UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

December 18, 2008

EPA-SAB-09-007

The Honorable Stephen L. Johnson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: SAB Advisory on Aquatic Life Water Quality Criteria for Contaminants of Emerging Concern

Dear Administrator Johnson:

The Science Advisory Board (SAB) Ecological Processes and Effects Committee, augmented with additional experts, reviewed the EPA White Paper titled *Aquatic Life Criteria for Contaminants of Emerging Concern* ("White Paper"). EPA's 1985 *Guidelines for Deriving Numerical National Water Quality Criteria for the Protection of Aquatic Organisms and Their Uses* ("Guidelines") specify procedural and data requirements for deriving ambient water quality criteria for the protection of aquatic life (aquatic life criteria). The Agency is faced with a number of technical issues and challenges in deriving aquatic life criteria for contaminants of emerging concern (CECs). To address these technical issues, the Office of Water and Office of Research and Development have proposed recommendations for interpreting and/or adapting principles in the 1985 Guidelines. EPA's White Paper describes the proposed recommendations, focusing in particular on CECs that disrupt endocrine function in animals. The White Paper also explores these recommendations in the context of a case example CEC, ethynylestradiol, a synthetic pharmaceutical estrogen.

EPA's Office of Water (OW) requested that the SAB: 1) comment on the technical merit, practicality, and implementability of recommendations in the White Paper; 2) comment on whether the White Paper identifies the appropriate issues to be addressed in deriving aquatic life criteria for CECs; 3) suggest ways to improve the utility of the ethynylestradiol case example; and 4) offer other suggestions to assist the Agency in implementing recommendations in the White Paper. The enclosed advisory report provides the advice and recommendations of the SAB.

Overall, the SAB finds that, in the White Paper, EPA has identified appropriate technical issues to be considered in deriving aquatic life criteria for CECs. However, EPA was constrained by the 1985 Guidelines which, although excellent when developed, were never envisioned for use with the current CECs. The 1985 Guidelines established a complex process to evaluate risk by using information from many areas of aquatic toxicology. The SAB finds that the derivation of aquatic life criteria needs to be more broadly risk-based, using a transparent and consistent framework that provides necessary flexibility not presently possible within the algorithm approach of the 1985 Guidelines. Hence, the SAB recommends that, to the extent practicable, the derivation of aquatic life criteria be risk-based using the principles defined in EPA's 1998 *Guidelines for Ecological Risk Assessment* and the more recent *Advice to EPA on Advancing the Science and Application of Ecological Risk Assessment: A Report of the U.S. EPA Science Advisory Board* (U.S. EPA Science Advisory Board, 2007).

Within the context of risk-based aquatic life criteria, the SAB recommends that EPA consider issues in addition to those identified in the White Paper, and that the Agency customize and update the 1985 Guidelines to address these issues. In particular, we urge EPA to include consideration of probable direct and/or indirect impacts on food webs, ecological processes and services, and endangered or unique species of special value or concern. These issues could be incorporated through development of a conceptual model as exemplified in Figure 1 of the enclosed report. We also recommend that EPA develop multiple lines of evidence, consider uncertainty, and bolster consideration of mode of action in the criteria development process. We suggest that mammalian pharmacology data available from the drug discovery process, genomics/proteomics/metabolomics, and quantitative structure activity relationships (QSARs) be used to screen CECs for modes of action and assess potential multiple modes of action for individual CECs. To increase efficiency, parallel processes could then be considered when developing aquatic life criteria for compounds with similar modes of action.

The SAB generally supports EPA's proposed approaches for interpreting and/or adapting principles in the Guidelines to address technical issues discussed in the White Paper. However, we have noted specific concerns about these approaches and provide recommendations to improve the White Paper. We emphasize that many CECs will require special consideration because they do not fit the effect model discussed in the White Paper (i.e., disruption of endocrine function), or may be not be well enough understood to allow appropriate judgment of their mode of action. In addition, we note that specific issues such as the potential for joint interactions affecting toxicity exist for many CECs that may occur in mixtures in the environment and which may also interact with environmental variables such as temperature. Such possible interactions should be considered. As more information is developed to account for the interactive effects of CECs, it is possible that water quality criteria may be revised up or down for individual CECs based upon data on joint interactions; use of such data would produce more risk-based criteria.

The SAB finds that the ethynylestradiol illustrative example in the White Paper is a well-written and thorough review of the existing literature. It illustrates the complexities inherent in generating aquatic life criteria for CECs. However, we do provide recommendations to clarify the example and make it more useful.

The SAB also provides other suggestions to assist EPA in implementing the proposed recommendations in the White Paper. These suggestions focus on: data collection and research activities; developing tissue residue-based criteria; developing exposure and effect indicators that could be used in future derivation of criteria; special considerations for sensitive or commercially/recreationally important species; and obtaining input from private industry and state governments.

Thank you for the opportunity to provide advice on this important topic. The SAB looks forward to receiving the Agency's response to this advisory and to updates on any additional follow-up activities.

Sincerely,

/Signed/ ***/Signed/***

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Science Advisory Board

Dr. Judith L. Meyer, Chair
Ecological Processes and Effects Committee

U.S. Environmental Protection Agency
Science Advisory Board
Ecological Processes and Effects Committee

Augmented for the Advisory on the EPA's Aquatic Life Water Quality Criteria

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List of Acronyms

ACR - Acute to Chronic Ratio
AhR - Aryl Hydrocarbon Receptor
ALC - Aquatic Life Criteria
AV - Acute Value
CCC - Criterion Continuous Concentration
CEC - Contaminant of Emerging Concern
CMC - Criterion Maximum Concentration
CV - Chronic Value
CYP3A - Cytochrome P450 3A
EC_{10} - Concentration causing an effect in 10 percent of the test organisms
EC_{20} - Concentration causing an effect in 20 percent of the test organisms
EC_x - Concentration causing an effect in x percent of the test organisms
EDC - Endocrine Disrupting Compound
EE2 - Ethynylestradiol
ELS - Early Life Stage Test
EPA - U.S. Environmental Protection Agency
ER - Estrogen Receptor
F_0 - The initial parent generation in a multigeneration reproduction study
F_1 - The first offspring generation in a multigeneration reproduction study
FDA - U.S. Food and Drug Administration
FFLC - Fish Full Life Cycle
FIFRA - Federal Insecticide Fungicide and Rodenticide Act
LC50 - Test concentration causing in mortality to 50% of the test population
LOEC - Lowest Observed Effect Concentration
LOEL - Lowest Observed Effect Level
NOAA - National Oceanic and Atmospheric Administration
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organization for Economic Cooperation and Development
ORD - U.S. Environmental Protection Agency Office of Research and Development
OSWER - U.S Environmental Protection Agency Office of Solid Waste and Emergency Response
OW - U.S. Environmental Protection Agency Office of Water
PBPK - Physiologically Based Pharmacokinetic Model
PDBE - Polybrominated diphenyl ether
PFOS - Perfluorinated octynyl sulfonate
PLC - Partial Life Cycle
QSAR - Quantitative Structure Activity Relationship
ROPC - Receptor of Potential Concern
SAB - U.S. Environmental Protection Agency Science Advisory Board
SETAC - Society of Environmental Toxicology and Chemistry
SSD - Species Sensitivity Distribution
SSRI - Selective Serotonin Reuptake Inhibitor
TSCA - Toxic Substances Control Act
USDA - U.S. Department of Agriculture

1. EXECUTIVE SUMMARY

EPA's Office of Water (OW) requested that the Science Advisory Board (SAB) provide advice on the Agency's proposed recommendations pertaining to derivation of water quality criteria for the protection of aquatic life (aquatic life criteria) for contaminants of emerging concern (CECs). The Agency's proposed recommendations are provided in a white paper titled *Aquatic Life Criteria for Contaminants of Emerging Concern* (White Paper). The White Paper, prepared by the EPA Office of Water/Office of Research and Development Emerging Contaminants Workgroup, was reviewed by the SAB Ecological Processes and Effects Committee (Committee). To augment the expertise on the Committee for this advisory activity, several environmental toxicologists with specific knowledge of the effects of endocrine disrupting chemicals also participated in the review.

EPA's Office of Water develops ambient water quality criteria that provide guidance to states and tribes for adoption of water quality standards. The EPA document, *Guidelines for Deriving Numerical National Water Quality Criteria for the Protection of Aquatic Organisms and Their Uses* (hereafter referred to as the "Guidelines") (Stephan et al., 1985), sets forth a methodology for deriving ambient water quality criteria for the protection of aquatic life. The Guidelines specify various data and procedural recommendations for evaluating risk and deriving criteria and also define general risk management goals for the criteria. Most of EPA's aquatic life criteria have been derived using methods in the Guidelines, and EPA has stated that the Agency intends to continue using the Guidelines to derive aquatic life criteria. However, EPA has also indicated that it faces a number of technical challenges in deriving aquatic life criteria for CECs. In its White Paper, the Agency described these technical challenges and proposed recommendations to interpret and/or adapt Guidelines principles to address the challenges. One of the Committee's key recommendations is that EPA incorporate risk assessment principles, as defined by the 1998 *Guidelines for Ecological Risk Assessment* (U.S. EPA, 1998), within the framework of the 1985 aquatic life criteria Guidelines. Criteria derived within the risk assessment framework will provide additional consistency with other ongoing work at EPA and will provide necessary flexibility not presently possible within the algorithm approach of the 1985 Guidelines. In this regard, it is suggested that EPA also consider recommendations and findings in the recent SAB report, *Advice to EPA on Advancing the Science and Application of Ecological Risk Assessment: A Report of the U.S. EPA Science Advisory Board* (U.S. EPA Science Advisory Board, 2007).

The term "contaminant of emerging concern" or CEC has been used by EPA to identify a variety of chemical compounds that have no regulatory standard, have been recently discovered in the natural environment because of improved analytical chemistry detection levels, and potentially cause deleterious effects to aquatic life at environmentally relevant concentrations. The Agency is particularly concerned about pharmacologically active chemical compounds and personal care products because: 1) they are commonly discharged at wastewater treatment plants, and 2) some of these compounds are designed to stimulate a physiological response in humans, plants, and animals.

The first part of EPA's White Paper (Part I), *General Challenges and Recommendations*, describes: 1) the technical challenges EPA faces in deriving aquatic life criteria for CECs; and 2) the proposed recommendations to address those challenges. The second part of the White Paper

(Part II), *Illustration of Recommendations Using Data for 17α – Ethynylestradiol (EE2)*, explores EPA's recommendations in the context of an example CEC, ethynylestradiol (EE2), which is a synthetic pharmaceutical estrogen. In its charge to the SAB, EPA requested comments on the technical merit, practicality, and implementability of recommendations in the White Paper to address: a) relevance of acute toxicity effect concentrations in setting aquatic life criteria for CECs; b) defining minimum data requirements regarding taxonomic coverage in toxicity testing; c) use of non-resident species in criteria development; d) defining appropriate chronic toxicity data; e) selection of effect endpoints upon which to base criteria; and f) involvement of an expert panel in the criteria development process. In addition, EPA asked the SAB to: comment on whether the Agency has identified the appropriate issues to be addressed in deriving aquatic life criteria for CECs; offer suggestions that may improve the utility of Part II of the White Paper; and offer suggestions that would assist the Agency in implementing proposed recommendations in the White Paper. In response to the charge questions, the Committee has provided comments and recommendations to improve the White Paper and assist EPA in deriving aquatic life criteria for contaminants of emerging concern.

Relevance of acute toxicity effect concentrations in deriving aquatic life criteria for CECs

Many CECs are physiologically active at concentrations orders of magnitude lower than those causing acute lethality, and concentrations sufficient to cause lethality may never occur in the environment. Therefore, in the White Paper the Agency recommends that, when sufficient information demonstrates a negligible risk of acute lethality for a CEC, the "criterion continuous concentration" (i.e., the concentration intended to protect against the longer term effects of exposure on survival, growth, and reproduction) be used to derive aquatic life criteria. In principle, the Committee supports EPA's suggestion to derive aquatic life criteria solely from criteria continuous concentrations (CCCs) for CECs when available information indicates that this is appropriate. However, we have recommended the following amendments in the White Paper:

- Not enough is known about some classes of CECs (e.g., nanoparticles) to determine whether acute toxicity needs to be taken into account in deriving aquatic life criteria. Therefore, all available data on any new class of CECs should be used in determining whether acute toxicity is likely to occur in environmentally relevant settings.

- Some CECs appear to have differing modes of action for acute toxicity vs. chronic toxicity. Lowest Observed Effect Concentrations (LOECs) and LC50s (test concentrations that result in mortality to 50% of the test population) are within one order of magnitude for some CECs, making acute toxicity relevant in deriving aquatic life criteria. Therefore, "criteria maximum concentrations" (CMCs) to protect against acute effects should be derived for compounds where LOECs are found to be within 1-2 orders of magnitude of LC50s.

- Pulsed discharges of CECs may occur during natural disasters and spills and result in atypically high concentrations in the environment. Therefore, criteria documents for CECs should always identify the CMC as a data gap when it is not used to derive criteria. Furthermore, as discussed in Section 4.1.1 of this report, aquatic life criteria derivations should consider whether concentrations capable of causing acute toxicity may occur during

these pulsed discharges. Under this scenario, it may be important to use CMCs in addition to CCCs in the aquatic life criteria derivation process.

- Mixtures of CECs with comparable modes of action may result in higher effective concentrations than would be expected based on the concentrations of any single compound. Therefore, research is needed to determine how aquatic life criteria for CECs can take into account the fact that aquatic organisms are exposed to mixtures of chemicals with similar modes of action.

- To maintain transparency in cases when CMCs are not used in criteria development, a summary of all available data that provide information on the relevance of acute toxicity should be included in any aquatic life criteria document.

