK models of TCE. Ample discussion was given to the data generated by the Lash laboratory, which was clearly the most extensive set of data relative to DCVG and DCVC levels in humans. These data indicated DCVG may be formed at levels similar to that of oxidative metabolites in humans. Based on

ED_002435_00003498-00038

these data, the conclusion that the GSH conjugation pathway plays an important role in kidney tumors/toxicity in both rodents and likely in humans is logical.

However the discussion of additional published in vitro studies that show disparately lower results for DCVG formation (beyond mercapturates) was not given a comparable level of attention. For example, the documents pointed out discrepancies between in vitro studies of DCVG formation conducted by the Green and Lash laboratories that report results differing by orders of magnitude. The studies from these labs reported very similar assay conditions using the same strain of rats, but differed in the analytical techniques used (HPLC-UV versus GC-MS). The analysis of these disparate results provided in the review was limited to nondescript statements that the differences may be "related to the different analytical methods employed such as detection of radiolabeled substrate vs. derivatized analytes" (section 3.3.2.7). Unfortunately, the authors of the original studies do not really provide technical explanations for the disparities either. Given such disparate results, the EPA has chosen to use the geometric mean of these two studies in estimating DCVG formation. This decision process and its impacts on the final rates for DCVG formation need to be more clearly spelled out in the discussion of these studies. The discrepancies in estimates of DCVG formation are among the most contentious issues associated with TCE risk analysis. Given the difficult task of drawing conclusions from such different results, the conservative approach the EPA has taken is defensible from a public safety policy perspective. From a strictly scientific perspective however, at a minimum, such large literature disparities call for a more complete discussion of the strengths and limitations of the analytical methodologies used than what is described in the review.

Recommendations:

- The issue of quantitative assessment of the metabolic flux of TCE through the GSH pathway vs. the oxidative metabolism pathway should be considered carefully since uncertainties exist with regard to the extent of formation of the dichlorovinyl metabolites of TCE between humans and rodents. EPA may need to provide appropriate reservations to the conclusions based on the limited data for GSH metabolites.
- The discussion of how each of the in vitro and in vivo data sets were used to estimate DCVG formation parameters for the PBPK model should be more transparent indicating strengths and weaknesses in the database.

ED_002435_00003498-00039

6. Mode of Action

Using the approach outlined in the U.S. EPA Cancer Guidelines (U.S. EPA, 2005a), does EPA's hazard assessment logically, accurately, clearly, and objectively represent and synthesize the available scientific evidence to support its conclusions regarding the mode(s) of action [MOA(s)] of TCE carcinogenicity and non-cancer effects? Specifically, please address the conclusions that the weight of evidence supports a mutagenic MOA for TCE-induced kidney tumors; that a MOA for TCE-induced kidney tumors involving cytotoxicity and compensatory cell proliferation, possibly in combination with a mutagenic MOA, is inadequately supported by available data; that there is inadequate support for PPARα agonism and its sequellae being key events in TCE-induced liver carcinogenesis; that there are inadequate data to specify the key events and MOAs involved in other TCE-induced cancer and non-cancer effects; and that the available data are inadequate to conclude that any of the TCE-induced cancer and non-cancer effects in rodents are not relevant to humans.

Response

6a Hazard Assessment and Mode of Action

The Panel agreed that the IRIS TCE hazard assessment logically, accurately, clearly, and objectively represented and synthesized the available scientific evidence to support its conclusions regarding the mode(s) of action [MOA(s)] of TCE carcinogenicity and non-cancer effects. For each end point, the hazard assessment described the possible MOA and underlying mechanisms. In general, the assessment provided explanations for inconsistent data or lack of results. For example, Section 4.8.3.3.2 provided a comprehensive, detailed, and very useful discussion of potential reasons for inconsistencies in the body of literature on TCE exposure *in utero* and heart defects.

The Panel agreed that the MOA for TCE nephrotoxicity involves conversion of TCE to GSH derived metabolites followed by conversion of the glutathione conjugate (DCVG) to the cysteine conjugate (DCVC) and activation by β-lyase in the kidney to the ultimate nephrotoxic species. Thus, the EPA's hazard assessment logically, accurately, clearly, and objectively represents and synthesizes the available scientific evidence to support the conclusion regarding the MOA for TCE kidney non-cancer toxicity. However, as discussed in the response to charge question 3, the Panel noted that uncertainties remain with regards to quantity of metabolites formed in humans and rodents. The panel concluded that the narrative presentation of the data, along with the evaluation of the strengths and weaknesses of each study, was appropriate with supplemental information.

Recommendations:

- The impact of the inconsistencies in data on the quantity of GSH pathway metabolites formed in humans and rodents should be presented more transparently.
- In the body of the document, MOA information should be systematized and broken down into key events for each proposed MOA. The EPA may consider using a tabular format to facilitate the ease of evaluation. Information on supporting/refuting (if any) evidence (with

ED_002435_00003498-00040

appropriate references indicated), human relevance (if available), and "strength" of each line of evidence/study should be included.

- EPA should consider tabular summaries by specific metabolites when studies used metabolite exposure rather than the parent compound.
- Data gaps should be clearly identified to help guide future research.
- Key conclusions supporting/refuting each key event should be presented in bullet form indicating where in the document a more detailed narrative/tables can be found.

6b MOA for TCE-Induced Kidney Tumors

The Panel agreed that the weight of evidence supported a mutagenic MOA for TCE-induced kidney tumors. However, the Panel concluded that the weight of evidence did not exclude the MOA for TCE-induced kidney tumors involving cytotoxicity and compensatory cell proliferation and including this MOA may more accurately reflect kidney tumor formation than a mutagenic mechanism alone. Furthermore, the combination of cytotoxicity, proliferation and DNA damage together may be a much stronger MOA than the individual components.

Recommendations:

- Modify the relevant text to reflect that the available data do, in fact, provide support for TCE-induced kidney tumors involving cytotoxicity and compensatory cell proliferation, possibly in combination with a mutagenic MOA, although not to the extent that support for a mutagenic MOA was provided.

6c Inadequate Support for PPARα agonism and its sequellae being key events in TCE-induced liver carcinogenesis

The Panel agreed that there was inadequate support for PPARα agonism and its sequellae being key events in TCE-induced human liver carcinogenesis. The Panel noted that PPARα agonists do not elicit peroxisomal proliferation in humans, a pathological change which is a hallmark effect of TCE and other peroxisome proliferators in rodents.

The Panel noted that a number of studies important for consideration of the relevance of PPARα mode of action to human liver carcinogenesis have been completed recently. These include, but are not limited to, studies in PPARα-null mice (Ito et al. 2007; Takashima et al. 2008; Eveillard et al. 2009), PPARα humanized transgenic mice (Morimura et al. 2006), and hepatocyte-specific constitutively-activated PPARα transgenic mice (Yang et al. 2007). The data from these animal models suggest that activation of PPARα is an important but not limiting factor for the development of mouse liver tumors and that additional molecular events may be involved.

The Panel noted the quantitative differences in the affinity of the various isoforms of PPARs to TCA, DCA and other model peroxisome proliferators are well established. Likewise, the quantitative differences in affinity between species are also known.

ED_002435_00003498-00041

Recommendations:

- Graphical or tabular presentation of these data to strengthen the comparative analysis between metabolites and chemicals.
- Including some of the analyses which compare the receptor transactivation potency and the carcinogenic potential of TCA, DCA and other model peroxisome proliferators from Guyton et al (2009) to strengthen the arguments.

6d Inadequate Data to specify Key Events and MOAs involved in other TCE-Induced Cancer and Non-Cancer Effects

The Panel agreed that the data are inadequate to specify the key events and MOAs involved in other TCE-induced cancer (lung, lymphoma) and non-cancer effects (central nervous system, immune system, respiratory tract toxicity, reproductive effects, developmental effects).

6e Human Relevance of TCE-Induced Cancer and Non-Cancer Effects in Rodents

The Panel agreed that the data are inadequate to conclude that any of the TCE-induced cancer and non-cancer effects in rodents are not relevant to humans.

Recommendations:

- The impact of potential overestimation of the extent of the GSH pathway in humans in Section 4.4.7 (Kidney) must be transparent
- The MOA for carcinogenicity should be described as complex rather than unknown in Section 4.5.7.4. Mode of Action (MOA). With respect to conclusions regarding the liver, while the complete MOA in animals may not be clear at this time, complex is a more appropriate descriptor since it is likely that key events from several pathways may operate leading to acute, sub-chronic and chronic liver toxicity of TCE.

ED_002435_00003498-00042

7. Susceptible Populations

Does EPA's hazard assessment logically, accurately, clearly, and objectively represent and synthesize the available scientific evidence to support its conclusions that the factors that could modulate susceptibility to TCE carcinogenicity and non-cancer effects include genetics, lifestage, background and co-exposures, and pre-existing conditions, but that only toxicokinetic variability in adults can be quantified given the available data?

Response

The Panel agreed that Section 4.10 of the Hazard Assessment provided a good review of potentially susceptible populations, and that the identified factors (genetics, lifestage, background, co-exposures and pre-existing conditions) may modulate susceptibility to TCE carcinogenicity and non-cancer effects. The review included adequate data to support factors that modulate exposure and pharmacokinetics in both animals and humans, but few data to demonstrate differing susceptibility to health effects from TCE exposure in either animals or humans. The Panel agreed with the conclusion that the existing data are inadequate to form a conclusion about whether the potentially modulating factors do or do not impact risk estimates for TCE and human health effects. The Panel agreed with the use of standard age-dependent adjustment factors in the protection of children.

***Recommendations*:**

- The Panel disagreed with the statement that "toxicokinetic variability in adults can be quantified given the existing data," as the main study characterizing toxicokinetic variability in adults was small ($n<100$) and was composed of subjects selected non-randomly. The Hazard Assessment document should note the limitations of the adult data for toxicokinetic modeling in terms of uncertainty and possible bias in section 4.10.3, and elsewhere in the document where these data are used for hazard characterization modeling.

- Section 4.10 of the Hazard Assessment should discuss explicitly the lack of data demonstrating modulation of health effects from TCE by the identified factors (genetics, lifestage, background, co-exposures, and pre-existing conditions), and the need for such data in risk assessment.

- EPA should make specific recommendations for studies that would fill the data gap for susceptible groups. For example, epidemiologic studies in which TCE exposure is well-characterized and in which internal comparisons can be made to determine whether there is effect modification, and animal studies comparing subgroups (e.g., based on genetics, obesity, multiple solvent exposures).

- Modulation of TCE exposure-related hypersensitivity dermatitis by genetic variation may be relevant for future study, given results of the study of hypersensitivity dermatitis in Asian workers reported in Li et al. (2007) and increasing industrial chemical exposures in China.

ED_002435_00003498-00043

- The wording in Section 4.10 was often not clear about whether it was describing results for a study that looked at effect modification of the TCE effect or not, as opposed to direct effects of age, gender, etc. Also, the draft document needs to state explicitly where effects of TCE within one subgroup were stated, whether the other subgroup was also examined in the same study.

- The Panel recommended that exposure to solvent mixtures should be added as a potential susceptibility factor (co-exposures) to Section 4.10, since exposure to more than one chemical to the same target organ likely increases risk.

- Section 4.10.2.4.1 (page 4-585) should be more accurately titled 'Obesity', rather than 'Obesity and metabolic syndrome'. As presently written, Section 4.10.2.4.1 gives no clear message as to how obesity affected the kinetics of TCE, and the section should be revised to provide clarification.

ED_002435_00003498-00044

8. Non-Cancer Dose-Response Assessment

EPA's dose-response assessment includes the development of a chronic inhalation Reference Concentration (RfC) and chronic oral Reference Dose (RfD) for non-cancer effects. Please address the following methods and results from EPA's non-cancer dose-response assessment in terms of the extent to which they are clearly and transparently described and technically/scientifically adequate to support EPA's draft RfC and RfD:

a. **The screening, evaluation, and selection of candidate critical studies and effects;**
b. **The points of departure, including those derived from benchmark dose modeling (e.g., selection of dose-response models, benchmark response levels);**
c. **The selected PBPK-based dose metrics for inter-species, intra-species, and route-to-route extrapolation, including the use of body weight to the ¾ power scaling for some dose metrics;**
d. **The selected uncertainty factors;**
e. **The equivalent doses and concentrations for sensitive humans developed from PBPK modeling to replace standard uncertainty factors for inter- and intra-species toxicokinetics, including selection of the 99th percentile for overall uncertainty and variability to represent the toxicokinetically-sensitive individual;**
f. **The qualitative and quantitative characterization of uncertainty and variability;**
g. **The selection of NTP (1988) [toxic nephropathy], NCI (1976) [toxic nephrosis], Woolhiser et al. (2006) [increased kidney weights], Keil et al. (2009) [decreased thymus weights and increased anti-dsDNA and anti-ssDNA antibodies], Peden-Adams et al. (2006 [developmental immunotoxicity], and Johnson et al. (2003) [fetal heart malformations] as the critical studies and effects for non-cancer dose-response assessment;**
h. **The selection of the draft RfC and RfD on the basis of multiple critical effects for which candidate reference values are in a narrow range at the low end of the full range of candidate critical effects, rather than on the basis of the single most sensitive critical effect.**

Response

8a The screening, evaluation, and selection of candidate critical studies and effects

The Panel agreed that the screening, evaluation, and selection of candidate critical studies and effects were generally adequate to support EPA's draft RfC and RfD. The Panel noted that a very large number of studies were considered and included in the tables, and agreed that it was appropriate to evaluate all studies showing dose-response for neurological, kidney, liver, immunologic, respiratory system, reproductive, and developmental effects, and body weight

ED_002435_00003498-00045

change. The Panel's comments on sub-question (a) related primarily to making the information presented in the document more clear and transparent to the reader, rather than to the screening, evaluation, and selection process itself.

The Panel believed that it was important that the reader easily be able to find the details of the studies included in the Chapter 5 tables.

For instance, four different studies with different durations were cited as "Crofton and Zhao (1997)" in Table 4-23, and it was not clear which duration was the basis for the cRfD in Table 5-1. In other cases, it was not stated whether the cRfD or cRfC was based on males or females when both were included in the study, or which strain was the basis when multiple strains were used. For example, from Table 5-2 and the text on p. 5-15 to 5-16, it was not clear which strain, gender, or exposure duration was used for the RfC for increased liver weight based on Kjellstrand et al. (1983b) (discussed in Chapter 4 and Appendix E). Another example for which cross-referencing the different sections of the document would be helpful is the information on the doses in the drinking water study of Keil et al. (2009). In the description of the study on p. 4-395, the doses were given as drinking water concentrations (ppb), but in Table 5-3, the LOAELs for this study were given in mg/kg/day, and the conversion from ppb in drinking water to mg/kg/day is found in Appendix E (p. E-34). A final example of where cross-referencing would be helpful relates to the studies of Carney et al. (2006) and Schwetz et al. (1975). These studies were listed in Table 5-4 (Reproductive Toxicity) because the key effect, decreased maternal body weight gain in a developmental study, was considered a "reproductive" effect. However, these studies were discussed under developmental toxicity in Chapter 4, making it difficult to locate them while reading the section on reproductive toxicity in Chapter 5.

Finally, it was stated on p. 5-1, point (1) that studies with "quantitative dose-response data" were considered. Some of the studies which were considered as the basis for RfCs and RfDs used only one dose of TCE and a control group (for example, Barrett et al., 1992). If a control group and a single treated group were considered adequate "quantitative dose-response data," this should be stated.

Recommendations:

- Chapter 5 should include a list of all non-cancer health effects and studies discussed in Chapter 4, noting those which were considered candidate critical effects and studies.
- Tables 5.1-5.5 should provide cross-references to the table or page in Chapter 4 and/or to the Appendices (such as Appendix E for hepatic studies) where the listed study was discussed, and should include more details (e.g. gender, strain, duration) of the studies selected as the basis for cRfDs and cRfCs when these details were needed to prevent ambiguity.
- Consistent dose units should be used in discussing the same study in different places in the document.

ED_002435_00003498-00046

8b The points of departure, including those derived from benchmark dose modeling (e.g., selection of dose-response models, benchmark response levels)

The Panel agreed that the derivation of the points of departure (PODs) was generally technically/scientifically adequate to support EPA's draft RfC and RfD. The Panel noted that the graphics in Appendix F provided a good presentation of the BMD analyses.

The Panel noted that, although BMD modeling was generally an appropriate approach for POD determination, the results of BMD modeling were very uncertain with some datasets. For example the log-logistic BMD analysis for toxic nephropathy in female Marshall rats in the NTP (1988) study, shown in Figure F-10, may greatly overestimate the risks at low doses. This modeling involved extrapolation from a high LOAEL at which a high percentage of the animals were affected.

Recommendation:

- Chapter 5 should include the information on POD derivation from Table F-13 of Appendix F, including approach, selection criterion and decision points.

8c The selected PBPK-based dose metrics for inter-species, intra-species, and route-to-route extrapolation, including the use of body weight to the ¾ power scaling for some dose metrics

The Panel agreed that the use of PBPK-based dose metrics for inter-species, intra-species, and route-to-route extrapolation modeling were, for the most part, technically and scientifically adequate to support EPA's draft RfC and RfD.

However, it was noted by the Panel that the RfDs and RfCs for kidney endpoints were highly sensitive to the rate of renal bioactivation of DCVC (ABioactDCVCBW34) in human versus rodents. Specifically, it was noted that p-cRfDs/RfCs based on this dose-metric were several hundred-fold lower than RfDs/RfCs for the same endpoints based on applied dose with standard uncertainty factors, while p-cRfDs/RfCs for endpoints based on other dose metrics were much closer to RfDs/RfCs based on applied dose and standard uncertainty factors.

In addition to the strong dependence of the p-cRfDs and p-cRfCs on the rate of renal bioactivation of DCVC, the Panel noted that the uncertainties about the in vitro and in vivo data used to estimate this dose metric were much greater than for other dose metrics. For example, there were very large discrepancies in the rates of human glutathione conjugation reported by Lash et al. (1999a) and Green et al. (1997a).

The Panel understood that the rationale for scaling the dose metric to body weight$^{3/4}$, in conjunction with the interspecies extrapolation, is that the PBPK model predicted the dose rate to the target tissue rather than the internal concentration of TCE. However, this distinction and the associated rationale would likely not be readily apparent to most readers of the document as currently written. Confusion might arise because, for other contaminants, PBPK models were used to estimate serum levels or other metrics of internal concentration, rather than delivered doses, and in such case, scaling of body weight$^{3/4}$ would not be used.

ED_002435_00003498-00047

The discussion of "empirical dosimetry" vs. "concentration equivalence dosimetry"as presented in the draft document would likely not be readily understandable to many readers. Furthermore, since body weight$^{3/4}$ scaling was used for all of the dose metrics discussed in sections 5.1.3.1.1-5.1.3.1.5, it may not be necessary to include the extensive discussion of the two dosimetry approaches in each of these sections.

Recommendations:

- The uncertainty about the rate of human glutathione conjugation found in Lash et al. (1999a) versus Green et al. (1997a) should be highlighted in the current assessment.
- The basis for the renal bioactivation dose metric should be more clearly and transparently presented and discussed in Chapter 3 and other appropriate sections. If this dose metric was derived indirectly from data on other metabolic pathways leading to and/or competing with bioactivation, this should be more clearly discussed.
- The rationale for scaling the dose metric to body weight$^{3/4}$, in conjunction with the interspecies extrapolation based on PBPK modeling, should be presented in a clearer and more transparent way (e.g. on pp. 5-33 – 5-36).
- The discussion of "empirical dosimetry" vs. "concentration equivalence dosimetry" should be made clearer and more transparent (pp. 5-33 – 5-36).

8d Uncertainty factors

The Panel agreed that, in general, the selection of uncertainty factors was clearly and transparently described and technically/scientifically adequate to support EPA's draft RfC and RfD. The uncertainty factors were consistently applied in Tables 5-8 to 5-13.
However it was noted that the uncertainty factors were appropriately applied only if the BMD-PBPK 99th percentile (HEC_{99} and HED_{99}) dose metrics were correctly derived.

The Panel recognized that EPA guidance defines the duration of subchronic rodent studies as 4 weeks to 90 days, and chronic rodent studies as 90 days to 2 years, and noted that some of the subchronic studies considered as the basis for risk assessment were of duration as short as 4 weeks (e.g. Isaacson, 1990). Also, some studies of duration only slightly greater than 90 days (e.g. 18 weeks for Kulig et al., 1987) were classified as chronic, as appropriate under the EPA definition of chronic as longer than 90 days. However, exposures for 18 weeks may not always accurately predict effects for lifetime duration, since 18 weeks is only a small percentage of a two year (104 week) rodent lifespan (less than 18%).

Recommendations:

- The definitions of chronic and subchronic studies should be provided in the document and a citation given.
- The discussion of the subchronic to chronic uncertainty factor on p. 5-6 should be clarified as far as durations of studies considered suitable as the basis of a chronic risk assessment.
- The draft document should include discussion of whether studies in the lower end of the range defined as subchronic (e.g. 4 weeks) are of sufficient duration to be used as the basis for a chronic (lifetime) risk assessment.

ED_002435_00003498-00048

- Studies only slightly longer than the minimum needed to be considered chronic should be noted as such, and the use of an uncertainty factor to account for less than lifetime exposure (of less than the full uncertainty factor of 10) could be considered for studies of such durations, especially for endpoints thought to progress in incidence or severity with time.

8e The equivalent doses and concentrations for sensitive humans developed from PBPK modeling to replace standard uncertainty factors for inter- and intra-species toxicokinetics, including selection of the 99th percentile for overall uncertainty and variability to represent the toxicokinetically-sensitive individual

The Panel generally agreed that this information is clearly and transparently described and technically/scientifically adequate to support EPA's draft RfC and RfD. It was noted that the 99th percentile estimates may be very sensitive to modeling assumptions, such as the choice of prior distribution and the shape of the distribution for population variability in the toxicokinetic parameters. The Panel concluded that the approach used, including the selections of idPODs and the extrapolations from rodent to human followed by consideration of the 99th percentile human estimates, was acceptable to address the sensitive population. It was also concluded that the approach used to simulate a large range of exposure doses in order to obtain the distribution for the relationship between human exposure and internal dose (page 5-68) was appropriate.

Recommendations:

- The Panel noted variability/uncertainty for the toxicokinetically-sensitive individual could be quantified in future work by considering distributions in addition to the distribution of the 99th percentile, such as the 95th percentile.
- A quantile regression looking simultaneously at several quantiles could be developed in the future and presented in future refinements of this assessment.

Additional issue related to sub-questions (c), (d), and (e) discussed by the Panel:

The question arose as to whether the general approach used in the draft document to develop p-RfDs and p-RfCs was appropriately protective, as opposed to being overly conservative. Specifically, the Panel noted that the PODs identified through BMD analysis were based on most sensitive species, strain, and sex, and that the idPODs based on lower bound estimates of the 1% or 5% response in animals were used as a central dose estimate in humans. It was also noted that uncertainty factors for interspecies and intra-human pharmacodynamic variability were applied to the 99th percentile estimates (i.e. the doses for the 1% most pharmacokinetically sensitive humans) of the internal dose (HEC_{99} and HED_{99}).

The Panel endorsed the use of BMD modeling instead of an approach based on an uncertainty factor for LOAEL-to-NOAEL extrapolation, and the use of PBPK modeling instead of default uncertainty factors for inter- and intra-species pharmacokinetic differences, when these approaches were supported by the data. The Panel recognized that these approaches were not

ED_002435_00003498-00049

intended to introduce greater conservatism, but rather to incorporate data to replace default assumptions when appropriate.

There was consensus among the Panel members that the general approach described above was consistent with accepted EPA methodology for RfD/RfC development. It was specifically noted that the uncertainty factors for interspecies and intra-human pharmacodynamic variability were intended to account for variability as well as uncertainty, and that some p-RfDs/p-RfCs based on PBPK modeling were higher than RfDs/RfCs for the same endpoints based on the default methodology. The Panel recommended that HEC_{50} and HED_{50} values be included in Tables 5-8 to 5-13 for informational purposes.

Finally, as discussed further under sub-question (h), the Panel concluded that the consistency of RfDs and RfCs, and that selected endpoints utilized relatively certain dose metrics, gave confidence in the PBPK approach. Dose metrics used for selected endpoinds and their levels of certainty are summarized as follows:

Dose Metric	**Level of Certainty**	**Dose Metric Use**
DCVC activation	uncertain	Renal endpoints
Total metabolism	Relatively certain	Decreased thymus weight, anti-ss and ds DNA antibodies
Total oxidative metabolism	Relatively certain	Cardiac malformations
Applied Dose (dose metric based on PBPK modeling not used		Developmental immunotoxicity

8f The qualitative and quantitative characterization of uncertainty and variability;

The Panel generally agreed that the uncertainties related to the RfC and RfD were clearly and transparently described and technically/scientifically adequate to support EPA's draft RfC and RfD.

It was noted that in the PBPK model, the uncertainty and variability were quantified with the posterior distributions, as appropriate for any Bayesian framework, while in the more general dose-response framework, the uncertainty is characterized with uncertainty factors which account for the main sources of variability and uncertainty. One Panel member commented that it was inconsistent to use a Bayesian approach in the PBPK modeling but not in the dose-response analysis, which uses numeric uncertainty factors, rather than distributions, which represent variability and uncertainty as a fixed effect.

The Panel recognized that the use of uncertainty factors in the TCE assessment followed the currently accepted EPA approach.

ED_002435_00003498-00050

Recommendations:

- The quantitative uncertainty analysis of PBPK model-based dose metrics for LOAEL or NOAEL based PODs (Section 5.1.4.2) should be revised to clarify the objective of this 2-D type analysis, as well as the methodology used.
- In future work, EPA could develop an approach using distribution to characterize uncertainty in a Bayesian framework.

8g The selection of NTP (1988) [toxic nephropathy], NCI (1976) [toxic nephrosis], Woolhiser et al. (2006) [increased kidney weights], Keil et al. (2009) [decreased thymus weights and increased anti-dsDNA and anti-ssDNA antibodies], Peden-Adams et al. (2006 [developmental immunotoxicity], and Johnson et al. (2003) [fetal heart malformations] as the critical studies and effects for non-cancer dose-response assessment

The Panel concluded that the choices of Keil et al. (2009) [decreased thymus weights and increased anti-dsDNA and anti-ssDNA antibodies], Peden-Adams et al. (2006) [developmental immunotoxicity], and Johnson et al. (2003) [fetal heart malformations] as critical studies and effects were technically/scientifically adequate to support EPA's draft RfC and RfD. The Panel noted that questions related to the use of cardiac malformations from Johnson et al. (2003) as a critical endpoint were adequately addressed in the response to Charge Question 3. It was noted that BMD modeling for the data from Johnson et al. (2003) was highly sensitive to model choice. It was also noted that, although a tremendous amount of information was available on liver toxicity, hepatic effects were not a critical endpoint because they were less sensitive than other endpoints.

The Panel expressed concerns about the use of NTP (1988) [toxic nephropathy], NCI (1976) [toxic nephrosis], and Woolhiser et al. (2006) [increased kidney weights] as critical studies and effects. For all three of these studies, uncertainties exist for the PBPK modeling based on renal bioactivation of DCVC, as discussed in sub-question (c) above.

Additional issues related to choice of toxic nephropathy in female Marshall rats from NTP (1988) as a critical effect and study include excessive mortality due to dosing errors and possibly other causes, and a high level of uncertainty in the extrapolation to the BMD due to the use of very high doses and a high incidence (>60%) of toxic nephropathy at both dose levels used. It was also noted that the incidence of this effect was lower in this study in other strains of rats and in male Marshall rats, suggesting that the sensitivity for this effect was highest in the female Marshall rats.

It should be noted that the uncertainties noted by the Panel about the quantitative risk assessment based on toxic nephropathy in NTP (1988) did not indicate that there was uncertainty that TCE caused renal toxicity in this study. The Panel noted that renal cytomegaly, which was not selected as a critical effect, occurred at a very high frequency in both sexes of all four strains used in this study, with 90-100% incidence in almost all dosed groups, and toxic nephropathy also occurred in all treated groups. In contrast, neither renal cytomegaly nor toxic nephropathy was seen in any of 396 control animals in study, which included groups of 50 males and females of the four different rat strains.

ED_002435_00003498-00051

Additional issues related to the choice of toxic nephrosis in mice from NCI (1976) were that BMD analysis was not supported because the effect occurred in nearly 100% of animals in both dose groups, and that a high level of uncertainty was associated with extrapolation from the LOAEL at which nearly 100% animals were affected. It was noted by the Panel that toxic nephrosis did not occur in any control animals of either sex in this study.

Thus, although the numerical values for the RfD and RfC based on the renal endpoints were highly uncertain, TCE could clearly cause renal toxicity in both sexes of the four strains of rats tested, as well as in both sexes of mice, when administered in sufficient doses.

8h The selection of the draft RfC and RfD on the basis of multiple critical effects for which candidate reference values are in a narrow range at the low end of the full range of candidate critical effects, rather than on the basis of the single most sensitive critical effect.

The Panel supported the selection of a draft RfC and a draft RfD based on multiple candidate reference values in a narrow range which was at the low end of the full range of candidate reference values developed, rather than basing these values on the single most sensitive critical endpoint. This approach was supported by the Panel because it was a very robust approach that increases confidence in the final RfC and RfD.

Reference Concentration

As noted in the draft assessment, the proposed RfC, 0.001 ppm (5 ug/m^3), was within a factor of 3 of the p-cRfCs for the six critical endpoints selected. The Panel agreed with the use of PBPK modeling for route-to-route extrapolation for the five p-cRfCs which were based on oral studies.

EPA stated in the draft document (p. 5-83) that there was high confidence in the three p-cRfCs based on renal endpoints [increased kidney weight (Woolhiser et al., 2006), toxic nephrosis (NCI, 1976), and toxic nephropathy, (NTP,1988)] because of the clearly adverse nature of the effects, the fact that two of them were based on chronic studies, and high confidence in its estimate of the dose metric which was clearly related to toxicity, while there was somewhat less confidence in the three p-cRfCs based on other endpoints [decreased thymus weight and anti-DNA antibodies (Keil et al., 2009) and cardiac malformation (Johnson et al., 2003)]. As stated in the response to (g), TCE can clearly cause significant renal toxicity when administered in sufficient doses. Thus, the Panel agreed that kidney toxicity was indisputably a key effect of TCE from a hazard identification perspective. However, as discussed above, the Panel concluded that the three p-cRfCs for renal endpoints were based on an uncertain dose metric, especially in regard to the relative rate of formation of the toxic metabolite in humans and animals. Although there was somewhat less confidence in the immune and cardiac malformation endpoints from a hazard identification perspective, for reasons discussed extensively in other sections of this response, there was sufficient confidence in them to consider them critical endpoints to support the RfC. While the confidence in these three endpoints was less than for the kidney endpoints as far as hazard identification, the three p-cRfCs for these endpoints were based on relatively certain dose metrics.

ED_002435_00003498-00052

Although there was much greater pharmacokinetic uncertainty for the RfCs based on the three studies with renal endpoints [(Woolhiser et al., NCI (1976), and NTP (1988)], they provided additional support for the RfC.

The Panel noted that the same final RfC, 0.001 ppm, was supported by the p-cRfCs based on both the three principal studies (0.0003 ppm, 0.0004 ppm, and 0.003 ppm) and the supporting (kidney) studies (0.0006 ppm, 0.001 ppm, and 0.002 ppm), and concluded that the use of p-cRfCs for multiple critical effects to derive the final recommended RfC reduced uncertainty and better characterizes variability. It was noted that, in general, this approach may create more work for the risk assessors and the users of the risk assessment than use of the single most sensitive endpoint. However, it was recognized that, even if the RfC were to be based on the single most sensitive endpoint, it would be necessary to develop p-cRfCs for multiple endpoints in order to rigorously determine which study and endpoint provides the most sensitive RfC. It was also noted that a single RfC value was provided to users of the risk assessment.

