Draft from Committee members on 4/23: Handout for meeting

1. **Clarifications regarding steps in the process that will make it more transparent**

General

- Overall, the process is explained well in the Federal Register Notice. Style in the Register seems to dictate an amazing lack of commas, but one can wade through without confusion caused by this style, even if it makes for slow reading at times.
- Can the primary documents (MMWR reports, book chapters, etc.) be made available on the web site? (If not all, then some. Yes, the references are given but having the actual documents there would be more helpful.)
- The Federal Register notice describes the process that the USEPA used to obtain the CCL3. There are numerous challenges that must be overcome when winnowing the universe of chemical contaminants down to a CCL. The USEPA has documented the decision-making process and has described their attempts to identify biases in their evaluation processes and to obtain expert feedback to assure that important compounds are not excluded from the process. In general, the approach is scientifically justified and well documented.
- In several places the USEPA employs approaches for screening data that are not supportive of their stated intent of offering equal protection to water consumers. For example, on page 9640, they define prevalence as "…the percent of public water systems or monitoring sites across the nation with detections, number of states with releases…" Neither of these measures takes into account the number of people who are potentially exposed to contaminants through these drinking water systems. In other words, a chemical that is used in two or three small states would receive greater weighting than a chemical used in a large, populous state.
- The number of contaminants on the CCL keeps increasing in every iteration and yet regulatory determinations are only made for 5-10 contaminants every five years. The continued increase in contaminants on the list may give the public a sense that water quality is declining with time. What plans does the USEPA have to reduce the number of contaminants on the CCL?
- On a related issue, how is the UCMR working? Are the data being collected in a manner that will expedite regulatory decisions? If not, how can it be improved?
- Various times in the Federal Register document, the USEPA mentions the role of various expert panels and reviewers who were solicited for opinions. While it might not be appropriate to list the names in the Federal Register, it would enhance transparency if the document could include a link to a web site that includes the names of various panel members.
- To improve transparency between the CCL2 and the CCL3, the EPA should list all contaminants from CCL2 that are not included in CCL3, and provide the reason the contaminant is not in CCL3
- There was some concern that the areas without full transparency could impede the ability of anyone to go through the same exercise the EPA has done, which was an enunciated criterion for transparency made by the NRC and NDWAC.
- The screening criteria (Exhibit 14, page 9645 Federal Register document (73, #35, Feb 21 2008) were clearly enunciated and described.

- Although this was not clear from the description published in the Federal Register, there was an hierarchical approach to the data sources used for health effects. For full transparency, the manuals and the order of reference should be spelled out. In discussion, the perception of disease severity by infectious diseases physicians differed from that displayed in the manuals, which then influenced the scoring system. It appears the SAB felt that the insertion of expert opinion might most profitably occur after a consistently applied scoring system had been applied to the microbial candidates.
- Perhaps what is less clear is the information that was not used in developing candidates for CCL inclusion. It would be useful to note that peer research articles in journals and periodicals received somewhat less attention as data sources than disease monitoring or surveillance data from other agencies, state or municipal sources. It may well merit inclusion of a brief discussion of the reason why this information is downplayed as this type of information is perhaps more current with respect to sensitivity, selectivity and specificity that derived from some more standard methods? This may well be more of a fact for chemical CCL development but it is also true for microbial candidates. It appears particularly relevant over the issue of relative use of non cultural detection methods in determining occurrence of microorganisms as described in section b. Occurrence Protocol, page 9646 of the CFR. In fact the last state of column two of that page is simply wrong and should be removed or better justified. This statement says that "because viability and infectivity cannot be determined by non cultural methods, the public health significance of non-cultural detections is unknown". This is not true simply because insufficient research has been supported to develop the statistical correlation and mechanistic basis to evaluate the public health relevance of the non-cultural detection of PCCL agents.
- Draw more diagrams indicating how you assemble the PCCL list, how you go from the PCCL to the CCL. Add these as appendices as necessary.
- Provide clear definition of WBSO used in scoring process eg must be reported by CDC
- Describe hierarchy of sources/information used to determine common health effects
- An important issue with respect to transparency is the disconnect between the initial approach to determining the chemical CCL list from the PCCL list, and the post-processing method that was finally adopted. The initial approach was a complex methodology which included a set of decision rules and the implementation of advanced statistical models. The Federal Register notice needs to acknowledge early on that this approach was ultimately changed in significant ways upon examination of the method's results by EPA personnel. This internal panel of experts found that the initial classification scheme, resulting from a methodology recommended by previous external expert panels and implemented by the EPA, yielded "list" decisions which the internal panel felt did not adequately represent those contaminants of most concern and which encouraged the listing of some chemicals which the EPA experts felt did not belong on the list.

- In order to bring the listing recommendations into line with what the internal panel believed they should be, the methodology was changed to yield a list the panel was more confident of. In doing so, the panel noted several deficiencies in the methodology previously undertaken, particularly the undue importance assigned to the LD50 values. The most important difference in the new methodology as compared with the previous one was the starting point of the classification process: while the initial approach essentially began with the modeling activities using a training set of chemicals (some on the PCCL and some not), the new approach began by subsetting the PCCL into 3 groups depending on the type of data available to characterize the contaminant. For each group, a new decision rule was employed to each contaminant in the group to decide whether or not the contaminant should be moved forward to the CCL list. These decision rules are indicated in the bullets in Section III A4 on page 9644, but the explanations attached to each bullet need to be expanded so that the decision rules are more clearly explicated.
- In summary, the discussion in the Federal Register notice regarding the methodology for moving chemicals from the PCCL to the CCL is organized in a chronological manner. This presentation implies significance to a complex and somewhat cumbersome initial methodology which was ultimately subsumed within a new methodological framework. The new framework, which forms the actual basis for the recommended list, needs to be more fully explained. It also needs to be incorporated in a more prominent position in the Federal Register notice e.g. in II C Summary of the Approach used.