Defining minimum data requirements regarding taxonomic coverage in toxicity testing

In the White Paper, EPA has recommended that, for CECs without complete chronic toxicity data sets to fulfill minimum data requirements, there be an evaluation of whether sufficient information exists to conclude that certain taxa would not be sensitive to a particular chemical. Thus, EPA recommends that the minimum data requirements for taxonomic coverage (specified in the Guidelines) be viewed as information requirements instead of toxicity test requirements. The Committee understands and appreciates the desirability of avoiding the extra work required to develop chronic data on species that are unlikely to be sensitive to certain CECs. However, we emphasize that it is equally important to perform adequate testing to ensure protection of aquatic life. We generally support the broad taxonomic coverage requirements in the Guidelines but agree that these could be viewed as information requirements instead of test requirements. We find that, if sufficient information exists on the insensitivity of certain taxa to particular chemicals, expert judgment concerning data development should prevail. This would result in a more focused approach to data development, keeping in mind weight of evidence rather than a requirement for testing all taxa specified in the Guidelines. As indicated below, we have provided specific recommendations to improve the process of determining appropriate taxonomic coverage to develop aquatic life criteria for CECs:

- EPA needs to define what constitutes a sufficiently robust set of chronic data for criteria development. Although the example used in the White Paper generally illustrates EPA's proposed process for making decisions concerning taxonomic coverage, it would be helpful if EPA were more explicit in identifying what constitutes a "sufficiently robust set of chronic data" and "a reasonable understanding of the mode of action for the chemical that may allow inferences."

- The White Paper should place greater emphasis on information useful for development of aquatic life criteria, rather than just toxicity test requirements. Incorporating effects on ecological processes (e.g., food webs, nutrient cycling, primary production) rather than only target species would be valuable in criteria development, and would follow more recent scientific thinking.

- As further discussed in Section 4.1.2 of this advisory report, EPA should consider shifting from an approach requiring a minimum level of taxonomic coverage to the approach of determining receptors of potential concern (ROPCs).

- Examples showing the unanticipated effects of CECs on non-target organisms (e.g., the impact of antibiotics on plants and effect of atrazine on the quality of algae available as food for other species) should be used in Part I of the White Paper to help describe how the aquatic life criteria development process needs to be more flexible depending on the compounds under evaluation.

Use of non-resident species in criteria development

Historically, EPA has not included data from toxicity testing with non-resident species in the actual criteria derivation process. In the White Paper, EPA recommends that "non-resident" species data be used in the aquatic life criteria derivation process if such data would enable a better estimation of species sensitivity distributions. The Committee agrees; we find that the exclusion of non-resident species data from criteria derivation is biologically and practically inconsistent with the intent of the Guidelines (i.e., providing an objective, internally consistent, appropriate, and feasible way of deriving national criteria). We have provided a number of specific recommendations concerning the use of non-resident species data:

- Because of the frequent use of non-resident species in toxicity testing, such species could potentially be over-represented in aquatic life criteria databases. Therefore, the proportion of the data set that should include resident species should be carefully evaluated by an expert advisory panel assembled to review each criterion.

- Although non-resident species can be used for criteria development, in no case should a criterion be developed on the basis of non-resident species data alone. Although the Guidelines have been designed to protect aquatic communities (including endangered species), EPA should support research that addresses the suitability of the use of surrogate species in assessing the responses of various resident aquatic species (e.g., endangered or long-lived species and species with varying life history strategies) to endocrine disrupting and other CECs.

- Differences in strains, husbandry, health, and parasite and pathogen load (i.e., other stressors) contribute to variations in toxicity test response and thus should be considered in the criteria development process.

- Issues to be considered in prioritizing species responses should include their vulnerability, endangerment status, and recreational, commercial and ecological value.

- Non-resident and resident species data must meet test guidelines for data and method validity.

Defining appropriate chronic toxicity data

In the White Paper, EPA recommends that the Guidelines requirements for chronic toxicity test data be tightened by requiring at least one full life-cycle test for a fish (life-cycle tests are already required for invertebrates) unless there is a compelling body of information indicating that life processes outside the early life stage or partial life-cycle exposure/observation window are not critical to capturing the biologically important effects of chronic exposure to the chemical. As further discussed in Section 4.1.4 of this report, the Committee strongly supports the use of fish full life-cycle test data in appropriate cases to develop aquatic life criteria. We find that it would be useful to develop a tiered testing approach to determine an appropriate rationale for use of data from fish full life-cycle, partial life-cycle, and possibly multigenerational testing to derive aquatic life criteria for CECs with parallel modes of action. We have provided additional recommendations concerning the requirement for chronic toxicity data.

- EPA should critically review data dealing with transgenerational responses of aquatic species and evaluate whether this additional testing would provide significant new information to inform the criteria development process.

- Test guidelines should include flexibility to include assessment of key developmental events, and professional judgment from an expert panel should be used to evaluate the relevance of non-traditional endpoints such as immune function and organism behavior. Behavioral endpoints (e.g., predator-prey interactions) may hold some promise for criteria development if the assays can be related to population-level responses and variability can be understood.

Selection of effect endpoints upon which to base criteria

In the White Paper, EPA has identified a number of endpoints that could be considered (in addition to the "traditional" endpoints of survival, growth, and reproduction) in developing aquatic life criteria for CECs. Moreover, the Agency has recommended more thorough exploration of the use of such endpoints in criteria development. Generally, the Committee agrees that EPA should continue to explore the possibility of using sublethal endpoints in helping to set aquatic life criteria. However, we caution EPA that such "non-traditional" endpoints must ultimately be linked to population endpoints (i.e., potential impacts to populations must be considered, not solely effects on individual organisms). We have provided a number of recommendations concerning use of these endpoints:

- EPA should use "non-traditional measures" to develop an understanding of and confirm mode of action of CECs.

- As further discussed in Section 4.1.5 of this advisory report, EPA should use human health information and toxicology tools (genomics/physiologically-based pharmacokinetic models [PBPKs]) to reduce the uncertainty of aquatic life criteria for CECs.

- EPA should consider the following key points concerning use of the non-traditional endpoints discussed in the White Paper: 1) vitellogenin in males and juveniles is an indicator

Involvement of an Expert Panel

Because the development of aquatic life criteria for CECs may be dependent on technical interpretations of a wide range of toxicological information, EPA has proposed that expert panels be used to provide professional judgment during criteria development. The Committee strongly supports the use of panels comprised of experts with a balanced range of perspectives to provide professional judgment during the process of developing aquatic life criteria. However, we note that the use of expert panels could lead to less consistency in how aquatic life criteria are determined if the panels are not selected carefully. To help alleviate this potential problem, we recommend that EPA develop specific guidance on the role of expert panels in problem formulation, data evaluation, and generation of advice to support criteria development. Specifically, we recommend that:

- The process for the use and selection of expert panels be described in detail and that it be transparent.

- The panels be given clear charges and understanding of their roles in the process.

- EPA take advantage of similar expert panel processes occurring in Europe and Asia to the extent possible.

Technical issues addressed in the White Paper

The Committee was asked to comment on whether EPA has identified the appropriate technical issues in the White Paper, and whether there are additional important issues that the Agency has not identified. We find that EPA has identified appropriate technical issues in the White Paper. However, as further discussed in Section 4.1.6 of this advisory report, we recommend that the Agency address additional issues to customize and update the 1985 Guidelines and thereby increase the flexibility and specificity of the aquatic life criteria derivation process. The following additional issues are of particular importance:

- In the White Paper, EPA should articulate principles that can be applied when modifying the 1985 Guidelines to develop water quality criteria for CECs. In particular, as further discussed in Section 4.2 of this advisory report, these principles should address: 1) obtaining a wide range of inputs from diverse perspectives; 2) developing a conceptual model as exemplified in Figure 1 of this report; 3) developing criteria for using multiple lines of evidence; and 4) identifying/including uncertainties (quantitative and qualitative) associated with criteria development.

- It is particularly important that understanding and presenting uncertainty become an intrinsic part of the aquatic life criteria development process. For example, the uncertainties inherent in understanding modes of action, concentration-response relationships, extrapolation of sensitivities, and derivation of ecological effects should be quantified and/or described in a narrative sense.

- EPA should bolster the consideration of mode of action in the aquatic life criteria derivation process. It is important that aquatic life criteria for CECs take into account the fact that aquatic organisms are exposed to mixtures of these chemicals. As more information becomes available to account for the interactive effects of CECs, it is possible that water quality criteria may be revised up or down for individual CECs based upon data on joint interactions. Use of such data would produce more risk-based criteria. Understanding the mode of action of a compound is very important in estimating mixture interactions. In fact, pharmacological mode of action is the basis for evaluating multiple drug prescriptions in humans by pharmacists. EPA should use mammalian pharmacology data available from the drug discovery process, genomics/proteomics/metabolomics and quantitative structure activity relationships (QSARs) to screen CECs for modes of action, identify CECs that may act in an additive manner as mixtures, and assess potential multiple modes of action for individual CECs. The Committee strongly recommends enhancing the communication and data transfer capabilities between agencies such as the U.S. Food and Drug Administration (FDA) and EPA to provide mode of action information.

- In deriving aquatic life criteria for CECs, EPA should bolster consideration of ecology and indirect ecological effects and also give special consideration to the protection of threatened and endangered species.

Part II of the White Paper

Part II of the White Paper uses ethynylestradiol (EE2) as a model chemical to illustrate the technical issues presented and provide a basis for understanding the recommendations in Part I. The Committee was asked to offer suggestions to improve the utility of Part II. The Committee finds that Part II is a well-written and thorough review of the existing literature on EE2. We agree that EE2 is an appropriate initial focal CEC given the extensive data available relative to other CECs and the ease with which it illustrates the complexities inherent in generating CEC-specific water quality criteria. We have provided a number of specific recommendations to improve Part II:

- EPA should explicitly recognize that EE2 is unique in being a data-rich CEC. The White Paper should highlight the fact that the Agency's interest in CECs goes beyond endocrine-active substances, and discuss how the process outlined for EE2 might be applied to other substances, particularly those for which less data are available and which have different modes of action.

- The Committee suggests that some of the illustrative pieces of Part II could also be presented in Part I in the form of succinct text boxes illustrating key concepts derived from the various

recommendations, and that the recommendations could be best illustrated if the text boxes were not restricted to EE2 but rather included other CECs.

- Part II should discuss how the individual effects of EE2 on biota might be changed by mixtures of compounds, especially those with similar modes of action.

- As stated previously, a criterion should not be developed on the basis of non-resident species data alone. Therefore, Part II should indicate that resident species data, especially data from life-cycle tests using resident species, remain extremely valuable and that results from non-resident species tests may not be generalized to resident species without comparative sensitivity studies.

- The possibility of transgenerational effects should be explicitly addressed in Part II.

- A broader array of endpoints should be included in Part II. For example, although EE2 is a potent estrogen receptor agonist, it can also affect the central nervous system (through steroid biotransformation), and an endpoint should be considered to reflect this. Part II should also note that relevant and reproducible endpoints indicative of adverse population level effects need to be used.

- As further discussed in Section 4.3 of this advisory report, the use of weight of evidence is implicit in the evaluation done in Part II, and should be explicitly discussed. Furthermore, when appropriate data are available, EC_x values (i.e., concentration causing an effect in x percent of the test organisms) should be used in Part II instead of NOECs/LOECs (i.e., no observed effects concentrations/lowest observed effects concentrations). The use of the EC_x values takes advantage of more of the information from a toxicity test, and confidence intervals can be generated. The raw data from most toxicity tests can be used to calculate an EC_x value. The selection of a specific EC_x value for derivation of an aquatic life criterion depends upon the level of protection or effect that decision makers are willing to accept or detect in the field. However, an EC_{20} has been used for most species and an EC_{10} has been used for threatened and endangered species. The Committee notes that if data are not available to calculate an EC value, EPA should recommend in Part II that such values be developed and used in future criteria derivation. Published data sets are available for much of the fathead minnow and other species toxicity tests conducted at EPA's Duluth Laboratory and other laboratories. If the data are available then the regression should be calculated. The Committee also notes that if the data are not available then the value of the NOEL/LOEL (no observed effect level/lowest observed effect level) should be carefully evaluated. Without information on the variability of the test results, and consequently the statistical power, it is not clear what the values represent.

- As further discussed in Section 4.3 of this report, the clarity and transparency of Part II could be improved in a number of areas.

Suggestions to assist EPA in implementing recommendations discussed in the White Paper

In Section 4.4 of this advisory report, the Committee has provided comments and recommendations to assist EPA in implementing the approaches discussed in the White Paper. The following key recommendations are provided:

- As noted at the beginning of this Executive Summary, the principles for conducting Ecological Risk Assessment should be incorporated into the process of deriving aquatic life criteria for CECs. The Committee recommends that, pending revision of the 1985 Guidelines, EPA develop a separate process document that discusses the intended application of aquatic life criteria for CECs. This process document should establish linkages between the Guidelines, EPA's Ecological Risk Assessment Principles (U.S. EPA, 1992, 1998), the recent SAB report, *Advice to EPA on Advancing the Science and Application of Ecological Risk Assessment: A Report of the U.S. EPA Science Advisory Board* (U.S. EPA Science Advisory Board, 2007), and the White Paper.

- EPA should prioritize the list of CECs for which aquatic life criteria will be developed. Data needs for these chemicals should be identified, and EPA should fund the research and data collection activities necessary to support aquatic life criteria development for CECs. In this regard, the Committee recommends that EPA's Office of Water and Office of Research and Development look for opportunities to leverage EPA research with ongoing research in other federal agencies, international agencies, and industry groups.

- EPA should incorporate use of conceptual models and ecosystem-based criteria into the process of deriving aquatic life criteria for CECs. The Committee notes that EPA programs are moving toward developing more comprehensive ecosystem-relevant criteria that take into consideration population-community structure, ecosystem functions and processes, and ecosystem services. Accordingly, the Committee notes that it is important to develop the link between the protected resource, the assessment endpoint, and the measurement endpoint, and a conceptual model would clarify those linkages.

- For bioaccumulative CECs where food chain transfer is a concern, EPA should consider developing tissue-based criteria (i.e., expressing the criterion as a concentration of the pollutant in fish tissue rather than a concentration in the water).

- EPA should also consider expanding the definition of CECs to include chemicals and other substances of increasing environmental concern due to anthropogenic activities and inadequate regulatory approaches. The White Paper focuses on endocrine disrupting chemicals. However, the Committee notes that some CECs do not fit the effect model of endocrine disrupting chemicals, or are not well enough understood at this time to allow a judgment of their mode of action. Nanoparticles are an example of such a class of compounds. Additional work is needed to further develop recommendations for deriving aquatic life water quality criteria for these other kinds of chemicals.