Reference Dose

As discussed in the draft document, the proposed RfD, 0.0004 mg/kg/day, was within 25% of the p-cRfDs for the four critical endpoints selected (toxic nephropathy (NTP, 1988), decreased thymus weight [(Keil et al, 2009), developmental immunotoxicity (Peden-Adams et al., 2006), and cardiac malformations (Johnson et al., 2003)]. All four p-cRfDs were based on oral exposure, and three of them were based on drinking water exposure, a route relevant to environmental exposures. EPA stated in the draft document (p. 5-83) that there was high confidence in the p-cRfD based on a renal endpoint (toxic nephropathy, (NTP, 1988)) because of the clearly adverse nature of the effects in a chronic study and the high confidence in the estimate of the dose metric which was clearly related to toxicity, while there was somewhat less confidence in the three p-cRfCs based on other endpoints [decreased thymus weight (Keil et al., 2009), developmental immunotoxicity (Peden-Adams et al., 2006), and cardiac malformations (Johnson et al., 2003)]. As stated in the response to (g), TCE could clearly cause significant renal toxicity when administered in sufficient doses. Thus, as in the RfC discussion above, the Panel agreed that kidney toxicity was indisputably a key effect of TCE from a hazard identification perspective. However, as discussed above, the Panel concluded that the p-cRfD for the kidney endpoint was based on an uncertain dose metric in regard to the relative rate of formation of the toxic metabolite in humans and animals. Although there was somewhat less confidence in the immune and cardiac malformation endpoints from a hazard identification perspective, for reasons discussed extensively in other sections of this response, there was sufficient confidence in them to consider them critical endpoints to support the RfC. While the confidence in these three endpoints was less than for the kidney endpoints as far as hazard identification, the three p-cRfCs for these endpoints were based on relatively certain dose metrics.

Although there was greater pharmacokinetic uncertainty for the p-cRfD based on the renal endpoint (NTP, 1988), it provided additional support for the final RfD.

The Panel noted that the same final RfD, 0.0004 mg/kg/day was supported by the p-cRfCs based on both the three principal studies (0.0004 mg/kg/day, 0.0005 mg/kg/day, and 0.0005 mg/kg/day) and the supporting (kidney) study (0.0003 mg/kg/day), and concluded that the use of

ED_002435_00003498-00053

p-cRfDs for multiple critical effects to derive the final recommended RfD reduced uncertainty and better characterizes variability. As discussed above for the RfC, it was noted that, in general, this approach may create more work for the risk assessors and the users of the risk assessment than use of the single most sensitive endpoint. However, it was recognized that, even if the RfD were to be based on the single most sensitive endpoint, it would be necessary to develop p-cRfCs for multiple endpoints in order to rigorously determine which study and endpoint would give the most sensitive RfD. It was also noted that a single RfD value was provided to users of the risk assessment.

Recommendations:

- The two endpoints for immune effects from Keil et al. (2009) and the cardiac malformations from Johnson et al. (2003) should be considered the principal studies supporting the RfC.
- The endpoints for immune effects from Keil et al. (2009) and Peden-Adams et al. (2009) and the cardiac malformations from Johnson et al. (2003) should be considered as the principal studies supporting the RfD.

ED_002435_00003498-00054

9. Cancer Dose-Response Assessment

In accordance with the approach outlined in the U.S. EPA Cancer Guidelines and Supplemental Guidance (U.S. EPA, 2005a; U.S. EPA, 2005b), EPA's dose-response assessment includes the development of an inhalation unit risk and oral unit risk for the carcinogenic potency of TCE. Please address the following methods, results, and conclusions from EPA's cancer dose-response assessment in terms of the extent to which they are clearly and transparently described and technically/scientifically adequate to support EPA's draft inhalation and oral unit risks:

a. **the estimation of unit risks for renal cell carcinoma from the Charbotel et al. (2006) case-control study;**
b. **the adjustments of renal cell carcinoma unit risks to account for the added risk of other cancers using the meta-analysis results and Raaschou-Nielsen et al. (2003);**
c. **the estimation of human unit risks from rodent bioassays;**
d. **in accordance with the approach in the U.S. EPA Cancer Guidelines (U.S. EPA, 2005a) and the conclusions as to MOA (above), the use of linear extrapolation from the point of departure (POD) for the cancer dose-response assessment of TCE;**
e. **the applications of PBPK modeling, including the selection of dose metrics and the use of PBPK model predictions for inter-species, intra-species, and route-to-route extrapolation based on internal dose, and their preference over default approaches based on applied dose;**
f. **the qualitative and quantitative characterization of uncertainty and variability;**
g. **the conclusion that the unit risk estimates for TCE based on human epidemiologic data and those based on rodent bioassay data are consistent overall; and,**
h. **the preference for the unit risk estimates for TCE based on human epidemiologic data over those based on rodent bioassay data.**

9a Estimation of Unit Risks for Renal Cell Carcinoma

The Panel agreed that the analysis of the Charbotel et al. (2006) data was well described and scientifically appropriate and that the study should be used to estimate unit risks. The Panel did, however, agree that some more discussion was needed on cutting oils and whether or not it was necessary to adjust for exposure to cutting oils when computing an odds ratio or relative risk relating TCE exposure to kidney cancer. As noted in the document (p. 5-136), Charbotel et al. (2006) found a marginally significant relationship between cutting and petroleum oils and RCC (p-value < 0.1) though the relationship disappeared after adjustment for other variables. Given that there was some suggestion of a relationship, the Panel recommended that the EPA take a closer look at the literature to determine if there were other studies which suggested that exposure to cutting oils was a risk factor for kidney cancer.

ED_002435_00003498-00055

Recommendations:

- The Panel believed that the EPA should provide a more detailed discussion of the limitations of their analysis. In particular, the model described on p. 5-131 made some very restrictive assumptions: linear dose-response and exposure was measured without error. In addition, the life table analysis applied the same estimated RR to each age interval; another restrictive assumption. While the Panel understood that these assumptions were necessary due to limited data, there was inadequate discussion of how violations of these assumptions may affect the results.

- Finally, in constructing the life table, the EPA used background kidney cancer rates in the US though the Charbotel et al. (2006) data were based on a French cohort. Hence, a comparison of background cancer rates in France and the U.S. would be helpful in supporting their conclusions.

9b Adjustment of Renal Cell Carcinoma Unit Risks

The Panel agreed that the analysis and presentation should be accepted in its current form.

9c Estimation of Human Unit Risks from Rodent Bioassays

EPA also calculated cancer unit risk estimates based on chronic bioassays on rats and mice. Five inhalation bioassays and 7 oral bioassays were selected for dose-response analyses. Dose-response modeling using the linearized multistage model was performed using applied doses as well as PBPK model-based internal doses. Bioassays for which time-to-tumor data were available were analyzed using a Multistage Weibull model. A cancer potency estimate for different tumor types combined were derived from bioassays in which there was more than one type of tumor response in the same sex and species. Unit risk estimates based on PBPK model-estimated internal doses were then extrapolated to human population unit risk estimates using the human PBPK model. Based on these results, the most sensitive bioassay (i.e. the one with the greatest unit risk estimate) was considered as a candidate unit risk estimates for TCE.

Recommendations:

- The Panel agreed that the analysis and results were appropriate but recommended that the EPA providemore details about their implementation and potential biases. For instance, in bioassays in which mortality occurred before time to first tumor, the authors simply adjusted their denominators to equal the number alive at time to first tumor. This approach assumed that drop-out prior to time to first tumor was unrelated to future risk of a tumor which could result in biased estimates.
- In addition, more information was needed on the priors used in their Bayesian analysis of combined risk across tumor types.

9d Use of Linear Extrapolation for Cancer Dose-Response Assessment

The Panel agreed that the analysis was consistent with current cancer guidelines. There was sufficient evidence to conclude that a mutagenic MOA was operative for TCE-

ED_002435_00003498-00056

induced kidney tumors, so linear extrapolation was used to derive unit risk estimates for this site. For all other tumor types, linear extrapolation was used as the default approach, in accordance with EPA's cancer guidelines. Hence, the Panel recommended accepting the analysis and presentation of the results in its present form.

9e Application of PBPK Modeling

The Panel agreed that the PBPK models provided valuable information to the risk assessment and agreed that the internal dose should be preferred over applied dose as it was the only way one could, at the mechanistic level, combine information about pharmacokinetics and pharmacodynamics.

9f Qualitative and Quantitative Characterization of Uncertainty and Variability

The Panel agreed that consideration of uncertainty and variability was adequate. The Panel believed that the characterization of uncertainty and variability in the PBPK models was exceptionally strong. Use of AIC to select the best fit model was an adequate way to address model uncertainty. However, the authors' use of a 0.05 significance level for goodness of fit tests was inappropriate; typically, larger type-I error rates are used in such tests (e.g., values between 0.1 and 0.2) since one usually does not want to reject the null hypothesis that the model fits the data.

9g Conclusion on the Consistency of Unit Risk Estimates Based on Human Epidemiologic Data and Rodent Bioassay Data

The Panel agreed with this conclusion. For inhalation, the most sensitive rodent bioassay responses based on the preferred dose metrics ranged from 2.6×10^{-3} per ppm to 8.3×10^{-2} per ppm across the sex/species combinations. For oral exposure, the most sensitive bioassay responses based on the preferred dose metrics ranged from 2.3×10^{-3} per mg/kg/d to 2.5×10^{-1} per mg/kg/d across the sex/species combination. For both routes of exposure, the most sensitive sex/species response was male rat kidney cancer based on the preferred dose metric. When the human epidemiologic data were considered, a cancer inhalation unit risk estimate of 2.2×10^{-2} per ppm and oral unit risk estimate of 5×10^{-2} per mg/kg/d were obtained, which are both within the ranges reported in the aforementioned animal studies.

9h Preference for the Unit Risk Estimates based on Human Epidemiologic Data

The Panel agreed that human data, when available, should be preferred over rodent data when estimating unit risk, since within-species uncertainty was easier to address than between-species uncertainty.

ED_002435_00003498-00057

10. Age-Dependent Adjustment Factors

Based on the conclusions that the weight of evidence supports a mutagenic MOA for TCE-induced kidney cancer and that the MOAs for TCE-induced liver cancer and lymphomas are not known, the Age-Dependent Adjustment Factors (ADAFs) are only applied to the kidney cancer component of the unit risk estimates. Please address the extent to which the recommended approach to applying the ADAFs in this situation is clearly, transparently, and accurately described.

Response

The Panel concluded that EPA has done an excellent job of describing and presenting the ADAF computations for both oral and inhalation situations. Application of ADAFs in the TCE analysis consistently followed recommendations in U.S. EPA Cancer Guidelines (U.S. EPA, 2005a) and Supplemental Guidance (U.S. EPA, 2005b). All of the steps were clearly presented for inhalation exposure. However, the discussion for the oral exposure route was shortened and referred back to the inhalation section, making understanding of the example less easy to follow.

EPA supplemental guidance recommends adjustment for children based on the presumption that children <16 years of age are intrinsically more susceptible than adults to mutagenic carcinogens because of biochemical and physiological factors related to the development of many organs and tissues during this time period; the rationale for the application of an ADAF is not based on the assumption that children have greater exposure on a per body weight basis than adults.

The Panel recognized that EPA wished to maximize utility in its IRIS database for TCE and other chemicals for which ADAFs were applied by providing slope factors and unit risk factors that allow users to compute risks for situation-specific drinking water intake values and for exposures to different age groups. Drinking water concentrations for specified lifetime cancer risk levels (10^{-4}, 10^{-5}, 10^{-6}) are routinely included in IRIS assessments in which ADAFs are not applied; this information is very helpful to public health professionals who use the IRIS database to evaluate situations of water contamination. For IRIS assessments in which ADAFs are applied, as in TCE, it would be useful to users to include this information, using representative drinking water intakes for various age groups. Other drinking water estimates may be used if determined to be more applicable.

The Panel was somewhat concerned that the use of ADAFs was in conflict with the assumptions that underlie the life-table analysis described in Section 5.2.2.1.2 and Appendix H. As indicated on p. 5-131, lines 25-28, the life-table method used to calculate lifetime extra risks from the Charbotel et al. (2006) study assumed that relative risk (RR) was independent of age; as seen in Table H-1, the same estimate of RR was used in each age interval of the life-table to compute the exposed RCC hazard rate (column L). However, ADAFs were applied under the assumption that children were more susceptible to the mutagenic effects which implied that RRs were age-dependent. The Panel recommended that EPA clarify whether this conflict in assumptions truly exists and if so, what impact it

ED_002435_00003498-00058

might have on risk estimation and how it may be resolved in the future. For example, it might make more sense to apply ADAFs during the life-table analysis instead of at the end of the analysis, following estimation of the unit risk.

Recommendations:

- The Panel recommended that the statement on page 5-151, lines 14-18, be expanded to better explain why age-dependent adjustment factors were used for <16 years of age, but not for the elderly, and why EPA did not directly produce age dependent unit risks per mg/kg/d.

- Include all details presented for the inhalation sample calculations as was done for the oral exposure sample calculations.

- IRIS assessments in which ADAFs are applied, such as TCE, should include estimated drinking water concentrations for specified lifetime cancer risk levels (10^{-4}, 10^{-5}, 10^{-6}), using representative drinking water intakes for various age groups, while noting that other drinking water estimates may be used if preferred.

- Include in the documentation a discussion of the perceived conflict between the use of ADAFs and the assumptions underlying the life table analysis of the Charbotel et al. (2006) data.

ED_002435_00003498-00059

11. Additional key studies

Please identify any additional studies that would make a significant impact on the conclusions of the Toxicological Review and should therefore be considered in the assessment of the noncancer and cancer health effects of TCE.

Response

The Panel has identified additional studies to be considered in the assessment:

11a Fetal Cardiac Effects

Some recent publications confirm and reinforce the results obtained in the Johnson et al. (2003) study, so maybe they could be cited to make a stronger argument. They are listed as follows:

Caldwell, PT; Thorne, PA; Johnson, PD et al. (2008) Trichloroethylene disrupts cardiac gene expression and calcium homeostasis in rat myocytes. Toxicol Sci 104: 135-143.

Györke S, Terentyev D. (2008) Modulation of ryanodine receptor by luminal calcium and accessory proteins in health and cardiac disease. Cardiovasc Res. 77(2):245-55. Epub 2007 Oct 15. Review. PubMed PMID: 18006456.

Lehnart SE, Mongillo M, Bellinger A,et al.(2008) Leaky Ca2+ release channel/ryanodine receptor 2 causes seizures and sudden cardiac death in mice. J Clin Invest. 118(6):2230-45. PubMed PMID: 18483626; PubMed Central PMCID: PMC2381750.

Lebeche D, Davidoff AJ, Hajjar RJ. (2008) Interplay between impaired calcium regulation and insulin signaling abnormalities in diabetic cardiomyopathy. Nat Clin Pract Cardiovasc Med. 5(11):715-24. Epub 2008 Sep 23. Review. PubMed PMID: 18813212.

Pace, BM; Lawrence, DA; Behr, MJ; et al. (2005) Neonatal lead exposure changes quality of sperm and number of macrophages in testes of BALB/c mice. Toxicology 210: 247-256.

Yano M, Yamamoto T, Kobayashi S. et al. (2008) Defective Ca2+ cycling as a key pathogenic mechanism of heart failure. Circ J. 72 Suppl A:A22-30. Epub Sep 4. Review. PubMed PMID: 18772523.

11b Kidney Effects

Jacob, S; Héry, M ; Protois, JC ; et al. (2007) New insight into solvent-related end-stage renal disease : occupations, products and types of solvents at risk. Occup Environ Med 64: 843-848.

ED_002435_00003498-00060

12. Research Needs

Please discuss research likely to substantially increase confidence in the database for *future* assessments of TCE.

Response

12a PBPK Model

The Panel concluded the analysis presented in the TCE Review Document defined how EPA expects to use PBPK models to integrate what is known about animal and human biology with TCE mode of action information and available animal and human study data to improve the transparency and accuracy of chemical risk assessments. This is a substantial piece of research and the EPA is to be applauded for this effort. The Panel discussed additional research, which could further improve the TCE risk assessment as well as influence the broader use of PBPD models in risk assessment.

The current model does not account for the temporal variability of the inputs and outputs in humans. Future development of the trichloroethylene PBPK model requires accommodation in the model for inter-individual temporal variability in the population. This is particularly important for modeling both sub-chronic and chronic exposures. If anything, the model should be most accurate in modeling the effects of human exposure over an extended period. Support for adding an inter-individual temporal component to the model can be found in a number of places in the report. For example on page 3-108 (lines 14-16) the text reads: "However, data from Chiu et al. (2007) indicated substantial interoccasion variability, as the same individual exposed to the same concentration on different occasions sometimes had substantial differences in urinary excretion.'' In this paper Chiu et al. (2007), found that there was variability in urinary excretion from the same individual exposed to the same concentration on different occasions. Also, Fisher et al. (1998) (see Table 3-45, page 3-111) documents an occasion in which a female was exposed to both 50 and 100 ppm. Assuming the same subject-specific estimates across the two occasions at different doses resulted in over-prediction at the higher exposure.

To substantially improve the PBPK model for trichloroethylene, EPA should perform a global sensitivity analysis. A formal Bayesian sensitivity analysis is one approach available, but even a more traditional approach to model sensitivity would provide useful information. In addition, the impact of changing priors and/or incorporating correlations among parameters should be examined. Because key dose metrics include upper tails from the predicted posterior distribution, future work should evaluate the sensitivity of the predictions to distributional assumptions for the random effects, for example by replacing uniform priors with normal or lognormal priors or by modifying the bounds on the priors. In future studies, the EPA should perform at least a limited analysis of sensitivity of results to model form (especially sensitivity to different assumed GSH pathways).

However, the hierarchical approach formulated in this report also made important assumptions about the relationship between the PBPK model parameters across the different

ED_002435_00003498-00061

species. These assumptions should be used consistently throughout the model development and not just in the case where there is limited prior information about a particular species.

Recommendations:

- Continue to look for data to support further refinement of priors, especially improving non-informative priors to informative priors and wide priors to narrower priors.

- Develop more efficient sophisticated model algorithms/environments to improve the simulation and reduce run time.

- Incorporate inter-individual temporal variability in future enhancements of the PBPK model for TCE.

- Perform a sensitivity analysis that ranges from the traditional assessment of the impact of parameter changes on final model predictions to an examination of the effect of changing prior distributions.

12b Derivation of RfD and RfC

Recommendations:

- The uncertainty about the rate of human glutathione conjugation found in Lash et al. (1999a) versus Green et al. (1997a) should be highlighted in the current assessment and addressed by sensitivity analysis in future refinements of this assessment.

- The variability/uncertainty for the toxicokinetically-sensitive individual could be quantified in future work by considering distributions in addition to the distribution of the 99th percentile, such as the 95th percentile. A quantile regression looking simultaneously at several quantiles could be developed in the future and presented in future refinements of this assessment.

- In future work, EPA could develop an approach using distribution to characterize uncertainty in a Bayesian framework.

12c Susceptibility Factors

Recommendations:

- There is a need for data examining potential modulation of health effects of TCE by t factors such as genetics, lifestage, background, co-exposures, and pre-existing conditions).

- Modulation of TCE exposure-related hypersensitivity dermatitis by genetic variation may be relevant for future study, given results of the study of hypersensitivity dermatitis in Asian workers reported in Li et al. (2007) and increasing industrial chemical exposures in China.

ED_002435_00003498-00062

12d Male Reproductive System

Recommendations:

- For in utero exposure studies in rodents using lower doses of TCE and metabolites, where effects (carcinogenic and non-carcinogenic) can be observed trans-generationally, attention should be directed to epigenetic changes as possible MOA for TCE-mediated effects on the reproductive systems.

ED_002435_00003498-00063

REFERENCES

Barrett, L; Torch, S; Leray, CL; et al. (1992) Morphometric and Biochemical studies in trigeminal nerves of rat after trichloroethylene or dichloroacetylene oral administration. Neurotoxicology 13:601-614.

Blechzcz, BRA; Gores, GJ (2008) Cholangiocarcinoma. Clin Liver Disease 12 :131-150.

Boyer, As; Finch, WT; Runyan, RB (2000) Trichloroethylene inhibits development of embryonic heart valve precursors in vitro. Toxicol Sci 53: 109-117.

Carney, EW; Thorsrud, BA; Dugard, PH; et al. (2006) Developmental toxicity studies in Crl:Cd (SD) rats following inhalation exposure to trichloroethylene and perchloroethylene. Birth Defects Research (Part B)77:405-412.

Charbotel, B; Fevotte, J; Hours, M; et al. (2006) Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II. Epidemiological aspects. Ann Occup Hyg 50(8): 777-787.

Chiu, WA; Bois, FY (2007) An approximate method for population toxicokinetic analysis with aggregated data. J. Agric Biol Environ Stat 12: 346-363.

Chiu, WA; Okino, MS; Evans, MV (2009) Characterizing uncertainty and population variability in the toxicokinetics of trichloroethylene and metabolites in mice, rats, and humans using an updated database, physiologically based pharmacokinetic (PBPK) model, and Bayesian approach. Toxicol Appl Pharmacol. Doi:10.1016/n.taap.2009.07.032.

Crofton, KM; Zhao, X (1997) The ototoxicity of trichloroethylene: extrapolation and relevance of high-concentration, short-duration animal exposure data. Fundam Appl Toxicol 38(1): 101-106.

El-Serag, HB (2007) Epidemiology of hepatocellular carcinoma in USA. Hepatology Res 37(Suppl 2):S88-S94.

Evans, MV; Chiu, WA; Okino, MS; et al. (2009) Development of an updated PBPK model for trichloroethylene and metabolites in mice, and its application to discern the role of oxidative metabolism in TCE-induced hepatomegaly. Toxicol Appl Pharmacol 236: 329-340.

Eveillard, A; Lasserre, F; de Tayrac, M; et al. (2009) Identification of potential mechanisms of toxicity after di-(2-ethylhexyl)-phthalate (DEHP) adult exposure in the liver using a systems biology approach. Toxicol Appl Pharmacol 236(3): 282-292.

Fisher, JW; Mahle, D; Abbas, R (1998) A human physiologically based pharmacokinetic model for trichloroethylene and its metabolites, trichloroacetic acid and free trichloroethanol. Toxicol Appl Pharmacol 152(2): 339-359.

ED_002435_00003498-00064

Green, T; Dow, J; Ellis, MK; et al. (1997a) The role of glutathione conjugaton in the development of kidney tumours in rats exposed to trichloroethylene. Chem Biol Interact 105(2):99-117.

Greenland, S (2004) Model-based estimation of relative risks and other epidemiologic measures in studies of common outcomes and in case-control studies. Am J Epidemiology 160: 301-305.

Guyton, KZ; Chiu, WA; Bateson, TF; et al. (2009) A reexamination of the PPAR-α activation mode of action as a basis for assessing human cancer risks of environmental contaminants. Environ Health Perspect 117(11): 1664-1672.

Hack, CE; Chiu, WA; Zhao, QJ; et al. (2006) Bayesian population analysis of a harmonized physiologically based pharmacokinetic model of trichloroethylene and its metabolites. Regul. Toxicol Pharmacol 46: 63-83.

Isaacson, LG; Spohler, SA; Taylor, DH (1990) Trichloroethylene affects learning and decreases myelin in the rat hippocampus. Neurotoxicol Teratol 12(4):375-381.

Ito, Y; Yamanoshita, O; Asaeda, N; et al. (2007) Di(2-ethylhexyl)phthalate induced hepatic tumorigenesis through a peroxisome proliferator-activated receptor α-independent pathway. J Occup Health 49:172-182.

Jacob, S; Héry, M ; Protois, JC ; et al. (2007) New insight into solvent-related end-stage renal disease : occupations, products and types of solvents at risk. Occup Environ Med 64: 843-848.

Johnson, PD; Goldberg, SJ; Mays, MZ; et al. (2003) Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. Environ Health Perspect 111(3): 289-292.

Keil, DE; Peden-Adams, MM; Wallace, S; et al. (2009) Assessment of trichloroethylene (TCE) exposure in murine strains genetically-prone and non-prone to develop autoimmune disease. J. Environ Sci Health A Environ Sci Eng Toxic 44:443-453.

Kjellstrand, P; Holmquist, B; Mandahl, N; et al. (1983b) Effects of continuous trichloroethylene inhalation on different strains of mice. Acta Pharmacol Toxicol (Copenh) 53(5):369-374.

Kim, S; Kim, D; Pollack, GM; et al. (2009) Pharmacokinetic analysis of trichloroethylene metabolism in male B6C3F1 mice: Formation and disposition of trichloroacetic acid, S-(1,2-dichlorovinyl)glutathione and S-(1,2-dichlorovinyl)-L-cysteine. Toxicol Appl Pharmacol 238(1):90-99.

Kulig, BM. (1987) The effects of chronic trichloroethylene exposure on neurobehavioral functioning in the rat. Neurotoxicol Teratol 9(2): 171-178.

Lash, LH; Lipscomb, JC; Putt, DA; et al. (1999a) Gluthione conjugation of trichloroethylene in human liver and kidney: kinetics and individual variation. Drug Metab Dispos 27(3):351-359.

ED_002435_00003498-00065

Li, H; Dai, Y; Huang, H; et al. (2007) HLA-B*1301 as a biomarker for genetic susceptibility to hypersensitivity dermatitis induced by trichloroethylene among workers in China. Environ Health Perspect 115(11):1553-1556.

Mishima, N; Hoffman, S; Hill, EG; et al. (2006) Chick embryos exposed to trichloroethylene in an ex vivo culture model show selective defects in early endocardial cushion tissue formation. Birth Defects Res A Clin Mol Terratol 76:517-527.

NCI (National Cancer Institute). (1976) Carcinogenesis bioassay of trichloroethylene. Division of Cancer Cause and Prevention, National Cancer Institute, U.S. Department of Health, Education, and Welfare, DHEW Publication No. (NIH) 76-802, Technical Report Series No. 2,218 pages, NCI-CG-TR-2; NTIS PB254122. Available online at Neghab, M; Qu, S; Bai, CL; et al. (1997) Raised concentration of serum bile acids following occupational exposure to halogenated solvents, 1,1,2-trichloro-1,2,3-trifluoroethane and trichloroethylene. Int Arch Occup Environ Health 70: 187-194.

Niklasson, M: Tham, R; Larsby, B; et al. (1993) Effects of toluene, styrene, trichloroethylene and trichloroethane on the vestibule and opto-oculo motor system in rats. Neurotoxicol Teratol 15(5): 327-334.

Morimura, K; Cheung, C; Ward, JM; et al. (2006) Differential susceptibility of mice humanized for peroxisome proliferator-activated receptor {alpha} to Wy-14,643 induced liver tumorigenesis. Carcinogenesis 27:1074-1080.

NRC (National Research Council) (2006) Key scientific issues in the health risk assessment of trichloroethylene. Washington: National Academy Press.

NTP (National Toxicology Program). (1988) Toxicology and carcinogenesis studies of trichloroethylene (CAS no. 79-01-6) in four strains of rats (ACI, August, Marshall, Osborne-Mendel) (gavage studies). Public Health Service, U.S. Department of Health and Human Services; NTP TR-273; NIH Publication No. 88-2529. Available from the Information Service, Springfield, VA; PB88-218896. Available online at http://ntp/niehs.nih.gov/htdocs/LT_rpts/tr273.pdf

Pace, BM; Lawrence, DA; Behr, MJ; et al. (2005) Neonatal lead exposure changes quality of sperm and number of macrophages in testes of BALB/c mice. Toxicology 210: 247-256.

Peden-Adams, MM; Eudaly, JG; Lee, AM et al. (2008) Developmental effects of trichloroethylene (TCE) on immunity: studies in MRL (+/+) mice. J. Environ Sci Health A Tox Hazard Subst Environ Eng A43 (12):1402-1409.

Raaschou-Nielsen, O; Hansen, J; McLaughlin, JK; et al. (2003) Cancer risk among workers at Danish companies using trichloroethylene: a cohort study. Am J Epidemiol 158(12):1182-1192.

ED_002435_00003498-00066

Ramdhan, DH; Kamijima, M; Yamada, N; et al. (2008) Molecular mechanisms of trichloroethylene-induced hepatoxicity mediated by CYP2E1. Toxicol Appl Pharmacol 231:300-307.

Schwetz, BA; Leong, BKJ; Gehring, PJ (1975) The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform, and methylene chloride on embryonal and fetal development in mice and rats. Toxicol Appl Pharmacol 32: 84-96.

Sweeney, LM; Kirman, CR; Gargas, ML; et al. (2009) Contribution of trichloroacetic acid to liver tumors observed in perchloroethylene (perc)-exposed mice. Toxicology 260(1-3):77-83.

Takashima, K; Ito, Y; Gonzalez, FJ; et al. (2008) Different mechanisms of DEHP-induced hepatocellular adenoma tumorigenesis in wild-type and PPAR alpha-null mice. J Occup Health 50(2):169-180.

Tham, R; Bunnfors, I; Eriksson, B; et al. (1984) Vestibulo ocular disturbances in rats exposed to organic solvents. Acta Pharmacol Toxicol 54(1):58-63.

U.S. EPA (Environmental Protection Agency). (2005a) Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001B. Available online at http://www.epa.gov/iris/backgr-d.htm.ES

U.S. EPA (Environmental Protection Agency). (2005b) Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. Risk Assessment Forum, Washington, DC; EPA/630/R-03/003F. Available online at http:www.epa.gov/iris/backgr-d.htm

Woolhiser, MR; Krieger, SM; Thomas, J; et al. (2006) Trichloroethylene (TCE): Immunotoxicity potential in CD rats following a 4-week vapor inhalation exposure. Dow Chemical Company, Toxicology & Environmental Research and Consulting, Midland, MI, Study ID 031020, July 5, 2006, unpublished.

Yang, Q; Ito, S; Gonzalez, FJ (2007) Hepatocyte-restricted constitutive activation of PPAR alpha induces hepatoproliferation but not hepatocarcinogenesis. Carcinogenesis 28(6):1171-1177.

Zandi-Nekad, K; Eddy, AA; Glassock, RJ; et al (2004) Why is proteinuria an ominous biomarker of progressive kidney disease? Lodmeu Omt 66: S76-89.

Zhang, J and Yu, KF (1998) What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 280: 1690-1691.

ED_002435_00003498-00067

Appendix A: Editorial Comments

Chapter 4

Typographical corrections - In the section on vestibular function – (headaches, dizziness, nausea) there is a typo on p 4-101 that should be corrected. LOAEL 1000 ppm human study (Kylin et al., 1967); 2700 ppm in rats (Tham et al 1984, Niklasson et al., 1993) and rabbits (Tham et al, 1983).

In the kidney section, there needs to be added mention of the 18% increase in kidney weight (in male mice only) seen in the largely immunotoxicity study conducted by Peden-Adams (2008).

Editorial Footnote #1 on page 146: "Elevation of NAG in urine is a sign of proteinuria, and proteinuria is both a sign and a cause of kidney malfunction (Zandi-Nejad et al., 2004). " Beta – N-acetylglucosaminidase (NAG) is an enzyme released by the proximal tubules. Usually total NAG is measured, however, this is comprised of NAG B, which reflects necrosis, and NAG A, which reflects milder forms of proximal tubule perturbation.

The last sentence on p4-173 line 32, 33 needs to be reworded as it is unclear. Additionally, there is a double period on line 23, p4-199.

Chapter 5

p. 5-33, line 25. Does "delivered dose" mean "administered dose"? If so, the term "administered dose" would be clearer.

p. 5-37, line 17. Should "kidney tumors" be changed to "kidney toxicity", since this section discusses non-cancer effects?

p. 5-10, line 9, Barrett et al., 1992, was referred to as an "acute study". On p.4-91, Table 4-21, it was shown that Barrett et al., 1991, was acute and Barrett et al., 1992, was subchronic (10 weeks). This should be corrected.

p. 5-2, point (7), the use of the 99th percentile HEC and HED estimates was discussed. The reason for choosing 99th percentile instead of 95th percentile was explained later in the chapter (p. 5-45). A reference to this discussion (p. 5-48) here would be helpful for clarification, since the 95th percentile was more commonly used in other risk assessments.

Table 5-23, NCI (1976), last bullet. 0.9 ug/m^3 should be corrected to 9 ug/m^3.
p. 5-24, lines 31-32. Change to "within 2-fold of each other" (1.1-1.9 mg/kg/day).