<u>Specific to Pathogens</u>

- The cutoff point in the ranking list (currently <7.1) is not justified. It's not clear to me that a difference of 0.5 is meaningful and yet it is used to break the list.
- First, the process as outlined in the documentation was overall judged a relatively transparent one. Having said that, during our discussions a number of suggestions were made that are likely to improve transparency and the validity of the process. One over-arching comment was that given the relatively limited number of microbial pathogens proposed for inclusion on the CCL, reviews of the scientific literature beyond the references used might be possible. In addition, the input of expert opinion for the microbial pathogens appeared to have influenced the scoring system. In contrast, for the chemical contaminants, the final expert opinion appears to have influenced the choice of the chemical contaminants, rather than the scoring system.
- The potential problems caused by highly endemic (but never detected as outbreaks) diseases is not explained fully
- There is a lack of data/discussion about the prevalence of organisms in sewage and wastewater
- The exclusion of outbreak and occurrence data from other parts of the world (especially Europe and Canada) is not justified. It would be very helpful to provide the reader with the current best estimate of the total annual number of known cases for each organism. (This is not a request for the waterborne

burden, just the total number of known cases). This will provide important background to the reader.

- The important issue of secondary transmission (and how it might impact burden) is not discussed in the document.
- It would be useful to provide information on the regulatory decisions of other countries (in particular the EU and Canada).
- Exceptions to the process for Arcobacter and MAC were made but it is possible that other organisms would change position if outside data/input were sought.
- A useful supplementary table would have been a tally of published (waterborne-attributed) case reports for each of the organisms. If there are 0 for some organisms, that would be useful information to have in the document.
- Exhibit 15, evidence of Waterborne Disease Outbreaks (WBDO) using the CDC surveillance database – this generated much discussion. Specifics included the inability to differentiate between pathogens that had caused many, many outbreaks and others that over the period in question (1973 on) only 2 outbreaks, and the lack of specific identified pathogens for the majority of studied outbreaks.
- In General the CFR description of the process for selection of microorganisms for the CCL is well written and describes a very comprehensive evaluation of the universe of microbial pathogens which was initially analyzed for those organisms that may require PCCL consideration. The analytical protocol employed in developing the CCL 3 list while not as discretely quantitative in terms of dose response relationship as chemical proposed for CCL 3 inclusion does have a quantitative underpinning that is superior to previous CCL formulations which appeared far more subjective. Advice and guidance by the NAS/NRC, NDWAC and others is clearly documented as to the analysis and selection procedure of microorganisms for the CCL. The sources of information and data used in candidate selection are clear and the effort to be inclusive in receiving information from NGOs, the public, professional organizations and municipalities is apparent.
- The relative weighting of WBDO, Occurrence and Health Effect Scoring and data normalization is well describe but not transparent. Moving form the PCCL to CCL in this regard is also less clear than needed and it is somewhat ambiguous as to how these ultimate scores were developed to provide the basis for PCCL analysis and CCL inclusion or exclusion. In particular, the use of “Occurrence” does not appear to be a quantitatively robust term and the 1-3 ranking scale may have far less utility initially expected. An occurrence term of 3 only means that it has been found in drinking water in the US, but it doesn’t mean that it is found in all drinking water. In fact it may mean that it was only found once in drinking water and if so the exposure potential to susceptible populations within the US may be quite low and the overall risk to US populations would be quite low. As a result, organisms such as Naegleria or Vibrio may receive a Pathogens PCCL score higher than scientifically expected because of the Occurrence weighting. An Environmental Frequency

(EF) or Distribution score for pathogens rather than or in addition to Occurrence score may be needed. An EF score should provide more information in terms of the number and distribution across the US for which the pathogen has been actually detected (by any method including non-cultural) in the respective drinking or source waters. Such information would provide a much more quantitative risk based approach for inclusion in the PCCL-CCL process.

Specific to Chemicals

- In a similar manner, the section on chemical contaminants indicates how the list of contaminants was scored during the review process. The section for microbial contaminants actually lists the scores for various contaminants. While it might take up too much space to include this information in the Federal Register notice, it would enhance transparency if these various determinations were summarized somewhere.
- The listing criteria should include an element that evaluates the analytical method used to quantify the contaminant concentration.
- Page 9641: It is unclear how fate parameters like the octanol/water partition coefficient were used in the evaluation. More details are needed.
- Exhibit 9: Units are needed on LD50 and related parameters.
- The approach used for developing the CCL from the universe of possible chemicals assumes that the data used for contaminant ranking (i.e., health effects and occurrence) are not influenced by professional judgment. In reality, decisions to conduct health effects studies and monitoring are based upon the perception of members of the research and regulatory community that the compounds could cause a problem. For example, USGS scientists employ professional judgment when they decide to allocate resources to developing new analytical methods for chemicals that may be included in the NAWQA program, while public health experts often conduct toxicology studies in response to concerns from regulators (e.g., MTBE health effects studies conducted over the past decade).
- The failure of the current process to acknowledge this fact has two implications: 1. It leads to a false sense that the algorithms employed to identify the CCL is an objective way to identify the contaminants of greatest concern from the entire universe of chemicals in commerce. Unless an approach is used that does not bias the results to focus on chemicals for which expert opinions have already been made, the universe of possible health threats will not be assessed properly. This shortcoming should lead the agency to allocate more resources to approaches such as computational toxicology, improvement of chemical release databases and environmental fate models. These are areas where ORD has considerable expertise (e.g., the ORD lab in Athens, GA) that can be better integrated into the process.
- The final CCL gives equal weight to all chemicals when in reality, some chemicals are likely to be ready for regulatory determination while others will require a significant amount of additional research before a regulatory determination can be made. For example, there appears to be a strong consensus among experts that NDMA, MTBE perchlorate and PFOA are a high priority for

the Agency because there is a high degree of certainty about their toxicity, occurrence and treatability. In fact, there are numerous cases in which water supplies contaminated with these chemicals have been the subject of intense public concern. In several cases, state agencies have passed regulations in response to these chemicals. In contrast, proposed CCL chemicals such as Germanium, hexane and quinoline appear to be on the list mainly because they scored highly in one category (e.g., production volume for hexane and toxicity for Germanium). This does not mean that further inquiry on these compounds is unwarranted. Rather, the likelihood that regulatory determinations can be made on these chemicals prior to substantial new data collection (e.g., the UCMR program) is extremely low.