- In Section 4.4 of this advisory report the Committee recommends additional research to address important issues such as: the effects of mixtures of CECs, interactions between CEC

and other stressors, modes of action of CECs, comparative sensitivities of resident and non-resident species, and use of field study results to inform the derivation of aquatic life criteria. The Committee also recommends that the discussion of taxonomic coverage in the White Paper be expanded to include specific recommendations concerning derivation of criteria to protect marine organisms. EPA's 1985 Guidelines call for assessment of marine organisms in the same manner as freshwater organisms. However, due to specific issues unique to marine organisms, such as physiological requirements (e.g., maintenance of salt balance) and life-history strategies (e.g., reproduction tied to tidal cycles), more specific guidance for CECs is likely needed. We suggest that such guidance may be best addressed by convening a "Pellston" type workshop (Society of Environmental Toxicology and Chemistry, 2008) that is comprised of experts from multiple disciplines and types of organizations.

2. INTRODUCTION

EPA's Office of Water (OW) requested that the Science Advisory Board (SAB) provide advice on the Agency's proposed recommendations pertaining to derivation of water quality criteria for the protection of aquatic life (aquatic life criteria) for contaminants of emerging concern (CECs) such as pharmaceuticals and personal care products that are commonly discharged in municipal wastewaters. EPA's proposed recommendations are provided in a white paper titled *Aquatic Life Criteria for Contaminants of Emerging Concern* (White Paper). The White Paper, prepared by the EPA Office of Water and Office of Research and Development Emerging Contaminants Workgroup, was reviewed by the SAB Ecological Processes and Effects Committee (Committee). To augment the expertise on the Committee for this advisory activity, several environmental toxicologists with specific knowledge of the effects of endocrine disrupting chemicals also participated in the review. The Committee held a public teleconference on June 23, 2008 to discuss its charge and receive a briefing from EPA, met on June 30th – July 1, 2008, and held a follow-up discussion in a public teleconference on September 16, 2008.

EPA's Office of Water is charged with protecting aquatic life, wildlife, and human health from the adverse water-mediated effects of anthropogenic pollutants. In support of this mission, OW develops ambient water quality criteria that serve as guidance to states and tribes for adoption of water quality standards. The EPA guidance document, *Guidelines for Deriving Numerical National Water Quality Criteria for the Protection of Aquatic Organisms and Their Uses* (Guidelines) (Stephan et al., 1985), sets forth a methodology for deriving ambient water quality criteria for the protection of aquatic life. The Guidelines specify various data and procedural recommendations for criteria derivation and also define general risk management goals for the criteria. Most of EPA's aquatic life criteria have been derived using methods in the Guidelines. EPA has informed the Committee that the Agency intends to continue using the Guidelines to derive aquatic life criteria. However, EPA has also stated that it faces a number of technical challenges in deriving aquatic life criteria for CECs. The white paper describes these technical challenges and proposes recommendations to interpret and/or adapt Guidelines principles to address the challenges.

The term CEC has been used by EPA to identify a variety of chemical compounds that have no regulatory standard, have been recently discovered in the natural environment because of improved analytical chemistry detection levels, and potentially cause deleterious effects to aquatic life at environmentally relevant concentrations. The Agency has indicated that it is particularly concerned about pharmacologically active chemical compounds and personal care products that are commonly discharged at wastewater treatment plants and may stimulate physiological responses in humans, plants, and animals. Many of these compounds are known to disrupt endocrine function in animals, and are thus referred to as endocrine disrupting chemicals. These chemicals may demonstrate low acute toxicity but cause significant reproductive effects at very low levels of exposure. In addition, the effects of exposure of aquatic organisms to CECs during the early stages of life may not be observed until adulthood. These chemicals may also have very specific modes of action that affect only certain types of aquatic animals (e.g., vertebrates such as fish). Therefore, EPA has suggested that traditional chronic toxicity test

endpoints specified in the Guidelines may not be sufficiently comprehensive, and Guidelines requirements for taxonomic coverage in toxicity testing may not be appropriate to derive aquatic life criteria for these chemicals. The White Paper focuses on recommendations to derive aquatic life criteria for endocrine disrupting chemicals.

The first part of EPA's White Paper (Part I), *General Challenges and Recommendations*, describes: 1) the technical challenges facing EPA in deriving aquatic life criteria for CECs; and 2) the recommendations to address those challenges. The second part of the White Paper (Part II), *Illustration of Recommendations Using Data for 17α – Ethynylestradiol (EE2)*, explores EPA's recommendations in the context of an example CEC, ethynylestradiol (EE2), which is a synthetic pharmaceutical estrogen. In its charge to the SAB, OW requested comments on the technical merit, practicality, and implementability of recommendations in the White Paper to address: a) relevance of acute toxicity effect concentrations in setting aquatic life criteria for CECs; b) defining minimum data requirements regarding taxonomic coverage in toxicity tests; c) use of non-resident species in criteria development; d) defining appropriate chronic toxicity data; e) selection of effect endpoints upon which to base criteria; and f) involvement of an expert panel in the criteria development process. In addition, OW asked the SAB for: comments on whether the Agency has identified the appropriate issues to be addressed in deriving aquatic life criteria for CECs; suggestions to improve the utility of Part II of the White Paper; and suggestions to assist the Agency in implementing proposed recommendations in the White Paper.

The Committee generally supports EPA's proposed approaches for interpreting and/or adapting Guidelines principles to address the technical challenges discussed in the White Paper. However in this advisory report we have recommended improvements to the approaches proposed in the White Paper. In addition, we have noted a number of specific technical and practical issues and caveats that should be considered by EPA when implementing the proposed approaches.

The Committee finds that, in the White Paper, EPA has identified appropriate technical issues and challenges to developing aquatic life criteria for CECs. However, we recommend that the Agency address additional issues to customize and update the Guidelines and thereby increase the flexibility and specificity of the aquatic life criteria derivation process. We find that EPA could clarify the process of developing aquatic life criteria for CECs by articulating a clear set of principles that could be applied when modifying the Guidelines. We also emphasize the importance of developing a conceptual model, as exemplified in Figure 1 of this advisory report, to guide the process of developing aquatic life criteria for CECs. The Committee finds that Part II of the White Paper is a well-written and thorough review of the existing literature on EE2 that illustrates the complexities inherent in generating aquatic life criteria for CECs. However, we have provided recommendations to improve the usefulness of this case example. In particular we suggest that EPA more explicitly describe how the illustration in Part II was developed from the recommendations in Part I of the White Paper.

The Committee has also provided other suggestions to assist EPA in implementing the proposed recommendations in the White Paper. These suggestions focus on: improved data collection and research activities; development of tissue residue-based criteria (i.e., expressing the criterion as a concentration of the pollutant in fish tissue rather than a concentration in the water) for bioaccumulative CECs where food chain transfer is a concern; use of indicators for

future development of criteria; special considerations for endangered or commercially/recreationally important species; obtaining input from private industry and state governments; and consideration of a mixture strategy for CECs.

3. CHARGE TO THE COMMITTEE

EPA's Offices of Water (OW) and Research and Development (ORD) sought advice from the Science Advisory Board on the scientific and technical merit of a draft white paper on aquatic life water quality criteria (ALC) for contaminants of emerging concern (CEC). The white paper developed by the EPA Emerging Contaminants Workgroup describes how the Agency intends to address the challenges it faces in developing ALC for CECs. The specific charge questions below were provided to the Committee:

1. The following recommendations have been developed to address important technical challenges and issues in deriving water quality criteria for CECs. Please comment on the technical merit, practicality, and implementability of the recommendations addressing the following issues as described in Part I of the white paper and the ethynylestradiol (EE2) case study in Part II.

   a. Relevance of Acute Toxicity Effect Concentrations in Setting ALC for CECs:

   Criteria consist of a Criterion Maximum Concentration (CMC), intended to address acute lethality and a Criterion Continuous Concentration (CCC), intended to address effects of chronic exposures on survival, growth, and reproduction. Many CECs are physiologically active at concentrations orders of magnitude lower than those causing acute lethality, and the high concentrations sufficient to cause lethality may never occur in the environment. Rather than rotely requiring a robust acute toxicity data set for such chemicals, the workgroup recommends that aquatic life criteria consist of only a CCC and that no CMC be derived, when sufficient information demonstrates risks of acute lethality are negligible.

   b. Defining Minimum Data Requirements Regarding Taxonomic Coverage:

   If an acute criterion is not calculated, then the CCC cannot be calculated using the acute to chronic ratio (ACR) approach and must be instead calculated directly from chronic toxicity data. Procedures for this are included in the Guidelines (pages 40-42), but they require that acceptable chronic toxicity tests be conducted for a broad range of taxonomic groups. In the case of many CECs, toxicological research tends to focus on organisms for which the mode of action is most relevant (e.g., vertebrates for estrogen mimics) and may have limited data coverage for other taxonomic groups that will likely be less sensitive. To avoid generation of resource-intensive chronic toxicity data for insensitive species that will have little impact on the final criterion, the workgroup recommends interpreting the minimum data requirements for taxonomic coverage as <u>information</u> requirements instead of <u>toxicity test</u> requirements. By this we mean that, rather than requiring a specific chronic toxicity test, the data requirement for certain taxonomic group expected to be insensitive might be met by a body of information demonstrating insensitivity of the taxon to the CEC.

c. Use of Non-Resident Species in Criteria Development:

Historically, EPA has not used data derived from toxicity testing with non-resident species in the actual criteria derivation process. Excluding species simply because they are not resident may be unnecessarily restrictive for the purposes of deriving national criteria, and may actually increase rather than decrease uncertainty. The workgroup recommends that non-resident species be considered for use in criteria derivation calculations, focusing on those species with widely used and standardized test methods and for which there is reason to believe that they would represent the sensitivity of comparable resident species. Furthermore, the workgroup specifically suggest accepting data for zebrafish (*Danio rerio*) and Japanese medaka (*Oryzias latipes*), to reflect international efforts toward data equivalency.

d. Defining Appropriate Chronic Toxicity Data:

For fish, the Guidelines allow the use of early life stage (ELS; egg to juvenile) exposures in lieu of full life-cycle (F_0 egg to F_1 offspring) or partial life-cycle (F_0 adult to F_1 juvenile) exposures for determining chronic toxicity of chemicals, unless there is reason to believe this is inappropriate. Current understanding of many CECs, particularly endocrine disrupting compounds (EDCs), is that important effects of these chemicals may not occur, or at least not be expressed, until after the ELS exposure window; in fact, partial life-cycle exposures may also miss important effects, such as those on sexual development. For such chemicals, it is clear that the definition of an acceptable chronic test must include consideration of key windows of exposure and effect (e.g., to include sexual development and reproduction in assessments of steroid hormone agonists/antagonists). However, even more broadly, the workgroup recommends that the Office of Water consider amending the chronic data acceptability requirements in the Guidelines to require at least one full life-cycle test for a fish (for invertebrates, life-cycle tests are already required) unless there is a compelling body of information indicating that life processes outside the early life stage or partial life-cycle exposure/observation window are not critical to capturing the biologically important effects of chronic exposure to the chemical. This amended requirement would include all chemicals, not just EDCs/CECs.

e. Selection of Effect Endpoints upon Which to Base Criteria

Aquatic life criteria typically are based on direct measures of survival, growth, and reproduction; other measures of response are generally not included unless they can be shown to be closely linked to expected changes in population dynamics. The workgroup supports this existing guidance, but recognizes that many CECs, particularly those with very specific modes of action like steroid hormone agonists/antagonists, will have data for a wide variety of histological, biochemical, physiological, or behavioral endpoints that may warrant consideration as measures of biologically important effects. The degree to which such measures can be used to infer population level effects is likely endpoint-, chemical-, and/or organism-specific, and developing a universal list of recommended endpoints is therefore beyond the scope of the workgroup's activities. Rather, the recommendation here is simply that criteria development more thoroughly explores such possibilities.

f. Involvement of an Expert Panel:

While not addressed explicitly in the Guidelines, the complexities involved in the assessment of many CECs, and the reliance on professional judgment in making some of the determinations required under the workgroup's recommendations, make clear the need to bring the best scientific knowledge to bear in the development of criteria for CECs, as well as other chemicals. The workgroup supports the recommendation from a Society of Environmental Toxicology and Chemistry (SETAC) Pellston workshop held in 2003 (Mount et al., 2003) indicating that criteria development should involve recruitment of an expert panel early in the process to insure that all relevant issues are considered during initial development of the criterion and to provide scientific perspective on decisions that are made as part of the process. Such a panel would not undermine the authority of the Agency to make policy decisions regarding criteria, but would ensure that such policy decisions are made from the best possible technical foundation. It is envisioned that expert panels would be formed around specific chemicals, or perhaps groups of chemicals with chemical or toxicological similarities (e.g., same mode of action).

2. Please comment on whether EPA has identified the appropriate issues to be addressed in deriving ALC for CECs. Are there additional important issues that EPA has not identified?

3. Part II of this white paper was specifically developed as a companion to Part I and focuses on the use of ethynylestradiol as a model chemical to illustrate the technical issues presented by the workgroup, as well as providing a basis for understanding the recommendations. Does the Committee have suggestions that may improve the utility of Part II of this white paper for the purposes stated above?

4. Does the Committee have suggestions that would assist EPA in implementing the proposed recommendations discussed in the white paper, particularly with respect to developing the necessary scientific data and information and/or providing expert scientific input at the appropriate stages of the risk assessment process?

4. RESPONSE TO CHARGE QUESTIONS

In the responses to each of the charge questions, the Committee has listed the key findings and comments as bullets. These comments are followed by numbered lists of the key recommendations.

4.1 Charge Question 1. Please comment on the technical merit, practicality, and implementability of recommendations addressing the following issues as described in Parts I and II of EPA's white paper on Aquatic Life Criteria for Contaminants of Emerging Concern: a) relevance of acute toxicity effect concentrations in setting aquatic life criteria for contaminants of emerging concern; b) defining minimum data requirements regarding taxonomic coverage; c) use of non-resident species in criteria development; d) defining appropriate chronic

toxicity data; e) selection of effect endpoints upon which to base criteria; and f) involvement of an expert panel.