ED_002435_00003498-00068

Print

U. S. SENATOR
David Vitter

Fax Transmittal

To: Paul Anastas, Linda Birnbaum

From: Senator David Vitter

Fax Number:

Date: 1/31/2012

Number of Pages Including Cover: 3

Message:

This Fax Was Sent From The Following Office (Check One Box):

C **Acadiana**
800 Lafayette Street
Lafayette, LA 70501
(337) 262-6898
(337 262-6373 fax

C **Northeast Louisiana**
1217 North 19th Street
Monroe, LA 71201
(318) 325-8120
(318) 325-9165 fax

C **Southeast Louisiana**
2800 Veterans Blvd., Suite 201
Metairie, LA 70002
(504) 589-2753
(504) 589-2607 fax

C **Baton Rouge/River Parishes**
858 Convention Street
Baton Rouge, LA 70802
(225) 383-0331
(225) 383-0952 fax

C **Northwest Louisiana**
920 Pierrmont Road, Suite 113
Shreveport, LA 71106
(318) 861-0437
(318) 861-4865 fax

C **Southwest Louisiana**
3221 Ryan Street, Suite E
Lake Charles, LA 70601
(337) 436-0453
(337) 436-3163 fax

C **Central Louisiana**
2230 S. MacArthur Dr., Suite 4
Alexandria, LA 71301
(318) 448-0169
(318) 448-0189 fax

Website With Email Access
vitter.senate.gov

G **Washington, D.C.**
516 Hart Senate Building
Washington, DC 20510
(202) 224-4623
(202) 228-5061 fax

If you received this fax in error,
please notify us by telephone so that we may arrange for the return of the documents.

Congress of the United States

Washington, DC 20510

January 31, 2012

Dr. Linda Birnbaum
Director
National Toxicology Program
P.O. Box 12233, Mail Drop B2-01
Research Triangle Park, North Carolina 27709

Dr. Paul Anastas
Assistant Administrator
Office of Research and Development
Mail Drop: D343-04
109 Alexander Drive
Durham, NC 27711

Dear Director Birnbaum and Dr. Anastas:

We write to request the release of the joint U.S. Environmental Protection Agency (EPA) and National Institute of Environmental Health Sciences (NIEHS) Pathology Working Group's (PWG) report on research conducted by the Ramazzini Institute in Italy.

In 2010, EPA "halted progress on four pending draft assessments that contained data from the Ramazzini Institute -- including those of methanol, the fuel additives methyl tertiary butyl ether (MTBE) and ethyl tert-butyl ether (ETBE), and the plastic ingredient acrylonitrile -- as well as existing assessments of vinyl chloride and 1,1 dichloroethylene (DCE)."[1] EPA's actions were based on questions raised by an NTP review of "results and methods of Ramazzini's studies on methanol's carcinogenicity."[2] An EPA press release last year announcing the PWG stated that the review would take months and specifically, that the "results will be made public."[3] Yet, we are compelled to write today amidst media reports indicating that while the report was finalized, "Anastas wants to meet with Birnbaum to agree on the interpretation before it is released."[4]

Moreover, EPA's denial of a staff request for a copy of the report has required us to express our frustration with your withholding of important scientific information related to chemical assessments. During this past year, both the National Academy of Sciences (NAS),

---

[1] Maria Hegstad, "Agencies Slated to Soon Release Study on Controversial Italian Cancer Data," InsideEPA.com, January 25, 2012, available at: http://insideepa.com/201201252388232/EPA-Daily-News/Daily-News/agencies-slated-to-soon-release-study-on-controversial-italian-cancer-data/menu-id-95.html (hereinafter Hegstad article)
[2] Ibid.
[3] EPA Press Release, "EPA Announces Plan of Action to Address Four IRIS Assessments," April 11, 2011, available at:
http://yosemite.epa.gov/opa/admpress.nsf/48f0fa7dd51f9e9885257359003f5342/f88161843dbdd2a98525786f005b734b1OpenDocument
[4] Hegstad article, *supra*, note 1

and the Government Accountability Office (GAO), have reported significant concerns with the IRIS program. This has led to bipartisan letters of concern to both of your agencies, as well as the FY 2012 appropriations conference report language directing your agencies to contract with the NAS to conduct additional reviews of the quality of work at NTP and EPA.

It is our understanding that EPA and NTP received the PWG report last November. While your respective agencies continue to deliberate over your interpretation of the PWG report, we request that you provide a copy so that we may review the PWG's findings.

Accordingly, we request a complete and unredacted copy of the PWG report on the Ramazzini Institute, as well as the following:

1. A summary of the weight of evidence placed on the Ramazzini Institute's work in IRIS' assessment for reference doses of methanol.

2. An update on the status of EPA's position on whether to accept recent peer review of the non-cancer effects of methanol.

3. A list of all chemical assessments that include, or may include in the future, work performed at the Ramazzini Institute.

Further, pending a complete analysis of the work performed at the Ramazzini Institute, we urge you to carefully consider all assessments currently under review that incorporate studies from the Ramazzini Institute. In light of the readily available nature of the information we are requesting, we look forward to your response by February 7, 2012.

Sincerely,

David Vitter
United States Senate

Rep. Paul Broun, MD
Chairman
House Science, Space, and Technology
Subcommittee on Investigations & Oversight

James Inhofe
United States Senate

Rep. Andy Harris, MD
Chairman
House Science, Space, and Technology
Subcommittee on Energy & Environment

Message

From: Deener, Kathleen [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=B9A2FF1C086249EA8F6414AFDE8A5E54-DEENER, KATHLEEN]
Sent: 6/24/2014 8:56:21 PM
To: Cogliano, Vincent [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=51f2736376ac4d32bad2fe7cfef2886b-Cogliano, Vincent]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]; Walsh, Debra [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d4fd965338fc4d449c2954945c41de46-Walsh, Debra]; Olden, Kenneth [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8979224c77ea4d559f70cab1688f28aa-Olden, Kenneth]; Flowers, Lynn [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1a4411c874d041b9a8badfc32b91bd70-Flowers, Lynn]; Jones, Samantha [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=eac77fe3b20c4667b8c534c90c15a830-Jones, Samantha]; Perovich, Gina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6e3c19d7f4db41bfa2477aa27ad83945-Perovich, Gina]; Sams, Reeder [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7d5b479ccd894cea99ae55df20de6971-Sams, Reeder]
Subject: FW: Low dose arsenic study --Communications outreach
Attachments: Arsenic_Study_Briefing_Participants_Final.docx; arsenic press releaseJune23.docx; ArsenicTalking pointsJune24.docx

Heads up re: soon to be published NTP study on low level arsenic exposure. It will be online next week in the Archives of Toxicology. NIH has shared their press release and talking points.

Kacee Deener, MPH
Communications Director
National Center for Environmental Assessment
(ph) 703.347.8514 | (blackberry) 202.510.1490
deener.kathleen@epa.gov

From: Mackar, Robin M (NIH/NIEHS) [E] [mailto:rmackar@niehs.nih.gov]
Sent: Tuesday, June 24, 2014 2:30 PM
To: Bartolucci, Noah (FDA/OC); Burden, Bernadette (CDC/OD/OADC); Deener, Kathleen; Linnenbrink, Monica; Mattas-Curry, Lahne
Cc: Flowers, Christine B (NIH/NIEHS) [E]; bucher@niehs.nih.gov; wolfe@niehs.nih.gov; Birnbaum, Linda (NIH/NIEHS) [E]; Waalkes, Mike (NIH/NIEHS) [E]; Miller, Mark (NIH/NIEHS) [E]
Subject: Low dose arsenic study --Communications outreach

Good afternoon.

For those of you who don't know me, I work in the communications office that supports the National Institute of Environmental Health Sciences and the National Toxicology Program.

We have a low dose arsenic paper that is coming out online next week in the journal Archives of Toxicology. The paper "Lung tumors in mice induced by "whole life" inorganic arsenic exposure at human relevant doses" is the first study to show that mice exposed to human relevant does of arsenic in drinking water (50 ppb and 500 ppb) developed lung cancer as adults.

Several weeks ago NTP briefed program staff from your agency about the study findings (see attached list). At the time, we told them as soon as we knew the paper was accepted we would let them know and work with their

communications staff to prepare for any media and public interest this paper may generate. We just heard the paper was accepted and will be online very shortly. The journal is not planning to do its own press release.

We have drafted a press release, attached, that we would like to get approved by **NIH to release on July 2th**. Before starting this through the NIH/HHS review process tomorrow afternoon or Thursday morning, we would like to give you an opportunity to take a quick look.

Also attached is some talking points and internal questions and answers we developed for our spokespeople (Dr. Mike Waalkes, lead author and Chief, NTP Toxicology Laboratory and NIEHS/NTP Director Linda Birnbaum)

Please let me know if you have any questions or need additional information. This is coming sooner than we anticipated, but want us all to be prepared as possible to respond to inquiries. Christine Bruske Flowers, NIEHS Communications Director, and I will be facilitating the media inquiries.

Attachment 1 - Arsenic study Briefing Participants
Attachment 2 – Draft NIEHS press release
Attachment 3 – Internal talking points/q's and a's

Robin Mackar
Office of Communications and Public Liaison
National Institute of Environmental Health Sciences/National Toxicology Program
National Institutes of Health
PO Box 12233, Research Triangle Park, NC 27709
919-541-0073; rmackar@niehs.nih.gov
NIH . . . Turning Discovery Into Health

Message

From: Landrigan, Philip [phil.landrigan@mssm.edu]
Sent: 8/12/2014 1:36:18 PM
To: Fiorella Belpoggi - Istituto Ramazzini [belpoggif@ramazzini.it]
CC: Huff, James (NIH/NIEHS) [G] [huff1@niehs.nih.gov]; Lunn, Ruth (NIH/NIEHS) [E] [lunn@niehs.nih.gov]; Dana Loomis [LoomisD@iarc.fr]; Neela Guha [guhan@iarc.fr]; kmb@sciencecorps.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=87242a9a179c44f192044d296259f748-kmb@science]; Kathryn Guyton [GuytonK@iarc.fr]; Cooper, Glinda [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=72c2e0a2283f42cc8f8cf3b22387505e-Cooper, Glinda]; Cogliano, Vincent [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=51f2736376ac4d32bad2fe7cfef2886b-Cogliano, Vincent]; morando soffritti [soffrittim@ramazzini.it]; frank mirer [fmirer@hunter.cuny.edu]; peter infante [pinfante@starpower.net]; Elihu D Richter [elihudrichter@gmail.com]; danny teitelbaum [toxdoc@ix.netcom.com]; Kathleen Ruff [kruff@bulkley.net]; joe ladou [drjoeladou@gmail.com]; Lauren Zeise [laurenzeise@gmail.com]; jsass@nrdc.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=71d3e1cd2cfe4b2bae6d327b1eacf155-jsass@nrdc.org]; colin soskoine [Colin.Soskolne@ualberta.ca]; Caldwell, Jane [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7a8f79de73e34dbaba09a77eae794461-Caldwell, Jane]; Dunnick, June (NIH/NIEHS) [E] [dunnickj@niehs.nih.gov]; bucher@niehs.nih.gov [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c421f94a4d20447ca67ed6ab9ee8b03a-bucher@niehs.nih.gov]; Birnbaum, Linda (NIH/NIEHS) [E] [birnbaumls@niehs.nih.gov]
Subject: Re: R: NAS formaldehyde -- endorses RoC/NTP [AGAIN!!!!!]

Bravo, Fiorella

Sent from my iPhone

> On Aug 12, 2014, at 8:09 AM, "Fiorella Belpoggi - Istituto Ramazzini" <belpoggif@ramazzini.it> wrote:
>
> Dear all,
> We published our paper on formaldehyde carcinogenicity in 1989, after 25
> years we take our revenge! Long term bioassays are predictive, it is just a
> matter of time...
>
> Dr. Fiorella Belpoggi
> Director
> Cesare Maltoni Cancer Research Center
> Ramazzini Institute
> Via Saliceto, 3
> 40010 Bentivoglio (Bologna)
> Italy
> Tel. +39-051-6640460
> Fax. +39-051-6640223
> e-mail: belpoggif@ramazzini.it
> www.ramazzini.org
>
> Confidentiality Statement:This email message, including any attachments, is
> for the sole use of the intended recipient(s) and may contain confidential
> and privileged information. Any unauthorized use, disclosure or distribution
> is prohibited. If you are not the intended recipient, please contact the
> sender by reply email and destroy all copies of the original message.
>
> -----Messaggio originale-----
> Da: Huff, James (NIH/NIEHS) [G] [mailto:huff1@niehs.nih.gov]
> Inviato: venerdì 8 agosto 2014 17:40
> A: Lunn, Ruth (NIH/NIEHS) [E]; Dana Loomis; Neela Guha; kathy burns; Kathryn
> Guyton; Cooper, Glinda; vincent cogliano; fiorella belpoggi; morando
> soffritti; frank mirer; peter infante; Elihu D Richter; danny teitelbaum;
> phil landrigan; Kathleen Ruff; joe ladou; Lauren Zeise; jennifer sass
> [NRDC]; colin soskoine; Jane Caldwell; Dunnick, June (NIH/NIEHS) [E]
> Cc: Bucher, John (NIH/NIEHS) [E]; Birnbaum, Linda (NIH/NIEHS) [E]
> Oggetto: NAS formaldehyde -- endorses RoC/NTP [AGAIN!!!!!]
>
> ruth
> way to go - two in a row - wonderful.
> Onwards and upwards for PUBLIC HEALTH.

> james
>
>
> On /Fri8Aug/14 11:17 AM, "Lunn, Ruth (NIH/NIEHS) [E]" <lunn@niehs.nih.gov>
> wrote:
>
>
> Here is the brief release NAS has on their website about the formaldehyde
> report.
>
>
https://urldefense.proofpoint.com/v1/url?u=http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID%3D18948&k=PFsgZv%2B4TEaU9fTpAWpLNw%3D%3D%0A&r=XlW7xWdP1tUIjrsQYpVoUqD02yeMZWjRHRTD3XqH0Lc%3D%0A&m=rHMHHMK6doZX4nVDALN8%2FWZ39h4Fo7L5oLDUb9wv5L4%3D%0A&s=ddf61a43568425e7bdfb542dc8c50c6f4035b37f45872261971e25a03e8ba2f0
>
> [cid:3490342740_2317033]FOR IMMEDIATE RELEASE Formaldehyde Confirmed as
> Known Human Carcinogen A new report
>
<https://urldefense.proofpoint.com/v1/url?u=http://www.nap.edu/catalog.php?record_id%3D18948&k=PFsgZv%2B4TEaU9fTpAWpLNw%3D%3D%0A&r=XlW7xWdP1tUIjrsQYpVoUqD02yeMZWjRHRTD3XqH0Lc%3D%0A&m=rHMHHMK6doZX4nVDALN8%2FWZ39h4Fo7L5oLDUb9wv5L4%3D%0A&s=3cc7d928bcd498fa2bbc3ac14ebea119da62d09ca9ea39727eea2f10bc0a9c60> from the
National Research
> Council has upheld the listing of formaldehyde as "known to be a human
> carcinogen" in the National Toxicology Program 12th Report on Carcinogens
> (RoC). The committee that wrote the Research Council report found that the
> listing is supported by sufficient evidence from human studies that indicate
> a causal relationship between exposure to the chemical and at least one type
> of human cancer. The committee reached the same conclusion after conducting
> both a peer review of the RoC and an independent assessment of the
> formaldehyde literature. The NTP is an interagency program that produces the
> RoC. Formaldehyde is a substance of interest for the RoC because many
> people in the United States are exposed, either through environmental
> sources such as combustion processes and tobacco smoke, or in occupational
> settings that include the furniture, textile, and construction industries.
> Formaldehyde is also produced naturally by human cells. It was first listed
> by NTP as "reasonably anticipated to be a human carcinogen" in 1981 before
> being upgraded to "known carcinogen" in the 2011 RoC. Based on RoC listing
> criteria, a substance can be classified as known to be a human carcinogen if
> there is sufficient evidence of carcinogenicity from studies in humans that
> indicate a causal relationship between exposure to the substance and human
> cancer. In its peer review of the RoC, the Research Council committee found
> that NTP described the strengths and weaknesses of relevant studies in a way
> that was consistent and balanced, but noted that it would be more complete
> if it also discussed why weaker evidence did not alter the conclusion. In
> addition, NTP did not include a description of its interpretation of
> "limited" and "sufficient" evidence for human studies, which factors into
> whether a chemical is listed as reasonably anticipated to be or known to be
> a human carcinogen. The Research Council committee defined "limited
> evidence" in humans to be two or more studies of varied design that suggest
> an association between formaldehyde and a specific type of cancer but that
> cannot exclude alternative explanations such as chance, bias, or confounding
> factors. Evidence was deemed to be "sufficient" if those alternative
> explanations could be ruled out with confidence. On this basis, the
> committee agreed that there is sufficient evidence to support an association
> between formaldehyde and cancer in humans. In its independent assessment,
> the committee considered human, animal, and mechanistic studies published
> through November 8, 2013 that focused on nasopharyngeal cancer, sinonasal
> cancer, and myeloid leukemia. It found sufficient evidence of
> carcinogenicity in human and animal studies and "convincing relevant
> information" that formaldehyde induces mechanistic events associated with
> the development of cancer in humans. Based on these findings, the committee
> concluded that formaldehyde should be listed in the RoC as "known to be a
> human carcinogen." Contacts: Lauren Rugani, Media Officer Christina
> Anderson, Media Assistant Office of News and Public Information
> 202-334-2138; e-mail news@nas.edu <mailto:news@nas.edu>
> www.national-academies.org/newsroom
> <https://urldefense.proofpoint.com/v1/url?u=http://www.national-
academies.org/newsroom&k=PFsgZv%2B4TEaU9fTpAWpLNw%3D%3D%0A&r=XlW7xWdP1tUIjrsQYpVoUqD02yeMZWjRHRTD3XqH0Lc%3D%0A&m=rHMHHMK6doZX4nVDALN8%2FWZ39h4Fo7L5oLDUb9wv5L4%3D%0A&s=7695a2131ceb6cdcad529112480bccbd73269a13f7cb3959393af131f26f4349> Twitter: @NAS_news
>
<https://urldefense.proofpoint.com/v1/url?u=https://twitter.com/NAS_news&k=PFsgZv%2B4TEaU9fTpAWpLNw%3D%3D%0A&r=XlW7xWdP1tUIjrsQYpVoUqD02yeMZWjRHRTD3XqH0Lc%3D%0A&m=rHMHHMK6doZX4nVDALN8%2FWZ39h4Fo7L5oLDUb9wv5L4%3D%0A&s=671fdf1018306daa799603e81ab1e631fbb9f165cb4e51d6cf1f260469cd0fe3> and @NASciences
>
<https://urldefense.proofpoint.com/v1/url?u=https://twitter.com/NASciences&k=PFsgZv%2B4TEaU9fTpAWpLNw%3D%

3D%0A&r=XlW7xWdP1tUIjrsQYpVoUqD02yeMZWjRHRTD3XqH0Lc%3D%0A&m=rHMHHMK6doZX4nVDALN8%2FWZ39h4Fo7L5oLDUb9wv5L4
%3D%0A&s=d33de55d7f69cba7975099a7a10cea44bdeffc2575cde86a411e38c80eda8d7a> RSS feed:
>
https://urldefense.proofpoint.com/v1/url?u=http://www.nationalacademies.org/rss/index.html&k=PFsgZv%2B4TE
aU9fTpAWpLNw%3D%3D%0A&r=XlW7xWdP1tUIjrsQYpVoUqD02yeMZWjRHRTD3XqH0Lc%3D%0A&m=rHMHHMK6doZX4nVDALN8%2FWZ39h4
Fo7L5oLDUb9wv5L4%3D%0A&s=11a684970a8f166b62f769c947e5a9765cb2e18c065a4211a60a31455c7e7137
>
<https://urldefense.proofpoint.com/v1/url?u=http://www.nationalacademies.org/rss/index.html&k=PFsgZv%2B4T
EaU9fTpAWpLNw%3D%3D%0A&r=XlW7xWdP1tUIjrsQYpVoUqD02yeMZWjRHRTD3XqH0Lc%3D%0A&m=rHMHHMK6doZX4nVDALN8%2FWZ39h
4Fo7L5oLDUb9wv5L4%3D%0A&s=11a684970a8f166b62f769c947e5a9765cb2e18c065a4211a60a31455c7e7137> Flickr:
>
https://urldefense.proofpoint.com/v1/url?u=http://www.flickr.com/photos/nationalacademyofsciences/sets&k=
PFsgZv%2B4TEaU9fTpAWpLNw%3D%3D%0A&r=XlW7xWdP1tUIjrsQYpVoUqD02yeMZWjRHRTD3XqH0Lc%3D%0A&m=rHMHHMK6doZX4nVDA
LN8%2FWZ39h4Fo7L5oLDUb9wv5L4%3D%0A&s=23a4eab1f79597f8cd9614c5ab7255cf0a51bd83109d20d86d727d840ae6a9b8
>
<https://urldefense.proofpoint.com/v1/url?u=http://www.flickr.com/photos/nationalacademyofsciences/sets&k
=PFsgZv%2B4TEaU9fTpAWpLNw%3D%3D%0A&r=XlW7xWdP1tUIjrsQYpVoUqD02yeMZWjRHRTD3XqH0Lc%3D%0A&m=rHMHHMK6doZX4nVD
ALN8%2FWZ39h4Fo7L5oLDUb9wv5L4%3D%0A&s=23a4eab1f79597f8cd9614c5ab7255cf0a51bd83109d20d86d727d840ae6a9b8>
> _____
> _____ Pre-publication copies of Review of the Formaldehyde Assessment in
> the National Toxicology Program 12th Report on Carcinogens
>
<https://urldefense.proofpoint.com/v1/url?u=http://www.nap.edu/catalog.php?record_id%3D18948&k=PFsgZv%2B4
TEaU9fTpAWpLNw%3D%3D%0A&r=XlW7xWdP1tUIjrsQYpVoUqD02yeMZWjRHRTD3XqH0Lc%3D%0A&m=rHMHHMK6doZX4nVDALN8%2FWZ39
h4Fo7L5oLDUb9wv5L4%3D%0A&s=3cc7d928bcd498fa2bbc3ac14ebea119da62d09ca9ea39727eea2f10bc0a9c60> available
from the National
> Academies Press on the Internet at www.nap.edu
<https://urldefense.proofpoint.com/v1/url?u=http://www.nap.edu/&k=PFsgZv%2B4TEaU9fTpAWpLNw%3D%3D%0A&r=XlW
7xWdP1tUIjrsQYpVoUqD02yeMZWjRHRTD3XqH0Lc%3D%0A&m=rHMHHMK6doZX4nVDALN8%2FWZ39h4Fo7L5oLDUb9wv5L4%3D%0A&s=e4
28020cbb5246137266757c2e219bfea14de76342ff164a028a4838547890d0> or by
> calling 202-334-3313 or 1-800-624-6242. Reporters may obtain a copy from
> the Office of News and Public Information (contacts listed above). # #
> # NATIONAL RESEARCH COUNCIL Division on Earth and Life Studies Board on
> Environmental Studies and Toxicology Committee to Review the Formaldehyde
> Assessment in the National Toxicology Program 12th Report on Carcinogens
> Alfred O. Berg*(chair) Professor and Chair Emeritus Department of Family
> Medicine University of Washington Seattle John C. Bailar III* Professor
> Emeritus University of Chicago Mitchellville, Md. A. Jay Gandolfi Professor
> Emeritus College of Pharmacy University of Arizona Tucson David Kriebel
> Co-Director Lowell Center for Sustainable Production; and Professor
> Department of Work Environment University of Massachusetts Lowell John B.
> Morris Board of Trustees Distinguished Professor; Professor of Pharmacology
> and Toxicology Department of Pharmaceutical Sciences; and Interim Dean
> University of Connecticut School of Pharmacy Storrs Kent E. Pinkerton
> Director Center for Health and the Environment; Professor Department of
> Pediatrics School of Medicine; and Professor Department of Anatomy,
> Physiology, and Cell Biology School of Veterinary Medicine University of
> California Davis Ivan Rusyn Professor Department of Environmental Sciences
> and Engineering; Director Laboratory of Environmental Genomics; and Director
> Carolina Center for Computational Toxicology Gillings School of Global
> Public Health University of North Carolina Chapel Hill Toshihiro Shioda
> Associate Professor of Medicine Harvard Medical School; and Director
> Molecular Profiling Laboratory Massachusetts General Hospital Cancer Center
> Charlestown Thomas J. Smith Professor Emeritus Department of Environmental
> Health Environmental Science and Engineering Program Harvard School of
> Public Health Boston Meir Wetzler Chief Division of Leukemia Department of
> Medicine Roswell Park Cancer Institute; and Professor of Medicine School of
> Medicine and Biomedical Sciences University at Buffalo State University of
> New York Buffalo Lauren Zeise Deputy Director for Scientific Affairs Office
> of Environmental Health Hazard Assessment California Environmental
> Protection Agency Oakland Patrick Zweidler-McKay Section Chief Pediatric
> Leukemia and Lymphoma; and Associate Professor Department of Medicine
> Division of Pediatrics The Children's Cancer Hospital The University of
> Texas M.D. Anderson Cancer Center Houston STAFF Heidi Murray-Smith Study
> Director _____ *Member, Institute of Medicine
>
>
>
> Robin Mackar
> Office of Communications and Public Liaison National Institute of
> Environmental Health Sciences National Institutes of Health PO Box 12233,
> Research Triangle Park, NC 27709 919-541-0073; rmackar@niehs.nih.gov NIH . .
> . Turning Discovery Into Health
>
>
>
>

Message

From: Kathy Burns [kmb@sciencecorps.org]
Sent: 8/12/2014 6:45:33 PM
To: 'Fiorella Belpoggi - Istituto Ramazzini' [belpoggif@ramazzini.it]; 'Huff, James (NIH/NIEHS) [G]' [huff1@niehs.nih.gov]; 'Lunn, Ruth (NIH/NIEHS) [E]' [lunn@niehs.nih.gov]; 'Dana Loomis' [LoomisD@iarc.fr]; 'Neela Guha' [guhan@iarc.fr]; 'Kathryn Guyton' [GuytonK@iarc.fr]; Cooper, Glinda [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=72c2e0a2283f42cc8f8cf3b22387505e-Cooper, Glinda]; Cogliano, Vincent [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=51f2736376ac4d32bad2fe7cfef2886b-Cogliano, Vincent]; 'morando soffritti' [soffrittim@ramazzini.it]; 'frank mirer' [fmirer@hunter.cuny.edu]; 'peter infante' [pinfante@starpower.net]; 'Elihu D Richter' [elihudrichter@gmail.com]; 'danny teitelbaum' [toxdoc@ix.netcom.com]; 'phil landrigan' [phil.landrigan@mssm.edu]; 'Kathleen Ruff' [kruff@bulkley.net]; 'Lauren Zeise' [laurenzeise@gmail.com]; jsass@nrdc.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=71d3e1cd2cfe4b2bae6d327b1eacf155-jsass@nrdc.org]; 'colin soskoine' [Colin.Soskolne@ualberta.ca]; Caldwell, Jane [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7a8f79de73e34dbaba09a77eae794461-Caldwell, Jane]; 'Dunnick, June (NIH/NIEHS) [E]' [dunnickj@niehs.nih.gov]
CC: bucher@niehs.nih.gov [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c421f94a4d20447ca67ed6ab9ee8b03a-bucher@niehs.nih.gov]; 'Birnbaum, Linda (NIH/NIEHS) [E]' [birnbaumls@niehs.nih.gov]
Subject: Ramazzini, predictive models and some humility

Dear Fiorella,
I'm very glad that you pointed out that it has been 25 years since your study was published. Imagine the potential lives saved and suffering avoided if there was reliance on your study and others that provided fair warning, but were insufficiently relied on in policy actions. It is becoming more difficult to obtain protective policies, even when overwhelming evidence of the potential for harm exists.

But the question I want to pose is whether we still need to rely on the types of bioassays you conducted. Can the now-numerous predictive toxicity models adequately characterize the range of toxic effects from chemicals such as formaldehyde? Animal studies are ethically objectionable to many of us and far slower than ideal (though nothing compared to industry-orchestrated delays). But is there sufficiently sophisticated knowledge of biological interactions to (largely) walk away from bioassays in favor of algorithms? Do we really know enough about cell signaling, RoS impacts, concurrent organ pathology induction and a host of other processes - <u>and their interactions</u> - to have confidence in the modeling conclusions?

Your work and that of others was fundamentally important and I think it will continue to be so for the foreseeable future.
Regards,
Kathy

Confidential Communication.

-----Original Message-----
From: Fiorella Belpoggi - Istituto Ramazzini [mailto:belpoggif@ramazzini.it]
Sent: Tuesday, August 12, 2014 8:09 AM
To: 'Huff, James (NIH/NIEHS) [G]'; 'Lunn, Ruth (NIH/NIEHS) [E]'; 'Dana Loomis'; 'Neela Guha'; 'kathy burns'; 'Kathryn Guyton'; 'Cooper, Glinda'; 'vincent cogliano'; 'morando soffritti'; 'frank mirer'; 'peter infante'; 'Elihu D Richter'; 'danny teitelbaum'; 'phil landrigan'; 'Kathleen Ruff'; 'joe ladou'; 'Lauren Zeise'; 'jennifer sass [NRDC]'; 'colin soskoine'; 'Jane Caldwell'; 'Dunnick, June (NIH/NIEHS) [E]'
Cc: 'Bucher, John (NIH/NIEHS) [E]'; 'Birnbaum, Linda (NIH/NIEHS) [E]'
Subject: R: NAS formaldehyde -- endorses RoC/NTP [AGAIN!!!!!]

Dear all,
We published our paper on formaldehyde carcinogenicity in 1989, after 25 years we take our revenge! Long term bioassays are predictive, it is just a matter of time...

Dr. Fiorella Belpoggi
Director
Cesare Maltoni Cancer Research Center
Ramazzini Institute
Via Saliceto, 3
40010 Bentivoglio (Bologna)
Italy
Tel. +39-051-6640460
Fax. +39-051-6640223
e-mail: belpoggif@ramazzini.it
www.ramazzini.org

Confidentiality Statement:This email message, including any attachments, is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized use, disclosure or distribution is prohibited. If you are not the intended recipient, please contact the sender by reply email and destroy all copies of the original message.