- Within the presentation of the chemical contaminants (the part that I focused on particularly), the final step from the PCCL to the CCL included a judgment by a panel of internal EPA experts. This is the one aspect of the entire process for the chemical contaminants that requires greater explanation in the primary document (the Register Notice) and also greater explanation in the backup documents. In the primary document, the basis for making the types of judgments that they made should be explained; that is, what was flawed about the analysis to that point that an expert panel would be better at, and specifically what kinds of judgments were made either to decide not to list something that the models judged to be L or L? or to not list something that the models judged to be NL? or NL. By a considerable margin, this is the weakest part of the chemical contaminant discussion.
- A far more minor point where I thought clarity was missing was in the presentation of the potency scoring equations (Exhibit 9). Being a relatively mathematical person in my thinking, I found it frustrating. As a minimum, the units used for the various measures must be included. What the log value is depends on the number, and what the number is depends on the units; as far as I could find, the units of some of the measures were not in the Notice. Having them in the supporting material is insufficient—the Notice has to be able to stand alone in matters like this.

2. Suggestions to improve the process for future CCLs

Pathogen

- There is no sensitivity analysis of the pathogen weighting criteria, i.e., the results are not shown to be robust to small changes in the scoring. For example, a change of only "1" unit in WBDO score would move some organisms on/off the list.
- The WBDO data do not appear to take into account the geographic concentration/dispersion of the outbreaks
- Strong objection: A choice was made to use only data sources with entries for all of the organisms. This led to heavy reliance on CDC databases and lack of use of the published scientific literature. This process would not, prima facie, represent the "best available science."
- Significant limitations in understanding which microbial pathogens should be considered for the CCL3 list include the lack of occurrence data, very limited surveillance for most of the microbial pathogens, and the broad range of health effects. The CDC WBDO database, for example, is widely acknowledged to be an incomplete reflection of the true number of outbreaks, nor does it capture the burden of disease relating to endemic, lower level transmission. Thus, the SAB considers this a clarion, wake-up call for the acquisition of better data on occurrence and surveillance regarding human disease.
- In addition, since so many drinking water supplies have sewage inputs, there was some discussion of scoring pathogens for their presence in sewage or wastewater, or for their presence in animal wastes that enter the water supply. Information about occurrence in sewage, wastewater, or animal wastes could be used to supplement information about occurrence in source water.
- The pathogens people were surprised to see on the CCL list included Entamoeba histolytica and Vibrio chlerae, and people were surprised not to see adenovirus or Mycobacteria. While there was general agreement that the existence of a WBDO should bring special attention to a microbial pathogen, the WBDO grading system did not appear to be able to provide to the scoring algorithm the full breadth or range of data available.

Chemicals

- Consideration of regulating chemicals with similar mechanisms of action, and microbial pathogens with similar health effects (for example, diarrhea, pneumonia, meningitis). This could include classes of compounds and microbes rather than individual ones.
- EPA has noted that adjustments were made by an internal evaluation team made up of EPA experts to the list of potential CCL3 chemicals created by application of the characterization model to the list of PCCL chemicals. This resulted in the addition to, or removal of, some number of candidates from the model-generated CCL3 list.
- As stated in the document entitled Contaminant Candidate List 3 Chemicals: Classification of the PCCL to CCL, “The Evaluation Team recognized that the relationship between Potency and Magnitude was important when deciding whether or not to list a chemical, but only when the Magnitude data represented concentration in ambient or finished water. Accordingly, calculation of the ratio between the health-based value and the 90th percentile concentration in finished

or ambient water was added as a post-model process. To calculate the health-concentration ratio, the data that provided the Potency score were converted to the Health Reference Level (HRL) benchmark that the Agency has used for Regulatory Determination. For non-carcinogens, the HRL is equivalent to the lifetime health advisory value. The lifetime health advisory value is obtained by multiplying the RfD times 70 kg, dividing by a water intake of 2 L/day and multiplying by a 20% relative source contribution (unless there are data to suggest that the 20% is inappropriate)."

- As noted above, derivation of an HRL for non-cancer effects includes the RfD as one factor in the equation. The Food Quality Protection Act of 1996 requires EPA's Office of Pesticide Program to make a finding with regard to the application of an additional 10-fold safety factor to the RfD to assure protection of children's health. Application of this additional safety factor to an RfD yields the Population Adjusted Dose or PAD. If it is concluded that the extra safety factor can be removed, the RfD and PAD become the same. In those cases in which the extra safety factor is retained or only partially reduced, the PAD becomes smaller than the RfD.
- It would seem appropriate to use the PAD rather than the RfD in the calculation on an HRL for a food use pesticide. Therefore, the Committee recommends that the Agency recalculate the health-concentration ratios for those pesticides on the PCCL that have PADs smaller than their RfD, since it is possible that additional substances may qualify for consideration for inclusion on the draft CCL3 because their revised ratio is now 10 or less.
- The process for selecting the toxins was really not presented in the documents, and should be explained clearly somewhere. The process for selecting the chemicals was quite clear and logically presented until after the three models were run and the resulting lists were created. At that point, the presentation became very murky. The Committee specifically raised numerous questions about the bullet points in section 4 on p. 9644 of the FR notice. It was not clear from the text that the 36 chemicals in the high certainty bin, for example, were included irrespective of the model results, whereas the 24 pesticides chosen from the medium certainty bin included only those with an L or an L-L? ranking. This needs to be clarified. In addition, there needs to be a clearer written justification for diverting from the results of the model at the end of the process.
- Committee members raised concerns that it was very difficult to figure out what the supporting data were for each of the chemicals that did get onto the list. For example, it is not shown what level of certainty "bin" each came from, what the data were in the exposure and health effects category, and what the modeled list-not list determinations were for these. A table presenting these results would be very helpful. In addition, it would be helpful to show similar results for at least a subset of the chemicals on the PCCL to help inform the reader as to why these were not selected. Chemicals that especially should have their results shown include any that were on the CCL2 and any that were nominated by public commenters but were not listed.

- Overall, the process from creation of the "universe" to the cut to the PCCL and ultimately to the CCL3 was very well done. The EPA is to be commended for the massive and systematic effort that was accomplished, and accomplished well.
- It would seem wise to include the SAB DWC earlier in the process. At this point, the EPA is basically asking for our blessing on a process that is a fait accompli. Getting buy-in from the DWC throughout the process and not just at the end would seem to take better advantage of the expertise of the committee.
- A potential serious flaw in the process is the choice to use individual chemicals only and not to consider classes of related compounds. I recognize the difficulty of deciding on classes and then figuring out a whole new process to determine concentrations and health effects, but the current process leaves out the possibility that several related chemicals might behave collectively and cause adverse health effects that the individual compounds do not. I believe that this situation must be corrected in the next iteration. (One might ask the question of what would happen if the THMs were evaluated individually—would we have no THM regulations?) This process might rely heavily on expert opinion, but could be supplemented with the same modeling that was done this time around.