4.1.1 Relevance of Acute Toxicity Effect Concentrations

As discussed in EPA's White Paper, aquatic life water quality criteria consist of a Criterion Maximum Concentration (CMC) intended to protect against severe acute effects of exposure to contaminants, and a Criterion Continuous Concentration (CCC) intended to protect against the longer term effects of exposure on survival, growth, and reproduction. EPA's Guidelines (Stephan et al., 1985) specify various data and procedural recommendations for criteria derivation. The CMC is determined based on available acute values (AVs). Acute values are median lethal concentrations or median effect concentrations from aquatic animal acute toxicity tests (48 to 96 hours long) meeting certain data quality requirements. The CCC is generally determined based on available chronic values (CVs), which are either: a) the geometric mean of the highest no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC) for effects on survival, growth, or reproduction in aquatic animal chronic tests; or b) in some recent criteria the EC_{20} (the test concentration that would cause a reduction in survival, growth, or reproduction in 20% of the test population) based on concentration-effect regression analyses of the toxicity test data. If chronic toxicity test data are not available for at least eight genera of aquatic organisms with a specified taxonomic diversity, the CCC is derived on the basis of an acute to chronic ratio (ACR) (i.e., the ratio of the AV to CV from parallel acute and chronic tests for at least three species with a specified taxonomic diversity). EPA's White Paper states that many CECs are physiologically active at concentrations orders of magnitude lower than those causing acute lethality, and that concentrations high enough to cause acute lethality may never occur in the environment. Therefore, in the White Paper the Agency recommends that, when sufficient information demonstrates a negligible risk of acute lethality for a CEC, the ALC for that contaminant could consist of only a CCC.

In principle, the Committee supports EPA's recommendation to derive aquatic life criteria directly from CCCs thus forgoing CMCs and ACRs. The Committee recognizes that, for many CECs, acute toxicity may only occur at concentrations several orders of magnitude greater than those likely to occur in the aquatic environment. The Committee also recognizes that the suggestion to forgo derivation of CMCs is not designed to truncate the aquatic life criteria development process, but rather is designed to allocate resources to areas most likely to affect the final aquatic life criteria and to avoid delaying implementation of aquatic life criteria due to a lack of data for species that are not likely to be sensitive. It is noted, however, that in cases of emergency releases of CECs (e.g., during floods or equipment failure), the potential for acute toxicity would need to be considered. Therefore, criteria documents for CECs should always identify the CMC as a data gap when it is not used to derive criteria.

Caveats concerning use of the Criterion Continuous Concentration for aquatic life water quality criteria

Although the Committee generally supports EPA's recommendation to derive aquatic life criteria for CECs directly from CCCs, we note that the following points should be considered by the Agency when implementing this recommendation:

- Some CECs do not fit the effect model of endocrine disrupting chemicals. Foremost on the Committee's list of concerns is that some CECs do not fit the effect model of endocrine disrupting chemicals (EDCs), or are not well enough understood at this time to allow a judgment of their mode of action. Nanoparticles are an example of such a class of compounds. Additional work is needed to further develop recommendations for deriving aquatic life water quality criteria for these other kinds of chemicals. EPA's White Paper focuses in particular on CECs that disrupt endocrine function in animals. Thus, many of the Committee's comments address deriving ALCs for CECs with modes of action similar to those of EDCs.

- For some CECs, acute toxicity may occur in environmental settings. The Committee notes that for some CECs, the LOECs and LC50s (test concentrations that result in mortality to 50% of the test population) are within one order of magnitude of each other, indicating that acute toxicity may occur in environmental settings. For these chemicals derivation of a CMC may be appropriate. Examples of such chemicals include fluoxetine (a selective serotonin reuptake inhibitor or SSRI) and gemfibrozil (a blood cholesterol regulator).

- Some compounds have differing modes of action for acute and chronic toxicity. The Committee is particularly concerned that some compounds may have differing modes of action for acute and chronic toxicity. In these cases, acute toxicity may be of concern in environmental settings and it may be appropriate to derive both a CMC and CCC.

- Pulsed discharge may result in high ambient concentrations of CECs. The Committee is concerned that the pulsed nature of some CEC releases (for example: pulsed industrial discharge; tidal action in the marine environment; and recurring natural events such as fluctuations in environmental concentrations of contaminants in ephemeral waterbodies due to evaporation and hurricanes that can cause flooding and release of untreated sewage) may result in short-term concentrations of CECs that could exceed what would generally be considered environmentally relevant concentrations. Although CCCs may be applicable in these situations, the Committee finds that acute toxicity should be considered to account for the effects of compounds where extreme pulses may occur more frequently than the three-year benchmark set by the Guidelines.

- Consideration of mixture effects is important. An additional concern of the Committee is the need for the consideration of mixture effects in determining whether acute toxicity could occur in natural settings. The White Paper explicitly references common modes of action for multiple compounds (as in the examples of EE2, estrone, and estradiol). The Committee feels strongly that mixture effects of compounds with similar modes of action should be taken into account in determining whether acute toxicity may occur in environmental situations. Thus a mixtures strategy is needed to guide development and interpretation of aquatic life criteria for CECs.

Committee recommendations concerning the relevance of acute toxicity effect concentrations

As a consequence of the Committee's discussion and concerns listed above, we provide the following recommendations to amend the White Paper text concerning derivation of aquatic life criteria on the basis of the Criterion Continuous Concentration:

1. Part 1 of EPA's White Paper contains a bulleted list (on page 28) identifying the kinds of information that should be reviewed in order to determine whether the differences between the CMCs and CCCs would be great enough to conclude that the CMC is not needed to develop ALC. The Committee finds that this list is very helpful. It addresses some of the concerns raised during the Committee's deliberation and it may be particularly useful in providing lines of evidence to determine whether acute toxicity data are needed. Therefore, we encourage expansion of this list in the final White Paper to include additional information addressing the points mentioned above.

2. The Committee suggests that all available data on any new class of CECs should be used in determining whether acute toxicity is likely to occur in environmentally relevant settings. These data should be summarized to document when additional data are needed, or when it is justifiable to move aquatic life criteria development forward without the derivation of CMCs.

3. The Committee recommends that CMCs be derived for compounds where LOECs are found to be within 1-2 orders of magnitude of LC50s.

4. The Committee recommends that the likelihood of pulses of exposure to contaminants be considered in determining the range of environmentally relevant concentrations for criteria development.

5. The Committee suggests that EPA consider the mixture effects of compounds with similar modes of action when determining the range of environmentally relevant concentrations for criteria development.

The Committee finds that, together with those in the White Paper, these considerations should allow a robust determination of whether CMCs are necessary for derivation of ALC for CECs.

4.1.2 Defining Minimum Data Requirements Regarding Taxonomic Coverage

EPA's draft White Paper states that a consequence of dropping acute toxicity testing requirements for deriving aquatic life criteria for CECs is the inability to calculate a CCC using the ACR approach. The Committee notes that CCCs could, however, be developed directly from sufficiently robust sets of chronic data using procedures in the Agency's Guidelines (Stephan et al., 1985, pages 40-42). These procedures require that acceptable chronic toxicity tests be conducted for a broad range of taxonomic groups. EPA has suggested that, if insufficient data from actual toxicity tests are available to fulfill the minimum data requirements for CECs, a reasonable understanding of the toxicological mode of action for a chemical may allow inferences as to what taxa (and endpoints) are most likely to be insensitive, and measured chronic values for those taxa might not be needed. Thus, in the White Paper, EPA has

recommended that, for CECs without complete chronic toxicity data sets to fulfill minimum data requirements, there be an evaluation of whether sufficient information exists to conclude that certain taxa would not be sensitive to the chemical. To accomplish this, EPA recommends interpreting the minimum data requirements for taxonomic coverage as "information requirements" instead of "toxicity test requirements." EPA notes that this would avoid generation of resource-intensive chronic toxicity data for insensitive species that would have little impact on the final criterion. The Committee agrees with EPA's recommendation. However, as further discussed below, the Agency needs to define: 1) what constitutes a sufficiently robust set of chronic data for criteria derivation, and 2) what constitutes a reasonable understanding of the mode of action for the chemical that may allow inferences concerning the insensitivity of particular taxa. In addition, the Committee has noted a number of concerns that should be addressed by EPA as it implements the proposed approach.

The Committee finds that the White Paper contains a comprehensive discussion of the issue of taxonomic coverage for developing aquatic life criteria. EPA's 1985 Guidelines require that data be available for the following organisms: a salmonid in the class Osteichthyes, a second family in the class Osteichthyes, a third family in the phylum Chordata, a planktonic crustacean, a benthic crustacean, an insect, a family in a phylum other than Arthropoda or Chordata, and a family in any order of insect or other phylum not already represented. This requirement is the same for freshwater as well as marine organisms. In the White Paper, EPA notes these taxonomic coverage requirements but recommends movement to a more "expert judgment" approach that is logical and should address some of the unique properties of CECs. The Committee understands and appreciates the desirability of avoiding the extra work required to develop chronic data for species that are unlikely to be sensitive to certain CECs. On the other hand, we emphasize that it is equally important to perform adequate testing to ensure protection of aquatic life. Therefore it is important to define what constitutes a sufficiently robust set of chronic data for criteria derivation and also to provide additional guidance concerning the data needed to infer that various taxa are insensitive to chemicals with specific modes of action.

As further discussed in Section 4.2 of this report, the derivation of aquatic life criteria should be risk-based and include consideration of probable direct and/or indirect impacts on food webs; ecological processes and services; and unique, endangered, and sensitive species. Thus, a major factor in determining that toxicity test data are not needed for particular taxa should be an assessment of the potential consequences of incorrectly concluding that a contaminant would have no effect. The ecological data requirements for supporting a conclusion of no effect (i.e., the level of "power" deemed sufficient for detecting a specified consequential effect) depend at least in part on an assessment of the social and biological values at risk and the potential for consequential losses. Moreover, because goals for aquatic life criteria should extend to the protection of ecosystems and their services rather than individual targeted organisms or specific subsystems, there is a need to assure that biological assessments adequately address a broad range of taxa and environmental contexts.

Concerns regarding taxonomic coverage for testing CECs

The Committee emphasizes that there are instances in which CECs have been shown to have unanticipated effects on non-target organisms. Examples include the impact of antibiotics on

plants (Brain et al., 2008) and atrazine effects on the quality of algae (Pennington and Scott, 2001). These types of examples should be used in Part I of the White Paper to help describe how the aquatic life criteria development process might need to be more flexible depending on the compounds under evaluation. In addition, we note the following important points to be considered concerning appropriate taxonomic coverage for deriving aquatic life criteria for CECs:

- There is a need to maintain broad taxonomic coverage for development of aquatic life criteria. The White Paper suggests that knowing certain modes of action could potentially focus testing on a particular type of organisms (e.g., vertebrates for "estrogenic" compounds). This suggestion is not wholly supported by the Committee. As stated in the 1985 Guidelines, the procedure for estimating the 5th percentile final chronic value is to use the four lowest values in the data set. This approach considers primarily vertebrates, and it is appropriate for EE2. However, it is not always appropriate (e.g., in the case of the weak estrogenic compound bisphenol A) to give primary consideration to vertebrates. Staples et al. (2008) compared four species sensitivity distribution methods to develop a predicted no-effect concentration for the aquatic environment for bisphenol A. Their study indicated that when using the Guidelines approach, the four lowest predicted values belonged to three invertebrates and one vertebrate. Clearly, this finding suggests that there is a need to maintain a broad taxonomic coverage in the development of aquatic life criteria.

- Little is known of chronic effects of CECs on "wild type" species. The Committee is concerned that much of the toxicity testing for CECs has been done on animals that are highly amenable to laboratory conditions and little is known of chronic effects of chemicals on "wild types." There is also some probability that criteria protecting "lab species" might not protect species of special concern like the endangered short-nosed sturgeon, several species of Pacific salmon, or the bull trout. Research is needed to evaluate the differences and similarities between life-histories and sensitivities of endangered/threatened and standard laboratory animals used for toxicity testing in order to have more confidence that surrogate species will provide sufficient information to develop protective criteria.

- Modes of action are not known for some CECs. The Committee notes that it is not safe to assume that a known mode of action is the only mode of action for a CEC. Different organisms may be affected in different ways by the same compound both as adults and at earlier stages of development. There is also the potential for synergism among CECs in mixtures and in interactions with environmental variables. It is the exception rather than the rule that modes of action are known for CECs.

Committee recommendations to improve the process of determining appropriate taxonomic coverage

Although the example used in Part II of EPA's White Paper to illustrate derivation of aquatic life criterion for an endocrine disrupting chemical is data-rich, the Committee notes that the same cannot be said for all or even most CECs. As EPA correctly states in the White Paper, in many cases non-traditional endpoints (i.e., endpoints not traditionally measured in toxicity testing) will almost certainly need to be considered for CECs. However, the use of non-traditional endpoints

requires an understanding of their relevance to the health of the organism, and ultimately the population, and also an understanding of the variability inherent in the measure. The key to determining appropriate taxonomic coverage and endpoints is ecological relevance. These considerations call for keeping the taxonomic coverage as broad as possible, considering the trophic position of the test organisms, and establishing a clear process or set of guidelines to determine the "insensitivity" of taxa. The Committee provides the following recommendations to improve the process of determining appropriate taxonomic coverage for criteria development:

1. EPA needs to define what constitutes a sufficiently robust set of chronic data. Although the example used in the White Paper generally illustrates EPA's proposed process for making decisions concerning taxonomic coverage, it would be helpful to be more explicit in identifying what constitutes a "sufficiently robust set of chronic data" and "a reasonable understanding of the mode of action for the chemical that may allow inferences." The language in the White Paper introduces uncertainty in both the general approach and in setting up specific test conditions.

2. EPA should consider emphasizing in the White Paper information necessary for development of aquatic life criteria rather than just toxicity test requirements. To that end, guidance on information needed to determine effects on ecological processes (e.g., food webs, nutrient cycling, and primary production) rather than only target species would be valuable in criteria development, and would follow more recent scientific thinking. In addition, there is a need for consideration of appropriate conceptual models that include fate pathways and exposure to the CECs. An understanding of exposure pathways could help direct testing toward more relevant species.

3. An approach that might be considered by EPA would be to shift from a minimum level of required taxonomic coverage toward determining receptors of potential concern (ROPCs). EPA acknowledges in the White Paper example illustrating development of an aquatic life criterion for EE2 that certain types of organisms might be differentially sensitive or impacted by a compound. The Committee notes that, if sufficient information exists on sensitivity, then expert judgment concerning data development should prevail. This would result in a more focused approach to data development keeping in mind a weight of evidence rather than a broad requirement for testing all eight taxa specified in the Guidelines. This would be a more flexible risk-based rather than set approach and would be consistent with the risk-assessment terminology used throughout Part I of the White Paper.