-----Messaggio originale-----
Da: Huff, James (NIH/NIEHS) [G] [mailto:huff1@niehs.nih.gov]
Inviato: venerdì 8 agosto 2014 17:40
A: Lunn, Ruth (NIH/NIEHS) [E]; Dana Loomis; Neela Guha; kathy burns; Kathryn Guyton; Cooper, Glinda; vincent cogliano; fiorella belpoggi; morando soffritti; frank mirer; peter infante; Elihu D Richter; danny teitelbaum; phil landrigan; Kathleen Ruff; joe ladou; Lauren Zeise; jennifer sass [NRDC]; colin soskoine; Jane Caldwell; Dunnick, June (NIH/NIEHS) [E]
Cc: Bucher, John (NIH/NIEHS) [E]; Birnbaum, Linda (NIH/NIEHS) [E]
Oggetto: NAS formaldehyde -- endorses RoC/NTP [AGAIN!!!!!]

ruth
way to go — two in a row — wonderful.
Onwards and upwards for PUBLIC HEALTH.
james

On /Fri8Aug/14 11:17 AM, "Lunn, Ruth (NIH/NIEHS) [E]" <lunn@niehs.nih.gov> wrote:

Here is the brief release NAS has on their website about the formaldehyde report.

http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=18948

[cid:3490342740_2317033]FOR IMMEDIATE RELEASE Formaldehyde Confirmed as Known Human Carcinogen A new report

<http://www.nap.edu/catalog.php?record_id=18948> from the National Research Council has upheld the listing of formaldehyde as "known to be a human carcinogen" in the National Toxicology Program 12th Report on Carcinogens (RoC). The committee that wrote the Research Council report found that the listing is supported by sufficient evidence from human studies that indicate a causal relationship between exposure to the chemical and at least one type of human cancer. The committee reached the same conclusion after conducting both a peer review of the RoC and an independent assessment of the formaldehyde literature. The NTP is an interagency program that produces the RoC. Formaldehyde is a substance of interest for the RoC because many people in the United States are exposed, either through environmental sources such as combustion processes and tobacco smoke, or in occupational settings that include the furniture, textile, and construction industries. Formaldehyde is also produced naturally by human cells. It was first listed by NTP as "reasonably anticipated to be a human carcinogen" in 1981 before being upgraded to "known carcinogen" in the 2011 RoC. Based on RoC listing criteria, a substance can be classified as known to be a human carcinogen if there is sufficient evidence of carcinogenicity from studies in humans that indicate a causal relationship between exposure to the substance and human cancer. In its peer review of the RoC, the Research Council committee found that NTP described the strengths and weaknesses of relevant studies in a way that was consistent and balanced, but noted that it would be more complete if it also discussed why weaker evidence did not alter the conclusion. In addition, NTP did not include a description of its interpretation of "limited" and "sufficient" evidence for human studies, which factors into whether a chemical is listed as reasonably anticipated to be or known to be a human carcinogen. The Research Council committee defined "limited evidence" in humans to be two or more studies of varied design that suggest an association between formaldehyde and a specific type of cancer but that cannot exclude alternative explanations such as chance, bias, or confounding factors. Evidence was deemed to be "sufficient" if those alternative explanations could be ruled out with confidence. On this basis, the committee agreed that there is sufficient evidence to support an association between formaldehyde and cancer in humans. In its independent assessment, the committee considered human, animal, and mechanistic studies published through November 8, 2013 that focused on nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia. It found sufficient evidence of carcinogenicity in human and animal studies and "convincing relevant information" that formaldehyde induces mechanistic events associated with the development of cancer in humans. Based on these findings, the committee concluded that formaldehyde should be listed in the RoC as "known to be a human carcinogen." Contacts: Lauren Rugani, Media Officer Christina Anderson, Media Assistant Office of News and Public Information 202-334-2138; e-mail news@nas.edu <mailto:news@nas.edu> www.national-academies.org/newsroom <http://www.national-academies.org/newsroom> Twitter: @NAS_news <https://twitter.com/NAS_news> and @NASciences <https://twitter.com/NASciences> RSS feed: http://www.nationalacademies.org/rss/index.html <http://www.nationalacademies.org/rss/index.html> Flickr: http://www.flickr.com/photos/nationalacademyofsciences/sets <http://www.flickr.com/photos/nationalacademyofsciences/sets>

_____ Pre-publication copies of Review of the Formaldehyde Assessment in the National Toxicology Program 12th Report on Carcinogens <http://www.nap.edu/catalog.php?record_id=18948> available from the National Academies Press on the Internet at www.nap.edu <http://www.nap.edu/> or by calling 202-334-3313 or 1-800-624-6242. Reporters may obtain a copy from the Office of News and Public Information (contacts listed above). # #

NATIONAL RESEARCH COUNCIL Division on Earth and Life Studies Board on Environmental Studies and Toxicology Committee to Review the Formaldehyde Assessment in the National Toxicology Program 12th Report on Carcinogens Alfred O. Berg*(chair) Professor and Chair Emeritus Department of Family Medicine University of Washington Seattle John C. Bailar III* Professor Emeritus University of Chicago Mitchellville, Md. A. Jay Gandolfi Professor Emeritus College of Pharmacy University of Arizona Tucson David Kriebel Co-Director Lowell Center for Sustainable Production; and Professor Department of Work Environment University of Massachusetts Lowell John B. Morris Board of Trustees Distinguished Professor; Professor of Pharmacology and Toxicology Department of Pharmaceutical Sciences; and Interim Dean University of Connecticut School of Pharmacy Storrs Kent E. Pinkerton Director Center for Health and the Environment; Professor Department of Pediatrics School of Medicine; and Professor Department of Anatomy, Physiology, and Cell Biology School of Veterinary Medicine University of California Davis Ivan Rusyn Professor Department of Environmental Sciences and Engineering; Director Laboratory of Environmental Genomics; and Director Carolina Center for Computational Toxicology Gillings School of Global Public Health University of North Carolina Chapel Hill Toshihiro Shioda Associate Professor of Medicine Harvard Medical School; and Director Molecular Profiling Laboratory Massachusetts General Hospital Cancer Center Charlestown Thomas J. Smith Professor Emeritus Department of Environmental Health Environmental Science and Engineering Program Harvard School of Public Health Boston Meir Wetzler Chief Division of Leukemia Department of Medicine Roswell Park Cancer Institute; and Professor of Medicine School of Medicine and Biomedical Sciences University at Buffalo State University of New York Buffalo Lauren Zeise Deputy Director for Scientific Affairs Office of Environmental Health Hazard Assessment California Environmental Protection Agency Oakland Patrick Zweidler-McKay Section Chief Pediatric Leukemia and Lymphoma; and Associate Professor Department of Medicine Division of Pediatrics The Children's Cancer Hospital The University of Texas M.D. Anderson Cancer Center Houston STAFF Heidi Murray-Smith Study Director _____ *Member, Institute of Medicine

Robin Mackar
Office of Communications and Public Liaison National Institute of Environmental Health Sciences National Institutes of Health PO Box 12233, Research Triangle Park, NC 27709 919-541-0073; rmackar@niehs.nih.gov NIH . . . Turning Discovery Into Health

Message

From: Foster, Paul (NIH/NIEHS) [E] [foster2@niehs.nih.gov]
Sent: 11/20/2014 5:41:30 PM
To: Flowers, Lynn [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1a4411c874d041b9a8badfc32b91bd70-Flowers, Lynn]; Olden, Kenneth [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8979224c77ea4d559f70cab1688f28aa-Olden, Kenneth]; Walsh, Debra [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d4fd965338fc4d449c2954945c41de46-Walsh, Debra]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]; D'Amico, Louis [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=78a91f83c4414910be286efe02004dbc-D'Amico, Louis J.]; Bussard, David [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cf26b876393e44f38bdd06db02dbbfe5-Bussard, David]; Sonawane, Bob [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a30dc04805854452837bcabc6b2954ab-Sonawane, Bob]; Makris, Susan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7654051d8d1240a39dfa9463c9b0b7e5-Makris, Susan]; Cogliano, Vincent [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=51f2736376ac4d32bad2fe7cfef2886b-Cogliano, Vincent]; Perovich, Gina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6e3c19d7f4db41bfa2477aa27ad83945-Perovich, Gina]; Strong, Jamie [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ea753aafefb74c268550fe6a2c187838-Benedict, Jamie]; Murray, Ed (ATSDR/DTHHS/OD) [hem0@CDC.GOV]; Todd, Glenn D. (Dan) (ATSDR/DTHHS/ETB) [gdt1@CDC.GOV]; Raffaele, Kathleen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cc48281bbab34bf5bf3ab1a63780d5ca-Kathleen Raffaele]; Morris, Jeff [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=55c34872e6ea40cab78be910aec63321-Morris, Jeff]; Barone, Stan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a4f8618acbba418da24c110f3123a2af-Barone, Stan]; Abadin, Henry (ATSDR/DTHHS/ETB) [hga0@CDC.GOV]; Foster, Stiven [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=43d242767f304355ad415ec856988213-sfoste02]
Subject: RE: addnl information: TCE Rat Cardiac Malformations w/W. Caffey Norman (HSIA) & others

Lynn,

I think a follow up meeting when have had a chance to see the proposal sounds very sensible.

Paul

Paul M.D. Foster, Ph.D., A.T.S.
Senior Scientist
Chief, Toxicology Branch
Division of the National Toxicology Program (NTP)
National Institute of Environmental Health Sciences (NIEHS)
PO Box 12233 (MD K2-12)
Research Triangle Park
NC 27709

Tel: (919) 541-2513
Fax: (301) 480-2999
Email: foster2@niehs.nih.gov

National Institute of Environmental Health Sciences
National Toxicology Program
U.S. Department of Health and Human Services

From: Flowers, Lynn [mailto:Flowers.Lynn@epa.gov]
Sent: Thursday, November 20, 2014 10:56 AM
To: Olden, Kenneth; Walsh, Debra; Vandenberg, John; D'Amico, Louis; Bussard, David; Sonawane, Bob; Makris, Susan; Cogliano, Vincent; Perovich, Gina; Strong, Jamie; Murray, Ed (ATSDR/DTHHS/OD); Foster, Paul (NIH/NIEHS) [E]; Todd, Glenn D. (Dan) (ATSDR/DTHHS/ETB); Raffaele, Kathleen; Morris, Jeff; Barone, Stan; Abadin, Henry (ATSDR/DTHHS/ETB); Foster, Stiven
Subject: addnl information: TCE Rat Cardiac Malformations w/W. Caffey Norman (HSIA) & others

Hello everyone: As an update to Nov 3, 2014 meeting with the HSIA folks, Caffey Norman sent the email below to Ken Olden, Linda Birnbaum and Ed Murray last week.
We talked here in NCEA about getting back together with you all and I was just about to set something up as a de-brief from that meeting when I saw the email below.
At least the tenor of the email is that they may be entertaining moving away from a "definitive" cardiac defect study.

Regardless of how you read the email, my proposal now is to wait to get back together until we receive the proposal in December.
How about we reconvene in January to discuss?
I can get something on the calendar when we receive the proposal.
By the way, we just got an inquiry from CalEPA regarding the status of the HSIA proposal from 2013 that they have a copy of. The word is out...
Thanks!
Lynn

From: Norman, Caffey [mailto:caffey.norman@squirepb.com]
Sent: Friday, November 14, 2014 4:03 PM
To: Olden, Kenneth; Meadows, Leslie
Cc: 'birnbaumls@niehs.nih.gov'; Murray, Ed (ATSDR/DTHHS/OD) (hem0@cdc.gov)
Subject: TCE Case Study

Dear Dr. Olden,

Thank you for arranging and participating in the November 3 meeting with HSIA representatives to discuss our proposal for a developmental study of TCE focused on the cardiac abnormality endpoint. We understand from this meeting that a broader science approach is desired, and are developing a concept document for data collection that would contribute to the understanding of gestational pharmacokinetics and windows of sensitivity by using dosimetry to allow for bridging across existing inhalation, gavage, and drinking water data. Such a TCE dataset would serve as a case study to compare internal levels of TCE/TCA in maternal and fetal compartments, and thus provide information more generally useful in exploring windows of susceptibility.

We plan to circulate the concept document to you and the other participants by December 12, 2014.

With best regards,

W. Caffey Norman
Partner
Squire Patton Boggs (US) LLP
2550 M Street, NW
Washington, DC 20037
T +1 202 457 5270
F +1 202 457 6315
M +1 202 460 9495
Caffey.Norman@squirepb.com |
squirepattonboggs.com

Lynn Flowers, PhD, DABT
Associate Director for Health
National Center for Environmental Assessment
US EPA
Washington, DC
703-347-8537

Message

From: Kadeli, Lek [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=39EFEE1E9A134AFCBFDBE386067C3462-KADELI, LEK]
Sent: 1/12/2015 9:00:31 PM
To: ORD-ALL Feds and NonFeds and RSLs [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2c735272eef941588aefd9a05ed28823-ORD-ALL Feds and NonFeds and RSLs]
CC: Kavlock, Robert [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=eebac67f01094409a7fdaa955a837884-Kavlock, Robert]
Subject: RE: Welcoming New Members to our Team

Dear ORD Family,

It is Dr. Bob Kavlock's and my great pleasure to welcome Dr. Tom Burke to ORD. I look forward to working with Tom, Bob, and all of you to carry out the Administrator's priorities and to address today's scientific and environmental challenges.

Best,

Lek

From: KeyesFleming, Gwendolyn
Sent: Monday, January 12, 2015 3:05 PM
To: Assistant Administrators; Regional Administrators
Cc: AO Staff Office Directors and AA's; AO-OCHP-Everyone; AO-IO-Everyone; Wiedeman, Allison; Kitamura, Louise; Morales, Esther; DAA; DRA
Subject: Welcoming New Members to our Team

Dear Colleagues:

Please join me in welcoming additions to our EPA family, including a new senior leader in the Office of Research and Development, a returning friend to the Administrator's Office, and the expansion of duties for a respected colleague in the Administrator's Office.

It all starts with science, so I'm pleased to announce that Dr. Thomas Burke joins EPA today as the Deputy Assistant Administrator for the Office Research and Development and Science Advisor. Most recently, he served as the Jacob I. and Irene B. Fabrikant Professor and Chair in Health, Risk and Society and the Associate Dean for Public Health Practice and Training at the Johns Hopkins Bloomberg School of Public Health. He also was a Professor in the Department of Health Policy and Management, with joint appointments in the Department of Environmental Health Sciences and the School of Medicine Department of Oncology. Additionally, he served as the Director of the Johns Hopkins Risk Sciences and Public Policy Institute. His research includes the development of new approaches to environmental health risk assessment and environmental health surveillance, and their applications to environmental health policy. On November 7, 2013 the President nominated Dr. Burke to be Assistant Administrator for EPA's Office of Research and Development.

Prior to his time at Johns Hopkins, Tom was Deputy Commissioner of Health for the State of New Jersey and Director of the Office of Science and Research in the New Jersey Department of Environmental Protection. In New Jersey, he directed initiatives that influenced the development of national programs, such as Superfund, the Safe Drinking Water Act, and the Toxics Release Inventory. Tom also served as a member of EPA's Science Advisory Board, as well as on advisory boards for the Centers for Disease Control and Prevention and on various committees for the National Academy of Sciences. He received his Ph.D. in epidemiology from the University of Pennsylvania, his M.P.H. from the University of Texas, and his B.S. from Saint Peter's College. We look forward to Tom's leadership as he works closely with Lek Kadeli and others in ORD to continue advancing our scientific research that so importantly factors into our policy decisions. Given his deep scientific and management background, Tom is uniquely well positioned to provide

invaluable expertise in shaping the Agency's science efforts. We would like to thank Dr. Bob Kavlock who has been serving as the interim Science Advisor for his excellent service.

We welcome Luseni Pieh back to EPA as the Deputy Chief of Staff for Programs and Strategic Initiatives. Lou, as you may recall, was EPA's White House Liaison before he went to the White House to serve as Senior Director for Cabinet Affairs, covering EPA, DOE, DOI, DOT, and USDA. Previously, he was a lawyer at a Milwaukee law firm where he focused on environmental issues. Lou earned his L.L.M. in Natural Resources and Environmental Law and Policy from the University of Denver, his J.D. from Indiana University, and his B.A. from Michigan State. As Deputy Chief of Staff he will help coordinate day to day interactions between the Administrator's Office and programs offices and regions on key emerging issues that span national programs and/or regional offices.

Matthew Fritz will begin this year with an expanded set of responsibilities by adding policy to his title of Deputy Chief of Staff for Policy and Operations. Matt will continue to help manage the day-to-day operations of the Office of the Administrator and continue to facilitate policy work on Bristol Bay, the Clean Water Plan, emergency response, homeland security, and other emerging issues. Prior to his service with EPA, he worked for 17+ years at the Connecticut Department of Environmental Protection where he served as Bureau Chief for Outdoor Recreation, overseeing the operations of more than 100 state parks, 14 campgrounds, dozens of historic sites, and more than 100 boat launches. Not one to serve in only one position at a time, while he was bureau chief, Matt also worked for former Governor Jodi Rell overseeing Connecticut's implementation of the American Recovery and Reinvestment Act. He previously served for three years as Chief of Staff for the Commissioner of CDEP and held a variety positions at CDEP overseeing communications and education on a variety of environmental issues.

Please join me in welcoming Tom and Lou to EPA and thanking Matt for taking on additional responsibilities.

Message

From: Gwinn, Maureen [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4BDC5237A5C440A7B664518E23EB5647-GWINN, MAUREEN]
Sent: 2/12/2015 2:03:40 AM
To: Ross, Mary [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=98359cd1f66f46ec91d327e99a3c6909-Ross, Mary]
CC: Flowers, Lynn [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1a4411c874d041b9a8badfc32b91bd70-Flowers, Lynn]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]; Walsh, Debra [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d4fd965338fc4d449c2954945c41de46-Walsh, Debra]; Cogliano, Vincent [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=51f2736376ac4d32bad2fe7cfef2886b-Cogliano, Vincent]; Perovich, Gina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6e3c19d7f4db41bfa2477aa27ad83945-Perovich, Gina]; Bussard, David [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cf26b876393e44f38bdd06db02dbbfe5-Bussard, David]; Gatchett, Annette [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f12d699a71f84e21bddbb876dae7f96c-Gatchett, Annette]; Birchfield, Norman [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c910f2fd28414e819b6afe6dda525e9f-Birchfield, Norman]; Berner, Ted [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f1949c9653024d3cb4aa4c2bd69c4fde-Berner, Ted]
Subject: Re: Senior Leader Update & Items of Interest

Thanks! Interesting info.

I think I heard about Ruth via SHC children's health group. It will surprise no one that Bob S knows her well :)

Sent from my iPhone

On Feb 11, 2015, at 8:30 PM, Ross, Mary <Ross.Mary@epa.gov> wrote:

> Thanks, Lynn. I remember hearing that Dr. Etzel was coming into OCHP, I don't remember where. It'll be interesting to see how she leads it.
>
> ---
>
> **From:** Flowers, Lynn
> **Sent:** Wednesday, February 11, 2015 7:51 PM
> **To:** Vandenberg, John; Ross, Mary; Walsh, Debra; Cogliano, Vincent; Perovich, Gina; Bussard, David; Gwinn, Maureen; Gatchett, Annette; Birchfield, Norman; Berner, Ted
> **Subject:** Fwd: Senior Leader Update & Items of Interest
>
> This is interesting. Besides a shout out to Mary (yeah), a new director for OCHP is named -- Ruth Etzel? This was news to me...,
>
> Sent from my iPhone
>
> Begin forwarded message:
>
> **From:** "Meiburg, Stan" <Meiburg.Stan@epa.gov>
> **Date:** February 10, 2015 at 11:39:33 AM EST
> **To:** "EPA-Hqtrs. Senior Executives" <EPAHqtrs._Senior_Executives@epa.gov>, EPA-Regional Senior

Executives <EPARegional_Senior_Executives@epa.gov>, EPA-Senior Level <CNEPASenior_LevelOScientific_Technical@epa.gov>
Cc: "Baldwin, Mark" <Baldwin.Mark@epa.gov>, "Reeder, John" <Reeder.John@epa.gov>
Subject: Senior Leader Update & Items of Interest

EPA Colleagues:

Greetings from Washington. I've been thinking about ways we can foster a greater sense of community and collaboration across One EPA. Obviously this isn't something I can do by myself—it will take all of us working together to connect the important networks and groups that we use to do our work.

One thing I thought I would try is for me to periodically communicate directly with you, our senior managers and senior leaders. My hope is that you will find occasional concise updates helpful, and that they would give you information you can share with your own leadership team. I have no pride of authorship, and if you have suggested items to include in these updates, or any other suggestions for improved communications generally, please don't hesitate to let me know, or contact Mark Baldwin (cc'd on this note) on my immediate staff.

Agency Updates and Happenings

- <!--[if !supportLists]--><!--[endif]-->FY16 Pres. Bud: On February 2nd, the President released the proposed budget for FY16. The President's budget proposes to fund EPA at $8.6 billion dollars, which is roughly a $450 million increase from FY15 enacted and a substantial increase over last year's PresBud. Highlights include a $120 million increase to improve air quality and address climate change (Goal 1); a $70 million increase to protect America's waters (Goal 2); a $178 million increase to clean up communities, advance sustainability, and address EJ impacts (Goal 3); a $47 million increase to address chemical safety (Goal 4); and a $66 million increase for enforcement and Next Generation compliance strategies and tools (Goal 5). For more information visit: http://www2.epa.gov/planandbudget/fy2016
- <!--[if !supportLists]--><!--[endif]-->Joint Congressional Hearing on the Clean Water Rule: On Wednesday, the Administrator and Assistant Secretary of the Army Jo-Ellen Darcy testified before the U.S. Senate Committee on Environment and Public Works and the U.S. House Committee on Transportation and Infrastructure on the proposed Clean Water Rule. The Administrator was very effective in defending our work on this rule in the face of some stiff challenges. To see the hearing visit: https://www.youtube.com/watch?v=FYB8iQ-3sgo
- <!--[if !supportLists]--><!--[endif]-->EPA Alumni Association MOU: On February 25th, I will be signing a new MOU with the EPA Alumni Association. The goal of the MOU is to promote mentoring opportunities and promote the preservation of EPA's rich history. Bob Wayland is the President of the Association; I know many of you remember Bob and it is a great honor to reconnect with him and some of our most distinguished former colleagues who love this agency; we will benefit tremendously from their continued service.
- <!--[if !supportLists]--><!--[endif]-->Regional trips: Since I came back in October, I have been to Regions 2, 4, 5, and 10, and I am planning to go to Region 8 later this month. Other such trips are being scheduled: I am looking forward to the chance to see many of you, meet as many people as possible and learn about some of the great things you are doing.
- <!--[if !supportLists]--><!--[endif]-->Headquarters visits: I am also trying to get around here in DC! I have been able to speak at all hands meetings for OP and OARM, and look forward to other such opportunities!

Agency Business

- <!--[if !supportLists]--><!--[endif]-->Environmental Justice Month: Starting on February 16 through March 16, EPA will be holding events to promote Environmental Justice. For more information please contact Mustafa Ali at Mustafa.ali@epa.gov

- <!--[if !supportLists]--><!--[endif]-->Limited English Proficiency Workgroup: Under EO 13166 "Improving Access to Services for Persons with Limited English Proficiency (LEP)" all federal agencies are required to ensure persons who are LEP have meaningful access to services, programs or activities that are available to the public. Under the leadership of the Office of Civil Rights, EPA is forming an internal workgroup tasked with identifying LEP gaps and needs in the agency and developing new policies and procedures to be implemented by the end of FY15. For more information, please contact Lilian Dorka at Dorka.lilian@epa.gov.

Transitions:
I had the honor of participating in retirement ceremonies over the last couple of months for George Pavlou, DRA in Region 2; Bharat Mathur, DRA in Region 5; and Mike Stahl, DAA in OITA. I know you will join me in wishing the very best to our wonderful colleagues, and others recently retired, who are moving to new opportunities and horizons in their journey.

Link of the Week:
EPA's Cross-Agency Strategies-- http://workplace.epa.gov/realizingoneepa/

Recent SES Arrivals & Reassignments (some new, some longstanding distinguished colleagues)

- <!--[if !supportLists]--><!--[endif]-->Dr. Ruth Etzel, Director for the Office of Children's Health Protection
- <!--[if !supportLists]--><!--[endif]-->Anne Heard, Deputy Regional Administrator for Region 4 (It was my great pleasure to make this announcement during a visit to Region 4 in December)
- <!--[if !supportLists]--><!--[endif]-->Deb Thomas, Deputy Regional Administrator for Region 8
- <!--[if !supportLists]--><!--[endif]-->Catherine McCabe, Deputy Regional Administrator for Region 2
- <!--[if !supportLists]--><!--[endif]-->Bob Kaplan, Deputy Regional Administrator for Region 5
- <!--[if !supportLists]--><!--[endif]-->Kathleen Salyer, Deputy Director for OSWER's Office of Resource Conservation and Recovery
- <!--[if !supportLists]--><!--[endif]-->Thomas Dussault, Deputy Director for OARM's Office of Acquisition Management
- <!--[if !supportLists]--><!--[endif]-->Denise Polk, Deputy Director for OARM's Office of Grants and Debarments
- <!--[if !supportLists]--><!--[endif]-->Lilian Dorka, Deputy Director for the Office of Civil Rights
- <!--[if !supportLists]--><!--[endif]-->Pamela Mazakas, Deputy Director for OECA's Office of Criminal Enforcement, Forensics and Training
- <!--[if !supportLists]--><!--[endif]-->Andrew Battin, Director for OCFO's E-Enterprise for the Environment Program
- <!--[if !supportLists]--><!--[endif]-->David Evans, Deputy Director for OW's Office of Wetlands, Oceans and Watersheds
- <!--[if !supportLists]--><!--[endif]-->Dr. Mary Ross, Deputy Director for Management, for ORD's National Center for Environmental Assessment
- <!--[if !supportLists]--><!--[endif]-->Tim Watkins, Deputy Director for Management, for ORD's National Exposure Research Laboratory

Other Senior Leadership Arrivals

- <!--[if !supportLists]--><!--[endif]-->Ron Carlton, Counselor to the Administrator for Agriculture Policy, AO
- <!--[if !supportLists]--><!--[endif]-->Dr. Thomas Burke, Deputy Assistant Administrator for Research and Development and Science Advisor, ORD
- <!--[if !supportLists]--><!--[endif]-->Luseni Pieh, Deputy Chief of Staff for Programs and Strategic Initiatives, AO

- <!--[if !supportLists]--><!--[endif]-->Randy Hill, Deputy Assistant Administrator, Office of International and Tribal Affairs

A. Stanley Meiburg, Ph.D.
Acting Deputy Administrator
U.S. Environmental Protection Agency
MC-1102A
1200 Pennsylvania Avenue, NW
Washington, DC 20460

United States
Environmental Protection
Agency

Summary of Nominations for the Fourth Contaminant Candidate List

Office of Water (4607M)
EPA 815-R-15-001
January 2015

Contents

1.0 Introduction **1**

2.0 Requesting Nominations **3**

3.0 Nominated Contaminants **4**

3.1 Chemical Nominations 4

3.1.1 Analysis of Nominated Chemical Contaminants 5

3.2 Microbial Nominations 7

3.2.1 Analysis of Nominated Microbial Contaminants 7

4.0 References **8**

5.0 Appendices **A-1**

Appendix 1. Chemical Contaminants Nominated
Appendix 2. Microbial Contaminants Nominated
Appendix 3. References Provided with Chemical Nominations
Appendix 4. References Provided with Microbial Nominations
Appendix 5. Complete List of References Provided with CCL 4 Nominations
Appendix 6. Outcome of Nominated Chemicals in the CCL 4 Process
Appendix 7. Outcome of Nominated Microbes in the CCL 4 Process

ED_002435_00004768-00003

ED_002435_00004768-00004

Exhibits

Exhibit 1. Chemicals on the Final CCL 4 Included in Nominations 7

ED_002435_00004768-00005

ED_002435_00004768-00006

Acronyms and Abbreviations

ATSDR	Agency for Toxic Substances and Disease Registry
AWWA	American Water Works Association
CASRN	Chemical Abstract Service Registry Number
CCL	Contaminant Candidate List
CCL	EPA's First Contaminant Candidate List
CCL 2	EPA's Second Contaminant Candidate List
CCL 3	EPA's Third Contaminant Candidate List
CCL 4	EPA's Fourth Contaminant Candidate List
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
EPA	United States Environmental Protection Agency
HA	Health Advisories
HPC	Heterotrophic Plate Count
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MDEP	Massachusetts Department of Environmental Protection
MDH	Minnesota Department of Health
MTBE	Methyl tertiary butyl ether
NJDEP	New Jersey Department of Environmental Protection
NPDWR	National Primary Drinking Water Regulations
NRDC	National Resource Defense Council
OSHA	Occupational Safety and Health Administration
PCCL	Preliminary Contaminant Candidate List
PFOA	Perfluorooctanoic acid
PWSs	Public Water Systems
REDs	Reregistration Eligibility Decision
SDWA	Safe Drinking Water Act
TT	Treatment Technique
U.S.	United States of America
USDA	United States Department of Agriculture
USGS	United States Geological Survey
WHO	World Health Organization

ED_002435_00004768-00007

ED_002435_00004768-00008

1.0 Introduction

Section 1412(b)(1) of the Safe Drinking Water Act (SDWA), as amended in 1996, requires EPA to publish the Contaminant Candidate List (CCL) every five years. The SDWA specifies that the list must include contaminants that are not subject to any proposed or promulgated National Primary Drinking Water Regulations (NPDWRs), are known or anticipated to occur in public water systems (PWSs) and may require regulation under the SDWA. EPA uses this list of unregulated contaminants to help the agency identify priority contaminants for regulatory decision making and to prioritize research and data collection efforts. SDWA also requires the agency to consult with the scientific community, including the Science Advisory Board, and provide notice and opportunity for public comment prior to the publication of the Final CCL. In addition, SDWA directs the agency to consider the health effects and occurrence information for unregulated contaminants to identify those contaminants that present the greatest public health concern related to exposure from drinking water.

EPA published the third CCL (CCL 3), which listed 116 contaminants on October 8, 2009 (74 FR 51850 (USEPA, 2009a)). In developing the CCL 3, EPA implemented a multi-step process to select contaminants for the final CCL 3, which included the following key steps:

(1) The identification of a broad universe of potential drinking water contaminants (CCL 3 Universe);
(2) Screening the CCL 3 Universe to a Preliminary CCL (PCCL) using screening criteria based on the potential to occur in PWSs and the potential for public health concern; and
(3) Evaluation of the PCCL contaminants based on a more detailed review of the occurrence and health effects data using a scoring and classification system to identify a final list of 116 CCL 3 contaminants; and
(4) Incorporating public input and expert review in the CCL 3 process.

Steps 1, 2 and 3 in the process are described in detail in the CCL 3 support documents:

- *Final CCL 3 Chemicals: Identifying the Universe* (USEPA, 2009b);
- *Final CCL 3 Chemicals: Screening to a PCCL* (USEPA, 2009c);
- *Final Contaminant Candidate List 3 Chemicals: Classification of the PCCL to the CCL* (USEPA, 2009d);
- *Final CCL 3 Microbes: Identifying the Universe* (USEPA, 2009e);
- *Final CCL 3 Microbes: Screening to the PCCL* (USEPA, 2009f); and
- *Final CCL 3 Microbes: PCCL to CCL Process* (USEPA, 2009g).

These documents can be found on the EPA web site at: http://www2.epa.gov/ccl/contaminant-candidate-list-3-ccl-3 or at http://www.regulations.gov (docket ID: EPA-HQ-OW-2007-1189).

After a Final CCL is published, SDWA section 1412(b)(1)(B)(ii) as amended in 1996, requires EPA at five year intervals to make determinations of whether to regulate or not to regulate no fewer than five contaminants from the CCL in a process called regulatory determinations. This

ED_002435_00004768-00009

is a separate process from the listing of contaminants on the CCL. The 1996 SDWA Amendments specify three criteria to determine whether a contaminant may require regulation:

- the contaminant may have an adverse effect on the health of persons;
- the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in PWSs with a frequency and at levels of public health concern; and
- in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by PWSs.

If EPA determines that these three statutory criteria are met and makes a final determination to regulate a contaminant, the agency has 24 months to publish a proposed Maximum Contaminant Level Goal[1] (MCLG) and NPDWR[2]. After the proposal, the agency has 18 months to publish and promulgate a final MCLG and NPDWR (SDWA section 1412(b)(1)(E))[3].

On February 11, 2011, as a separate action, the agency issued a positive regulatory determination for perchlorate, a chemical listed in CCL 1, CCL 2 and CCL 3 (76 FR 7762 (USEPA, 2011)). Recently, EPA has published preliminary regulatory determinations for five unregulated contaminants on the CCL 3 (79 FR 62716 (USEPA, 2014)). The five contaminants include: dimethoate; 1,3-dinitrobenzene; strontium; terbufos and terbufos sulfone. The agency is making preliminary determinations to regulate one contaminant (strontium) and to not regulate four contaminants (dimethoate; 1,3-dinitrobenzene; terbufos; and terbufos sulfone). Therefore, the agency is removing perchlorate and these five contaminants from the Draft Fourth CCL (CCL 4), pending the result of the final regulatory determinations for CCL 3.

EPA conducted an abbreviated evaluation and selection process for the CCL 4. This abbreviated CCL 4 process includes a three pronged approach: (1) carrying forward CCL 3 contaminants (minus those with regulatory determinations), (2) seeking and evaluating nominations from the public for additional contaminants to consider and (3) evaluating any new data for those contaminants with previous negative regulatory determinations from CCL 1 or CCL 2 for potential inclusion on the CCL 4.

As part of the process to develop the CCL 4, EPA published a *Federal Register* notice (77 *FR* 27057 (USEPA, 2012)) requesting that the public submit nominations for chemical and microbial contaminants to be considered for inclusion in the CCL 4. EPA also requested supporting information that has been made available since the development of the CCL 3 or existing information that was not considered in the development of the CCL 3, which shows that the nominated contaminant may have an adverse health effect on people and occurs or is likely to occur in public water systems. EPA reviewed the nominations and supporting information provided by nominators to determine if any new data were provided that had not been previously

[1] The MCLG is the "maximum level of a contaminant in drinking water at which no known or anticipated adverse effect on the health of persons would occur, and which allows an adequate margin of safety. Maximum contaminant level goals are non-enforceable health goals." (40 C.F.R. 141.2; 42 U.S.C. 300g-1)

[2] An NPDWR is a legally enforceable standard that applies to public water systems. An NPDWR sets a legal limit (called a maximum contaminant level or MCL) or specifies a certain treatment technique (TT) for public water systems for a specific contaminant or group of contaminants. The MCL is the highest level of a contaminant that is allowed in drinking water and is set as close to the MCLG as feasible using the best available treatment technology and analytical methods and taking cost into consideration.