<u>General</u>

- The response to public comments was deficient. The comments from some members of the public were mischaracterized by EPA (ie. presented as saying "all unlisted pesticides" when actually a very specific and short list of pesticides had been nominated). In addition, with the exception of the pharmaceuticals, EPA failed to respond with any rationale for failing to list the other nominated substances. The Agency should provide more information on the chemicals nominated by the public and the reasons why they did not meet the criteria for listing.
- It is unclear whether this new CCL process is a significant improvement over the old process. Although it did "cast the net wider", the less well-known chemicals that were included in the Universe did not make the cut because of lack of data. In the end, despite the lengthy process, the final CCL3 was really developed by a group of experts at a series of meetings. This raises the question of whether EPA should consider a more streamlined process of creating the CCL and should instead focus on generating more data to fill the gaps, and on actually regulating some chemicals.
- If EPA does use this process again, it will be important to attempt to incorporate the lessons learned at the end of the selection process into an earlier phase of the process for the next round. Specifically, the models will need to take into consideration the level of certainty, and also some measure of the ratio between the level of concern and the potential drinking water level. However some members of the Committee cautioned against using the 90th percentile of the measured water concentrations in combination with a 10-fold ratio. It is clear that the very skewed distributions of concentrations in water could mean that some water utilities could be in a zone of concern and the chemical would still be screened off the list using these criteria.

- The Committee agreed that it will be very important to incorporate information on wastewater concentrations into the exposure side of the assessment. This will be important both because wastewater will increasingly be processed into potable water in the future, and because wastewater reflects a wide variety of important contaminants including pharmaceuticals, personal care products, and other emerging contaminants.
- EPA has noted that adjustments were made by an internal evaluation team made up of EPA experts to the list of potential CCL3 chemicals created by application of the characterization model to the list of PCCL chemicals. This resulted in the addition to, or removal of, some number of candidates from the model-generated CCL3 list.
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- It would seem appropriate to use the PAD rather than the RfD in the calculation on an HRL for a food use pesticide. Therefore, the Committee recommends that the Agency recalculate the health-concentration ratios for those pesticides on the PCCL that have PADs smaller than their RfD, since it is possible that additional substances may qualify for consideration for inclusion on the draft CCL3 because their revised ratio is now 10 or less.
- Please use computational toxicology to generate lists of toxins and carcinogens, and to group them by classes, and to predict which compounds in a class are carcinogenic. Regulate the most potent carcinogens.
- Decide on a level below which a cancer slope factor will cause a chemical carcinogen not to be regulated on the CCL list, because carcinogenesis slope

factors and the mutagenicity of mutagenic carcinogens varies over six orders of magnitude.

- Develop quick risk assessment procedures as quick screens to prioritize carcinogens (risk for cancer = cancer slope factor x concentration x #people exposed = number of cancers due to this chemical; risk for toxin = 1/LD50 x concentration x # of people exposed = number of diseases and deaths due to this toxin). Triage chemicals onto and off of the CCL by the quantitative values obtained in these quick calculations.
- The same exceptions made for Arocbacter and MAC in how a WBSO is defined should be applied to the other patogens for which there is a high-quality peer-reviewed report of an outbreak
- Now that the information sources and scoring protocols are standardized for the CCL pathogens hold another expert workshop to ensure the experts' scores are consistent with EPA internal scoring. Reproducibility would augment transparency
- Concerning H. Pylori and the relevance of the scoring process for chronic health effects, it appears the first two health outcome categories (pathogen causes significant mortality and pathogen causes pneumonia ? cancer) are applicable to the chronic effects of H. pylori. The scoring does not distinguish acute from chronic effects. Several important additional points arise from the above analysis:
  - If transparency is to be defined as having reproducible listing results, more information must be provided. With respect to the classification models, this means that the training set of chemicals should be provided, along with the attributes assigned to each chemical and the expert judgement as to whether the model should classify the chemical as a "list" or "no-list" chemical. Also, parameters chosen for the models e.g. stopping rules or specification decisions should be provided (in addition to what is provided in Appendix E.)
  - Since the classification models are only used for chemicals in the medium certainty bin, the models should be re-trained using only training chemicals that would fall into this bin. This will provide calibrated models that are narrowly focused on exactly the chemical subgroup which is germane to the application of the models.
- Prioritization within the CCL is important. This may also require reformulating or retraining the models, since the dependent model variable must now indicate not only whether a chemical should be studied for listing, but with what urgency the chemical should be studied.
- The improvements recommended in the selection process are entirely consistent with the theme of adaptive management recommended by NWDAC and endorsed in the Federal Register notice. Thus, the methodology for the listings can be adapted as more experience with the CCL listing process is gained. The post-processing changes recommended by the internal EPA panel are perfect examples of how the actual implementation of a methodology provides empirical data (i.e. the initial listing recommendations from the classification models) which can be analyzed and fed back to provide guidance and criteria for improving the selection methodologies.

- The data bases used by the EPA in these analyses do not include much of the journal literature, which could be a rich source of information for its analyses. While these sources would be difficult to search for the universe of chemicals, it is recommended that these data be included in the PCCL to CCL process. The use of advanced text-processing software should be investigated for this application. E-government initiatives throughout the federal government, as well as a lively and innovative academic community in this area, are potential sources of help for EPA in pursuing this approach.