4. Examples showing the unanticipated effects of CECs on non-target organisms (e.g., the impact of antibiotics on plants and atrazine effects on the quality of algae) should be used in Part I of the White Paper to help describe how the aquatic life criteria development process might need to be more flexible depending on the compounds under evaluation.

5. The Committee recommends that the discussion of taxonomic coverage in the White Paper be expanded to include specific recommendations concerning the marine environment. EPA's 1985 Guidelines call for assessment of marine organisms in the same manner as freshwater organisms. However, a discussion of testing marine organisms was omitted from EPA's White Paper. We note that including consideration of testing marine organisms would

be consistent with the approach taken by the European Union as it developed its Water Framework Directive (European Commission, 2008). Due to specific issues unique to marine organisms, such as physiological requirements (e.g., maintenance of salt balance) and life-history strategies (e.g., reproduction tied to tidal cycles), more specific guidance for CECs is likely needed. The Committee suggests that this guidance may be best addressed by convening a "Pellston" type workshop (Society of Environmental Toxicology and Chemistry, 2008) that is comprised of experts from multiple disciplines and types of organizations. Since testing requirements for marine organisms are already being considered by EPA, this should be stated in the White Paper.

4.1.3 Use of Non-resident Species in Criteria Development

EPA's Guidelines limit the data used for aquatic life criteria development to tests with native species while allowing use of non-resident species data to provide additional narrative evidence for criteria development. In its White Paper, EPA suggests that excluding species from testing simply because they are not resident may be unnecessarily restrictive for the purposes of deriving national criteria, and may actually increase rather than decrease uncertainty. The White Paper recommends that these "non-resident" species data be used in the aquatic life criteria derivation process if the non-resident species data would enable better estimation of species sensitivity distributions (SSDs). EPA recommends that criteria derivation calculations focus on test data from species for which widely used and standardized test methods are available, and for which there is reason to believe that data would represent the sensitivity of comparable resident species. EPA specifically recommends accepting data for zebrafish (*Danio rerio*) and Japanese medaka (*Oryzias latipes*), to reflect international efforts in harmonization of test methods. As further discussed below, the Committee agrees with this recommendation.

Benefit of using non-resident species data

The Committee finds that the exclusion of non-resident species data from criteria derivation is biologically and practically inconsistent with the intent of the Guidelines (i.e., providing an objective, internally consistent, appropriate, and feasible way of deriving national criteria). Furthermore, we find that, as advocated by the White Paper authors, use of such data would greatly benefit the development of scientifically sound aquatic life criteria CECs. Although geographic differences in species tolerance to contaminants have been documented (Chapman et al., 2006), it is important to note that the U.S. covers a wide range of geographic areas (from tropical [Florida, Hawaii] to arctic [Alaska]). Previous criteria development has focused on temperate species. Thus, inclusion of non-resident species has the potential to cover not only data needs but also the geographic (e.g., temperature) range of biota in the U.S. and arguably could increase the protectiveness of the derived criteria.

The White Paper states that only "species with recognized international equivalency [will] be included in criteria derivation with the full weight given to data from resident species." This approach supports international test harmonization efforts. Specifically, the White Paper recommends use of zebrafish and Japanese medaka. These two species have been largely used for EDC testing and have shown sensitivity similar to native fathead minnows and other species. Tests conducted with the zebrafish and Japanese medaka provide insight into the biochemical

and physiological mechanisms involved in the toxicity of CECs. It is important to match the mode of action with the appropriate test species. The conservative nature of the endocrine system, a target for most endocrine disrupting chemicals and likely many CECs, renders the exclusion of non-resident species from aquatic life criteria development biologically indefensible. Certainly the use of any test species would be useful if it could aid in the interpretation of modes of action, relative taxa tolerance, and endpoint sensitivity comparisons. For example, studies with surrogate species have been conducted to demonstrate the toxicity of CECs to resident species, such as the Rio Grande silvery Minnow and the North American Sturgeon, that are too endangered for laboratory testing (Beyers, 1995; Dwyer et al., 2000). Additional studies of the sensitivity of marine and freshwater test species are cited in the recommendations below. In such cases test data from closely related non-resident species may provide laboratory evidence useful in the development of protective aquatic life criteria for the endangered resident species

Concerns regarding the use of non-resident species data

Although the Committee supports the use of non-resident species data for deriving aquatic life criteria for CECs, we note the following concerns that should be considered by EPA:

- Non-resident species are defined in different ways. The Committee notes that EPA's Guidelines define "non-resident" species as those not native to the continental United States and Canada. However, non-resident species have been defined in other ways. At the federal level, they have been defined as species that are not native to North America. Many states use the term non-resident species to mean species not native to their specific region. Hence local criteria are sometimes derived substituting species found locally. The definition of "non-resident" (or non-native) and invasive species should be clearly stated in EPA's White Paper. The White Paper should indicate whether organisms that have migrated (or invaded or been stocked) are considered "resident." In this regard, the Committee notes that global climate change and other factors associated with the migration of organisms potentially make the definition of resident or non-resident species a moving target.

- It is important to consider the concept of "representative" species in criteria derivation. An underlying assumption in the exclusion of non-resident species data from criteria derivation is that non-resident species do not represent the response expected from native species in a geographic area. It is more important to consider the ecophysiological make-up of a species and its alignment with the ecological conditions in which the exposure occurs than the geographic home range of the species. It would be easy to postulate a case where resident or native warm water species are not as representative of risks to resident cold water species as the response of a non-resident cold water species which occupies the same or similar niche in a different geography.

- Non-resident species data may dominate the criteria derivation process. The Committee is concerned that non-resident species and their large respective databases could dominate the criteria derivation process. The recommendation to use non-resident species data, as presented in the White Paper, is reasonable when looking at criteria derivation from a continental perspective. However, including non-resident species data in the criteria

derivation process could lead to inappropriately biased criteria development in certain sensitive geographic areas, such as cold water and oligotrophic systems. More detailed information is needed in the White Paper to address this concern.

- Variation in test organism response is often unknown. The Committee notes that variation among the strains of test organisms used in laboratory studies is often unknown. Therefore, it is difficult to understand whether the variation observed between native and non-native species is within the uncertainty of the test data for either species. Differences in husbandry, health, parasite and pathogen load (i.e., other stressors) may contribute to differences in test results between resident and non-resident species. Within Pacific herring of Puget Sound there are apparent stock differences in the frequency of malformations of new hatchlings that are not related to spawning site (Hershberger et al., 2005). Differences in sensitivity have also been observed for clones of *Daphnia magna* (Baird et al., 1990). While the issue of response variation should be considered, many studies have shown parallel responses when fairly close relatives are used.

Committee recommendations regarding the use of non-resident species data

Excluding the use of use non-resident species data from the process of developing aquatic life criteria for CECs may result in failure to meet the minimum data requirements. Therefore, the Committee finds that use of available data for non-resident species is warranted. Although the use of resident species information is preferable to non-resident species, data from tests using non-resident species, such as zebrafish and Japanese medaka, can provide extremely useful information on modes of action. The appropriate use of non-resident species data in criteria development will allow better estimation of species sensitivity distributions and also improve international harmonization and equivalency efforts. The Committee provides the following recommendations concerning the use of non-resident species data:

1. As noted above, non-resident species could potentially be over-represented in aquatic life criteria databases. The proportion of the data set that should include resident species is a matter that should be carefully evaluated by the expert advisory panel assembled to review each criterion.

2. In no case should a criterion be developed on the basis of non-resident species data alone. Certainly if it is shown that non-resident species are ecologically relevant and appropriately sensitive then they should be used for criteria derivation as long as the studies meet appropriate quality criteria. Test species used in toxicity testing tend to be easy to rear and test, and have appropriate sensitivity levels. However, other factors should be considered when ample data are available for prioritizing species responses for criteria development. These factors include vulnerability; endangerment status; and recreational, commercial or ecological value. In order to protect endangered species, studies should be completed to compare toxicity test responses of common test species and endangered organisms and thereby determine the relevance of surrogates in the criteria development process. Previously EPA and the U.S. Fish and Wildlife Service (Besser et al., 2005; Dwyer et al., 1999, 2005; and Sappington et al., 2001) compared the sensitivity of common freshwater and marine testing species with protected/endangered fish species and found that these surrogate

test species (e.g., rainbow trout) may equally protect endangered species. However, these surrogate fish species do not necessarily provide protection for other threatened and endangered non-fish species such as marine mammals, wildlife, and birds that reside and feed in aquatic ecosystems and provide ecosystem goods and services. Additional consideration of these other non-fish protected species is required in developing risk-based approaches for CECs that fully protect all threatened and endangered species.

3. The statement that criteria would be developed "…with full weight given to data from resident species" should include a qualifier concerning the validity of the data. An available resident species study with no obvious protocol, no measurement of test concentrations, or other protocol concerns should be assigned a lower priority than a fully valid Organization for Economic Cooperation and Development (OECD)/EPA guideline study with a non-resident species. However, the Committee qualifies this recommendation by emphasizing that all scientifically valid data should be used in setting criteria.

4. Differences in strains, husbandry, health, and parasite and pathogen load contribute to response variation and should be considered in the aquatic life criteria development process.

5. Non-resident as well as resident species test data must meet Guidelines requirements for data and method validity.

4.1.4 Defining Appropriate Chronic Toxicity Data

EPA's Guidelines state that acceptable chronic tests for derivation of aquatic life criteria are full life-cycle exposures (F_0 egg to F_1 offspring) for vertebrates and invertebrates, as well as partial life-cycle (adult to juvenile) and early life-stage (egg to juvenile) tests for fish. EPA's White Paper states that some CECs may have potent effects on life processes that lie outside the exposure period represented by early life stage tests or effects may not be manifested until later in development. Thus, early life stage tests might not be good predictors of chronic toxicity for these chemicals. In the White Paper, EPA recommends that the Guidelines requirements for chronic toxicity data be tightened by requiring at least one full life-cycle test for a fish (for invertebrates, life-cycle tests are already required) unless there is a compelling body of information indicating that life processes outside the early life stage or partial life-cycle exposure/observation window are not critical to capturing the biologically important effects of chronic exposure to the chemical.

The Committee strongly supports EPA's recommendation to amend the chronic data acceptability requirements in the Guidelines. However, we are divided in our assessment of the "guilty until proven innocent" approach in the White Paper (page 17). Some Committee members view it as appropriate while others view it as extremely precautionary. The White Paper states that "…it is probably wiser to require that the chronic toxicity data for fish include exposure and observation over a full life-cycle unless there is an affirmative reason to believe that it is not necessary." The statement is used in the context of requiring a full life cycle study instead of relying on an early life stage test for fish. Some Committee members find that the statement does not appear to fit the process of setting aquatic life criteria, whereas others find it to provide an important perspective for establishing aquatic life criteria.

The Committee also supports extending the recommendation to amend the chronic data acceptability requirement to all chemicals, not just endocrine disrupting chemicals and CECs. The Committee finds that EPA's recommendation is justified based on evidence showing that a number of chemicals may exert effects during the period of gonadal differentiation, and that these effects may not be manifested until much later in life. Including at least one full life cycle test in the test guidelines for fish ensures that these types of effects are captured.

Issues to be considered in defining appropriate chronic toxicity data

Although the Committee supports EPA's recommendations concerning use of chronic toxicity data for development of aquatic life criteria, we note the following issues that should be addressed in defining appropriate chronic toxicity test data:

- Transgenerational effects of CECs are potentially important and should be considered. There is evidence for some chemicals that exposure in one generation creates effects in a later generation that were not observed in prior generations even in the same life stage. Accordingly, the chronic toxicity data requirements include a full life-cycle test to be conducted for at least one species of fish. There is still some uncertainty as to whether a full life-cycle test might underestimate the chronic effects that would be seen in exposures extending over more than two generations (multigenerational testing). We do not recommend adding a requirement for multigenerational testing to the Guidelines, but suggest that EPA critically review data dealing with transgenerational responses of aquatic species and evaluate whether this additional testing provides significant new information that informs the evaluation process. This critical review should examine the utility of multigenerational tests relative to proposed fish full life-cycle (FFLC) tests as well as partial life-cycle (PLC) tests and early life-stage studies. The intent of this recommendation is to ensure that a full range of development (e.g., early life stage to adult) is evaluated sufficiently to assure adequate aquatic life protection. The Committee generally supports the concept of fish full life-cycle testing because it spans the entire exposure window in the early life-cycle to adults. The Committee also supports further development of a tiered testing approach to derive an appropriate rationale for the use of FFLC, PLC, and possibly multigenerational testing for chemicals with parallel modes of action. In this regard, it is noted that the decision to use data from partial versus full life-cycle and/or multigenerational tests requires a consideration of tradeoffs between the costs of additional testing and the social and biological values at risk and the potential losses from missing an important effect.

- Flexibility in test guidelines is needed to include key developmental events. Test guidelines must have the flexibility to include assessment of key developmental events (e.g., metamorphosis in amphibians, acquisition of saltwater tolerance), particularly if these processes are identified in a ROPC.

- Test methods should include non-traditional measures that may be linked to ecologically relevant endpoints. There is a need to ensure that the test methods include provisions to consider non-traditional endpoints such as immune function and organism behavior. These endpoints may directly impinge on ecologically-relevant endpoints such as growth,

reproduction and survival. In this case, professional judgment from an expert panel is needed to determine the relevance of these non-traditional endpoints.

The Committee also notes the following practical issues that should be addressed if the chronic toxicity data recommendation in the White Paper is to be implemented:

- Surrogate test species may be needed. A key issue to be addressed is the suitability of surrogate test species. Surrogates may be needed in the case of: 1) long-lived species with delayed sexual maturity; 2) organisms of large size (which precludes their suitability as a test species in the laboratory), 3) endangered species, and 4) species for which there is little knowledge of the husbandry conditions or background biology. There is also uncertainty in how differences in the physiology and life history strategies (i.e., long-lived versus short-lived species, differences in maternal-fetal transport of contaminants) may affect the response of aquatic species to CECs and endocrine disrupters. Many of these issues represent significant data gaps that need to be addressed. In these cases, expert opinion may be needed to assist EPA in determining the suitability of surrogate test species for use in criteria development.