[3] The statute authorizes a nine month extension of this promulgation date.

ED_002435_00004768-00010

evaluated for CCL 3. The agency also collected additional data for the nominated contaminants, when it was available, from both CCL 3 data sources that had been updated and from new data sources that were not available at the time of CCL 3. A complete list of references provided by nominators can be found in Appendices 3, 4 and 5 of this document. A more detailed description of the CCL data sources collected by EPA may be found in the support document *Data Sources for the CCL 4* (USEPA, 2015a)).

This document describes EPA's request for contaminant nominations and summarizes the nominations received by EPA. In addition, it describes EPA's analysis of the nominated contaminants and reports on their status in the Draft CCL 4. The specific contaminants nominated, the information provided by the nominators and the outcome of the nominated contaminants in the CCL 4 process are included in Appendices 1 through 7 of this document. More detailed information on the CCL 4 is available in the CCL 4 support documents found on the CCL 4 Web site at: http://www2.epa.gov/ccl/contaminant-candidate-list-4-ccl-4. The original nomination letters submitted via the docket and nominations submitted via the Web site can be found in the docket at http://www.regulations.gov (docket ID: EPA-HQ-OW-2012-0217).

2.0 Requesting Nominations

The agency sought nominations for contaminants to be considered for possible inclusion in the CCL 4 by framing the SDWA requirements in a series of questions to document the anticipated or known occurrence in PWSs and the adverse health effects of potential contaminants. The agency requested that the public respond to those questions and provide the documentation and rationale for including a contaminant for consideration in the CCL 4 process. The questions posed to the public were:

- What is the contaminant's name, Chemical Abstract Service Registry Number (CASRN), and/or common synonym (if applicable)?
- What factors make this contaminant a priority for the CCL 4 process (e.g., widespread occurrence; anticipated toxicity to humans; potentially harmful effects to susceptible populations (e.g., children); potentially contaminated source water (surface or ground water) and/or finished water; release to air, land and/or water; contaminant is manufactured in large quantities with a potential to occur in source waters)?
- What are the new significant health effects and occurrence data that are available since CCL 3 or existing information that was not considered in CCL 3, which you believe supports the CCL requirement(s) that a contaminant may have an adverse effect on the health of persons and is known or anticipated to occur in PWSs?
- Please provide complete citations, including author(s), title, journal and date. Contact information for the primary investigator would also be helpful.

Nominations were received via the EPA Web site and via the EPA docket (docket ID: EPA-HQ-OW-2012-0217). The agency compiled the information from the nominations process to identify the contaminants nominated, the rationale for the nomination and to compare the supporting data submitted to information gathered by EPA. Where new information was of sufficient quality that

ED_002435_00004768-00011

information was used in the analysis; EPA analyzed the nominated contaminants using the CCL 3 process, which is described briefly in Section 1, to select the Draft CCL 4.

3.0 Nominated Contaminants

EPA received nominations for 59 unique contaminants for the CCL 4 submitted by 10 organizations and individuals. These 59 nominations include 5 microbial and 54 chemical contaminants. Eight contaminants were nominated by more than one nominator. Aldicarb, bisphenol A, carbaryl, chlorpyrifos, *Toxoplasma gondii*, and microcystin LR were each nominated by two separate nominators. Manganese and perfluorooctanoic acid (PFOA) were nominated by three different nominators each.

The agency did not require nominators to provide their name or an affiliated organization. Two nominators remained anonymous while providing documentation and rationale for the contaminants. Two other individuals identified themselves but did not provide an organization affiliation.

The organizations that nominated contaminants were:

- American Water Works Association (AWWA),
- Natural Resources Defense Council (NRDC),
- State of Massachusetts Department of Environmental Protection (MDEP),
- State of Minnesota Department of Health (MDH),
- State of New Jersey Department of Environmental Protection (NJDEP), and
- U.S. Department of Agriculture (USDA).

EPA received three general types of nominations:

- specific individual chemicals,
- specific individual organisms, and
- groups of contaminants (Heterotrophic Plate Count (HPC) was considered as a group).

The AWWA also provided a letter with recommendations for the CCL 4 process. The full text of this letter can be found at http://www.regulations.gov (docket ID: EPA-HQ-OW-2012-0217).

3.1 Chemical Nominations

There were a total of 54 unique chemical contaminant nominations for the CCL 4. The full list of chemical nominations and the supporting information provided by the nominators can be found in Appendix 1. The references provided by the nominators for chemical nominations can be found in Appendix 3.

ED_002435_00004768-00012

3.1.1 Analysis of Nominated Chemical Contaminants

SDWA specifies that the CCL only includes those contaminants without any proposed or promulgated NPDWRs. There are two nominated contaminants covered under the existing NPDWR for beta photon emitters (strontium 90 and cesium 137) (40 CFR §141.66 (d)(1)); therefore, these will not be considered for CCL 4. Radon was also nominated but is not eligible for CCL 4 since a proposed NPDWR has been developed (64 FR 59245, November 2, 1999 (USEPA, 1999). Aldicarb was nominated but is not eligible for CCL 4 since it has an existing NPDWR (40 CFR §141.61(c)); (Note, in response to an administrative petition the agency issued an administrative stay of the effective date of the maximum contaminant levels (MCLs) for aldicarbs).

For the remaining 50 nominated chemicals, EPA reviewed the nominations and supporting information provided by nominators to determine if any new data were provided that had not been previously evaluated for CCL 3. In addition to the data provided by nominators, and the data EPA collected previously under CCL 3, EPA collected data for the nominated contaminants, when it was available, from both CCL 3 data sources that have been updated and from new data sources that were not available at the time of CCL 3. A list and description of these data sources can be found in the *Data Sources For the CCL 4* (USEPA, 2015a) support document. If new data were available, EPA screened and scored the nominated contaminants using the same process as was used in CCL 3. Five of the nominated chemicals were on CCL 3 and were carried forward to the CCL 4 along with the other CCL 3 contaminants. The five chemicals are: perfluorooctanoic acid (PFOA), Microcystin-LR, methyl tertiary butyl ether (MTBE), alpha-hexachlorocyclohexane and permethrin. Microcystin-LR is included within the group of cyanotoxins in the Final CCL 3 and the Draft CCL 4.

Forty of the nominated chemicals were previously included in the CCL 3 Universe, and were carried forward to the CCL 4 Universe. In addition to these forty, EPA has added three nominated chemicals to the CCL 4 Universe (octylphenol ethoxylate, oxacillin and virginiamycin) based on health effects and/or occurrence data that is newly available since the development of the CCL 3. Seven of the nominated chemicals did not have enough data in order to be added to the CCL 4 Universe. EPA screened all of the nominated chemicals in the CCL 4 Universe according to the screening criteria developed for CCL 3 and based on that evaluation, twenty of the nominated chemicals were included in the PCCL 4. Eighteen of those 20 chemicals were also included in the PCCL 3 and EPA added two new chemicals (manganese and nonylphenol) to the PCCL 4. The data used to screen the nominated chemicals from the CCL 4 Universe to the PCCL 4 can be found in the *Screening Document for the Draft PCCL 4 Nominated Contaminants* (USEPA, 2015b). EPA further evaluated the nominated chemicals on the PCCL 4 based on the classification process developed in CCL 3 and determined that manganese and nonylphenol should be added to the Draft CCL 4 (in addition to the chemicals carried forward from the CCL 3 to the CCL 4) based on new health and/or occurrence information that warrants further evaluation. The data which was used to further evaluate the nominated contaminants from the PCCL 4 and to select those that were included in the Draft CCL 4 can be found in the *Contaminant Information Sheets for the Draft PCCL 4 Nominated Contaminants* (USEPA, 2015c).

ED_002435_00004768-00013

Manganese is an element that naturally occurs in oxide forms and in combinations with other elements in many minerals. Small amounts, found in foods, are an essential nutrient for humans and animals. Manganese ores are used in a variety of applications in the US. Its principal use is in steel production to improve hardness, stiffness and strength (ATSDR, 2012). In 2003 and as part of the CCL 1 Regulatory Determination process, EPA made a negative regulatory determination for manganese based on the health and occurrence data available at that time. However, CCL 4 nominators cited more than 20 recent studies that indicate concern for neurological effects in children and infants exposed to excess manganese, which were not available at the time manganese was considered for Regulatory Determination 1 or CCL 3. In addition, new monitoring studies from USGS and drinking water monitoring information from several States support an earlier survey (i.e., the National Inorganics and Radionuclides Survey) that indicates manganese is known to occur in drinking water. EPA believes the new health effects information and additional occurrence data merit listing manganese in the Draft CCL 4.

Nonylphenol is used in the preparation of lubricating oil additives, resins, plasticizers and antioxidants for plastics and rubber. Additionally, sixty percent of nonylphenol is used in the production of nonylphenol ethoxylates, which are found in detergents and used in the treatment of textiles. Nonylphenol was previously considered for CCL 3. It was included in the CCL 3 Universe, but was not included on the PCCL 3 or CCL 3. Updated health and occurrence data (since the development of the CCL 3) are now available for nonylphenol, and these data (as follows) were considered in evaluating nonylphenol for the Draft CCL 4. Nonylphenol and some of its degradation products have been found to have estrogenic activity in rats and mice (WHO, 2004). Monitoring data are available from a USGS National Reconnaissance monitoring study of ambient water (Kolpin et al., 2002). EPA believes this updated health data and additional occurrence data show that nonylphenol is anticipated to occur in PWSs and has potential adverse health effects; therefore, it merits listing on the Draft CCL 4.

EPA considered adding dicofol to the Draft CCL 4; however, both recent manufacturers of the pesticide ceased all production as of May 17, 2011 and agreed to an EPA registration cancellation, which effectively prohibits all labeled uses of existing stocks after October 31, 2016. Use of dicofol has declined significantly in recent years. The chemical properties of dicofol indicate that it is has low mobility in water because it is expected to adsorb to organic matter in soil and sediment and it has moderately low solubility in water. Therefore, EPA did not list dicofol on the Draft CCL 4 because it is not known or anticipated to occur in drinking water due to its low mobility. Additionally, the registration cancellation, which will prohibit use of existing stocks beyond October 2016, is expected to further lessen any potential occurrence in drinking water.

Exhibit 1 shows the nominated chemicals that were included in the Draft CCL 4. In addition, Appendix 6 shows a list of the nominated chemicals and whether they were included in the CCL 4 Universe, PCCL 4 or Draft CCL 4.

ED_002435_00004768-00014

Exhibit 1. Nominated Chemicals Included in the Draft CCL 4

Contaminant Name	CASRN
*alpha-hexachlorocyclohexane	319-84-6
manganese	7439-96-5
*methyl tertiary butyl ether (MTBE)	1634-04-4
*microcystin-LR	101043-37-2
nonylphenol	25154-52-3
*perfluorooctanoic acid (PFOA)	335-67-1
*permethrin	52645-53-1

*Indicates that this chemical was carried forward from CCL 3 to the Draft CCL 4

3.2 Microbial Nominations

Five unique microbial nominations were submitted by the public in response to EPA's request for nominations for contaminants to be considered for possible inclusion in the Draft CCL 4 (77 FR 27057). The following organisms or group of organisms were nominated: Heterotrophic Plate Count bacteria, Adenovirus, *Naegleria fowleri, Toxoplasma gondii* and *Vibrio chloerae. Toxoplasma gondii* was nominated by two different nominators. Adenovirus and *Naegleria fowleri* were included in the Final CCL 3 and are being carried forward to the Draft CCL 4. Additional information on the nominated microbes and the information submitted by the nominators can be found in Appendix 2.

3.2.1 Analysis of Nominated Microbial Contaminants

EPA reviewed the nominated microbial contaminants and the supporting information provided by nominators to determine if any new data were provided that had not been previously evaluated. The agency also collected additional data for the nominated microbial contaminants, when it was available, from both CCL 3 data sources that had been updated and from literature searches covering the time between CCL 3 and CCL 4 (2007– 2012). If new data were available, EPA screened and scored the microbial contaminants nominated for CCL 4 using the same process that was used for CCL 3. The new data did not change the CCL 3 scores or listing decisions for the nominated microbial contaminants.

The group of HPC bacteria was nominated for the CCL 4; however, available epidemiological evidence shows no relationship between gastrointestinal illness and HPC bacteria in drinking water (Calderon, 1988; Calderon and Mood, 1991; Payment et al., 1997; WHO, 2003). Thus, EPA considers the potential health risk of HPC bacteria in drinking water as likely negligible and is not including HPC on the Draft CCL 4. In addition, HPC bacteria are addressed under the Surface Water Treatment Rule as a treatment technique (TT) where they can be monitored in lieu of a disinfectant residual.

Vibrio cholerae and *Toxoplasma gondii* will remain on the draft PCCL 4 and *Naegleria fowleri* and Adenovirus will be carried forward to the Draft CCL 4, along with the other microbes

ED_002435_00004768-00015

included on the Final CCL 3. A summary of the outcomes for the microbial contaminants for the CCL 3 and Draft CCL 4 can be found in Appendix 7.

4.0 References

Note: The following references apply to Sections 1.0, 2.0 and 3.0 above. References provided by CCL 4 nominators are listed in Appendix 5 below.

Calderon, R.L. 1988. Bacteria Colonizing Point-of-Entry Granular Activated Carbon filters and their Relationship to Human Health. EPA CR-813978-01-0, US Environmental Protection Agency, Washington, DC.

Calderon, R.L. and Mood, E.W. 1991. Bacteria Colonizing Point-of-Use Granular Activated Carbon Filters and their Relationship to Human Health. EPA CR 811904-01-0, US Environmental Protection Agency, Washington, DC.

Kolpin, D. W., E. T. Furlong, M. T. Meyer, E. M. Thurman, S. D. Zaugg, L. B. Barber, and H. T. Buxton. 2002. Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance. Environmental Science and Technology, v. 36, no. 6

Payment, P., J. Siemiatycki, L. Richardson, G. Renaud, E. Franco, and M. Prevost. 1997. A prospective epidemiological study of gastrointestinal health effects due to the consumption of drinking water. Int. J. Environ. Health Res. (7): 5-31.

USEPA, 1999. National Primary Drinking Water Regulations; Radon-222; Proposed Rule. Federal Register. Vol. 64, No. 211. p. 59245, November 2, 1999.

USEPA. 2009a. Drinking Water Contaminant Candidate List 3--Final. Federal Register. Vol. 747. No 194. p. 51850. October 8, 2009.

USEPA. 2009b. Final Contaminant Candidate List 3 Chemicals: Identifying the Universe. EPA 815-R09-006. August, 2009.

USEPA. 2009c. Final Contaminant Candidate List 3 Chemicals: Screening to a PCCL. EPA 815-R-09-007. August, 2009.

USEPA. 2009d. Final Contaminant Candidate List 3 Chemicals: Classification of the PCCL to the CCL. EPA. 815-R-09-008. August, 2009.

USEPA. 2009e. Final Contaminant Candidate List 3 Microbes: Identifying the Universe. EPA. 815-R-09-004. August, 2009.

USEPA. 2009f. Final Contaminant Candidate List 3 Microbes: Screening to the PCCL. EPA 815-R-09-0005. August, 2009.

ED_002435_00004768-00016

USEPA. 2009g. Final Contaminant Candidate List 3 Microbes: PCCL to CCL Process. EPA 815-R-09-009. August, 2009.

USEPA. 2011. Drinking Water: Regulatory Determination on Perchlorate. Federal Register. Vol. 76, No. 29. p. 7762, February 11, 2011.

USEPA. 2012. Request for Nominations of Drinking Water Contaminants for the Fourth Contaminant Candidate List. Federal Register. Vol. 77. No 89. p. 27057. May 8, 2012

USEPA. 2014. Announcement of Preliminary Regulatory Determination for Contaminants on the Third Drinking Water Contaminant Candidate List. Federal Register. Vol. 79, No. 202, p. 62716, October 20, 2014.

USEPA. 2015a. Data Sources for the CCL 4. EPA 815-R-15-004. January, 2015.

USEPA. 2015b. Screening Document for the Draft PCCL 4 Nominated Contaminants. EPA 815-R-15-002. January, 2015.

USEPA. 2015c. Contaminant Information Sheets (CISs) for the Draft Fourth Preliminary Contaminant Candidate List (PCCL 4) Nominated Contaminants. EPA 815-R-15-003. January, 2015.

WHO. 2003. Emerging Issues in Water and Infectious Disease Series: Heterotrophic Plate Counts and Drinking-water Safety. ed. J. Bartram, J. Cotruvo, M. Exner, C. Fricker, and A. Glasmacher. IWA Publishing, London, UK. p. 119 – 122.

WHO. 2004. Integrated Risk Assessment: Nonylphenol Case Study. ed. D. Bontje, J. Hermens, T. Vermeire, and T. Damstra. 63 pp. December, 2004. Available on the Internet at:http://www.who.int/ipcs/methods/Nonylphenol.pdf.

ED_002435_00004768-00017

5.0 Appendices

The appendices that follow provide tabulated summaries that present a list of the chemical and microbial contaminants nominated for consideration in CCL 4. Appendix 1 lists the chemical nominations, provides the chemical abstracts service registry number (CASRN) for each chemical contaminant, common name, nominating individual or organization, health effects information provided with the nomination, occurrence information provided with the nomination and additional information provided with the nomination. For the purpose of developing this appendix, EPA separated original text submitted with the nomination for each contaminant and placed it into the health effects information, occurrence information or additional information columns, as appropriate. EPA maintained the text submitted with each nomination verbatim; however, footnote numbers submitted in nominators' letters have been removed for clarity. The footnotes generally refer to references or comments and can be found in the original letters located in the docket.

Appendix 2 provides the same information for the microbial contaminants.

Appendix 3 lists the references provided with chemical nominations including: CASRN, contaminant name, nominating organization or individual and references cited. The references cited in Appendix 3 are in an abbreviated citation format (e.g., Fiore et al., 1986).

Appendix 4 lists the same information as Appendix 3; however, Appendix 4 covers microbial nominations.

Appendix 5 includes the complete list of full references provided with CCL 4 nominations for both microbial and chemical nominations. The original nomination letters and the nominations submitted via the Web site can be found in the docket at http://www.regulations.gov (docket ID: EPA-HQ-OW-2012-0217). The original documents contain all tables referenced in Appendix 1 and 2.

Appendix 6 shows the outcome of the nominated chemicals in the CCL 4 process (i.e., whether the nominated chemical was included in the CCL 4 Universe, PCCL 4 or Draft CCL 4). It also denotes the status of the nominated chemicals in the CCL 3 process. An "X" denotes that a chemical was included in that stage of the process. Note that nominated contaminants with an NPDWR or proposed NPDWR were not eligible for CCL 4, as explained in Section 3.1.1 above.

Appendix 7 shows the outcome of the nominated microbes in the CCL 4 process (i.e., whether the nominated microbe was included in the CCL 4 Universe, PCCL 4 or Draft CCL 4). It also denotes the status of the nominated microbe in the CCL 3 process. An "X" denotes that the microbe was included in that stage of the process.

ED_002435_00004768-00018

Appendix 1[4]. Chemical Contaminants Nominated

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
77439-76-0	3-chloro-4-dichloromethyl-5-hydroxy-2(5H)-furanone)	AWWA	None given	None given	None given
116-06-03	Aldicarb	AWWA	None given	None given	None given
116-06-3	Aldicarb	Natural Resources Defense Council	Aldicarb is an N-methyl carbamate insecticide that causes reversible red blood cell and plasma cholinesterase inhibition. This pesticide is classified as Toxicity Category 1 because of its high toxicity through all routes of exposure (oral, dermal and inhalation). Symptoms of acute aldicarb exposure observed in animal studies include decreased motor activity, lacrimation, tremors, salivation, pinpoint pupils, and decreased grip strength. A rat study by EPA/ORD demonstrated that young animals are more susceptible to aldicarb-induced brain cholinesterase inhibition than adults. Although it is generally believed that acute high level exposure to aldicarb will not cause chronic health effects, one case study by Grendon et al. (1994) in Washington State documented long-term health problems in men and sheep resulting from a single poisoning incident. EPA has not assessed the risks of chronic exposure to aldicarb in its 2006 Revised Human Health Risk Assessment (HRA). The Agency reasoned that since cholinesterase inhibition due to aldicarb exposure is reversed in less than 24 hours, such an assessment is unnecessary and chronic exposure can be treated as a series of acute exposures. However, EPA mentioned in the Revised HRA that effects such as pale kidneys and hydroceles in the oviducts occurred in dams in a developmental study, symptoms that suggest chronic damage not seen in acute single-exposure cases. In addition, some studies suggest that chronic exposure to aldicarb may have longer-term effects on the immune and nervous systems. Fiore et al (2006) analyzed immune function in two groups of women, one exposed to aldicarb at environmental concentrations in groundwater at levels below 61 ppb (23 subjects), and an unexposed group (27 subjects). No women in either group had known reasons for immune problems. The researchers found a significant association between aldicarb exposure and abnormalities in T-cell subset ratios. Hajoui et al. (1992) also found changes in the percentages of certain T-cell subsets after subchronic, but not chronic exposure.The results of a rat study by Smulders et al. (2003) suggest that exposure to carbamates such as aldicarb may also lead to chronic changes in the nervous system resulting from the inhibition of neuronal nicotinic acetylcholine receptors. A similar study of the carbamates fenoxycarb, carbaryl, and S-ethyl N,N-dipropylthiocarbamate (EPTC), which have the same mechanism of action, showed that increasing the pesticide dose or the length of exposure reduced the rate of reversal of acetylcholine receptor inhibition. Therefore, two mechanisms, cholinesterase inhibition and acetylcholine receptor inhibition may lead to chronic neurotoxicity from exposure to carbamate pesticides such	EPA placed aldicarb under Special Review in 1984 due to concerns about groundwater contamination. Aldicarb degradation in groundwater is slow. This chemical is persistent and mobile in soil, and degrades in the environment to aldicarb sulfoxide and aldicarb sulfone, both of which are cholinesterase inhibitors. In 1991 EPA established MCLs of 0.003 ppb for aldicarb, 0.004 ppb for aldicarb sulfoxide and 0.002 ppb for aldicarb sulfone, but these MCLs never went into effect. Instead, EPA issued a 7 ppb health advisory for each of the aldicarb species and for combined aldicarb residues. EPA based its drinking water risk assessment in the HRA on the highest aldicarb concentrations in groundwater found in eight regions where aldicarb was used. The concentrations ranged from 0 to 24 ppb. The region with no aldicarb detections was removed from the analysis. Surface water concentrations, on the other hand, were derived from models for lack of sufficient monitoring data.	None given

[4] For the purpose of developing this appendix, EPA separated original text submitted with the nomination for each contaminant and placed it into the health effects information, occurrence information or additional information columns, as appropriate. EPA maintained the text submitted with each nomination verbatim.