3. **Contaminant-specific recommendations**

- It doesn't make sense (at least from the "sniff test") to list Vibrio above adeno/enterovirus.
- Based on pathogen occurrence in source water and disease prevalence it makes no sense to list Entamoeba histolytica and Vibrio cholerae on the CCL 3 whereas Adneoviruses and Enteroviruses are off the list. The latter two pathogens are much more of a health problem in the USA.
- The Committee noted that acetochlor came out as an NL in the model, and metolachlor came out as an NL?, although both chemicals and their metabolites were placed on the CCL3. These results are surprising and Committee members were curious as to the explanation. Committee members seemed comfortable with the ‘chlor herbicides being included on the CCL3, but were wondering whether there might be a need for a change in the process or for clarification of the NL classifications.
  - Other pesticides that did not appear on the CCL3 that were mentioned as potentially worthy of listing included the triazine herbicides, carbaryl, aldicarb, chlorpyrifos, azinphos-methyl, other isomers of hexachlorocyclohexane, and iprodione. Information was provided to EPA on several of these chemicals by public commenters. These are chemicals that, at a minimum, should be included in a table showing why they did not meet the Agency’s criteria for listing.
  - In the case of pharmaceuticals, perflourinated surfactants and other contaminants that are prevalent in wastewater effluent the USEPA may want to consider using data obtained in wastewater effluent monitoring programs for the screening process. Numerous large water systems are subjected to large discharges of wastewater effluent and it is likely that the concentrations of contaminants measured in wastewater effluent could be used to predict concentrations in raw water. An approach for predicting the role of unplanned wastewater reuse that may be appropriate for predicting concentrations in raw water sources is presented in by Anderson et al. (1).
  - The absence of data on the occurrence of pharmaceuticals in surface waters is puzzling. Why weren’t the data from USGS or any of the numerous studies in the peer-reviewed literature included here.
  - PFOA data in effluent: Higgins et al.?
  - Bisphenol A and phthalate esters should probably be mentioned somewhere due to public interest and concern.
  - The final CCL gives equal weight to all chemicals when in reality, some chemicals are likely to be ready for regulatory determination while others will require a significant amount of additional research before a regulatory determination can be made. For example, there appears to be a strong consensus among experts that NDMA, MTBE perchlorate and PFOA are a high priority for the Agency because there is a high degree of certainty about their toxicity, occurrence and treatability. In fact, there are numerous cases in which water supplies contaminated with these chemicals have been the subject of intense public concern. In several cases, state agencies have passed regulations in response to these chemicals. In contrast, proposed CCL

chemicals such as Germanium, hexane and quinoline appear to be on the list mainly because they scored highly in one category (e.g., production volume for hexane and toxicity for Germanium). This does not mean that further inquiry on these compounds is unwarranted. Rather, the likelihood that regulatory determinations can be made on these chemicals prior to substantial new data collection (e.g., the UCMR program) is extremely low.

References

(1) Anderson, P. D.; D'Aco, V. J.; Shanahan, P.; Chapra, S. C.; Buzby, M. E.; Cunningham, V. L.; Duplessie, B. M.; Hayes, E. P.; Mastrocco, F. J.; Parke, N. J.; Rader, J. C.; Samuelian, J. H.; Schwab, B. W., Screening analysis of human pharmaceutical compounds in US surface waters. *Environmental Science & Technology* **2004**, *38*, 838-849.

Pesticides Proposed for Removal from, Addition to, Draft CCL3

Chemical	**Rationale for Removal**
3-Hydrocarbofuran	3-Hydroxycarbofuran has not been shown to form in the majority of environmental fate studies, with the exception of one study in which it was detected in low amounts as a result of soil photolysis [OPP Carbofuran RED]. Additionally, all uses of carbofuran are in process of being cancelled. Therefore, potential for exposure in drinking water will cease.
Ethylene oxide	Highly volatile. Virtually no possibility of contamination of water
Ethylene thiourea	Monitoring yielded no “hits” above detection limit of 0.1 ppb. Cumulative assessment from all sources (EBDC fungicides) led OPP to conclude “No concern.” [Mancozeb RED]
Fenamiphos	Cancellation of all domestic uses in 2002. While some import tolerances remain, possibility for d.w. exposure from domestic use no longer exists.
Molinate	Voluntary cancellation of all uses in 2005. Potential for exposure in drinking water will cease.
Nitrofen	All uses cancelled in 1983. Potential for exposure in drinking water no longer exists.
Thiodicarb	Thiodicarb degrades rapidly to methomyl in the environment. Focus should be on methomyl which could occur in surface and ground waters

Chemical	**Rationale for Inclusion**
Gamma-hexacyclohexane (Lindane) Beta-hexacyclohexane	Even though all pesticidal uses of Lindane have been cancelled, residues of Lindane and its isomers are persistent and will continue to be found in water (and, other environmental media) for an extended period

Methomyl	See Thiodicarb removal rationale above

Based on my review of the chemicals listed in Breakout Group #1, which is a subset of CCL3, I recommend regulating the following chemicals in the following order:

1) N-nitrosodimethylamine (NDMA, CAS # 62-75-9). For DMN, is metabolically activated by cytochrome P450, and this generates the electrophilic carbonium ion (methyldiazonium ion), which binds covalently to and alkylates DNA bases. DMN is strongly mutagenic and a potent hepato-canecrogen, and causes liver disease with jaundice and swelling. DMN is carcinogenic to all ten species tested in single bolus doses or multiple low doses. Liver, kidneys, thymus, spleen, lung, skin and trachea are the target organs for carcinogenesis by DMN. DMN is a mutagenic carcinogen in multiple organs and species. It clearly belongs on the CCL3 list, and should be a top priority for regulation because it is a mutagenic carcinogen in multiple organs and multiple species.

2) N-Nitrosodiethylamine (NDEA, CAS # 55-18-5). NDEA is a mutagenic carcinogen that is activated by cytochrome P450. It is a very strong multi-organ carcinogen in rodents. It clearly deserves to be on the CCL3 list, on the top tier, i.e., in category A.

3) N-nitroso-di-n-propylamine (NDPA, CAS # 621-64-7). NDPA is also activated by cytochrome P450 to a mutagen, and it is a mutagenic chemical carcinogen. It is justified to place this chemical on the CCL3 list, and it should be at the top tier of this list, in category A.

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4) N-nitrosopyrrolidine (NPYR, CAS # 930-55-2). NPYR is a nitrosamine used as a research chemical and may also be a disinfection by-product. Like all nitrosamines, which are mutagenic carcinogens, it should also be on the CCL3 list, in the top tier.