Committee recommendations regarding defining appropriate chronic toxicity data

As discussed above, the Committee strongly supports EPA's recommendation concerning the use of at least one full life cycle test for a fish in appropriate cases for testing all kinds of chemicals when deriving water quality criteria for the protection of aquatic life in marine and freshwater environments. We provide the following recommendations to implement the requirement for chronic toxicity data:

1. As discussed above, EPA should critically review data dealing with transgenerational responses of aquatic species and evaluate whether or not this additional testing provides significant new information that informs the evaluation process.

2. EPA should support research that addresses the suitability of the use of surrogate species in assessing the response of aquatic species (e.g., endangered or long lived species; species with varying life history strategies) to CECs.

3. Test guidelines should include flexibility to include assessment of key developmental events, and professional judgment from an expert panel should be used to evaluate the relevance of non-traditional endpoints such as immune function and organism behavior.

4.1.5 Selection of Effect Endpoints for Criteria Development

In the White Paper, EPA has stated that the selection of endpoints appropriate to the derivation of aquatic life criteria must be tied to the goal of aquatic life criteria (i.e., to protect aquatic organisms and their uses). EPA further states that survival, growth, and reproduction are processes directly related to this goal. The Agency notes, however, that there are many more biological responses that have been observed in response to toxicant exposure. In the White Paper, EPA has identified a number of sublethal endpoints that could be considered in

developing aquatic life criteria for CECs. The Agency has recommended that the use of such endpoints be more thoroughly explored for development of aquatic life criteria.

Points to be considered in selecting effect endpoints

Generally, the Committee agrees that EPA should continue to explore the possibility of using sublethal endpoints to help set aquatic life criteria. However, we caution EPA that non-traditional endpoints must ultimately be linked to the population, and not solely to individual-level endpoints. The ultimate goal of any aquatic life criterion is to protect populations of aquatic organisms from the "harmful" effects of chemicals (or other stressors). Thus, reproduction, growth and survival are the predominant effect endpoints currently utilized in laboratory studies supporting criteria development. The Committee discussed: 1) the usefulness of information provided by the non-traditional endpoints identified in the White Paper; and 2) whether the endpoints might provide information to assess effects on populations, particularly when considering mixtures and indirect effects. We provide the following comments to be considered by EPA in selecting effect endpoints to develop criteria for CECs:

- Contaminants effects should be linked to different levels of biological organization. Definitions of "biologically important effect" and what constitutes a "good population" are needed. We also note that not all biological responses represent an "adverse" effect. This is consistent with a principle laid out in the White Paper (i.e., the White Paper states that chemicals such as endocrine disrupters have been shown to produce a wide variety of measurable changes at many different levels of biological organization, and the challenge is to select from among those endpoints that have sufficiently clear connection to expected effects on populations or communities of aquatic organisms).

- Activational biological effects can provide useful information. CECs often induce changes in behaviors, secondary sexual characteristics, or levels of hormones or hormone-induced products. Many of these responses are transitory or may revert to their prior or normal condition with cessation of exposure. Accordingly, it is often difficult to interpret these activational responses in relation to higher level biological effects. Nevertheless, these endpoints do provide useful information, particularly regarding mode of action. Consideration of such effects would certainly help reduce uncertainty in a risk assessment paradigm. While it is clear that these endpoints alone could not be utilized to set criteria, the Committee notes that sublethal endpoints integrated with toxicodynamic and kinetic factors could provide useful data in a problem formulation step related to some CEC, and could also be used to help identify data gaps that may be filled to reduce uncertainty and aid in criteria development.

- Use of non-traditional sublethal endpoints holds promise but further validation of such endpoints is needed. Behavioral endpoints related to population (e.g., predator-prey interactions) and reproduction may hold some promise for criteria development if the assays can be validated and variability can be understood. The implicit model for considering behavioral endpoints is that biological changes in individual organisms in response to contaminants may produce changes in individual characteristics and behavior which may have implications for populations and ecosystems. It is also noted, however, that social

factors can affect the behavior of individuals, which in turn can affect neurological and other systems and functions. Immune function and genetic variation are also endpoints that should be explored (Filby et al., 2007). In addition, models capable of extrapolating laboratory endpoints to the population level should be targeted for development (Ankley et al., 2008; Chandler et al., 2004). Exploration of endpoints related to ecological processes (e.g., primary productivity, decomposition rate) is also warranted.

- Research is needed to determine how aquatic life criteria for CECs can take into account the fact that aquatic organisms are exposed to mixtures of these chemicals. As noted previously, in developing aquatic life criteria for CECs it will be particularly important to consider the effects of mixtures. The Committee provides a number of comments in this regard. We note that understanding the mode of action of a compound is extremely important in estimating mixture interactions. Mixtures of CECs with comparable modes of action may result in higher environmental concentrations than would be expected for any single compound. In fact, pharmacological mode of action is the basis for evaluating multiple drug prescriptions in humans by pharmacists. For example, if it is known that a vertebrate is exposed to aryl hydrocarbon receptor (AhR) agonists and estrogen receptor (ER) agonists, it is likely that antagonism of each effect could occur. Information regarding mode of action should be made available to EPA from manufacturers or other governmental agencies (e.g., available from the U.S. Food and Drug Administration [FDA] or from testing under the requirements of the Federal Insecticide, Fungicide, and Rodenticide Act [FIFRA]). It is through use of this information that non-traditional measures can confirm similar or different modes of action in targeted ROPCs. The Committee strongly recommends enhancing the communication and data transfer capabilities between agencies such as FDA and EPA to provide these data.

- Mode of action fingerprints developed by evaluating combined sublethal endpoints should be linked to *in vivo* species testing. The Committee notes that much of the toxicity testing for compounds such as pharmaceuticals and personal care products has been conducted using mammals and other vertebrates. Additional data are needed for other "keystone" species. We suggest that the choice of species, critical life stages, and complicating stressors (i.e., salinity and temperature) could be potentially identified in a problem formulation/conceptual model stage of a risk assessment paradigm. If these data are not available, research and development could be undertaken to obtain mode of action "fingerprints" for a CEC or any other compound through combined sublethal endpoints (i.e., genomic-transcriptomic, proteomic, metabolomic) and toxicodynamic/kinetic feature evaluations within sentinel species (to cover taxonomic issues). It is likely that through this process additional "side-effects," or species-specific modes of action, could be obtained. These data could be integrated with "fingerprints" of other compounds with different modes of action and utilized to help address mixture issues or potential indirect effects. The toxicity to a particular species at a particular trophic position could then be modeled to assess indirect impacts on other populations.

- Additional research is needed to link biomarkers to effects. The Committee notes that the concept of using biological responses occurring prior to impacts on growth, reproduction, and survival has been proposed for more than 20 years as a way to detect adverse effects in a population before the population is altered. While there are examples of such "biomarkers of

effect," we find that the linkages between biochemical, histological, and behavioral endpoints and reproduction, growth, and survival are likely life-stage dependent and are difficult to validate, particularly in the field. We note that "biomarkers of exposure" are available but research is needed to interpret their significance.

- Vitellogenin production is an excellent biomarker of exposure to feminizing chemicals. One of the best examples of exposure biomarkers is the biological response of vitellogenin production in male or juvenile animals. Vitellogenin is an excellent *in vivo* biomarker for exposure to feminizing chemicals. If the response is measured in the whole animal, it incorporates estrogenic as well as anti-androgenic or other modes of action that can cause a feminized response (production of an egg-yolk precursor). It is important to point out that this assay is not identical to estrogen receptor (ER) - based *in vitro* bioassays. Some compounds such as EE2 are very potent ER agonists but also have other modes of action that may alter endocrine systems (Tabb and Blumberg, 2006) such as the inhibition of several isoforms of cytochrome P450 (e.g., CYP3A), which are important in the clearance of endogenous steroids (Parkinson, 2001). Nonylphenols also have multiple modes of action other than direct binding to the ER that lead to enhanced estradiol synthesis (Harris et. al, 2001; Kazeto et al., 2004; Martin-Skilton et al., 2006; Meucci et al., 2006; Thibaut and Porte, 2004). So the observation of vitellogenin induction within an oviparous male or juvenile organism does not indicate total specificity with regard to mode of action. Anything that increases endogenous estrogen biosynthesis or diminishes clearance would also provide this biological response. The Committee notes that the reduction of vitellogenin in females may not indicate anti-estrogenic effects or even alterations of endocrine activity, as basic hepatotoxicants in females can elicit a similar effect. However, we point out that the correlations between fecundity and vitellogenin in females have been observed to be strong even though this may not indicate mode of action (Miller et al, 2007) (see discussion below). Additional studies are needed to examine hepatotoxicants or compounds with modes of action exclusive of endocrine targets.

- The linkage of vitellogenin production to biological effects is limited. While the linkage of vitellogenin to exposure is reasonably solid, linkages of vitellogenin in males/juveniles to higher biological effects such as altered reproduction, survival and growth are limited, even though the relationship may make intuitive sense. Several studies have shown relationships between vitellogenin and reproduction in the laboratory, often at concentrations beyond probable effect concentrations (Thorpe et al., 2007), but few examples of population alterations have been noted in the field. Even in the United Kingdom, where gender shifts to females were originally noted and correlated with vitellogenin induction within males, intersex individuals, and other histological anomalies, overall abundance declines within the species of interest have not been reported. In fact, only one study (Kidd et al., 2007) has linked population crash with vitellogenin or histopathological alterations in fish. A similar occurrence has been noted in laboratory studies where vitellogenin expression may or may not be linked to intersex (Grim et al., 2007), which in turn may or may not lead to gender shifts. Even the relatively clear signal of gender shift, while clearly impacting reproduction in laboratory animals optimized to a specific gender ratio, may not significantly impact field populations in an uncharacterized species (Munday et al., 2006). Clearly, a better understanding of the population dynamics of a ROPC is needed to determine the phenotypic

plasticity of the gender ratio. Thus, gender shifts should be viewed with caution, particularly in species that have not been well studied.

Committee recommendations regarding selection of endpoints

The Committee agrees that EPA should continue to explore the possibility of using sublethal endpoints in helping to set aquatic life criteria. We provide the following recommendations in this regard:

1. EPA should pursue the use of "non-traditional measures," or endpoints for criteria development, as discussed in the White Paper. The Agency should ensure that such measures can be tied to impacts on populations or ecological processes, not just to effects on individual organisms.

2. EPA should use "non-traditional measures" when appropriate to develop an understanding of and confirm mode of action.

3. EPA should use human health information and toxicology tools (genomics/ PBPKs) when appropriate and available to reduce the uncertainty of aquatic life criteria.

4. EPA should consider the following key points concerning use of the non-traditional endpoints discussed in the White Paper: 1) vitellogenin in males and juveniles is an indicator of exposure to a feminizing stressor(s), but its linkage to population effects is limited; 2) strong correlations between vitellogenin and fecundity have been observed in females, but this is not necessarily tied to altered endocrine mode of action; 3) Anomalous intersex is indicative of a gender stressor(s), but has not been strongly tied to population effects; and 4) gender ratio can be indicative of endocrine alteration, but baseline information on appropriate life history is necessary for this evaluation.

4.1.6 Involvement of an Expert Panel

Because development of aquatic life criteria for CECs may be dependent on technical interpretations of a wide range of toxicological information, EPA has proposed that expert panels be used to provide professional judgment during criteria development. The Committee concurs that strong, active participation by a panel of outside experts will be necessary to ensure that the approaches used (including the designs for toxicity testing, the selected endpoints, and the necessary species and tests to be used, i.e., the ROPCs) are the most appropriate for the compound under scrutiny. As the EPA moves away from firm requirements for species and tests, it will become increasingly important that expert panels comprising diverse expertise be utilized to ensure that the best data are selected for necessary decisions. The National Academy of Sciences and Society of Environmental Toxicology and Chemistry have suggested similar approaches. In a recent report dealing with ecological risk assessment in environmental decision making (U.S. EPA Science Advisory Board, 2007), the SAB strongly recommended that expert panels be used to provide assistance to EPA during the problem formulation phase of ecological risk assessments. The same recommendations are appropriate for development of aquatic life criteria. Involving a suite of experts with a balanced range of perspectives during the very early

stages of problem formulation, and continuing their involvement as external reviewers at strategic junctures throughout the process, will significantly improve quality, utility, and defensibility of the criteria. It is noted that implementing a risk-based approach to deriving aquatic life criteria that protect ecosystems and their valued services will necessitate including social scientists, economists, and relevant publics/stakeholders on expert panels.

Committee recommendations concerning the use of expert panels

As stated above, the Committee concurs with the use of expert panels to provide professional judgment during the process of developing aquatic life criteria. We offer the following recommendations concerning the formation and use of expert panels:

1. The process for the use and selection of expert panels should be described in detail and should be transparent. The process used to select and convene the panels, the general attributes of panel composition, and methods used to address issues such as identification and elimination of conflicts of interest must be described (U.S. EPA, 2006). In this regard, one possible model to be considered is the process used to select SAB committees and panels, whereby national and international experts are identified from multiple sectors representing broad disciplinary expertise and professional affiliation (e.g., academic, appropriate governmental agencies [such as FDA], non governmental organizations, and private industry).

2. The charge to the panel and the expected end result must be clearly defined.

3. There are likely similar expert panel processes occurring elsewhere. The Committee recommends that EPA determine whether similar processes are underway in Europe and Asia, and if so, consider them as models to provide additional insight and/or expertise.

4. The Committee is concerned that the use of expert panels could lead to less consistency in how aquatic life criteria are determined. To help alleviate this potential problem, we recommend that EPA develop specific guidance on the roles of expert panels in problem formulation, data evaluation, and the generation of recommendations leading to criteria derivation.

4.2 Charge Question 2. Please comment on whether EPA has identified the appropriate issues to be addressed in deriving ALC for CECs. Are there additional important issues that EPA has not identified?