ED_002435_00004768-00019

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			as aldicarb. This raises concerns about chronic low-level exposure such as may result from aldicarb contamination of drinking water. Acute dietary exposure estimates from food alone exceeded the level of concern for children 1 to 2 years old (159% of the acute Population Adjusted Dose, or aPAD), and children 3 to 5 years old (129% aPAD), so that any additional exposures from drinking water would increase these risks of concern. The highest exposure from groundwater calculated for the regions where this pesticide was detected was 945% aPAD for the 95th percentile of the most exposed population sub-group. For the general U.S. population and other sub-groups, exposure ranged from 20% aPAD to 393% aPAD. It is clear from EPA's own analysis that aldicarb is a water contaminant that poses health risks of concern at levels found in food and drinking water. Given that food exposure alone exceeds levels of concern for children, drinking water exposure creates an additional unacceptable risk. EPA must move to establish a protective MCL for aldicarb.		
68555-24-8	Alkylphenol mono- to tri-oxylates	Natural Resources Defense Council	Alkylphenols were first reported to be estrogenic in the 1930s. In 1991, publication of the effects of nonylphenol on cultured human breast cancer cells led to health concerns. Estrogenic effects have also been shown in the mouse. Estrogenic effects are present at tissue concentrations of 0.1 μM for octylphenol and 1 μM for nonylphenol. A recombinant yeast screen using the human estrogen receptor has shown similar results.	An estimated 450,000,000 pounds of alkylphenol polyethoxylates (APEs) are produced annually in the United States, and about half that amount is estimated to be released to wastewater. Alkylphenol polyethoxylates do not break down effectively in sewage treatment plants or in the environment. Instead they degrade to alkylphenols and alkylphenol ethoxylates, which persist for longer. Nonylphenol and its ethoxylates, and other alkylphenols, have been detected in wastewater and in waterways.	None given
26787-78-0	Amoxicillin	Natural Resources Defense Council	Widespread exposure to antibiotics is contributing to the growth of bacterial resistance, and this problem is of grave concern. In the past several decades almost every bacteria that can cause infections in humans has developed resistance to at least one antibiotic, and some are resistant to multiple antibiotics. The Centers for Disease Control and Prevention (CDC) have identified antibiotic resistance as one of the most pressing public health problems to face our nation. Infections caused by bacteria with resistance to at least one antibiotic have been estimated to kill over 60,000 hospitalized patients each year. Antibiotic resistance is caused by a number of factors including repeated and improper use of antibiotics in both humans and animals. Scientists also agree that exposure to low levels of antibiotics actually promotes bacterial resistance by exerting selective pressure for genes that promote resistance. Beta-lactam antibiotics are a broad class of antibiotics which include penicillin derivatives, cephalosporins, monobactams, carbapenems and Beta-lactamase inhibitors. Methicillin, a form of penicillin, had been relied upon as an common effective treatment for Staphylococcus aureus infections but now many strains of S. aureus bacteria are resistant to methicillin (MRSA or methicillin-resistant Staphylococcus aureus.) Unfortunately, MRSA is resistant to much of the entire class of penicillin-like antibiotics called beta-lactams. Therefore, EPA must include penicillin, amoxicillin, oxacillin and methicillin on the CCL4.	Antibiotics are found in wastewater because the body does not completely metabolize all drugs, so both the metabolized and unmetabolized drug are excreted by humans into wastewater. For example,when amoxicillin is ingested, 60-75% of the antibiotic is excreted unchanged into the urine. This antibiotic, now in the environment, may encounter other bacteria and promote resistance. It is unknown how much of an impact current low levels of antibiotics in drinking water are having on the problem of bacterial resistance. However, the potential has been recognized for many years.	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
86-50-0	Azinphos-methyl	Natural Resources Defense Council	Azinphos-methyl (CAS # 86-50-0) is an organophosphate pesticide classified as toxicity category 1 for oral exposure. Exposure to azinphos-methyl causes plasma, red blood cell and brain cholinesterase inhibition, with symptoms including headache, nausea, vomiting, dizziness, anxiety, muscle tremors and weakness. Studies by Souza et al. (2004, 2005) found that azinphos-methyl affected human placental enzymatic activity, which may have adverse consequences for fetal development. Exposure to organophosphate pesticides (OPs) such as azinphos-methyl has been associated with lower performance on neurobehavioral tests in exposed adults. Children are more vulnerable than adults to the neurotoxic effects of OPs and may suffer developmental effects from low-level chronic exposures.	Azinphos-methyl has a high potential to pollute surface waters due to runoff and spray drift. Data on environmental concentrations of azinphos-methyl in the United States are limited, but studies in South Africa suggest that under certain conditions azinphos-methyl may also reach high concentrations (>40 ppb) in groundwater. EPA indicated in its drinking water assessment in the Interim Reregistration Eligibility Decision (IRED) document for azinphos-methyl that the estimated environmental concentration (EEC) of this pesticide in surface water is 16 ppb at typical application rates in peaches. This concentration is over three times the acute drinking water level of comparison (DWLOC) the agency calculated for infants less than a year old (5 ppb), and over twice the DWLOC for children 1-6 years (6 ppb). The highest annual mean concentrations in surface water according to monitoring data and EPA models ranged from 0.27 ppb to 7.2 ppb. The latter concentration exceeds the chronic DWLOC the agency calculated for infants less than a year old (7 ppb). While EPA argued in the IRED that the phase-out of azinphos –methyl use on peaches will eliminate drinking water risks of concern, EPA is still allowing the use of azinphos¬methyl on apples (the most frequently treated crop) at application rates equal to or higher than those for peaches (1.0-1.5 lb ai/A per application, 4.5 lb ai/A per year maximum on apples vs. 1.125 lbs ai/A per application, 4.5 lbs ai/A per year maximum on peaches). Furthermore, the total amount of azinphos-methyl used on apples (890,000 lb active ingredient) is over seven times the amount used on peaches (120,000 lb). Therefore, the EPA assessment indicates that azinphos-methyl poses a risk to drinking water supplies. While EPA has issued a four-year limited registration for azinphos-methyl use on apples and seven other crops, the Agency has stated that these registrations may be extended, thus creating the need to regulate azinphos-methyl as a drinking water contaminant.	None given
1405-89-6	Bacitracin zinc	Natural Resources Defense Council	Widespread exposure to antibiotics is contributing to the growth of bacterial resistance, and this problem is of grave concern. In the past several decades almost every bacteria that can cause infections in humans has developed resistance to at least one antibiotic, and some are resistant to multiple antibiotics. The Centers for Disease Control and Prevention (CDC) have identified antibiotic resistance as one of the most pressing public health problems to face our nation. Infections caused by bacteria with resistance to at least one antibiotic have been estimated to kill over 60,000 hospitalized patients each year. Antibiotic resistance is caused by a number of factors including repeated and improper use of antibiotics in both humans and animals. Scientists also agree that exposure to low levels of antibiotics actually promotes bacterial resistance by exerting selective pressure for genes that promote resistance.	Antibiotics are found in wastewater because the body does not completely metabolize all drugs, so both the metabolized and unmetabolized drug are excreted by humans into wastewater. For example, when amoxicillin is ingested, 60-75% of the antibiotic is excreted unchanged into the urine. This antibiotic, now in the environment, may encounter other bacteria and promote resistance. It is unknown how much of an impact current low levels of antibiotics in drinking water are having on the problem of bacterial resistance. However, the potential has been recognized for many years. Large animal feeding operations generate a large amount of waste that can potentially contaminate groundwater and waterways contributing to antibiotic resistance and contamination of waterways with steroid hormones. As occurs in humans, some portion of the antibiotics administered to livestock will pass unchanged through their bodies and will be excreted in their waste. It has been estimated that	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			Massive quantities of antibiotics are used in agriculture both to treat infections and as food additives to promote growth and to compensate for conditions that contribute to infection. Animals raised in Concentrated Animal Feeding Operations (CAFOs) are at increased risk for infection due to close confinement and stress. In fact, it has been estimated that 70% of the antibiotics used in the U.S. are for animal husbandry. Improper use and overuse of antibiotics in livestock and poultry can cause resistance in strains of bacteria that can infect humans. Furthermore, half of the antibiotics used in livestock are in the same classes of drugs that are used in humans. As a result the U.S. Institute of Medicine (IOM) and the World Health Organization (WHO) both stated that the widespread use of antibiotics in agriculture is contributing to antibiotic resistance in humans.	between 25-75% of antibiotics are excreted unchanged in feces and can persist in the soil after land application. Manure is applied in large quantities as fertilizer in farm fields. In addition to potentially contaminating the food supply with antibiotic resistant bacteria, antibiotics in manure can persist in soil and promote the development of more antibiotic resistant bacteria. Animal waste and its associated contaminants can enter waterways through groundwater contamination, overflow of waste lagoons into surface water or by over-application of manure as fertilizer in farm fields. A recently published study found evidence of fecal contamination and increased levels of antibiotic resistant bacteria downstream of a swine concentrated feeding operation. Other studies have found antibiotic resistance in groundwater underlying a swine waste lagoon. As such, antibiotics that are used both for human medical needs and in large-scale agriculture operations at low levels in animal feed to promote animal growth must be included on the CCL4 and must be regulated. These antibiotics include bacitracin zinc, spiramycin, tylosin, and virginiamycin. Notably, these antibiotics were all banned for agricultural use in the European Union in 1998.	
25057-89-0	Bentazone	AWWA	None given	None given	None given
85-68-7	Benzyl butyl phthalate	Natural Resources Defense Council	Phthalates are endocrine disruptors that have been found to cause developmental and reproductive abnormalities in animal studies. Furthermore, studies have found an association between phthalate metabolite concentrations and obesity, insulin resistance and thyroid hormone levels in humans. Stahlhut et al.(2007) analyzed urinary concentrations of seven phthalate metabolites in 1,443 adult men and found a statistically significant positive association between concentrations of the metabolites MBzP, MEHHP, MEOHP and MEP and abdominal obesity. Concentrations of MBP, MBzP and MEP were positively and significantly associated with insulin resistance. In a different study, baby boys exposed to the phthalates, DMP, DEP or BBP, in their mother's breast milk were found to have hormonal disturbances at 3 months of age. Studies have found that di-isononyl phthalate (DiNP) is an anti-androgenic endocrine disruptor with developmental and reproductive toxicity. Exposures in pregnant rats have been shown to adversely affect development of the male reproductive tract. Adverse effects include a cluster of outcomes that has been called "phthalate e syndrome" and includes underdeveloped or absent reproductive organs, retained nipples, cryptorchidism, decreased anogenital distance (AGD), hypospadias, and decreased or abnormal sperm. DINP does not bind to the androgen receptor and these effects are likely mediated through interference with testosterone synthesis. Phthalates are ubiquitous in the U.S. population. Although significant exposure can occur due to consumer products, the contribution of drinking water to overall exposure deserves to be examined. The NHANES measured the concentrations of 12 phthalate metabolites in the urine of over 2,500 children	Phthalates enter the environment as a result of releases from industrial facilities that manufacture or use these compounds, from waste disposal sites, through the use of phthalate-containing products by consumers and through discharge of municipal wastewaters containing phthalates. Phthalates have been found in numerous hazardous waste sites: diethyl phthalate (DEP) has been identified at 348 sites, dibutyl phthalate (DBP) at 602 sites, dimethyl phthalate (DMP) at 167 sites, benzyl butyl phthalate (BzBP) at 413 sites, dicyclohexyl phthalate (DCHP) at one site, and di-n-octyl phthalate (DnOP) at 433 sites, among other phthalates. Phthalates have been detected in environmental water samples across the United States, which raises concerns about drinking water as a route of exposure. The maximum concentrations found for some of these phthalates are particularly alarming. The following data were found in a search for stream water samples analyzed for phthalates in the EPA STORET database. Results are for the period January 2000 through June 2012: Benzyl butyl phthalate (BzBP) was present in 789 (19.3 %) out of 4077 stream water samples analyzed for this chemical, with a maximum concentration of 1000 ug/L.	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			and adults. The highest average concentration was 163 ug/g creatinine for MEP, a metabolite of the plasticizer diethyl phthalate (see Table 3). [See the CDC report cited below] The Centers for Disease Control and Prevention (CDC) did not report what percentage of samples had detectable concentrations of each of the metabolites, but nine of the metabolites were found in the urine of at least half of the individuals. [See Table 3. CDC report of phthalate concentrations in urine; NHANES 1999 – 2000 and 2001 - 2002 located on page 27 of the NRDC Nomination Letter and Table 4 Frequency of detection of phthalate metabolites in human urine samples, United States located on pages 28 and 29 of the NRDC Nomination Letter.]		
80-05-7	Bisphenol A	Anonymous 201	Weak endocrine disruptor - principal concern is for potential reproductive and developmental effects in early life stages. EPA has considered exposures to children from drinking water and from the use of BPA in consumer products. EPA also examined potential ecological impact from the presence of BPA in the environment.	None given	None given
80-05-7	Bisphenol A	Natural Resources Defense Council	A number of recent studies have revealed that early life exposures to low-doses of BPA result in adverse effects later in life. The developing fetus is especially vulnerable. Although many of these studies were done in laboratory animals, the exposures occurred at concentrations currently found in the human population. Recent research finds low levels of BPA exposure causes harm in the mammary gland, prostate tissue, and brain. In rats, in utero exposure to BPA causes long-term effects on development of mammary tissue, causing preneoplastic lesions, increased susceptibility to cancer and increased sensitivity to a chemical known to cause breast cancer. Perinatal exposure to low levels of BPA causes precancerous prostate lesions (prostatic intraepithelial neoplasia) in rats. The effect appears to result from the failure in exposed animals of a gene to become hypermethylated as the rats age. Experiments with mice reveal that chronic adult exposure to BPA causes insulin resistance, a common problem in humans that can lead to Type II diabetes and heart disease. Recent human studies continue to find links between BPA and cardiovascular disease, obesity and metabolic changes affecting insulin levels, which could lead to diabetes. BPA has been shown to cause aneuploidy in mouse oocytes. Meiotic aneuploidy is the most common cause of miscarriage in women. In 2007, a group of 38 scientists issued a consensus statement expressing their concern that current levels of BPA exposure were contributing to the human health conditions of neurobehavioral problems, obesity, infertility and reproductive cancers. In addition, the U.S. National Toxicology Program has issued a draft report expressing "some concern" that BPA could cause neurobehavioral abnormalities, early onset puberty, and reproductive cancers, especially in fetuses, infants and children who are exposed.	BPA is produced at over one million pounds per year and is frequently found in the environment. BPA releases to the environment in the U.S. totaled 1.4 million pounds in 2006, including 3,410 pounds released directly to water and 108,805 pounds released to the air. BPA is a water contaminant. A study in Germany found BPA in surface water (0.0005 to 0.41 ug/L), in sewage effluents (0.018 to 0.702 ug/L), in sediments (0.01 to 0.19 mg/kg) and in sewage sludge (0.004 to 1.363mg/kg dw). Cousins et al. (2002) reviewed previously published monitoring data for the United States and found a median reported water concentration of 0.5 ug/l (below the detection limit of the studies) and a 90th percentile of 4.4 ug/l. The same study also suggested a half-life for BPA of 4.5 days in surface water, indicating that BPA can be transported hundreds of kilometers in rivers before levels fall below detection limits. In December, 2011, the International Chemical Secretariat in the E.U. reported that many drinking water pipes are being restored by relining them with epoxy resin that contains BPA, and that this BPA is leaching into the drinking water. Anecdotally, this practice seems to also be occurring in the U.S. This is another important source of exposure in the drinking water – and suggests that levels of BPA are even higher than articles suggest.	Bisphenol A - (4,4'-(1-ethylethylidene)bisphenol or 4,4'-Isopropylidenediphenol), (CASRN 80-05-7), is a monomer used as the building block of polycarbonate plastics and other plastics including epoxy resins. BPA is found in a wide variety of everyday consumer products, such as the coating of food and drink packaging, dental sealants, baby bottles, water bottles, microwave ovenware and eating utensils. As these products age, the polycarbonate polymer breaks down, releasing the BPA monomer.
1689-84-5	Bromoxynil	AWWA	None given	None given	None given
63-25-2	Carbaryl	AWWA	None given	None given	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
63-25-2	Carbaryl	Natural Resources Defense Council	Carbaryl (CAS # 63-25-2) is an N-methyl carbamate pesticide that acts as a neurotoxic acetylcholinesterase inhibitor and a "likely" carcinogen according to the Office of Pesticide Programs Cancer Assessment Review Committee. The systemic effects of carbaryl include headache, dizziness, weakness, shaking, nausea, stomach cramps, diarrhea, and sweating. Effects may also include loss of appetite, weakness, weight loss, and general malaise. Carbaryl is particularly toxic to the developing nervous system of fetuses, infants, and young children. Exposure to elevated levels of carbaryl may cause developmental neurotoxicity and "significant changes in some of the morphometric measurements of the brain". Given the limitations in the monitoring data that the Agency [EPA] has acknowledged, and the fact that the highest EEC estimated by EPA models was 55 times the acute DWLOC for children 1 to 2 years old, it is clear that carbaryl presents risks of concern from drinking water exposure and should be regulated as a drinking water contaminant by establishing an MCL.	Approximately 3.9 million pounds of carbaryl active ingredient are used annually in the U.S. When EPA issued its Revised Risk Assessment for carbaryl in 2003, its water assessment did not consider non-agricultural sources of carbaryl, which constitute a total of 40% of carbaryl use by weight, and which are the dominant sources of carbaryl pollution in surface water. Despite ignoring non-agricultural uses, the carbaryl health risk assessment in the Interim Reregistration Eligibility Decision (IRED) found that acute surface water risks presuming maximum label application rates exceeded the drinking water level of concern (DWLOC) for children and the general population when combined with estimated food exposures. U.S. Geological Survey National Water Quality Assessment (NAWQA) monitoring data presented in the carbaryl assessment demonstrated that streams draining urban areas had both higher concentrations of carbaryl and more frequent detections, when compared with streams draining agricultural or mixed land use areas. It is clear that contamination of water is predominantly from non-agriculture uses of carbaryl, and that by not considering these uses, the Agency dramatically underestimated the amount of carbaryl in drinking water (Estimated Environmental Concentration, or EEC), which is likely to be two-times higher than EPA estimates. Twenty-one percent of surface water samples in the NAWQA database contained detectable levels of carbaryl.EPA discussed in its IRED the limitations of existing monitoring data: "Carbaryl is fairly mobile, but is not likely to persist or accumulate in the environment. As such, it is difficult for monitoring studies to detect peak concentrations that can occur. EPA determined that currently available monitoring studies for carbaryl are limited in this regard, and did not use them to define peak values for carbaryl."As a result of these data limitations, EPA used models to estimate drinking water EECs for currently registered uses in the carbaryl IRED. The Agency reported that the acute drinking water EECs ranged from 23 to 410 ppb for acute exposure, and from 1.3 to 23 ppb for chronic exposure, which exceeded the acute DWLOC for children 1-2 years old (7.4 ppb) and for the general population (200 ppb). This is especially concerning, given that these calculations are likely to underestimate risk by excluding non-agricultural uses of carbaryl, which comprise 40% of total carbaryl used. Therefore, it is likely that actual EEC's are even higher, possibly 40% higher, than what the Agency calculates. The high toxicity of carbaryl, coupled with the high exceedances of acceptable levels in drinking water, make this level of risk to infants and children unacceptably high.	None given
10045-97-3	Cesium 137	Anonymous 197	Cs-137 is prevalent in atmosphere due to melt down underway in Japan of four reactors with 40 years of spent fuel on site. Cs-137 interferes with endocrine function and fetal development.	There are 23 nuclear power plants of exact design to the fatal power plants in Japan, failure due to earthquakes near population centers and water sources.	Monitoring existing conditions leads to rate of change analysis when done on a predictable time frame.
1897-45-6	Chlorothalonil	AWWA	None given	None given	None given
2821-88-2	Chlorpyrifos	AWWA	None given	None given	None given

ED_002435_00004768-00024

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
2921-88-2	Chlorpyrifos	Natural Resources Defense Council	With chlorpyrifos and other developmental neurotoxic chemicals, risk to the fetus, infant, and child comes primarily from the timing of exposure. Even a very small dose, for even a short duration, during a developmental period of vulnerability will result in permanent neural dysfunction. There is no demonstrated reliable threshold of safety for this highly toxic chemical, as indicated in the IRED, where a no-effect level could not be determined for developmental neurotoxicity. However, there is demonstrated evidence of neuropathology and increased vulnerability of fetuses when exposed to chlorpyrifos. EPA has acknowledged this susceptibility in the chlorpyrifos Human Health Risk Assessment: In conclusion, the weight of the evidence raises concern for an increase in both the sensitivity and susceptibility of the fetus or young animal to adverse biochemical, morphological, or behavioral alterations from chlorpyrifos treatment during brain development. With respect to cholinesterase inhibition, an increase in sensitivity of the young compared to adults was seen all along the dose response curve, even at relatively low doses." Using the PRZM/EXAMS screening model, EPA estimated that 90-day average and peak chlorpyrifos concentrations were 6.7 and 40 ppb respectively. Meanwhile, acute DWLOCs for infants less than a year old, children 1-6 years and females 13 to 50 years ranged from 0.9 to 9 ppb. Chronic DWLOCs for these population groups ranged from 0.2 to 0.72 ppb. EPA's modeling estimates therefore show that chlorpyrifos exposure in drinking water has the potential to expose vulnerable groups of the population to unacceptable levels of this chemical.	Chlorpyrifos (CAS # 2921-88-2) is an organophosphate pesticide used at approximately 21 to 24 million pounds active ingredient (a.i.) annually in the United States. Most chlorpyrifos is used in agriculture on crops such as corn and cotton, but other uses include golf courses, road medians, food processing plants, manufacturing plants, ship holds, railroad boxcars, and non-structural wood treatments. Chlorpyrifos is applied aerially, by chemigation, groundboom, hand wand, airblast sprayer, and other methods. Although EPA said in the IRED that the drinking water risk is below the level of concern, the Agency noted that there have been cases of high levels of drinking water well contamination associated with localized applications of chlorpyrifos as a subterranean termiticide. This was addressed, EPA said, by eliminating all termiticidal uses. However, despite EPA's assertions that only termiticidal use leads to water contamination problems, USGS and others have found contamination of ground and surface water with chlorpyrifos and its metabolites, and EPA's own modeling shows that it is likely that in certain areas of heavy use, chlorpyrifos (and its metabolites) present significant water risks. There is no evidence that the water risks of chlorpyrifos and its metabolites are limited to termiticidal use.There is extensive evidence of the potential of chlorpyrifos to contaminate surface and groundwater. Combined USGS data for state, local, national, and multi-state studies that measured chlorpyrifos concentrations in surface water detected the pesticide at 7 of 108 (6%) sites sampled. Chlorpyrifos has medium runoff potential due to its relatively low water solubility, 2 mg/L. A chlorpyrifos flux as a percentage of use of 0.15 has been measured in the Minnesota River. Chlorpyrifos is also used in non-agricultural settings and can drift or runoff directly into surface water bodies in areas of high population density.Data from the Mid-Continent Pesticide Study show that chlorpyrifos was present in the ground water in 4.2% of the wells sampled. Chlorpyrifos has been detected in 0.6% of wells sampled, according to the U.S. EPA's Pesticides in Ground Water Database. Long (1989) detected chlorpyrifos in the ground water of 30% of 56 sites examined beneath pesticide mixing and loading facilities in Illinois. The maximum concentration detected was 0.5 ppb.Water monitoring sample sites are not necessarily correlated with chlorpyrifos use sites, and in particular, may miss sites where multiple fields are treated with chlorpyrifos resulting in pooled runoff into a common water source. In fact, the IRED states, "it is not clear that they [monitoring data] represent the most vulnerable groundwater where chlorpyrifos is used most intensively" (IRED p.18). Monitoring of surface water is likely to be subject to the same problem. Levels of chlorpyrifos in pooled runoff sites are likely to be many times higher than single field sites. Similarly, data collection is not timed to correspond with worst-case scenarios, such as closely following chlorpyrifos applications, or following large storm runoff events, and thus most often misses these highly toxic environmental exposures.	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
84-74-2	Dibutyl phthalate	Natural Resources Defense Council	Phthalates are endocrine disruptors that have been found to cause developmental and reproductive abnormalities in animal studies.Furthermore, studies have found an association between phthalate metabolite concentrations and obesity, insulin resistance and thyroid hormone levels in humans. Stahlhut et al. (2007) analyzed urinary concentrations of seven phthalate metabolites in 1,443 adult men and found a statistically significant positive association between concentrations of the metabolites MBzP, MEHHP, MEOHP and MEP and abdominal obesity. Concentrations of MBP, MBzP and MEP were positively and significantly associated with insulin resistance. In a different study, baby boys exposed to the phthalates, DMP, DEP or BBP, in their mother's breast milk were found to have hormonal disturbances at 3 months of age. Studies have found that di-isononyl phthalate (DiNP) is an anti-androgenic endocrine disruptor with developmental and reproductive toxicity. Exposures in pregnant rats have been shown to adversely affect development of the male reproductive tract. Adverse effects include a cluster of outcomes that has been called "phthalate e syndrome" and includes underdeveloped or absent reproductive organs, retained nipples, cryptorchidism, decreased anogenital distance (AGD), hypospadias, and decreased or abnormal sperm. DINP does not bind to the androgen receptor and these effects are likely mediated through interference with testosterone synthesis. Phthalates are ubiquitous in the U.S. population. Although significant exposure can occur due to consumer products, the contribution of drinking water to overall exposure deserves to be examined. The NHANES measured the concentrations of 12 phthalate metabolites in the urine of over 2,500 children and adults. The highest average concentration was 163 ug/g creatinine for MEP, a metabolite of the plasticizer diethyl phthalate (see Table 3). [See the CDC report cited below.] The Centers for Disease Control and Prevention (CDC) did not report what percentage of samples had detectable concentrations of each of the metabolites, but nine of the metabolites were found in the urine of at least half of the individuals. [See Table 3. *CDC report of phthalate concentrations in urine; NHANES 1999 – 2000 and 2001 - 2002* located on page 27 of the NRDC Nomination Letter and Table 4 Frequency of detection of phthalate metabolites in human urine samples, United States located on pages 28 and 29 of the NRDC Nomination Letter.]	Phthalates enter the environment as a result of releases from industrial facilities that manufacture or use these compounds, from waste disposal sites, through the use of phthalate-containing products by consumers and through discharge of municipal wastewaters containing phthalates. Phthalates have been found in numerous hazardous waste sites: diethyl phthalate (DEP) has been identified at 348 sites, dibutyl phthalate (DBP) at 602 sites, dimethyl phthalate (DMP) at 167 sites, benzyl butyl phthalate (BzBP) at 413 sites, dicyclohexyl phthalate (DCHP) at one site, and di-n-octyl phthalate (DnOP) at 433 sites, among other phthalates. Phthalates have been detected in environmental water samples across the United States, which raises concerns about drinking water as a route of exposure. The maximum concentrations found for some of these phthalates are particularly alarming. The following data were found in a search for stream water samples analyzed for phthalates in the EPA STORET database. Results are for the period January 2000 through June 2012: Dibutyl phthalate (DBP) was found in 828 (19.9%) of the 4160 stream water samples for that period, with a maximum concentration of 2,760 ug/L.	None given
1918-00-9	Dicamba	AWWA	None given	None given	None given
62-73-7	Dichlorvos	Natural Resources Defense Council	Dichlorvos (CAS # 62-73-7), or DDVP, is an organophosphate insecticide widely used in agriculture. Like other organophosphates, dichlorvos is an acetylcholinesterase inhibitor. DDVP exposure may cause symptoms such as nausea, vomiting, dizziness, muscle spasms, and seizures. According to a 2000 EPA Cancer Assessment review, there is suggestive evidence that dichlorvos may cause cancer. The National Toxicology Program has stated that there is "clear evidence" of carcinogenic activity of dichlorvos in a mice study. One study has linked dichlorvos exposure to leukemia in children under 15. Another study has also found an association between dichlorvos exposure and leukemia in adult men. Furthermore, EPA has determined that "dichlorvos has been shown to be a direct acting mutagen by common *in vitro* bacterial	Dichlorvos is soluble in water and may enter surface waters in runoff. However, no data on its occurrence in surface waters has been collected; there is also little data on dichlorvos in groundwater. Two other pesticides, naled and trichlorfon, degrade to dichlorvos in the environment and represent additional inputs of dichlorvos to water. However, monitoring data on these two pesticides is also very limited. Given the lack of monitoring data, EPA used IR-PCA PRZM/EXAMS models to calculate estimated drinking water concentrations (EDWCs) of dichlorvos in surface water. The models produced estimates that were below the EPA level of concern. However; the complete lack of	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			genetic toxicity assays and *in vitro* mammalian test systems."	monitoring data raises questions about whether an exclusive reliance on modeling results is appropriate for a neurotoxic and potentially carcinogenic pesticide such as dichlorvos. EPA should collect data monitoring data for dichlorvos by requiring such data from the registrants or commissioning its own studies to better assess drinking water risks and set an MCL if necessary.	
115-32-2	Dicofol	Natural Resources Defense Council	Animal studies have found that dicofol causes toxicity in the liver, adrenal glands, kidneys, thyroid, reproductive organs, heart and stomach. Liver and thyroid effects occurred at relatively low doses (100 ppm and 10 ppm, respectively). Dicofol is a possible human carcinogen. Dicofol has shown endocrine disruptor activity in vivo and in vitro. This chemical has been shown to interfere with blastocyst implantation in rats. The first problem with the assessment is related to the way EPA calculated the Reference Dose (RfD). EPA is supposed to apply an additional safety factor of 10x to the RfD calculation to protect infants and children, who may have increased susceptibility to health effects from chemical exposures compared to adults. The Agency reduced the FQPA safety factor of 10x to 3x based on the lack of increased pre-natal or post-natal susceptibility to dicofol in developmental toxicity studies. However, EPA stated that a developmental neurotoxicity study was necessary because dicofol produced neurotoxicity in rats and such a study might identify an endpoint for dietary risk. Despite lacking such a study, EPA improperly reduced the safety factor to 3x. If the 10x factor had been applied as mandated by the Food Quality Protection Act, a more protective acute RfD of 0.015 mg/kg day-1 would have been chosen instead of the 0.05 mg/kg day-1 dose EPA used in its assessment. Had EPA applied the 10x safety factor, dicofol exposure from food alone would have exceeded the acute RfD and the EPA level of concern for all population groups (see Table 1) [See Table 1. Comparison of acute dietary exposure values from food at the 99.9th percentile located on page 16 of the NRDC nomination letter]. This would have resulted in a DWLOC of zero (0), so that any drinking water exposure would have been of concern. The unwarranted reduction of the FQPA safety factor also affected the outcome of the chronic dietary exposure assessment. As shown in Table 2 [See Table 2. Chronic dietary food exposure and risk estimate from Dicofol (in food alone) located on page 17 of the NRDC nomination letter.], if the 10x factor had been applied, chronic exposures from food alone for infants and children 1 to 6 years old would have exceeded the level of concern. Therefore, any drinking water exposure would have been of concern as well. [See Table 2. Chronic dietary food exposure and risk estimate from Dicofol (in food alone) located on page 17 of the NRDC nomination letter.]	Dicofol is an organochlorine pesticide used in agriculture, primarily on cotton and citrus crops. Approximately 860,000 pounds of active ingredient are used every year.EPA used its SCI-GROW model to estimate dicofol concentrations in groundwater and calculated a 90-day average peak concentration of 0.069 ppb. An overall mean surface water concentration of 0.5 ppb was estimated with the PRZM-EXAMS model. Both concentrations were below the Drinking Water Levels of Comparison (DWLOCs) for children and the general U.S. population for both acute and chronic exposure. However, there are some important shortcomings in EPA's assessment of dicofol exposure and risk. Another shortcoming in the EPA assessment is that the Agency relied on models to estimate environmental concentrations in surface and groundwater, but did not have a robust set of monitoring data. EPA should require the collection of surface and groundwater monitoring data in areas where dicofol is applied. The Agency should use these data to corroborate its exposure estimates and make a regulatory determination for dicofol under the SDWA.	None given
84-61-7	Dicyclohexyl phthalate	Natural Resources Defense Council	Phthalates are endocrine disruptors that have been found to cause developmental and reproductive abnormalities in animal studies. Furthermore, studies have found an association between phthalate metabolite concentrations and obesity, insulin resistance and thyroid hormone levels in humans. Stahlhut et al. (2007) analyzed urinary concentrations of seven phthalate metabolites in 1,443 adult men and found a statistically significant positive association between concentrations of the metabolites MBzP, MEHHP, MEOHP and MEP and abdominal obesity. Concentrations of MBP,	Phthalates enter the environment as a result of releases from industrial facilities that manufacture or use these compounds, from waste disposal sites, through the use of phthalate-containing products by consumers and through discharge of municipal wastewaters containing phthalates. Phthalates have been found in numerous hazardous waste sites: diethyl phthalate (DEP) has been identified at 348 sites, dibutyl phthalate (DBP) at 602 sites, dimethyl phthalate (DMP) at 167 sites, benzyl butyl phthalate (BzBP) at 413 sites,	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			MBzP and MEP were positively and significantly associated with insulin resistance. In a different study, baby boys exposed to the phthalates, DMP, DEP or BBP, in their mother's breast milk were found to have hormonal disturbances at 3 months of age. Studies have found that di-isononyl phthalate (DiNP) is an anti-androgenic endocrine disruptor with developmental and reproductive toxicity. Exposures in pregnant rats have been shown to adversely affect development of the male reproductive tract. Adverse effects include a cluster of outcomes that has been called "phthalate e syndrome" and includes underdeveloped or absent reproductive organs, retained nipples, cryptorchidism, decreased anogenital distance (AGD), hypospadias, and decreased or abnormal sperm. DINP does not bind to the androgen receptor and these effects are likely mediated through interference with testosterone synthesis. Phthalates are ubiquitous in the U.S. population. Although significant exposure can occur due to consumer products, the contribution of drinking water to overall exposure deserves to be examined. The NHANES measured the concentrations of 12 phthalate metabolites in the urine of over 2,500 children and adults. The highest average concentration was 163 ug/g creatinine for MEP, a metabolite of the plasticizer diethyl phthalate (see Table 3). [See the CDC report cited below.] The Centers for Disease Control and Prevention (CDC) did not report what percentage of samples had detectable concentrations of each of the metabolites, but nine of the metabolites were found in the urine of at least half of the individuals. [See Table 3. *CDC report of phthalate concentrations in urine; NHANES 1999 – 2000 and 2001 - 2002* located on page 27 of the NRDC Nomination Letter and Table 4 Frequency of detection of phthalate metabolites in human urine samples, United States located on pages 28 and 29 of the NRDC Nomination Letter.]	dicyclohexyl phthalate (DCHP) at one site, and di-n-octyl phthalate (DnOP) at 433 sites, among other phthalates. Phthalates have been detected in environmental water samples across the United States, which raises concerns about drinking water as a route of exposure. The maximum concentrations found for some of these phthalates are particularly alarming.	
84-66-2	Diethyl phthalate	Natural Resources Defense Council	Phthalates are endocrine disruptors that have been found to cause developmental and reproductive abnormalities in animal studies. Furthermore, studies have found an association between phthalate metabolite concentrations and obesity, insulin resistance and thyroid hormone levels in humans. Stahlhut et al. (2007) analyzed urinary concentrations of seven phthalate metabolites in 1,443 adult men and found a statistically significant positive association between concentrations of the metabolites MBzP, MEHHP, MEOHP and MEP and abdominal obesity. Concentrations of MBP, MBzP and MEP were positively and significantly associated with insulin resistance. In a different study, baby boys exposed to the phthalates, DMP, DEP or BBP, in their mother's breast milk were found to have hormonal disturbances at 3 months of age. Studies have found that di-isononyl phthalate (DiNP) is an anti-androgenic endocrine disruptor with developmental and reproductive toxicity. Exposures in pregnant rats have been shown to adversely affect development of the male reproductive tract. Adverse effects include a cluster of outcomes that has been called "phthalate e syndrome" and includes underdeveloped or absent reproductive organs, retained nipples, cryptorchidism, decreased anogenital distance (AGD), hypospadias, and decreased or abnormal sperm. DINP does not bind to the androgen receptor	Phthalates enter the environment as a result of releases from industrial facilities that manufacture or use these compounds, from waste disposal sites, through the use of phthalate-containing products by consumers and through discharge of municipal wastewaters containing phthalates. Phthalates have been found in numerous hazardous waste sites: diethyl phthalate (DEP) has been identified at 348 sites, dibutyl phthalate (DBP) at 602 sites, dimethyl phthalate (DMP) at 167 sites, benzyl butyl phthalate (BzBP) at 413 sites, dicyclohexyl phthalate (DCHP) at one site, and di-n-octyl phthalate (DnOP) at 433 sites, among other phthalates. Phthalates have been detected in environmental water samples across the United States, which raises concerns about drinking water as a route of exposure. The maximum concentrations found for some of these phthalates are particularly alarming. The following data were found in a search for stream water samples analyzed for phthalates in the EPA STORET database. Results are for the period January 2000 through June 2012:	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			and these effects are likely mediated through interference with testosterone synthesis. Phthalates are ubiquitous in the U.S. population. Although significant exposure can occur due to consumer products, the contribution of drinking water to overall exposure deserves to be examined. The NHANES measured the concentrations of 12 phthalate metabolites in the urine of over 2,500 children and adults. The highest average concentration was 163 ug/g creatinine for MEP, a metabolite of the plasticizer diethyl phthalate (see Table 3). [See the CDC report cited below.] The Centers for Disease Control and Prevention (CDC) did not report what percentage of samples had detectable concentrations of each of the metabolites, but nine of the metabolites were found in the urine of at least half of the individuals. [See Table 3. CDC report of phthalate concentrations in urine; NHANES 1999 – 2000 and 2001 - 2002 located on page 27 of the NRDC Nomination Letter and Table 4 Frequency of detection of phthalate metabolites in human urine samples, United States located on pages 28 and 29 of the NRDC Nomination Letter.]	Diethyl phthalate (DEP) was detected in 840 (20.1%) of the 4174 stream water samples analyzed. The maximum concentration found was 1000 ug/L.	
28553-12-0	Di-isononyl phthalate	Natural Resources Defense Council	Phthalates are endocrine disruptors that have been found to cause developmental and reproductive abnormalities in animal studies. Furthermore, studies have found an association between phthalate metabolite concentrations and obesity, insulin resistance and thyroid hormone levels in humans. Stahlhut et al. (2007) analyzed urinary concentrations of seven phthalate metabolites in 1,443 adult men and found a statistically significant positive association between concentrations of the metabolites MBzP, MEHHP, MEOHP and MEP and abdominal obesity. Concentrations of MBP, MBzP and MEP were positively and significantly associated with insulin resistance. In a different study, baby boys exposed to the phthalates, DMP, DEP or BBP, in their mother's breast milk were found to have hormonal disturbances at 3 months of age. Studies have found that di-isononyl phthalate (DiNP) is an anti-androgenic endocrine disruptor with developmental and reproductive toxicity. Exposures in pregnant rats have been shown to adversely affect development of the male reproductive tract. Adverse effects include a cluster of outcomes that has been called "phthalate e syndrome" and includes underdeveloped or absent reproductive organs, retained nipples, cryptorchidism, decreased anogenital distance (AGD), hypospadias, and decreased or abnormal sperm. DINP does not bind to the androgen receptor and these effects are likely mediated through interference with testosterone synthesis. Phthalates are ubiquitous in the U.S. population. Although significant exposure can occur due to consumer products, the contribution of drinking water to overall exposure deserves to be examined. The NHANES measured the concentrations of 12 phthalate metabolites in the urine of over 2,500 children and adults. The highest average concentration was 163 ug/g creatinine for MEP, a metabolite of the plasticizer diethyl phthalate (see Table 3). [See the CDC report cited below.] The Centers for Disease Control and Prevention	Phthalates enter the environment as a result of releases from industrial facilities that manufacture or use these compounds, from waste disposal sites, through the use of phthalate-containing products by consumers and through discharge of municipal wastewaters containing phthalates. Phthalates have been found in numerous hazardous waste sites: diethyl phthalate (DEP) has been identified at 348 sites, dibutyl phthalate (DBP) at 602 sites, dimethyl phthalate (DMP) at 167 sites, benzyl butyl phthalate (BzBP) at 413 sites, dicyclohexyl phthalate (DCHP) at one site, and di-n-octyl phthalate (DnOP) at 433 sites, among other phthalates. Phthalates have been detected in environmental water samples across the United States, which raises concerns about drinking water as a route of exposure. The maximum concentrations found for some of these phthalates are particularly alarming. The following data were found in a search for stream water samples analyzed for phthalates in the EPA STORET database. Results are for the period January 2000 through June 2012: Di-isononyl phthalate (DiNP) – No data available. [The Institute for Health and Consumer Protection (IHCP) of the European Chemicals Bureau estimated a half life in surface water for DINP of 50 days. According to the IHCP, 7 percent of the DINP in the influent in sewage treatment plants will be released in the effluent. See European Commission Joint Research Centre, Institute for Health and Consumer Protection, 1,2-Benzenedicarboxylic acid, Di-C8-10-Branched Alkyl Esters, C9-Rich and Di-"Isononyl" Phthalate (DINP), CAS Nos: 68515-48-0 and 28553-12-0, EINECS Nos: 271-090-9 and 249-079-5, Summary Risk Assessment Report, 2003. http://ecb.jrc.it/DOCUMENTS/Existing-	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			(CDC) did not report what percentage of samples had detectable concentrations of each of the metabolites, but nine of the metabolites were found in the urine of at least half of the individuals. [See Table 3. CDC report of phthalate concentrations in urine; NHANES 1999 – 2000 and 2001 - 2002 located on page 27 of the NRDC Nomination Letter and Table 4 Frequency of detection of phthalate metabolites in human urine samples, United States located on pages 28 and 29 of the NRDC Nomination Letter.]	Chemicals/RISK_ASSESSMENT/SUMMARY/dinpsum046.pdf. Given the widespread use and high production volumes of DINP, these releases could pose risks for water quality.]	
131-11-3	Dimethyl phthalate	Natural Resources Defense Council	Phthalates are endocrine disruptors that have been found to cause developmental and reproductive abnormalities in animal studies. Furthermore, studies have found an association between phthalate metabolite concentrations and obesity, insulin resistance and thyroid hormone levels in humans. Stahlhut et al. (2007) analyzed urinary concentrations of seven phthalate metabolites in 1,443 adult men and found a statistically significant positive association between concentrations of the metabolites MBzP, MEHHP, MEOHP and MEP and abdominal obesity. Concentrations of MBP, MBzP and MEP were positively and significantly associated with insulin resistance. In a different study, baby boys exposed to the phthalates, DMP, DEP or BBP, in their mother's breast milk were found to have hormonal disturbances at 3 months of age. Studies have found that di-isononyl phthalate (DiNP) is an anti-androgenic endocrine disruptor with developmental and reproductive toxicity. Exposures in pregnant rats have been shown to adversely affect development of the male reproductive tract. Adverse effects include a cluster of outcomes that has been called "phthalate e syndrome" and includes underdeveloped or absent reproductive organs, retained nipples, cryptorchidism, decreased anogenital distance (AGD), hypospadias, and decreased or abnormal sperm. DINP does not bind to the androgen receptor and these effects are likely mediated through interference with testosterone synthesis. Phthalates are ubiquitous in the U.S. population. Although significant exposure can occur due to consumer products, the contribution of drinking water to overall exposure deserves to be examined. The NHANES measured the concentrations of 12 phthalate metabolites in the urine of over 2,500 children and adults. The highest average concentration was 163 ug/g creatinine for MEP, a metabolite of the plasticizer diethyl phthalate (see Table 3). [See the CDC report cited below.] The Centers for Disease Control and Prevention (CDC) did not report what percentage of samples had detectable concentrations of each of the metabolites, but nine of the metabolites were found in the urine of at least half of the individuals. [See Table 3. CDC report of phthalate concentrations in urine; NHANES 1999 – 2000 and 2001 - 2002 located on page 27 of the NRDC Nomination Letter and Table 4 Frequency of detection of phthalate metabolites in human urine samples, United States located on pages 28 and 29 of the NRDC Nomination Letter.]	Phthalates enter the environment as a result of releases from industrial facilities that manufacture or use these compounds, from waste disposal sites, through the use of phthalate-containing products by consumers and through discharge of municipal wastewaters containing phthalates. Phthalates have been found in numerous hazardous waste sites: diethyl phthalate (DEP) has been identified at 348 sites, dibutyl phthalate (DBP) at 602 sites, dimethyl phthalate (DMP) at 167 sites, benzyl butyl phthalate (BzBP) at 413 sites, dicyclohexyl phthalate (DCHP) at one site, and di-n-octyl phthalate (DnOP) at 433 sites, among other phthalates. Phthalates have been detected in environmental water samples across the United States, which raises concerns about drinking water as a route of exposure. The maximum concentrations found for some of these phthalates are particularly alarming. The following data were found in a search for stream water samples analyzed for phthalates in the EPA STORET database. Results are for the period January 2000 through June 2012: Dimethyl phthalate (DMP) was present in 587 (15.9%) of 3687 stream water samples, with a maximum of 2,500 ug/L.	None given