5) Hydrazine (CAS# 302-01-2). . It is acetylated rapidly in most mammalian species and excreted in the urine as the di-acetyl metabolite. Hydrazine causes single carbon compounds to be incorporated to yield O-6-methylguanine and 7-methulgunaine in DNA. Hydrazine is a strong poison with strong caustic action on skin and mucous membranes. It is classified as a local irritant, convulsant, hepatotoxin, and hemolytic agent. It causes anorexia, vomiting, cardiac depression, and hypotension., bronchial mucous destruction, pulmonary edema, and delayed death in days. In animals, hydrazine causes liver damage, kidney damage, lung damage, muscle tremors, and is embryo-lethal. It is considered a possible human carcinogen (IARC class 2B) due to increased tumors in laboratory animals given hydrazine, but insufficient data in humans exists. Hydrazine is mutagenic in bacteria, viruses, and mammalian cell assays. Hydrazine certainly is justified being on the CCL3 list. Due to its mutagenicity, carcinogenicity in animals, and strong toxicity as a caustic agent, I recommend placing it at the top priority section of the CCL 3 list.

6) 1,3-butadiene: It is rapidly metabolized to butadiene mono-epoxide (BME) by cytochrome P450 enzymes, and also to butadiene diepoxide BDE). BME and BDE are thought to cause carcinogen-DNA adducts and mutagenesis, leading to carcinogenesis. 1,3-butadiene causes hemangiosarcomas, tumors of entdothelial origin, in B6C3F1mice, in the liver, lung, and kidney, and heart. 1,3-butadiene is a mutagenic carcinogen, which likely follows a linear, no threshold dose-response curve for carcinogenesis. At very high levels (2000- 8000 ppm), 1,3-butadiene caused CNS depression, as evidenced by blurred vision, drowsiness, fatigue, brachycardia, and hypotension. The LC50 in rats exposed to butadiene for 4 hrs is 129,000 ppm. In rats and mice, inhalation of butadiene is carcinogenic. The greatest threat from this chemical is carcinogenesis to humans at low doses, following a linear, no-threshold, dose-response curve. Hence, yes, 1,3-butadiene should remain on the CCL3 list. I would rank this in the "A" category, at the top of this list, because it is a mutagenic, multi-organ carcinogen.

7) Perchlorate (CAS # 14797-73-0). Perchlorate binds to the sodium-iodide (NIS) symporter, present in the basolateral membrane of thyroid follicular cells, which transports iodide into the thyroid gland. This can lead to hypothyroidism, compensatory hyperplasia. If sustained, this can lead to cancer of the thyroid gland. Since thyroid hormone is very important in growth and development, this situation is particularly dangerous when pregnant women who are already hypothyroid contact perchlorate in the drinking water, because their offspring may be born with neurological/intellectual deficits. Because of its widespread occurrence as a contaminant in drinking water, and because it can cause hypothyroidism in the offspring of pregnant women, and potentially cancer in humans, perchlorate deserves to be on the CCL3 list, and with a high priority, in group A.

8) Urethane (CAS 51-79-6). Urethane, or ethylcarbamate, or the ethyl ester carbamic acid, is used as a solvent for organic materials, pesticides, and fumigants and as a paint ingredient. It is also used as a chemical intermediate in the production of cross-linking agents in textiles and in the pharmaceutical industry. Urethane was designated as a carcinogen in l948, when its use as a veterinary anesthetic was stopped. It is activated in the liver by cytochrome P450 by two sequential steps. It is dehydrogenated, which generates vinyl carbamate, followed by epoxidation to form vinyl carbamate epoxide. Vinyl carbamate is believed to be the ultimate carcinogenic metabolite of urethane. IARC classified urethane as a probable human carcinogen, based on animal carcinogenicity data. Because it is such a strong mutagenic carcinogen, I recommend urethane stay on the CCL3 list as justified, and at the top of this list.

9) Toluene Diisocyanate. Toluene 2,4-diisocyanate is metabolized into 2,4-diaminotoluene in humans. Its mechanism of toxicity is as a cross-linking agent and sensitizer in humans. In humans, it is a strong irritant to the eyes, skin, and respiratory system. It is a lacrimating agent, a strong dermal and pulmonary sensitizer, and a suspected carcinogen. The ACGIH TLC for toluene diisocyanate

is 0.005 ppm. The LC50 (inhalation) is 14 ppm/4 hr in rats and 10 ppm/4 hr in mice. Since this is such a strong sensitizer, which causes dermal, pulmonary, and eye sensitization, this chemical should appear on the CCl3 list, at the first tier of priority, because as a cross-linking agent, it is also a suspect carcinogen.

10) O-Toluidine. (CAS 95-53-4). O-toluidine is used to produce dyes for textiles, rubber, pharmaceuticals, and pesticides, and as an accelerator in rubber vulcanization. . It interferes with enzymes associated with the detoxification process and monooxygenase systems, and also defats membranes. O-toluidine is a carcinogen The ACGIH TLV is 2 ppm. The oral LD50 in rats is 670 mg/kg for o-toluidine. Hence, this chemical clearly also belongs on the CCL3 list, and as a likely mutagenic carcinogen, in the top category of the list.

11) Vinclozolin. Vinclozolin is a member of the dicarboximide fungicide class that acts as an androgen receptor antagonist. Vinclozolin or its metabolites, competitively inhibit binding of androgen to the AR, leading to inhibition of androgen-dependent gene expression in vitro/in vivo. Vinclozolin delays pubertal maturation and reduces sex accessory glands and epididymal growth and increases serum LH , testosterone, and 5-androstane-3,17 diol levels. Administration of vinclozolin during sexual differentiation demasculinizes and feminizes the male rat offspring such that treated males display female-like AGD at birth, retained nipples, etc. Neoatal injection of vinclozolin demasculinized aggressive play behavior in male rats at 3 days of age, indicating CNS sexual differentiation was altered in an anti-androgen manner. Hence, it is also appropriate that vinclozolin be placed on the CCL3, and likely at the top of this list, due to its effects on hormones and changing sexual characteristics in animals. This could be very dangerous if this compound entered the water supply in significant quantities, and it might play havoc with affecting sexual orientation in the population exposed to this chemical at high concentrations. Even the mention of this possibility could shake the confidence of the public in the purity and safety of public drinking supplies. Hence, vinclozolin should certainly be on the CCL 3 list, and at a very high priority.