As stated previously, EPA's White Paper identifies technical issues that need to be addressed in deriving aquatic life criteria for CECs. The Committee was asked to comment on whether the Agency has identified the appropriate issues in the White Paper and whether there are additional important issues that EPA has not identified. The Committee finds that appropriate technical issues have been identified in the White Paper. However, EPA could clarify the process of developing aquatic life criteria for CECs by articulating a set of principles that could be applied when modifying the 1985 Guidelines to develop water quality criteria for such contaminants. We also emphasize the importance of developing a conceptual model to guide the process of

developing aquatic life criteria for CECs. The conceptual model should address more than the fate and direct effects of CECs. It should include consideration of probable direct and or indirect impacts on food webs, ecological processes and services, unique, endangered or keystone species or species of special societal value or concern. The example provided in Figure 1 illustrates components that could be included in such a conceptual model. Use of a conceptual model to

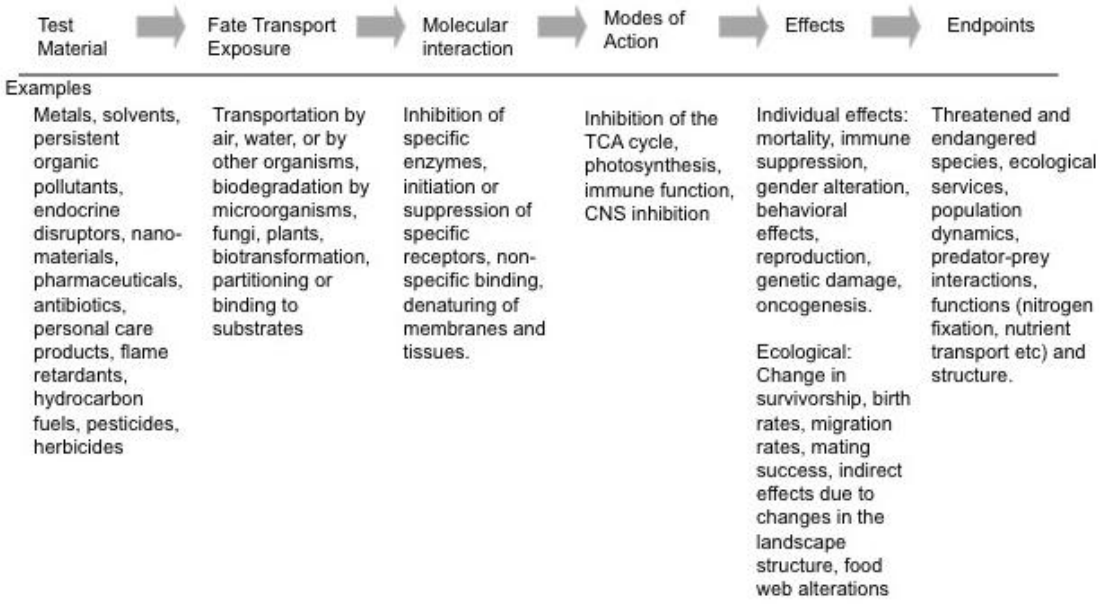

Figure 1. A Generalized Conceptual Model for Deriving Aquatic Life Criteria With Examples for Each Step

support criteria development would improve EPA's ability to address emerging questions about unique mechanisms, fate processes, and effects endpoints. Use of the conceptual model is further discussed below.

Committee recommendations concerning additional issues to be addressed

Although the Committee finds that EPA has identified appropriate technical issues in the White Paper, we recommend that the Agency address the additional issues listed below in order to customize and update the 1985 Guidelines and thereby increase the flexibility and specificity of the aquatic life criteria derivation process. It is important to note that several of the following recommendations (e.g., the recommended shift toward an ecological risk assessment model and the recommendation to seek inputs from diverse perspectives) will require explicit and systematic assessment of the concerns of relevant publics/stakeholders. This in turn will require greater involvement of social and economic sciences in the aquatic life criteria setting process, especially in the context of identifying and prioritizing contaminants of emerging concern.

1. In the White Paper, EPA should articulate principles that can be applied when modifying the 1985 Guidelines to develop water quality criteria for CECs. The Committee recommends that these principles be directly linked to EPA's Guidelines for Ecological Risk Assessment (U. S. EPA, 1992, 1998). The committee in fact recommends that the 1985 Guidelines be

updated to incorporate risk assessment principles and guidelines that did not exist when the Guidelines were developed over 20 years ago. In other words, the derivation of aquatic life criteria needs to be fully risk-based, using a transparent and consistent framework that provides necessary flexibility not presently possible within the algorithm approach of the 1985 Guidelines. A recent SAB report, *Advice to EPA on Advancing the Science and Application of Ecological Risk Assessment in Environmental Decision Making: A Report of the U.S. EPA Science Advisory Board*, (U.S. EPA Science Advisory Board, 2007) contains additional recommendations that may be considered in order to enable more effective use of ecological risk assessment in the derivation of aquatic life criteria.

2. In line with using a risk-based approach, principles for developing aquatic life criteria for CECs should include the following: seek a wide range of inputs from diverse perspectives; determine appropriate ROPCs; develop a robust conceptual model; develop multiple lines of evidence; and identify uncertainties (quantitative and qualitative) associated with criteria development. Each of these risk assessment-based principles is further discussed below:

   - Seek a wide range of inputs. EPA should seek input from a diversity of experts representing: Agency scientists, academic scientists, scientists in business and industry, state and tribal scientists, and the environmental community on the problem formulation, conceptual model development, modifications to the Guidelines dictated by the properties of a CEC, and the resulting recommendation for the aquatic life criterion. Adherence to this principle will ensure that the process stimulates a robust discussion and is informed by and acceptable from a diversity of perspectives. This diversity should include input from chemists, modelers, toxicologists, ecologists, and risk assessors.

   - Determine appropriate ROPCs. The process needs to clearly identify the need to determine appropriate receptors of potential concern and not simply focus on "traditional" test organisms.

   - Develop a robust conceptual model. At the start of the criterion development process, the available data on fate and effects should be examined and used to develop a conceptual model (e.g., Figure 1). Structure activity data and modes of action of similar compounds/materials should be consulted to inform model development. An expert panel should be convened to assist in the problem formulation and conceptual model development step. Uncertainty should be identified in the model and used to identify strategic efforts to reduce uncertainty. The conceptual model should include more than fate and effects data. It should include consideration of probable direct and or indirect impacts on food webs, ecological processes and services, and unique, endangered or keystone species or species of special societal value or concern (charismatic species).

   - Develop multiple lines of evidence. The committee finds that a multiple line of evidence approach has the potential to inform decision making and the criterion recommendation. It also can serve to reduce uncertainty when the lines converge and reinforce each other.

   - Identify uncertainties and conduct uncertainty analysis. As further discussed below, EPA should identify the uncertainties associated with the criteria developed for CECs. At all

stages of criteria development, uncertainty should be quantified and/or qualitatively discussed. Uncertainty should be used to focus and prioritize data generation efforts.

3. EPA should develop a system or process to assist the development of criteria for CECs. The system would establish a set of rules to enable analysis of information supplied by the user and lead to recommendations concerning one or more courses of user action. The Committee finds that such a system would be an important tool for capturing and maintaining the state of the art in aquatic life criteria development. It would serve as a vehicle for connecting fate and effects assessment tools and capturing expert knowledge, and it could serve as a platform for deriving priorities for future research in assessing the risks of contaminants to aquatic life and ecosystems.

4. The Committee strongly recommends that understanding and presentation of uncertainty become an intrinsic part of the aquatic life criteria development process. The presentation of uncertainty needs to be an explicit and transparent part of the analysis. For example, the uncertainties inherent in understanding modes of action, determination of concentration-response relationships, development of species sensitivity distributions, and derivation of ecological effects should be quantified or described in a narrative sense. An important aspect of this is developing an a priori understanding of the amount and types of uncertainties that preclude the derivation of an aquatic life criterion. These uncertainties can be classified into the categories listed below:

   - Uncertainties that preclude the derivation of an aquatic life criterion.

   - Areas in which uncertainties may be important and can be resolved with additional modeling, research or a better understanding of the relationship of the uncertainty to the standard setting process.

   - Uncertainties that do not preclude the setting of an aquatic life criterion but form the basis for future research programs.

   Identification of uncertainties in these categories can be addressed in development of the conceptual model in consultation with the expert panel.

5. EPA should bolster the consideration of mode of action and ecology in the aquatic life criteria derivation process. A better understanding of the molecular interactions and modes of action will reduce uncertainty in that aspect of the conceptual model. A better understanding of the ecological effects and context will allow more specific and flexible predictions of risks to individuals, populations and ecological structure and function. This will reduce predictive uncertainty. The Committee encourages the developers of the aquatic life criteria to further integrate these advances into the criteria derivation process.

6. In the White Paper, EPA should discuss the importance of considering environmental context (i.e., site specific considerations) in deriving aquatic life criteria for CECs. These modifying factors should be mentioned in the CEC criteria themselves. For example, characteristics of the receiving environment affect bioavailability and toxicity to organisms (e.g., trophic

status, dissolved organic carbon, pH, and substrate types) as well as longevity of their exposure due to impacts on the degradation and partitioning rates of these chemicals. Several CECs have the potential, based on their physical-chemical properties, to bioaccumulate and bioconcentrate, and this may result in diet-borne toxicity to a predator. Degradation/biotransformation products of CECs should be considered because there are instances where their toxicity is greater than the parent compound. In addition, the Committee recommends considering analytical chemistry because some aquatic life criteria have the potential to be set at concentrations that are at or below current (widely available) abilities to easily quantify CECs.

7. The Committee recommends that EPA keep abreast of the new science related to CECs in order to ensure that the latest approaches for assessing the effects of these chemicals are considered in criteria derivation. These types of effects may include impacts on natural selection and genetic diversity, indirect effects through changes in prey quality and quantity, and alteration of ecosystem function. We also point out that effects of CECs may be non-linear, which would pose challenges in derivation of aquatic life criteria. We note that consideration needs to be given to the diversity of phylogenies, functions, and habitats represented in the data used to establish an aquatic life criterion in order to ensure that the overall goals of the process (adequate, appropriate level of population-level protection) are met.

8. As mentioned previously, the Committee recommends that EPA use mammalian pharmacology data available from the drug discovery process, genomics/proteomics/metabolomics and QSARs to screen CECs for modes of action and assess potential multiple modes of action for individual CECs. This would facilitate exploration of the use of parallel processes to develop aquatic life criteria for CECs with similar modes of action. To increase efficiency when determining an aquatic life criterion for one compound (such as EE2), the process could be repeated (or developed in parallel) for compounds (such as estradiol or E2) with similar modes of action. In addition, some guidance should be provided for site-specific applications where mixtures of compounds occur that may have additive effects that exceed individual aquatic life criteria.

9. Natural history of a ROPC can determine the magnitude of effects of CECs and should therefore be considered in the derivation of aquatic life criteria. The timing of breeding seasons, immaturity periods, intrinsic rates of reproduction, survivorship, and life span all influence the magnitude and direction of possible changes in population size and age structure. Fisheries take should be considered for recreationally or commercially important species.

10. In developing aquatic life criteria for CECs, EPA should give special consideration to the protection of threatened and endangered species. Unlike other species, threatened and endangered species are managed so that effects on individuals, not populations, are avoided. Specific mortality of threatened and endangered individuals, along with the contribution of each to the survival of the population, are parameters requiring accuracy with a minimum of uncertainty. In certain cases specific populations or evolutionarily significant units are the assessment endpoints to be considered.

4.3 Charge Question 3. Part II of this white paper was specifically developed as a companion to Part I and focuses on the use of ethynylestradiol as a model chemical to illustrate the technical issues presented by the workgroup, as well as providing a basis for understanding the recommendations. Does the *Committee* have suggestions that may improve the utility of Part II of this white paper for the purposes stated above?

The Committee finds that Part II of EPA's white paper, which is intended to illustrate application of EPA's recommendations concerning aquatic life criteria for CECs (rather than serve as a comprehensive case-study) is a generally well-written and thorough review of the existing literature on EE2; however, some improvements are recommended to enhance clarity. The Committee agrees that EE2 is an appropriate initial focal CEC given: 1) the extensive data available relative to other CECs; and 2) the ease with which it illustrates the complexities inherent in generating CEC-specific water quality criteria to protect aquatic life. Nevertheless, there may be limitations as to how readily the insights gained from the EE2 illustration can be applied to other CECs. Therefore, the EE2 illustrative example should be presented more clearly as an illustration of the aquatic life criteria setting process, rather than the derivation of a criterion for a specific CEC that is important in its own right (although the latter is certainly true). In this regard, more frequent and elaborated discussions of how the EE2 example illustrates points raised in Part I would be very useful. That is, the EE2 example could be used more forcefully to illustrate important issues and principles applicable across the breadth of CECs. The following recommendations are provided to improve the usefulness of the EE2 example.

Committee recommendations to improve the usefulness of the illustrative example

1. In the White Paper, EPA should explicitly recognize that EE2 is unique in being a data-rich CEC. The White Paper should highlight the fact that the Agency's interest in CECs goes beyond endocrine-active substances, and discuss how the example of EE2 might be extrapolated to other substances, particularly to data-poor substances. EPA should consider conducting a similar assessment for a compound with a minimal data set (in contrast to the maximal set of data available for EE2) and evaluate the new approach accordingly. Other CECs with differing modes of action such as polybrominated diphenyl ethers (PDBEs), bisphenol A, and perfluorinated octynyl sulfonate (PFOS) could be considered. These are problematic and controversial CECs and concerns about these chemicals differ from the stated concern in the White Paper over pharmaceutical and personal care products entering the aquatic ecosystem from wastewater treatment plants. They are nonetheless important and instructive case studies that might shed new light on revising the 1985 Guidelines.

2. The Committee suggests that some of the illustrative pieces of Part II could also be included in Part I in the form of succinct text boxes illustrating key concepts derived from the various recommendations (e.g., why certain steps in the Guidelines were included and others were not). Further, we suggest that the recommendations could be best illustrated if the text boxes were not restricted to EE2 but rather included other CECs (e.g., non-endocrine-active

3. Regarding the scope of the material included in the EE2 example, we note that the White Paper fails to address how the influence of EE2 might be affected by mixtures of compounds, especially those with similar modes of action (e.g., estradiol, estrone), as well as environmental (e.g., temperature) and biological (e.g., disease, starvation) modifying factors. Although the Committee recognizes that various offices/groups within EPA are investigating mixtures of compounds, and the White Paper cannot address all relevant issues in the development of guidelines, the document needs to be explicit regarding the importance of considering multiple stressors as well as synergies among CECs. For example, the White Paper should, at the very least, state the rationale for not considering all estrogens within a given body of water, and should provide examples of mixtures and synergies that could affect the toxicity of EE2.