ED_002435_00004768-00030

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
117-84-0	Di-n-octyl phthalate	Natural Resources Defense Council	Phthalates are endocrine disruptors that have been found to cause developmental and reproductive abnormalities in animal studies. Furthermore, studies have found an association between phthalate metabolite concentrations and obesity, insulin resistance and thyroid hormone levels in humans. Stahlhut et al. (2007) analyzed urinary concentrations of seven phthalate metabolites in 1,443 adult men and found a statistically significant positive association between concentrations of the metabolites MBzP, MEHHP, MEOHP and MEP and abdominal obesity. Concentrations of MBP, MBzP and MEP were positively and significantly associated with insulin resistance. In a different study, baby boys exposed to the phthalates, DMP, DEP or BBP, in their mother's breast milk were found to have hormonal disturbances at 3 months of age. Studies have found that di-isononyl phthalate (DiNP) is an anti-androgenic endocrine disruptor with developmental and reproductive toxicity. Exposures in pregnant rats have been shown to adversely affect development of the male reproductive tract. Adverse effects include a cluster of outcomes that has been called "phthalate e syndrome" and includes underdeveloped or absent reproductive organs, retained nipples, cryptorchidism, decreased anogenital distance (AGD), hypospadias, and decreased or abnormal sperm. DINP does not bind to the androgen receptor and these effects are likely mediated through interference with testosterone synthesis. Phthalates are ubiquitous in the U.S. population. Although significant exposure can occur due to consumer products, the contribution of drinking water to overall exposure deserves to be examined. The NHANES measured the concentrations of 12 phthalate metabolites in the urine of over 2,500 children and adults. The highest average concentration was 163 ug/g creatinine for MEP, a metabolite of the plasticizer diethyl phthalate (see Table 3). [See the CDC report cited below.] The Centers for Disease Control and Prevention (CDC) did not report what percentage of samples had detectable concentrations of each of the metabolites, but nine of the metabolites were found in the urine of at least half of the individuals. [See Table 3. CDC report of phthalate concentrations in urine; NHANES 1999 – 2000 and 2001 - 2002 located on page 27 of the NRDC Nomination Letter and Table 4 Frequency of detection of phthalate metabolites in human urine samples, United States located on pages 28 and 29 of the NRDC Nomination Letter.]	Phthalates enter the environment as a result of releases from industrial facilities that manufacture or use these compounds, from waste disposal sites, through the use of phthalate-containing products by consumers and through discharge of municipal wastewaters containing phthalates. Phthalates have been found in numerous hazardous waste sites: diethyl phthalate (DEP) has been identified at 348 sites, dibutyl phthalate (DBP) at 602 sites, dimethyl phthalate (DMP) at 167 sites, benzyl butyl phthalate (BzBP) at 413 sites, dicyclohexyl phthalate (DCHP) at one site, and di-n-octyl phthalate (DnOP) at 433 sites, among other phthalates. Phthalates have been detected in environmental water samples across the United States, which raises concerns about drinking water as a route of exposure. The maximum concentrations found for some of these phthalates are particularly alarming. The following data were found in a search for stream water samples analyzed for phthalates in the EPA STORET database. Results are for the period January 2000 through June 2012: Di-n-octyl phthalate (DnOP) was found in 129 out of 2469 stream water samples, with a maximum concentration of 20 ug/L.	None given
115-29-7	Endosulfan	Natural Resources Defense Council	Endosulfan is an organochlorine insecticide and acaricide. Technical grade endosulfan is made of both alpha and beta stereoisomers whose toxicity is manifested through blockage of inhibitory GABA (gamma amino butyric acid) gated chloride channels, resulting in over-stimulation of the central nervous system. Endosulfan is a recognized neurotoxin and endocrine disruptor, making even extremely low-dose exposures of very great concern, especially to vulnerable populations such as children and fetuses. Endosulfan is similar in its acute oral toxicity to the related insecticides aldrin and dieldrin, except that it is slightly more toxic than these substances in female laboratory animals. Inhalation of endosulfan dust by humans has been	In 2010, EPA's pesticide office announced that it was cancelling all uses of endosulfan in the U.S. However, because endosulfan is persistent, past uses of this pesticide continue to contaminate our water. According to the EFED risk assessment for the RED on endosulfan, monitoring data show widespread contamination of surface water. EPA modeled surface water contamination and calculated acute estimated environmental concentrations ranging from 4.49 ppb to 23.86 ppb. Chronic EECs ranged from 0.53 ppb to 1.5 ppb. The acute and chronic EEC for endosulfan in groundwater was 0.012 ppb. EPA concluded in the RED that "residues of endosulfan in drinking water are of concern" for acute exposure for infants less than	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			associated with slight nausea, confusion, excitement, flushing, and dry mouth. Nine employees who had been working with 50-percent water-wettable endosulfan powder for only a few days had convulsions. Endosulfan is a significant endocrine disruptor and reproductive toxicant. This pesticide increases the rate of testosterone breakdown and excretion. In immature rats, endosulfan causes significant dose-related decreases in sperm counts, and causes sperm deformities at low exposure levels. In fish, endosulfan elevates levels of thyroxine and suppresses levels of triiodothyronine, probably by inhibiting the conversion of thyroxine to T3. The developing brain is potentially most severely affected by this pesticide via altered levels of critical neurotransmitters such as dopamine, noradrenaline and serotonin; the altered neurotransmitter levels are associated with deficits in learning and memory.	one year old and for children 1-6 years old. EPA determined that exposure from food alone created risks of concern for children 1 to 6 years old and set a DWLOC of zero ppb for this population.	
2164-17-2	Fluometuron	AWWA	None given	None given	None given
319-84-6	Hexachlorocyclohexane (alpha isomer)	AWWA	None given	None given	None given
165800-03-3	Linezolid	Natural Resources Defense Council	Widespread exposure to antibiotics is contributing to the growth of bacterial resistance, and this problem is of grave concern. In the past several decades almost every bacteria that can cause infections in humans has developed resistance to at least one antibiotic, and some are resistant to multiple antibiotics. The Centers for Disease Control and Prevention (CDC) have identified antibiotic resistance as one of the most pressing public health problems to face our nation. Infections caused by bacteria with resistance to at least one antibiotic have been estimated to kill over 60,000 hospitalized patients each year. Antibiotic resistance is caused by a number of factors including repeated and improper use of antibiotics in both humans and animals. Scientists also agree that exposure to low levels of antibiotics actually promotes bacterial resistance by exerting selective pressure for genes that promote resistance. Linezolid resistance in Staphylococcus aureus was reported in 2003. Community-acquired MRSA (CA-MRSA) has now emerged as an epidemic that is responsible for rapidly progressive, fatal diseases including necrotizing pneumonia, severe sepsis and necrotizing fasciitis. Outbreaks of CA-MRSA infections have been reported in correctional facilities, among athletic teams, among military recruits, in newborn nurseries, and among active homosexual men. Therefore, linezolid must be included on the CCL4.	Antibiotics are found in wastewater because the body does not completely metabolize all drugs, so both the metabolized and unmetabolized drug are excreted by humans into wastewater. For example, when amoxicillin is ingested, 60-75% of the antibiotic is excreted unchanged into the urine. This antibiotic, now in the environment, may encounter other bacteria and promote resistance. It is unknown how much of an impact current low levels of antibiotics in drinking water are having on the problem of bacterial resistance. However, the potential has been recognized for many years.	None given
330-55-2	Linuron	Natural Resources Defense Council	Linuron (CAS # 330-55-2) is an urea-based herbicide used primarily on soybeans (79 percent of usage). It has been shown to cause non-malignant testicular and liver tumors in animals. Investigation of the testicular tumors revealed that this herbicide acts by blocking the function of male androgens. In animals, at relatively low doses, linuron is a recognized anti-androgen. This chemical has been shown in laboratory studies to decrease male sex organ weights, cause testicular atrophy, delay puberty, and increase estrogen levels	About 400,000 pounds of linuron are used in U.S. agriculture each year. This herbicide persists for 1-5 months in soil, and has been shown to run off of fields into surface and groundwater supplies. EPA concluded in its Reregistration Eligibility Decision (RED) that linuron exceeded the Levels of Concern (LOC) for groundwater quality. EPA also expressed "moderate concerns" for drinking water supply systems relying on surface water sources.	Since linuron is not regulated under the Safe Drinking Water Act (SDWA), water supply systems are not required to sample or analyze for it. This is a particular problem because EPA admits that drinking water

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			in males. Casting further doubt on EPA's estimates of the risks of linuron in drinking water sources is the fact that the model used for surface water assessment was not tested against any data whatsoever. The exposure estimates (18 ppb) for infants and children exceed EPA's chronic DWLOC (6 ppb) by three-fold. This result is of particular concern in light of the serious flaws in the drinking water risk assessment that conspire to underestimate the actual risk. EPA admits that "residues of linuron and its metabolites in drinking water may represent a chronic human health risk..."	Several factors in EPA's drinking water exposure assessment raise concerns about groundwater contamination. In the groundwater portion of the assessment, data were present for only four states: Georgia, Missouri, Virginia, and Wisconsin. In Georgia linuron was found in groundwater in concentrations up to 5 ppb. EPA later cast doubt on the reliability of the data and removed it from consideration in the final RED, basing its decision on new information received from the State of Georgia. Valid groundwater detections in Missouri (up to 1.9 ppb), Virginia (up to 1.31 ppb in 4 of 8 wells) and Wisconsin (up to 2.7 ppb) may seriously underestimate linuron levels throughout the country because these three states are not among the 16-20 states where linuron is most heavily used. The sixteen states listed on page 3 of EPA's Overview of Linuron Risk Assessment appear to account for well over 80% of linuron use in the United States, so the complete absence of any data on groundwater in any of these states is a critical data gap. The USGS has also reported on areas where linuron is most heavily used on a per-acre basis. The USGS maps indicate that Indiana, Ohio, Michigan, Delaware, and Maryland are heavy use states. These states are not among the ones from which groundwater data are available. Strangely, only one of these (Michigan) is listed by EPA as among heavy use states.	treatment is unlikely to remove linuron and its degradates. The Agency must move rapidly to collect more data on linuron in water and must make a high priority of regulating linuron under the SDWA.
121-75-5	Malathion	AWWA	None given	None given	None given
7439-96-5	Manganese	Massachusetts Department of Environmental Protection	There has been an accumulating body of work since US EPA's last review of manganese suggesting an association between drinking water exposures in school age children and a variety of subtle neurological effects (see selected references in Appendix B). Effects in one of the more recent studies have been seen at manganese water concentrations below the current US EPA lifetime Health Advisory (HA) value, suggesting that the validity of that research finding be critically examined and that possibly the basis for the current HA be revisited. The effect — exposure duration relationship deserves attention in view of the fact that some children may have altered neurological function after exposures to manganese in water at concentrations greater than the lifetime HA level but after less than lifetime durations of exposure. New federal guidance could contribute towards providing protective guidance for sensitive subgroups for less than lifetime exposures. Identifying protective toxicity values for ingestion of manganese is particularly challenging because it is an essential element and there appears to be differential bioavailability of manganese between water and food stuffs. Present drinking water guidance (applicable to the entire population except for infants) is based upon a safe, no effect level of manganese derived from adult dietary intake studies. The recent studies with children suggest that they	Occurrence: From sampling across Massachusetts, we have manganese in groundwaters serving as sources of drinking water for public and private water supplies at concentrations above current health-based guidance concentrations (see Appendix A for examples);	We see a clear need for national level drinking water guidance for manganese which reflects emerging science. There is currently no clear, up-to-date, national uniform message about the health risks from ingestion of manganese in drinking water, resulting in states having to handle manganese issues individually. Our experience has been that manganese in drinking water is not perceived as a potential health issue, but rather purely an aesthetic one. We believe this to not be the case and strongly support the inclusion of manganese on the CCL4 list. Doing so would raise the prominence of this issue. Given the complexity of manganese's toxicity (exposure route and chemical form specific, essentiality versus toxicity,

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			should be evaluated as a susceptible subgroup of the population and that toxicity should be factored into setting manganese drinking water exposure limits, possibly along with considerations of essentiality. While infants have been singled out as of special concern by US EPA in its existing HA, we are especially concerned about bottle-fed infants due to their apparently low nutritional requirement for Mn in early life, their immature homeostatic mechanism for controlling Mn absorption and excretion, and potentially high levels of Mn in infant formulas.		differential life stage, susceptibility, emerging science not currently reflected in US EPA guidance), we believe that an examination of manganese toxicity for drinking water is in order. The current US EPA HA gives no guidance to the states in terms of what advice they should offer to regulated entities or private well owners, or what regulatory stance they should take with exceedances of HA levels, leaving states to craft their own positions on this issue. National leadership with a national primary drinking water standard would provide some uniformity in how manganese health risks are communicated and dealt with.
7439-96-5	Manganese	Minnesota Department of Health	Since US EPA's last review of manganese, a body of research has accumulated suggesting an association between drinking water exposures in school age children and a variety of subtle neurological effects (see manganese references in Appendix B). In two recent epidemiology studies, effects have been seen at manganese water concentrations below the current US EPA lifetime HA value, suggesting that the basis for the current HA should be revisited (Bouchard et al., 2011, Khan et al., 2011). The relationship between exposure duration and health effects deserves attention in light of the fact that some children have exhibited altered neurological function after exposures to manganese in water at concentrations greater than the lifetime HA level but after less than lifetime durations. New federal guidance could contribute towards providing protective guidance for sensitive subgroups for less than lifetime exposures. Identifying protective toxicity values for ingestion of manganese is particularly challenging because it is an essential element and there appears to be differential bioavailability of manganese between water and foodstuffs. Present drinking water guidance (applicable to the entire population except for infants) is based upon a safe, no effect level of manganese derived from adult dietary intake studies. The recent studies with children suggest that they should be evaluated as a susceptible subgroup of the population.	Manganese is commonly detected in groundwater in the United States at concentrations greater than the lifetime Health Advisory (HA) value of 300 ug/L. Twelve percent of 4,976 groundwater samples taken throughout the United States by the US Geological Survey from 1992 – 2003 exceeded the HA for manganese (Ayotte, Gronberg, & Apodaca, 2011). Manganese is found in groundwater throughout Minnesota, including groundwater that serves as source of drinking water for public and private water supplies, at concentrations above current health-based guidance concentrations (See Appendix A - Minnesota Department of Health nomination letter). Appendix A. Occurrence Information for Manganese in Groundwater in Minnesota Over 4000 groundwater well samples were collected from throughout Minnesota and analyzed for manganese. Almost two-thirds (61%) of wells which might serve as water sources for public supplies or private residences had manganese concentrations greater than the Secondary Maximum Contaminant Level of 0.050 mg/L. Twenty-one percent had concentrations greater than the lifetime health advisory value (See Table 1- Minnesota Department of Health nomination letter).	We are nominating manganese for CCL4 because it is frequently detected in public and private wells, and there is some recent evidence of health effects at concentrations below the current EPA health advisory value. Also, we have concerns about manganese exposures among sensitive populations such as infants and children, and for less than lifetime exposure durations. The current US EPA HA gives no guidance to the states in terms of what advice they should offer to regulated entities or private well owners, or what regulatory stance they should take when of HA levels are exceeded, leaving states to craft their own positions on this issue. National leadership with a national primary drinking water standard would provide some uniformity in how

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			While infants have been singled out as a special concern by US EPA in its existing HA, we are especially concerned about bottle-fed infants due to their apparently low nutritional requirement for Mn in early life, their naturally high blood Mn concentrations at birth, their immature homeostatic mechanism for controlling Mn absorption and excretion, and potentially high levels of Mn in infant formulas.		manganese health risks are communicated and dealt with.
7439-96-5	Manganese	NJ Department of Environmental Protection	Manganese in drinking water is of current interest to a number of states. State and EPA FSTRAC members have formed a partner group to evaluate recent health effects information relevant to drinking water exposure to manganese. The current EPA Health Advisory for manganese is based on the assumption that manganese exposure from drinking water is much lower than from the diet, and is not based on health effects. This manganese Health Advisory is several-fold higher than the secondary standard for manganese that is based on aesthetic effects. However, manganese occurs in NJ and other states in both public water supplies and private wells at levels which result in much higher exposures than those assumed by EPA in their comparison to dietary exposures. Also, several recent studies suggest that manganese by the oral route may cause neurodevelopmental effects. There is a need for an updated health assessment for manganese in drinking water based on current health effects data. This health assessment could be used for an updated Health Advisory or as the basis for a proposed MCLG.	None given	None given
61-32-5	Methicillin	Natural Resources Defense Council	Widespread exposure to antibiotics is contributing to the growth of bacterial resistance, and this problem is of grave concern. In the past several decades almost every bacteria that can cause infections in humans has developed resistance to at least one antibiotic, and some are resistant to multiple antibiotics. The Centers for Disease Control and Prevention (CDC) have identified antibiotic resistance as one of the most pressing public health problems to face our nation. Infections caused by bacteria with resistance to at least one antibiotic have been estimated to kill over 60,000 hospitalized patients each year. Antibiotic resistance is caused by a number of factors including repeated and improper use of antibiotics in both humans and animals. Scientists also agree that exposure to low levels of antibiotics actually promotes bacterial resistance by exerting selective pressure for genes that promote resistance. Beta-lactam antibiotics are a broad class of antibiotics which include penicillin derivatives, cephalosporins, monobactams, carbapenems and Beta-lactamase inhibitors. Methicillin, a form of penicillin, had been relied upon as an common effective treatment for Staphylococcus aureus infections but now many strains of S. aureus bacteria are resistant to methicillin (MRSA or methicillin-resistant Staphylococcus aureus.) Unfortunately, MRSA is resistant to much of the entire class of penicillin-like antibiotics called beta-lactams. Therefore, EPA must include penicillin, amoxicillin, oxacillin and methicillin on the CCL4.	Antibiotics are found in wastewater because the body does not completely metabolize all drugs, so both the metabolized and unmetabolized drug are excreted by humans into wastewater. For example, when amoxicillin is ingested, 60-75% of the antibiotic is excreted unchanged into the urine. This antibiotic, now in the environment, may encounter other bacteria and promote resistance. It is unknown how much of an impact current low levels of antibiotics in drinking water are having on the problem of bacterial resistance. However, the potential has been recognized for many years.	None given
298-00-0	Methyl parathion	AWWA	None given	None given	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
1634-04-4	Methyl tertiary butyl ether	NJ Department of Environmental Protection	A recent chronic cancer bioassay of MTBE by the drinking water exposure route in rats (Dodd et al., 2011) should be considered by USEPA. Previously, a chronic inhalation study in mice and rats (an exposure route that is not as relevant to drinking water exposure, Bird et al., 1997) and an oral gavage study in rats from the Ramazzini Institute in Italy, which USEPA has decided not to consider this study because of issues related to the pathology evaluations (http://www.epa.gov/iris/ramazzini.htm) were the only studies available as the basis for the assessment of the carcinogenic potential of MTBE in drinking water. The recent Dodd et al. (2011) study suggests that MTBE in drinking water may cause brain tumors in rats and should be considered by EPA.	None given	None given
101043-37-2	Microcystin-LR	Minnesota Department of Health	Liver toxicity has long been identified as the most sensitive toxicological endpoint for microcystin-LR. As part of the CCL3 process, EPA derived a draft RfD of 0.000003 mg/kg-d based on hepatotoxicity, using an estimated NOAEL of 3 ug/kg-d in mice from ingestion of water containing 20 ug/L microcystin-LR (Ueno et al., 1999). However, a more recent study reports male reproductive effects in mice exposed to lower doses of microcystin-LR in drinking water. (Chen et al., 2011). Significant decreases in testosterone and sperm motility and count were observed at doses as low as approximately 0.64 ug/kg-d. (This dose is estimated based on ingestion of water containing 3 ug/L microcystin-LR.) In addition to the Chen et al. study, there are a limited number of intraperitoneal injection studies in mice, rats and rabbits and in vitro studies in Sertoli cells which reported male reproductive effects on sperm, testes and Sertoli cells (Li, Y., J. Sheng, et al., 2008; Liu, Y., P. Xie, et al., 2010; Wang, X., F. Ying, et al.,2012). A recent oral study reported altered reproductive function and disruption in spermatogenesis in medaka fish (Trinchet, I., C. Djediat, et al., 2011) Because the Chen et al. study identifies a new toxicological endpoint at a dose level nearly five-fold lower than that used in EPA's draft RfD, and some supporting data also indicate potential reproductive toxicity, we believe microcystin-LR is worthy of consideration for updated guidance at the federal level.Because of the episodic nature of microcystin "outbreaks" in surface water (see Occurrence section), we believe that short-term exposures and effects should be given special consideration for this chemical.	Microcystin –LR is largely a surface water contaminant, and is commonly detected in lakes in temperate climates (Ohio Environmental Protection Agency, 2012; Boyer et al., 2005; Graham et al., 2004). Surface water is used as a drinking water source in many locations in the United States. Contamination of a surface water body with microcystin-LR is likely to be episodic in nature, exhibiting both seasonal variation (Billam et al., 2006) and aquatic concentrations that are highly sensitive to total phosphorus, total nitrogen, and other chemical parameters (Graham et al., 2004). Therefore, we believe that short-term exposures and effects should be given special consideration for this chemical. The use of "recycled" wastewater for drinking water is increasingly being viewed as a water supply management option in some areas of the United States (City of San Diego, 2012; Barringer, 2012). Wastewater, including treated wastewater, provides nutrients that can promote the growth of cyanobacteria in surface water (Ho et al., 2010). This indicates a potential future route of microcystin exposure via drinking water.	None given
101043-37-2	Microcystin-LR	Minnesota Department of Health	Liver toxicity has long been identified as the most sensitive toxicological endpoint for microcystin-LR. As part of the CCL3 process, EPA derived a draft RfD of 0.000003 mg/kg-d based on hepatotoxicity, using an estimated NOAEL of 3 ug/kg-d in mice from ingestion of water containing 20 ug/L microcystin-LR (Ueno et al., 1999). However, a more recent study reports male reproductive effects in mice exposed to lower doses of microcystin-LR in drinking water. (Chen et al., 2011). Significant decreases in testosterone and sperm motility and count were observed at doses as low as approximately 0.64 ug/kg-d. (This dose is estimated based on ingestion of water containing 3 ug/L microcystin-LR.) In addition to the Chen et al. study, there are a limited number of intraperitoneal injection studies in mice, rats and rabbits and in vitro studies in	Microcystin –LR is largely a surface water contaminant, and is commonly detected in lakes in temperate climates (Ohio Environmental Protection Agency, 2012; Boyer et al., 2005; Graham et al., 2004). Surface water is used as a drinking water source in many locations in the United States. Contamination of a surface water body with microcystin-LR is likely to be episodic in nature, exhibiting both seasonal variation (Billam et al., 2006) and aquatic concentrations that are highly sensitive to total phosphorus, total nitrogen, and other chemical parameters (Graham et al., 2004). Therefore, we believe that short-term exposures and effects should be given special consideration for this chemical. The use of "recycled" wastewater for drinking water is increasingly	We are nominating microcystin-LR for CCL4 because its oral RfD, while already low, may need to be revised downward in light of new toxicological data. Also, there is some concern that the human exposure to microcystin-LR in drinking water may increase due to more favorable conditions for algal growth in lakes and reservoirs (i.e., nutrients, temperature, wastewater releases), and new

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			Sertoli cells which reported male reproductive effects on sperm, testes and Sertoli cells (Li, Y., J. Sheng, et al., 2008; Liu, Y., P. Xie, et al., 2010; Wang, X., F. Ying, et al.,2012). A recent oral study reported altered reproductive function and disruption in spermatogenesis in medaka fish (Trinchet, I., C. Djediat, et al., 2011) Because the Chen et al. study identifies a new toxicological endpoint at a dose level nearly five-fold lower than that used in EPA's draft RfD, and some supporting data also indicate potential reproductive toxicity, we believe microcystin-LR is worthy of consideration for updated guidance at the federal level.	being viewed as a water supply management option in some areas of the United States (City of San Diego, 2012; Barringer, 2012). Wastewater, including treated wastewater, provides nutrients that can promote the growth of cyanobacteria in surface water (Ho et al., 2010). This indicates a potential future route of microcystin exposure via drinking water.	efforts to recycle wastewater into drinking water.
25154-52-3	Nonylphenol	Natural Resources Defense Council	Alkylphenols were first reported to be estrogenic in the 1930s. In 1991, publication of the effects of nonylphenol on cultured human breast cancer cells led to health concerns. Estrogenic effects have also been shown in the mouse. Estrogenic effects are present at tissue concentrations of 0.1 μM for octylphenol and 1 μM for nonylphenol. A recombinant yeast screen using the human estrogen receptor has shown similar results.	An estimated 450,000,000 pounds of alkylphenol polyethoxylates (APEs) are produced annually in the United States, and about half that amount is estimated to be released to wastewater. Alkylphenol polyethoxylates do not break down effectively in sewage treatment plants or in the environment. Instead they degrade to alkylphenols and alkylphenol ethoxylates, which persist for longer. Nonylphenol and its ethoxylates, and other alkylphenols, have been detected in wastewater and in waterways.	None given
9016-45-9	Nonylphenol ethoxylate	Natural Resources Defense Council	Alkylphenols were first reported to be estrogenic in the 1930s. In 1991, publication of the effects of nonylphenol on cultured human breast cancer cells led to health concerns. Estrogenic effects have also been shown in the mouse. Estrogenic effects are present at tissue concentrations of 0.1 μM for octylphenol and 1 μM for nonylphenol. A recombinant yeast screen using the human estrogen receptor has shown similar results.	An estimated 450,000,000 pounds of alkylphenol polyethoxylates (APEs) are produced annually in the United States, and about half that amount is estimated to be released to wastewater. Alkylphenol polyethoxylates do not break down effectively in sewage treatment plants or in the environment. Instead they degrade to alkylphenols and alkylphenol ethoxylates, which persist for longer. Nonylphenol and its ethoxylates, and other alkylphenols, have been detected in wastewater and in waterways.	None given
27193-28-8	Octylphenol	Natural Resources Defense Council	Alkylphenols were first reported to be estrogenic in the 1930s. In 1991, publication of the effects of nonylphenol on cultured human breast cancer cells led to health concerns. Estrogenic effects have also been shown in the mouse. Estrogenic effects are present at tissue concentrations of 0.1 μM for octylphenol and 1 μM for nonylphenol. A recombinant yeast screen using the human estrogen receptor has shown similar results.	An estimated 450,000,000 pounds of alkylphenol polyethoxylates (APEs) are produced annually in the United States, and about half that amount is estimated to be released to wastewater. Alkylphenol polyethoxylates do not break down effectively in sewage treatment plants or in the environment. Instead they degrade to alkylphenols and alkylphenol ethoxylates, which persist for longer. Nonylphenol and its ethoxylates, and other alkylphenols, have been detected in wastewater and in waterways.	None given
9036-19-5	Octylphenol ethoxylate	Natural Resources Defense Council	Alkylphenols were first reported to be estrogenic in the 1930s. In 1991, publication of the effects of nonylphenol on cultured human breast cancer cells led to health concerns. Estrogenic effects have also been shown in the mouse. Estrogenic effects are present at tissue concentrations of 0.1 μM for octylphenol and 1 μM for nonylphenol. A recombinant yeast screen using the human estrogen receptor has shown similar results.	An estimated 450,000,000 pounds of alkylphenol polyethoxylates (APEs) are produced annually in the United States, and about half that amount is estimated to be released to wastewater. Alkylphenol polyethoxylates do not break down effectively in sewage treatment plants or in the environment. Instead they degrade to alkylphenols and alkylphenol ethoxylates, which persist for longer. Nonylphenol and its ethoxylates, and other alkylphenols, have been detected in wastewater and in waterways.	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
66-79-5	Oxacillin	Natural Resources Defense Council	Widespread exposure to antibiotics is contributing to the growth of bacterial resistance, and this problem is of grave concern. In the past several decades almost every bacteria that can cause infections in humans has developed resistance to at least one antibiotic, and some are resistant to multiple antibiotics. The Centers for Disease Control and Prevention (CDC) have identified antibiotic resistance as one of the most pressing public health problems to face our nation. Infections caused by bacteria with resistance to at least one antibiotic have been estimated to kill over 60,000 hospitalized patients each year. Antibiotic resistance is caused by a number of factors including repeated and improper use of antibiotics in both humans and animals. Scientists also agree that exposure to low levels of antibiotics actually promotes bacterial resistance by exerting selective pressure for genes that promote resistance. Beta-lactam antibiotics are a broad class of antibiotics which include penicillin derivatives, cephalosporins, monobactams, carbapenems and Beta-lactamase inhibitors. Methicillin, a form of penicillin, had been relied upon as an common effective treatment for Staphylococcus aureus infections but now many strains of S. aureus bacteria are resistant to methicillin (MRSA or methicillin-resistant Staphylococcus aureus.) Unfortunately, MRSA is resistant to much of the entire class of penicillin-like antibiotics called beta-lactams. Therefore, EPA must include penicillin, amoxicillin, oxacillin and methicillin on the CCL4.	Antibiotics are found in wastewater because the body does not completely metabolize all drugs, so both the metabolized and unmetabolized drug are excreted by humans into wastewater. For example, when amoxicillin is ingested, 60-75% of the antibiotic is excreted unchanged into the urine. This antibiotic, now in the environment, may encounter other bacteria and promote resistance. It is unknown how much of an impact current low levels of antibiotics in drinking water are having on the problem of bacterial resistance. However, the potential has been recognized for many years.	None given
multiple CAS #s	Penicillin	Natural Resources Defense Council	Widespread exposure to antibiotics is contributing to the growth of bacterial resistance, and this problem is of grave concern. In the past several decades almost every bacteria that can cause infections in humans has developed resistance to at least one antibiotic, and some are resistant to multiple antibiotics. The Centers for Disease Control and Prevention (CDC) have identified antibiotic resistance as one of the most pressing public health problems to face our nation. Infections caused by bacteria with resistance to at least one antibiotic have been estimated to kill over 60,000 hospitalized patients each year. Antibiotic resistance is caused by a number of factors including repeated and improper use of antibiotics in both humans and animals. Scientists also agree that exposure to low levels of antibiotics actually promotes bacterial resistance by exerting selective pressure for genes that promote resistance. Beta-lactam antibiotics are a broad class of antibiotics which include penicillin derivatives, cephalosporins, monobactams, carbapenems and Beta-lactamase inhibitors. Methicillin, a form of penicillin, had been relied upon as an common effective treatment for Staphylococcus aureus infections but now many strains of S. aureus bacteria are resistant to methicillin (MRSA or methicillin-resistant Staphylococcus aureus.) Unfortunately, MRSA is resistant to much of the entire class of penicillin-like antibiotics called beta-lactams. Therefore, EPA must include penicillin, amoxicillin, oxacillin and methicillin on the CCL4.	Antibiotics are found in wastewater because the body does not completely metabolize all drugs, so both the metabolized and unmetabolized drug are excreted by humans into wastewater. For example, when amoxicillin is ingested, 60-75% of the antibiotic is excreted unchanged into the urine. This antibiotic, now in the environment, may encounter other bacteria and promote resistance. It is unknown how much of an impact current low levels of antibiotics in drinking water are having on the problem of bacterial resistance. However, the potential has been recognized for many years.	None given