12) Nitrobenzene (CAS# 98-95-3). It is metabolized in two ways: 1) reduction to aniline, followed by hydroxylation to aminophenols and b) direct hydroxylation of nitrobenzene to form nitrophenols, and reduction of these to aminophenols. Metabolites in urine are p-nitro and p-aminophenol. The mean lethal adult dose is 1-5 grams. Methemoblobinemia, headache, nausea, lethargy, depressed respiration, and cyanosis may occur on exposure to nitrobenzene. Tachycardia, hypotension, respiratory depression/failure, cardiac arrythmias, and liver damage may occur on exposure to nitrobenzene. Its poisoning resembles that of aniline. Nitrobenzene is a carcinogen in mice and rats by the inhalation route. Nitrobenzene has been shown not to be mutagenic in Salmonella typhimurium. There is ample justification for nitro-benzene to be placed on the CCL3 list, in the top tier of priority, due to its strong and unique set of toxicities and its carcinogenicity in rodents.

Second tier of compounds:

13) Cobalt (CAS # 7440-48-4): Cobalt is an essential trace element/metal to mammals, including humans, found in cyanocobaltamine (vitamin B_{12}), which protects against pernicious anemia and is required in production of red blood cells. It has been used medicinally in humans as cobaltous chloride to stimulate formation of red blood cells in individuals suffering from anemia, and as a germicide. Cobalt is absorbed easily orally, likely through the jejunum. Cobalt can be toxic, primarily in the occupational setting at high doses. It can cause respiratory irritation when inhaled. Cobalt depresses enzyme activities, including catalase and amino levulinic acid synthetase, cytochrome P450, and enzymes involved in cellular respiration. Cobalt also depresses and interferes with iodine metabolism, resulting in reduced thyroid activity, which can lead to goiter, when it is consumed in cobalt-contaminated water. Cobalt can also block the Krebs citric acid cycle, inhibiting cellular energy production. In industrial settings, inhalation of high concentrations of cobalt compounds has lead to hard-metal pneumoconiosis, which may lead to interstitial fibrosis, hypersensitivity reactions, and skin hypersensitivity reactions. Ingestion of cobalt can result in production of unusually high number of red blood cells. Addition of cobalt salts (once added to beer as a defoaming agent) has caused cardiomyopathy. The ACGIH TLV-TWA for cobalt (elemental and inorganic compounds is 0.02 mg/m^3. ACGIH classifies cobalt as an animal carcinogen. CAL- EPA classifies it a as a chemical carcinogen. Obviously, small amounts are needed as an essential trace element, and large amounts are problematic because of the toxic and carcinogenic effects of cobalt and its salts. It clearly deserves to be on the list, somewhere in the category of B.

15) 1,4-Dioxane. Humans contact dioxane by inhalation, ingestion, and dermal contact. Dioxane is metabolized to beta-hydroxyacetic acid (HEAA) in humans and rats, and HEAA can be metabolized to 1,3-dioxane-2-one, which is believed to be a hepatic carcinogen. Dioxane is a non-mutagenic carcinogen; it does not covalently bind to DNA. Its mode of carcinogenicity is not known. Dioxane is toxic to human only at high concentrations, such as occurred while men were working in a textile factory and inhaled large quantities of dioxane. Symptoms were irritation of the upper respiratory passage, coughing irritation of eyes, drowsiness, vertigo, headache, anorexia, stomach pains, nausea, vomiting, uremia, coma, congestion and edema of the lungs, and brain, liver, and kidney injury, and death. One worker died after working 1 week on a job where the average concentration of dioxane vapor was 470 ppm. Dioxane is classified as a B2, or probable, human carcinogen, by the U. S. EPA, based on adequate animal studies and inadequate human studies. Hence, dioxane clearly belongs on this CCL 3 list, due to its toxicity, carcinogenicity, and widespread occurrence, in the B or second priority category. .

16). 2-Methoxyethanol (ethylene glycol monomethyl ether). It is metabolized to methoxyacetic acid, likely via methoxyacetaldehyde. At high acute doses, it has a narcotic effect, and causes kidney and lung damage, with hemogobinuria. Toxicity is due to the metabolites, including methoxyacetaldehyde and methoxyacetate. It is teratogenic, due to the interference by methoxyethanol, or metabolites, with 1-carbon metabolism in synthesis of nucleic acid precursors. 200 ml is fatal for individuals compromised by alcoholism. A high doses MOE causes sleepiness, weakness, nausea, acidosis, CNS depression, neurological symptoms, anemia, and immune depression. It is a reproductive toxin in animals, and presumed to be one also in humans. This chemical should certainly be on the CCL3 list, likely with a designation of B.

17) Acetaldehyde (CAS # 75-07-0). Acetaldehyde is metabolized in the nasal cavity and liver to a number of metabolites. By inhalation acetaldehyde irritates the upper respiratory tract and can the skin and eyes. A STEL ceiling of 2 ppm has been recommended. The 4 hr LC50 is 13,300 ppm. Acetaldehyde is an animal carcinogen. By inhalation exposure, acetaldehye has produced nasal tumors in rats and laryngeal tumors in hamsters. In rats, acetaldehyde is teratogenic. It is mutagenic in many assays (SCEs, chromosomal aberrations) in mammalian cells in vitro. Acetaldehyde also deserves to be on the CCL3 list, at a second or category B priority on this list.

16. Hexane. Human exposure occurs by inhalation, ingestion, or dermal contact. Hexane is metabolized by cytochrome P450 enzymes at he two and three positions (hydroxylation). It can be metabolized to 2-hexanol and then to 2,5-hexandeiol by P450 and thence to 2,5 hexanedione, which is a more neurotoxic metabolite that produces polyneuropathy. Due to its neurotoxicity, the ACGIH recommended a TLV of 50 ppm, as an 8 hr TWA. Acute exposure to high levels of hexane causes CNS depression. 50 g of hexane may be fatal to humans. Workers exposed occupationally to n-hexane contract sensory polyenuropathy, sensorimotor polyneuropathy, and sensorimotor polyneuropathy with amyotropy, cranial nerve involvements (visual disorders and facial numbness). N-hexane is so far not classifiable for carcinogenicity at the present time. N-hexane is not mutagenic in Salmonella typhimurium with or without rat and hamster liver S-9. N-hexane should certainly be on this list due to its neurotoxicity, in a second category.