ED_002435_00004768-00038

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
335-67-1	Perfluorooctanoic acid	Eileen Murphy	http://www.c8sciencepanel.org/publications.html The C8 Panel has been reporting detrimental effects at relatively low exposure levels, particularly in children.	In areas where monitoring for PFOA (and other perfluorinated chemicals) occurs, it is detected at some level. Where there are known sources, levels are higher. However, PFOA is often detected in areas with no obvious source.	None given
335-67-1	Perfluorooctanoic Acid	Natural Resources Defense Council	None given	None given	None given
335671	Perfluorooctanoic Acid	NJ Department of Environmental Protection	Post et al. (2012) summarizes many recent toxicology and epidemiology studies relevant to the assessment of potential health effects of PFOA in drinking water. The studies cited in Post et al. (2012) should be considered by USEPA. Two additional very recent publications showing associations of PFOA exposure and kidney and testicular cancer in communities with drinking water exposure (C8 Science Panel, 2012), and with hypertension and elevated homocysteine (a marker for risk of heart disease; Min et al., 2012) in the general population should also be considered by USEPA. While the C8 Science Panel (2012) report is not a peer-reviewed publication, several publications on the cancer incidence study are cited as "in press" in the report; these publications are expected to be available in the near future and should be considered by USEPA.	The following information is a summary of information discussed in Post et al. (2012, citation below): Unlike most other commonly detected organic drinking water contaminants, PFOA and other perfluorinated chemicals do not degrade in the environment and persist indefinitely. PFOA and other perfluorinated compounds are highly water soluble, unlike most other persistent organic pollutants (e.g. PCBs, dioxins, chlordane) which bind preferentially to soil and sediments and are not highly water soluble. For this reason, drinking water is a major exposure route, while drinking water is not a major exposure route for these other persistent organic pollutants (e.g. PCBs, dioxins, chlordane). PFOA bioaccumulates from drinking water to serum with a serum:drinking water ratio of about 100:1 after ongoing exposure, and exposure to even relatively low drinking water concentrations substantially increases total exposure in humans. PFOA persists in humans with a serum half-life of several years. Exposure to PFOA in drinking water by breast-fed and formula-fed infants, a potentially susceptible subpopulation for PFOA's developmental effects, is higher than in adults using the same drinking water source. The review by Post et al. (2012) summarizes many recent studies of the environmental fate and transport, sources, and occurrence of PFOA in source waters (groundwater and surface water) and drinking water. These studies should be considered by USEPA.	None given
52645-53-1	Permethrin	AWWA	None given	None given	None given
732-11-6	Phosmet	Natural Resources Defense Council	Phosmet is a neurotoxicant that causes red blood cell, plasma, serum and brain cholinesterase inhibition. It also shows mutagenic activity. Phosmet interferes with human placental enzymatic activity, which may affect fetal development. EPA has stated in its Interim Reregistration Eligibility Decision (IRED) for phosmet that there is "suggestive evidence of carcinogenicity" based on increased incidence of liver adenomas and carcinomas in male mice, and of mammary gland tumors in females. The EPA IRED used modeling estimates to assess phosmet exposure through drinking water due to the limited amount of monitoring data available. Estimated environmental concentrations ranged from 0.4 to 140 ppb. While EPA concluded that drinking water exposure through surface and groundwater was not of concern, there are several flaws in the EPA analysis that undermine that conclusion, as explained below. The IRED drinking water assessment should not be relied upon to decide whether to regulate phosmet under the SDWA.	Phosmet is an organophosphate pesticide used primarily on apples, peaches, walnuts, almonds and pears. Approximately 1.25 million pounds of active ingredient are applied every year.Phosmet is mobile in runoff and has the potential to contaminate drinking water sources. EPA has done a drinking water risk assessment for phosmet as part of the pesticide reregistration process.	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			EPA determines whether the drinking water risks of a pesticide are of concern as part of its dietary risk assessment for that chemical. For drinking water risk to remain below the Agency's level of concern, the sum of food and drinking water exposures must be less than the Population Adjusted Dose (PAD). [The PAD is a term that expresses the dietary risk of a chemical, and reflects the Reference Dose, either acute or chronic, that has been adjusted to account for the FQPA safety factor (i.e., RfD/FQPA safety factor)]. A risk estimate that is less than 100% of the acute or chronic PAD does not exceed the Agency's risk concern.)The IRED risk summary for phosmet indicates that dietary risk, acute and chronic, is below the Agency's level of concern. However, the Agency had initially determined that acute dietary exposures were of great concern for infants and children, with up to 2000% of the acute Reference Dose (aRfD) consumed.. Such an exceedance in exposure from food alone means that any additional exposure from drinking water would create additional unacceptable risks. The assessment of food exposure was subsequently revised using a newly submitted acute neurotoxicity study by the registrant, reviewed by the Agency in February 1999, and by the hazard identification assessment review committee (HIARC) in July, 1999. This new acute neurotoxicity study in rats was used to raise the No Observable Adverse Effects Level (NOAEL) to 4.5 mg/kg/day, from the 1.1 value that had been used, based on a chronic toxicity study in rats. The result was a four-fold change, which also resulted in an increase in the PAD. The HIARC executive summary of the study states that "no effects of treatment were seen in the 3.0 or 4.5 mg/kg group", which is in agreement with the registrants conclusions. However, the study DER finds some critical problems with this study: -"Extremely high variability was noted in the data from the motor activity testing, raising questions about the sensitivity of the procedures used in this study. For example, an increase in subsession activity approaching 300% above control levels was not found to be statistically significantly different from controls." -"There was also some large variability in some of the blood cholinesterase measurements (especially for the red blood cells), such that decreases of 25% were not statistically significant. Again, it is possible that true differences caused by exposure to phosmet might be obscured by the high variability of the measure." In fact, the DER states that "the smallest statistically significant change detected in blood measures was 40% (DER p. 10) -"no information is available regarding the dose response curves for cholinesterase inhibition or behavioral effects. This is especially relevant since similar levels of inhibition (60-75%) were seen in brain and red blood cell cholinesterase at the high dose, with brain inhibition persisting throughout the study." NRDC suggests that this study is not sufficient to establish a NOAEL, since the variability in cholinesterase inhibition was so great that the study design did not provide any statistical power to detect treatment effects. Therefore, the increase in the PAD that made it possible for food and drinking water		

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			exposures to remain below the level of concern was not scientifically supported.Notwithstanding EPA's previous determination that phosmet in drinking water does not pose risks of concern (which, as noted above, was based on a flawed study), phosmet should be regulated as a water contaminant under the SDWA and an MCL should be established.		
57-83-0	Progesterone	Natural Resources Defense Council	While each of these compounds [See Table 5 Concentrations of reproductive hormones in U.S. streams (USGS, 2002) located on page 29 of the NRDC letter] is generally found at low concentrations, the potential effects on human health of mixtures of these compounds are unknown. Based on the individual effects of these chemicals, possible risks include defects of the reproductive system in individuals exposed during critical stages of development (e.g. testosterone).	The U.S. Geological Survey (USGS) conducted a study of 139 streams in 30 states that found widespread presence of estrogenic compounds, ovulation inhibitors and other reproductive hormones in surface water near urbanized and agricultural areas (see Table 5). [See Table 5 *Concentrations of reproductive hormones in U.S. streams (USGS, 2002)* located on page 29 of the NRDC letter] Wastewater treatment plants, the likely sources of most of these chemicals, do not treat sewage for these pollutants. Furthermore, drinking water treatment plants do not generally test or treat water for these contaminants, so the frequency of occurrence of these chemicals in treated drinking water and the degree of human exposure are not known. Additional monitoring of water sources and drinking water are necessary to determine the full extent of the contamination, to assess risks to human health, and to determine acceptable levels of exposure and appropriate regulatory action. EPA properly included many of these reproductive hormones on CCL3, although it has not made a final regulatory determination on any of them. However, considering that progesterone and testosterone also occur at similar concentrations and similar frequency as some of the hormones that were include, they should also be added to the CCL4.	None given
10043-92-2	Radon	NJ Department of Environmental Protection	Radon is a known human carcinogen. In New Jersey and other states where radon is prevalent in groundwater, the cancer risk from radon in drinking water is higher than for most other drinking water contaminants that are regulated based on their carcinogenicity. For example, the average level in NJ public water supplies is 921 pCi/L, and the lifetime cancer risk at this level (from inhalation plus ingestion) is 7 x 10-4.	Radon occurs widely in drinking water using groundwater sources in New Jersey and some other states. In New Jersey, the concentration of radon ranged from nondetectable levels to 41,000 pCi/L with an average concentration of 921 pCi/L in public water supplies, and from 50 pCi/L to 170,000 pCi/L with an average concentration of 5,040 pCi/L in private wells.	None given
8025-81-8	Spiramycin	Natural Resources Defense Council	Widespread exposure to antibiotics is contributing to the growth of bacterial resistance, and this problem is of grave concern. In the past several decades almost every bacteria that can cause infections in humans has developed resistance to at least one antibiotic, and some are resistant to multiple antibiotics. The Centers for Disease Control and Prevention (CDC) have identified antibiotic resistance as one of the most pressing public health problems to face our nation. Infections caused by bacteria with resistance to at least one antibiotic have been estimated to kill over 60,000 hospitalized patients each year. Antibiotic resistance is caused by a number of factors including repeated and improper use of antibiotics in both humans and animals. Scientists also agree that exposure to low levels of antibiotics actually promotes bacterial resistance by exerting selective pressure for genes that promote resistance.	Antibiotics are found in wastewater because the body does not completely metabolize all drugs, so both the metabolized and unmetabolized drug are excreted by humans into wastewater. For example, when amoxicillin is ingested, 60-75% of the antibiotic is excreted unchanged into the urine. This antibiotic, now in the environment, may encounter other bacteria and promote resistance. It is unknown how much of an impact current low levels of antibiotics in drinking water are having on the problem of bacterial resistance. However, the potential has been recognized for many years. Large animal feeding operations generate a large amount of waste that can potentially contaminate groundwater and waterways contributing to antibiotic resistance and contamination of waterways with steroid hormones. As occurs in humans, some portion of the	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			Massive quantities of antibiotics are used in agriculture both to treat infections and as food additives to promote growth and to compensate for conditions that contribute to infection. Animals raised in Concentrated Animal Feeding Operations (CAFOs) are at increased risk for infection due to close confinement and stress. In fact, it has been estimated that 70% of the antibiotics used in the U.S. are for animal husbandry. Improper use and overuse of antibiotics in livestock and poultry can cause resistance in strains of bacteria that can infect humans. Furthermore, half of the antibiotics used in livestock are in the same classes of drugs that are used in humans. As a result the U.S. Institute of Medicine (IOM) and the World Health Organization (WHO) both stated that the widespread use of antibiotics in agriculture is contributing to antibiotic resistance in humans.	antibiotics administered to livestock will pass unchanged through their bodies and will be excreted in their waste. It has been estimated that between 25-75% of antibiotics are excreted unchanged in feces and can persist in the soil after land application. Manure is applied in large quantities as fertilizer in farm fields. In addition to potentially contaminating the food supply with antibiotic resistant bacteria, antibiotics in manure can persist in soil and promote the development of more antibiotic resistant bacteria. Animal waste and its associated contaminants can enter waterways through groundwater contamination, overflow of waste lagoons into surface water or by over-application of manure as fertilizer in farm fields. A recently published study found evidence of fecal contamination and increased levels of antibiotic resistant bacteria downstream of a swine concentrated feeding operation. Other studies have found antibiotic resistance in groundwater underlying a swine waste lagoon. As such, antibiotics that are used both for human medical needs and in large-scale agriculture operations at low levels in animal feed to promote animal growth must be included on the CCL4 and must be regulated. These antibiotics include bacitracin zinc, spiramycin, tylosin, and virginiamycin. Notably, these antibiotics were all banned for agricultural use in the European Union in 1998.	
121831-99-0	Strontium 90	Anonymous 197	Public Health goals recommend a reasonable standard of 0.35 pCi/L based upon carcinogenic potency of 5.59 x 10E-11 pCi/L for Sr-90 in drinking water.	There are 23 nuclear power plants of exact design to the fatal power plants in Japan, failure due to earthquakes near population centers and water sources.	Monitoring existing conditions leads to rate of change analysis when done on a predictable time frame.
58-22-0	Testosterone	Natural Resources Defense Council	While each of these compounds (see Table 5) [See Table 5 Concentrations of reproductive hormones in U.S. streams (USGS, 2002) located on page 29 of the NRDC letter] is generally found at low concentrations, the potential effects on human health of mixtures of these compounds are unknown. Based on the individual effects of these chemicals, possible risks include defects of the reproductive system in individuals exposed during critical stages of development (e.g. testosterone).	The U.S. Geological Survey (USGS) conducted a study of 139 streams in 30 states that found widespread presence of estrogenic compounds, ovulation inhibitors and other reproductive hormones in surface water near urbanized and agricultural areas (see Table 5). [See Table 5 *Concentrations of reproductive hormones in U.S. streams (USGS, 2002)* located on page 29 of the NRDC letter] Wastewater treatment plants, the likely sources of most of these chemicals, do not treat sewage for these pollutants. Furthermore, drinking water treatment plants do not generally test or treat water for these contaminants, so the frequency of occurrence of these chemicals in treated drinking water and the degree of human exposure are not known. Additional monitoring of water sources and drinking water are necessary to determine the full extent of the contamination, to assess risks to human health, and to determine acceptable levels of exposure and appropriate regulatory action. EPA properly included many of these reproductive hormones on CCL3, although it has not made a final regulatory determination on any of them. However, considering that progesterone and testosterone also occur at similar concentrations and similar frequency as some of the hormones that were include, they should also be added to the CCL4.	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
52-68-6	Trichlorfon	Natural Resources Defense Council	Like the other organphosphates, trichlorfon is a neurotoxicant and cholinesterase inhibitor. Trichlorfon exposure is associated with kidney, lung and gastrointestinal abnormalities in animal studies. Anemia has also been reported, as well as benign pheochromocytomas. A statistically significant increase in mononuclear cell leukemia was also observed. Incidences of alveolar/bronchiolar adenomas, renal tubular adenomas and alveolar/bronchiolar carcinomas, while not statistically significant, occurred with frequencies "well outside of the historical control range for all three tumor types." While EPA decided to classify trichlorfon in Group E for carcinogenicity arguing that the statistically significant increases in tumors in the studies were seen in the lower but not the higher doses, we argue that the evidence remains suggestive given that separate studies found significant increases in the same types of tumors. In the studies analyzed by EPA during the reregistration process, trichlorfon also showed developmental toxicity in animals (decreased fetal body weight, delayed or reduced ossification) and mutagenic activity in an in vitro cytogenetic study in mammalian cells.	Trichlorfon is an organophosphate insecticide with agricultural non-food and feed crop uses (e.g. agricultural non-cultivated areas, ornamental trees, etc.), as well as indoor and outdoor residential use. Usage volume data for these registered uses is not available. Trichlorfon is highly mobile in soil, but EPA did not assess its groundwater contamination potential during the reregistration process for lack of appropriate data. Trichlorfon can enter surface waters in ground spray and runoff. Well samples from Georgia in the EPA Pesticides in Ground Water Database showed trichlorfon detections in 12 of 179 wells with concentration up to 10 ppb. EPA did not consider these samples useful, citing analytical uncertainties. Trichlorfon has a half-life in soil of 1 to 27 days, depending on soil type, which increases its potential to contaminate surface waters. However, the trichlorfon RED does not address drinking water risks. Despite the cancellation of feed and food crop uses, trichlorfon still has registered agricultural and residential outdoor uses that pose a risk of surface and possibly groundwater contamination. The scarcity of monitoring data on environmental concentrations should not lead to an assumption of negligible risk. The known toxicity of trichlorfon, its mobility and extended half-life in soil all make it a likely water contaminant in high use areas. EPA should require the collection of monitoring data for these areas to enable the Agency to assess water contamination risks and make a regulatory decision concerning trichlorfon.	None given
101-20-2	Triclocarban	Natural Resources Defense Council	Triclocarban is a possible endocrine disruptor An animal study indicates that triclocarban exposure enhanced the effects of testosterone both in vitro and in vivo in male rats.	Triclocarban (Urea, N-(4-chlorophenyl)-N'-(3,4-dichlorophenyl) 3,4,4'-Trichlorocarbanilide), an antimicrobial pesticide also known as TCC, has been widely detected in effluent from wastewater treatment plants (WWTPs) in the United States. TCC has also been frequently detected in environmental water samples. The half-life of TCC in sediment is 540 days. One study predicted the magnitude and frequency of TCC contamination nationwide based on experimental and modeling data to be 1150 ng/L and 60%, respectively; much higher than previously recognized by EPA (240 ng/L, 30%). Another study in the Greater Baltimore area found an average TCC level of 6.75 ug/L in wastewater samples, while river water samples had concentrations of up to 5.6 ug/L. These concentrations are higher than the Predicted Environmental Concentrations (PEC) calculated by the TCC Consortium in a report submitted to EPA in 2003 as part of the High Production Volume Chemical program, which estimated PECs from 0.0013 to 0.050 jtg/L. The actual measurements from the Greater Baltimore area study also exceed the TCC Consortium's Predicted No Effect Concentration of 0.146 ~g/L.	None given

ED_002435_00004768-00043

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
				A study of a 684 million liter per day typical activated sludge WWTP found a concentration of 6.1 ± 2.0 ug/L in the influent and 0.17 ± 0.03 ug/L in the effluent. Approximately 127 ± 6 g/d exited the plant in the effluent, a clear indication that conventional wastewater treatment may leave considerable levels of TCC in the water. Because of this, TCC concentrations tend to be higher downstream of WWTPs. The most important sources of triclocarban to the aquatic environment were estimated to be activated sludge treatment plants (contributing 39-67%), followed by trickling filters (31- 54%), combined sewer overflows (2-7%) and sanitary sewer overflows (<0.2%). Given these data, triclocarban should be added to the CCL4.	
3380-34-5	Triclosan	Natural Resources Defense Council	The chemical structure of triclosan is similar to other endocrine disrupting compounds and potential breakdown products of triclosan include dioxins. Recently, low levels of triclosan were found to interfere with the metamorphosis of frogs. Exposure to as little as 0.15 µg/L triclosan caused an earlier metamorphosis than normal, with effects on the tadpole brain and tail. Triclosan activates the human pregnane X receptor (hPXR), which is involved in the enzymatic metabolism of steroids and xenobiotics.	Triclosan (5-chloro-2-(2,4-dichlorophenoxy)-phenol), is a broad spectrum antimicrobial pesticide that is widely used in personal care products such as soaps, toothpastes, cosmetics, skin creams and deodorants; kitchen accessories such as cutting boards and utensils; and in textiles such as sportswear, shoes and carpets. Approximately three quarters of Americans between the ages of six to over 65 have triclosan in their urine. Triclosan has even been detected in human blood plasma and breast milk. Triclosan is produced at over one million pounds per year. Triclosan is one of the most frequently detected chemicals in streams across the U.S. Wild Atlantic bottlenose dolphins have been found with triclosan in their bodies. Triclosan has been found in wastewater treatment effluent and drinking water sources. Triclosan was detected in Louisiana sewage treatment plant effluent at 10-21 ng/l. Boyd (2004) reported triclosan concentrations of ND – 29 ng/l in two stormwater canals in New Orleans. Triclosan has also been detected in raw and finished drinking water samples from Southern California.	None given
1401-69-0	Tylosin	Natural Resources Defense Council	Widespread exposure to antibiotics is contributing to the growth of bacterial resistance, and this problem is of grave concern. In the past several decades almost every bacteria that can cause infections in humans has developed resistance to at least one antibiotic, and some are resistant to multiple antibiotics. The Centers for Disease Control and Prevention (CDC) have identified antibiotic resistance as one of the most pressing public health problems to face our nation. Infections caused by bacteria with resistance to at least one antibiotic have been estimated to kill over 60,000 hospitalized patients each year. Antibiotic resistance is caused by a number of factors including repeated and improper use of antibiotics in both humans and animals. Scientists also agree that exposure to low levels of antibiotics actually promotes bacterial resistance by exerting selective pressure for genes that promote resistance. Massive quantities of antibiotics are used in agriculture both to treat infections and as food additives to promote growth and to compensate for conditions that contribute to infection. Animals raised in Concentrated Animal Feeding	Antibiotics are found in wastewater because the body does not completely metabolize all drugs, so both the metabolized and unmetabolized drug are excreted by humans into wastewater. For example, when amoxicillin is ingested, 60-75% of the antibiotic is excreted unchanged into the urine. This antibiotic, now in the environment, may encounter other bacteria and promote resistance. It is unknown how much of an impact current low levels of antibiotics in drinking water are having on the problem of bacterial resistance. However, the potential has been recognized for many years. Large animal feeding operations generate a large amount of waste that can potentially contaminate groundwater and waterways contributing to antibiotic resistance and contamination of waterways with steroid hormones As occurs in humans, some portion of the antibiotics administered to livestock will pass unchanged through their bodies and will be excreted in their waste. It has been estimated that between 25-75% of antibiotics are excreted unchanged in feces and can persist in the soil after land application. Manure is applied in large	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			Operations (CAFOs) are at increased risk for infection due to close confinement and stress. In fact, it has been estimated that 70% of the antibiotics used in the U.S. are for animal husbandry. Improper use and overuse of antibiotics in livestock and poultry can cause resistance in strains of bacteria that can infect humans. Furthermore, half of the antibiotics used in livestock are in the same classes of drugs that are used in humans. As a result the U.S. Institute of Medicine (IOM) and the World Health Organization (WHO) both stated that the widespread use of antibiotics in agriculture is contributing to antibiotic resistance in humans. [Quotes from the Healthcare Without Harm factsheet. A*ntibiotic Resistance and Agricultural Overuse of Antibiotics*. 2005. http://www.noharm.org/us/food/issue *U.S. Institute of Medicine/National Academy of Science:* "Clearly, a decrease in antimicrobial use in human medicine alone will have little effect on the current [antibiotic-resistant] situation. Substantial efforts must be made to decrease inappropriate overuse in animals and agriculture as well." *World Health Organization:* "There is clear evidence of the human health consequences due to resistant organisms resulting from non-human usage of antimicrobials. These consequences include infections that would not have otherwise occurred, increased frequency of treatment failures (in some cases death) and increased severity of infections."]	quantities as fertilizer in farm fields. In addition to potentially contaminating the food supply with antibiotic resistant bacteria, antibiotics in manure can persist in soil and promote the development of more antibiotic resistant bacteria. Animal waste and its associated contaminants can enter waterways through groundwater contamination, overflow of waste lagoons into surface water or by over-application of manure as fertilizer in farm fields. A recently published study found evidence of fecal contamination and increased levels of antibiotic resistant bacteria downstream of a swine concentrated feeding operation. Other studies have found antibiotic resistance in groundwater underlying a swine waste lagoon. As such, antibiotics that are used both for human medical needs and in large-scale agriculture operations at low levels in animal feed to promote animal growth must be included on the CCL4 and must be regulated. These antibiotics include bacitracin zinc, spiramycin, tylosin, and virginiamycin. Notably, these antibiotics were all banned for agricultural use in the European Union in 1998.	
1404-90-6	Vancomycin	Natural Resources Defense Council	Widespread exposure to antibiotics is contributing to the growth of bacterial resistance, and this problem is of grave concern. In the past several decades almost every bacteria that can cause infections in humans has developed resistance to at least one antibiotic, and some are resistant to multiple antibiotics. The Centers for Disease Control and Prevention (CDC) have identified antibiotic resistance as one of the most pressing public health problems to face our nation. Infections caused by bacteria with resistance to at least one antibiotic have been estimated to kill over 60,000 hospitalized patients each year. Antibiotic resistance is caused by a number of factors including repeated and improper use of antibiotics in both humans and animals. Scientists also agree that exposure to low levels of antibiotics actually promotes bacterial resistance by exerting selective pressure for genes that promote resistance. Beta-lactam antibiotics are a broad class of antibiotics which include penicillin derivatives, cephalosporins, monobactams, carbapenems and Beta-lactamase inhibitors. Methicillin, a form of penicillin, had been relied upon as an common effective treatment for Staphylococcus aureus infections but now many strains of S. aureus bacteria are resistant to methicillin (MRSA or methicillin-resistant Staphylococcus aureus.) Unfortunately, MRSA is resistant to much of the entire class of penicillin-like antibiotics called beta-lactams. Therefore, EPA must include penicillin, amoxicillin, oxacillin and methicillin on the CCL4. Infections among hospital patients (nosocomial infections) from enterococci bacteria are very common. Such infections that result in human disease can	Antibiotics are found in wastewater because the body does not completely metabolize all drugs, so both the metabolized and unmetabolized drug are excreted by humans into wastewater. For example, when amoxicillin is ingested, 60-75% of the antibiotic is excreted unchanged into the urine. This antibiotic, now in the environment, may encounter other bacteria and promote resistance. It is unknown how much of an impact current low levels of antibiotics in drinking water are having on the problem of bacterial resistance. However, the potential has been recognized for many years.	None given

CASRN	Common Name	Nominator	Health Effects Information Provided with Nomination	Occurrence Information Provided with Nomination	Additional Information Provided with Nomination
			be fatal, particularly those caused by strains of vancomycin-resistant enterococci (VRE). During 2004, VRE caused about one of every three infections in hospital intensive-care units, according to the Centers CDC. As of 2007, the U.S. had reported seven cases of vancomycin-resistant *Staphylococcus aureus* (VRSA) infection. Therefore, vancomycin must be included on the CCL3.		
11006-76-1	Virginiamycin	Natural Resources Defense Council	Widespread exposure to antibiotics is contributing to the growth of bacterial resistance, and this problem is of grave concern. In the past several decades almost every bacteria that can cause infections in humans has developed resistance to at least one antibiotic, and some are resistant to multiple antibiotics. The Centers for Disease Control and Prevention (CDC) have identified antibiotic resistance as one of the most pressing public health problems to face our nation. Infections caused by bacteria with resistance to at least one antibiotic have been estimated to kill over 60,000 hospitalized patients each year. Antibiotic resistance is caused by a number of factors including repeated and improper use of antibiotics in both humans and animals. Scientists also agree that exposure to low levels of antibiotics actually promotes bacterial resistance by exerting selective pressure for genes that promote resistance. Massive quantities of antibiotics are used in agriculture both to treat infections and as food additives to promote growth and to compensate for conditions that contribute to infection. Animals raised in Concentrated Animal Feeding Operations (CAFOs) are at increased risk for infection due to close confinement and stress. In fact, it has been estimated that 70% of the antibiotics used in the U.S. are for animal husbandry. Improper use and overuse of antibiotics in livestock and poultry can cause resistance in strains of bacteria that can infect humans. Furthermore, half of the antibiotics used in livestock are in the same classes of drugs that are used in humans. As a result the U.S. Institute of Medicine (IOM) and the World Health Organization (WHO) both stated that the widespread use of antibiotics in agriculture is contributing to antibiotic resistance in humans. [Quotes from the Healthcare Without Harm factsheet. A*ntibiotic Resistance and Agricultural Overuse of Antibiotics*. 2005. http://www.noharm.org/us/food/issue *U.S. Institute of Medicine/National Academy of Science:* "Clearly, a decrease in antimicrobial use in human medicine alone will have little effect on the current [antibiotic-resistant] situation. Substantial efforts must be made to decrease inappropriate overuse in animals and agriculture as well." *World Health Organization*: "There is clear evidence of the human health consequences due to resistant organisms resulting from non-human usage of antimicrobials. These consequences include infections that would not have otherwise occurred, increased frequency of treatment failures (in some cases death) and increased severity of infections."]	Antibiotics are found in wastewater because the body does not completely metabolize all drugs, so both the metabolized and unmetabolized drug are excreted by humans into wastewater. For example, when amoxicillin is ingested, 60-75% of the antibiotic is excreted unchanged into the urine. This antibiotic, now in the environment, may encounter other bacteria and promote resistance. It is unknown how much of an impact current low levels of antibiotics in drinking water are having on the problem of bacterial resistance. However, the potential has been recognized for many years. Large animal feeding operations generate a large amount of waste that can potentially contaminate groundwater and waterways contributing to antibiotic resistance and contamination of waterways with steroid hormones. As occurs in humans, some portion of the antibiotics administered to livestock will pass unchanged through their bodies and will be excreted in their waste. It has been estimated that between 25-75% of antibiotics are excreted unchanged in feces and can persist in the soil after land application. Manure is applied in large quantities as fertilizer in farm fields. In addition to potentially contaminating the food supply with antibiotic resistant bacteria, antibiotics in manure can persist in soil and promote the development of more antibiotic resistant bacteria. Animal waste and its associated contaminants can enter waterways through groundwater contamination, overflow of waste lagoons into surface water or by over-application of manure as fertilizer in farm fields. A recently published study found evidence of fecal contamination and increased levels of antibiotic resistant bacteria downstream of a swine concentrated feeding operation. Other studies have found antibiotic resistance in groundwater underlying a swine waste lagoon. As such, antibiotics that are used both for human medical needs and in large-scale agriculture operations at low levels in animal feed to promote animal growth must be included on the CCL4 and must be regulated. These antibiotics include bacitracin zinc, spiramycin, tylosin, and virginiamycin. Notably, these antibiotics were all banned for agricultural use in the European Union in 1998.	None given