18) Ethylene Glycol (1,2-dihydroxy-ethane, CAS# 107-21-1). . Its use as a pesticide has been cancelled. The first step in the metabolism of ethylene glycol is alcohol dehydrogenase-catalyzed conversion of ethylene glycol to glycoaldehyde. The major metabolic end-products in animals are carbon dioxide in exhaled air, and glycolate and unchanged ethylene glycol in urine. Glyoxylate, hippurate, and oxalate may also be excreted in the urine. Metabolism occurs primarily in the liver and kidneys. Systemic toxic effects of ethylene glycol include metabolic acidosis and renal tubule necrosis, which are attributed to the metabolites. Inhalation causes upper respiratory tract irritation. Ingestion of large

amount of ethylene glycol causes CNS depression, cardiopulmonary disturbances, and renal distress. Cardiopulmonary disturbances include tachycardia, hypertension, congestive heart failure, pulmonary edema, and cardiomegaly. ACGIH has established a STEL-Celing of 39.4 ppm for mist and vapor combined. The lethal dose in humans for oral administration is 1.4 ml/kg. Ethylene glycol is an animal teratogen. Ethylene glycol was negative in the Salmonella and mouse lymphomas assays for induction of chromosomal aberrations and sister chromatid exchanges in CHO cells. Ethylene glycol is a very toxic. Because of its toxicity, it should remain on the CCL3 list. However, since it is non-mutagenic, it should be placed in the second tier of toxins/carcinogens.

17). Methyl tert-butyl ether (MTBE, CAS # 1634-04-4). In humans, MTBE can cause kidney failure or liver damage. It is an animal carcinogen and teratogen. The oral LD50 in rats is 4,000 mg/kg. The inhalation LC50 in rats is 2.3 ppm. Due to its foul taste and smell, in California, MTBE has been regulated in drinking water down to a level of 1 ppb. It is metabolized to tert-butyl alcohol and formaldehye, by CYP2A6 in humans. MTBE has been reported to cause kidney and testicular tumors, liver adenomas, leukemias, and lymphomas in rodents. It also causes endocrine dysregulation in rodents at high doses. EPA has set an advisory guidance range of 20 – 40 ugl/L for MTBE in water due to its objectionable taste and smell. It is mutagenic in a few test systems. MTBE should be on this CCL3 list, in the second priority of chemicals to be regulated, based on toxicity/carcinogenicity.

18) PFOA (Perfluoro-octanoic acid, CAS # 335-67-1). The Carcinogen Identification Committee (CIC) of OEHHA/California EPA, voted that not enough data exists on PFOAs to determine whether they are carcinogenic, and not to move them to the head of the priority list for listing as carcinogens. Similarly, the Developmental and Reproductive Toxins (DART) Committee of OEHHA also voted not to move these chemicals to the head of the priority list. However, data on PFOA and PFOS is accumulating rapidly. They do bio-accumulate, and they are now showing up at high levels in certain water systems (e. g., in Ohio). They do belong on the CCL3 priority list. I cannot say with what priority, because the data base is currently thin on these worrisome chemicals, which are widespread contaminants that bioaccumulate. Please take account of the very latest data on carcinogenicity (yes or no, and slope factors if yes), and any data on development/reproductive toxicity caused by these chemicals. .

20) Permethrin. Permethrin has also been combined with sulfur to treat human scabies and is the recommended treatment for scabies in patients with AIDS. Metabolism of permethrin occurs rapidly through ester cleavage and hydroxylation. Permethrin has a selective high affinity for membrane sodium channels. It slows the closing of the sodium channel, resulting in a prolonged tail current and repetitive firing of pre-synaptic and accompanying post-synaptic cells following a single action potential. High enough doses can cause complete polarization and blockade of nerve conduction. Permethrin also inhibits Ca, Mg

ATPase and calmodulin. Permethrin is neurotoxic in mammals, and produces type I motor symptoms characterized by hyper-excitation, enhanced startle respone, tremors, and prostration. Permethrin is an appropriate candidate for the CCL3 list. Due to its neurotoxicity in animals, and likely neurotoxicity in humans, it is a toxic chemical and should be on the CCL3 list, but toward the lower end of the highest category, because it is neurotoxic to mammals but because pyrethroids' toxicity is low for mammals, and because there have been few reported cases of human poisoning by permethrin.

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4. **Vanadium**. Vanadium is toxic to alveolar macrophages when inhaled, and may impair pulmonary resistance to infections and clearance of particulate matter. Its toxicity is attributed to its ability to inhibit enzymatic systems such as monoamine oxidase, ATPases, tryosinases cholinesterases, and cholesterol synthetases. Vanadate mimics insulin action in target tissue and can inhibit the sodium pump. Acute oral exposure causes abdominal cramping diarrhea, and black stools. Systemic symptoms of exposure to vanadium include peripheral vasoconstriction of the lungs, spleen, kidneys, and intestines. Fatal doses cause CNS depression with tremors, headache, and tinnitus. Chronic exposure can cause arrhythmias and bradycardia. Vanadium is a pulmonary toxicant (edema) in animals. Food (seafood, mush-rooms, dill seed, milk, meat, cereals, and vegetables) is the major source of human exposure. to its widespread interference with biochemical/lbiological processes/enzyme systems, vanadium should be on the CCL3 list, with a B priority.

4. **The Future: Emerging Issues/Research Needs.**

- How to deal with PFOA/PFOS. New research to determine whether they are carcinogenic, what the mechanism is, are they mutagenic carcinogens? Are they development and reproductive toxins, and what are the mechanisms of this and carcinogenicity?
- Further studies on the mechanisms of action of vinclozolin as a toxin/endocrine disruptor need to be conducted to solidify its risk assessment.
- Strong risk assessments on 1,3-butadiene need to be carried out, based on the science of its carcinogenicity.
- Studies on whether toluene diisocyanate is a carcinogen need to be carried out, and the molecular mechanisms of carcinogenesis, if it is a carcinogen, need to be conducted.
- Research to strengthen the risk assessments for perchlorate, to determine what maximal levels of perchlorate should be allowed in water systems, based on effects on T3 and T4 and inhibition of iodide binding to the NIS receptor.
- Research support for CCL