4. Regarding choice of taxa for criteria derivation, the Committee agrees that, although use of non-resident species to assess EE2 effects appears to fit this case example, such may not always be the case. As such, the document should indicate that: 1) resident species data, especially life-cycle tests from resident species, remain extremely valuable, and 2) results from non-residents, while providing useful information, may not be generalized to resident species unless data are available to compare the sensitivities of the non-resident and resident species. We are also concerned that certain sensitive taxa such as amphibians were not included in Table 3.2, and that the key issue of development time to sexual maturity for long-lived charismatic species, such as sturgeon, is not addressed in the document. Research should be conducted to develop comparisons between long-lived species and surrogate test species.

5. The Committee is concerned that transgenerational effects were not considered in Part II of the White Paper. On page 14 in Part II of the White Paper, EPA states that "it does not seem that the evidence for transgenerational effects is sufficient for requiring their inclusion in the definition of an acceptable chronic test." Given EE2's role as an endocrine disrupting chemical, it is surprising that transgenerational effects were not included in the treatment of EE2. Further, given the "guilty until proven innocent" rule mentioned previously, the Committee recommends that the possibility of transgenerational effects be explicitly addressed in this illustration. Although transgenerational effects may not be expected in the case of EE2, potential transgenerational consequences must be addressed in a clear and transparent manner to ensure the development of a process that can also be applied to substances for which transgenerational effects are expected.

6. The Committee recommends that a broader array of endpoints be included in Part II. For example, although EE2 is a potent estrogen receptor agonist, it also can affect the central nervous system through indirect effects (steroid biotransformation). Non-traditional endpoints such as genomic or physiologically based pharmacokinetic modeling (PBPK) studies might be considered. As noted previously, use of non-traditional endpoints requires an understanding of their relevance to the health of the organism and ultimately the population. The illustration in Part II needs to answer the question as to whether or not it is

possible to calculate population-scale impacts with EE2 and, if not, how a criterion can be developed that will truly protect populations within a reasonable level of uncertainty (consistent with the intent of the Guidelines).

7. Two key recommendations regarding Part I of the White Paper are repeated here for the sake of consistency. First, the use of weight of evidence is implicit in the evaluation, but it needs to be explicit in the Part II of the document. Interactions between weight of evidence and the Precautionary Principle (i.e., appropriate levels of uncertainty) should be clarified. Second, when appropriate data are available, ECx values (i.e., the concentration causing an effect in x percent of the test organisms) should be used rather than NOECs/LOECs (i.e., no observed effects concentrations/lowest observed effects concentrations). The EC_x value reflects the information in the entire concentration-response curve and confidence intervals can be calculated as part of the curve fitting process. In contrast, the use of NOECs or LOECs by hypothesis tests are dependent upon the test concentrations that are used, the variability of the experimental technique, and the power of the statistical test. It is also not possible to generate confidence intervals for the NOEC/LOEC determinations. When available, the data used in a NOEC/LOEC determination should be used to calculate the EC_x value. Curve fitting, which uses more of the information contained in a data set and enables derivation of confidence intervals in the estimation of the EC_x, is the preferred method for representing dose (concentration)-response information. The selection of a specific EC_x value for derivation of an aquatic life criterion depends upon the level of protection or effect that decision makers are willing to accept or detect in the field. However, an EC_{20} has been used for most species and an EC_{10} has been used for threatened and endangered species.

8. The Committee finds that the clarity and transparency could be improved in several areas. In particular, the authors need to more explicitly describe how the illustration was developed from the recommendations in Part I. Part II also needs to be more explicit regarding how specific conclusions and assessments were derived from the data. The following specific revisions are suggested:

   - Data used to arrive at the values shown in Table 3.1 need to be provided in an appendix.

   - Table 1 arguably includes chronic data (*Lytechinus* and *Strongylocentrotus* echinoderm embryo development tests and the *Acartia* embryo test) that, not surprisingly, provide the most sensitive responses. While the Committee concurs that there is "ample evidence that a CMC is not needed and that it is unnecessary to conduct further tests to meet the minimum data requirements," the differentiation between acute and chronic data needs to be clearer and more transparent along with the implications of including equivocal data. Confusion between acute and chronic data can result in unnecessary levels of uncertainty and variability in criteria development. We note that slide 11 of the presentation provided by Dr. Russell Erickson of EPA ORD at the Committee meeting on June 30 provides the requisite level of clarity and transparency and could usefully be included in the document.

   - More explicit discussion of what constitutes "sufficient information" at various decision points would be helpful.

- The validity of using non-resident species is justified by text referring to complex tables, which do not provide the level of clarity and transparency necessary. Given the importance of validating the use of non-resident species, a graphic representation of the data is required (e.g., SSDs or horizontal lines indicating ranges for survival, growth and reproduction showing where the non-resident species fit).

- The Committee suggests that the authors add a concluding section that summarizes how the process of developing an aquatic life criterion for EE2 was modified by use of the new/revised guidelines. Part II should also provide an overview of how the process is expected to ultimately influence the criteria derived (in other words, how the new recommendations changed the final outcome).

- The EE2 example in Part II relies on nominal concentrations in addition to measured concentrations. The Committee assumes that criteria will not be based on nominal concentrations. However, it is acknowledged that as long as measured concentrations are within 20% of the nominal concentrations employed in a study, the concentrations reported could be the nominal concentrations. This needs to be made clear in the document.

- The first two paragraphs on page 13 of Part II would benefit from additional information on the timing of exposures to clarify that a 16% reduction in growth occurred after 28 days (paragraph 1, line 4). The timing for lower reproduction at 0.2 and 1 ng/L (paragraph 1, line 9) should also be clarified. We have a similar suggestion for effects on fertilization success (paragraph 2, lines 7-8).

- EPA should include in the appendix the residency status of each species or genus. The authors refer to residency in interpretations, but this information is missing from the document.

- A list of acronyms such as that provided for Part I also would be useful for Part II.

- A few questions are raised regarding citations: (1) Wenzel et al. (2002) is cited in the text (p. 14, paragraph 3, line 3) but not in the References; should the date of the reference be 2001? (2) Is the Kolpin et al. (2002) reference correct (both here and in Part I) - it does not seem to apply as it is a 2-page response to a comment, not a full paper? (3) Lee and Choi (2006) is listed in the References as “in press” but surely this is not still the case 2 years later? (4) The reliance on McKim et al. (1978) is questioned regarding the assertion that a “factor of 2 difference is generally found for other chemicals” (page 13, incomplete paragraph beginning the page, last line). We note that the McKim et al. (1978) paper only referred to one chemical, copper, and was published thirty years ago in a journal that does not have a high level of peer review.

4.4. Charge Question 4. Does the Committee have suggestions that would assist EPA in implementing the proposed recommendations discussed in the white paper, particularly with respect to developing the necessary scientific data and information

and/or providing expert scientific input at the appropriate stages of the risk assessment process?

The Committee has provided comments and recommendations to assist EPA in implementing the proposed recommendations discussed in the White Paper. Many of our comments focus on actions that would assist in implementation of the recommendations in the White Paper. However, we have also provided broader suggestions to facilitate future development of aquatic life criteria for CECs. Some of our comments and recommendations elaborate upon points discussed in previous sections of this advisory report.

Points to be considered in implementing the proposed recommendations in the White Paper

- Developing new criteria for CECs will require intensive data collection/generation activities. In an ideal world, it would be the Committee's recommendation that the same level of effort required to register a new chemical or pesticide also be required to develop aquatic life criteria for CECs. Acknowledging that this may not be possible in a world of limited resources, it will be important that OW/ORD prioritize the list of CECs for which aquatic life criteria will be developed. EPA should also identify data needs for these chemicals and leverage research development activities to develop the necessary data. Prioritization of CECs and data needs is further discussed below. In addition, EPA should conduct research to evaluate the sensitivity of test organisms that could be used as surrogates for resident and endangered species. Research should also compare the sensitivity of traditional and non-traditional test endpoints.

- Leveraging research efforts of other agencies is essential. In a time of decreasing research funds within the federal government, it is important that OW/ORD seek opportunities to leverage research efforts of other government agencies (e.g., FDA, U.S. Department of Agriculture [USDA], National Oceanic and Atmospheric Administration [NOAA]). The Committee was informed that EPA and the FDA are coordinating data sharing. We recommend that this activity continue and further that it be broadened to include other government agencies. We further support international collaboration between EPA, the European Union, Environment Canada and other appropriate non-U.S. environmental agencies. In addition, it is apparent that the regulated community, industries, animal husbandry organizations (e.g., National Cattlemen's Beef Association) and Publicly Owned Treatment Works, are actively engaged in independent evaluation of CECs. Establishing a government/industry consortium may be a way of leveraging limited funds for broader data development opportunities.

- Aquatic life criteria derivation for CECs should be conducted with knowledge of data provided by the Toxic Substances Control Act (TSCA) new product review process. Chemical manufacturers provide data to EPA on new products in accordance with the TSCA pre-manufacture notification requirements. The search for possible CECs should begin at this stage. At a minimum, aquatic life toxicity data provided by manufacturers in this process could be used to help derive aquatic life criteria. EPA could also consider integrating parts of the aquatic life criteria setting process into the TSCA new product review to aid in the assessment of new product notifications. Data and other information supplied for the

new product review under TSCA could also help the Agency prioritize CECs for aquatic life criteria derivation.

- Linkages between ecological risk assessment and development of aquatic life criteria need to be articulated. The Committee finds that, in many ways, the 1985 Guidelines contain the same principles of evaluating ecological risk that were subsequently incorporated into the 1989 *Risk Management Guidance for Superfund, Volume 2: Environmental Evaluation Manual*, (U.S. EPA, 1989), and in the 1992 *Framework for Ecological Risk Assessment* (U.S. EPA, 1992). Furthermore, it was apparent from the presentations made by EPA to the Committee that the ecological risk assessment principles have been considered by OW and ORD in planning further development of aquatic life criteria for CECs. However, the link between the 1989 Risk Management Guidelines and the aquatic life criteria derivation process is not apparent. The white paper needs to explicitly consider and illustrate risk assessment principles (e.g., identification of ROPCs, development of a conceptual diagram as previously recommended by the Committee).

- Tissue-based criteria should be considered for bioaccumulative CECs where food chain transfer is a concern. As mentioned previously, EPA should consider developing tissue-based criteria (i.e., expressing the criterion as a concentration of the pollutant in fish tissue rather than a concentration in the water). Aquatic life may be impaired directly by eating contaminated food, or indirectly by loss of prey or other ecosystem alterations that could stem from CECs. EPA is developing residue-based criteria for selenium (2002 and 2004 draft criteria documents [U.S. EPA, 2007]). Arguably, selenium can be considered a contaminant of emerging concern, but it does not fit the definition provided in Section 1.1 of Part I of the White Paper. The Committee finds that it may be useful to consider using selenium as an example for development of tissue-based aquatic life criteria for CECs.

- Quantitative linkages are needed between mode of action indicators and population-level endpoints. The proposed recommendations in the White Paper are consistent with bettering the risk assessment process. However, it will be important to set priorities for technical research that addresses significant gaps in knowledge needed to develop: 1) new indicators; 2) modeling capabilities; and 3) tools that provide integration and linkage of data sources. As mentioned previously, one of the most important challenges facing EPA will be linking mode of action indicators of exposure/effects to known population-level effects measurement endpoints such as survival, growth, reproduction and development. Developing conceptual models will guide criteria development but quantitative linkages will be needed to discern how mode of action indicators connect with population-level end points. The White Paper (p. 20, lines 21- 21) states that it is important to clearly link mode of action indicators such as histopathology to growth, reproduction and development. The Committee notes that in some instances it may be possible to define scaled risk (e.g., level of biological response in cell, tissue, etc.) and relative risk. This will make it possible to develop mode of action fingerprints that may provide earlier warning and greater sensitivity in predicting population-level effects.

- Additional factors may need to be considered to protect certain species. As noted previously, development of aquatic life criteria to provide adequate levels of protection for endangered,

highly managed, protected and "charismatic" species (e.g., marine mammals, eagles, polar bears, sturgeon) may require consideration of additional factors. For example, in marine mammals a dive reflex can force more contaminant into tissue due to pressure gradients. Endangered species may have very different lag times for sexual differentiation and uptake characteristics of CECs than the commonly used test species. For example, sturgeons are both endangered and charismatic fishes, and they are known to readily accumulate many CECs for an extended developmental period prior to reproduction. Given their long lifespan, a life cycle chronic test to determine uptake would be impossible, and an early life cycle test would be inappropriate.

- There is a need to compile a list of priority CECs. To facilitate development of aquatic life criteria, the Committee finds that it would be useful for federal agencies working on CECs (e.g., EPA, the U.S. Geological Survey, the U.S. Food and Drug Administration, the National Oceanic and Atmospheric Administration, and others) to compile a list of priority CECs that may pose the greatest risks to aquatic life – in other words, use a risk assessment approach in a problem formulation exercise to determine contaminants of potential concern. It is noted that compilation of a list of priority CECs can be further facilitated by greater involvement of public/stakeholders and relevant social sciences. Related to effective prioritization of CECs for criteria derivation is the need for consistent classification of CECs into categories relevant to aquatic life criteria. As suggested in other parts of this advisory report, mode of action may be a very useful basis for such classifications, as well as for addressing the issues of mixtures of multiple contaminants and of environmental pulses and concentrations. Analytical chemistry methods should be developed for CECs that are not already being measured in aquatic environments. The Committee suggests that calculation of the ratios of the Maximum Environmental Concentrations to meaningful measures of biological effects (e.g., CCCs, or LC_xs from toxicity testing) could initially be used to develop a list of high priority CECs. This kind of exercise would likely, but not certainly, show that estrogens should be a top priority for aquatic life criteria, as indicated in the White Paper.

- There is a clear need for continued development of analytical capabilities to measure levels of CECs in the aquatic environment. The ability to detect many of the CECs at appropriate concentrations in a controlled laboratory setting may be entirely different from detecting those same low concentrations in the aquatic environment. Addressing such issues will help current long term monitoring programs (e.g., NOAA National Status and Trends and Mussel Watch programs, U.S. Geological Survey National Water Quality Assessment Program, EPA Environmental Monitoring and Assessment Program) implement a coordinated approach to better define CEC exposures in the environment. Efforts to develop methodological approaches for lowering limits of detection and standards for CECs should involve discussion among agencies as well as the regulated community. It may be important to include the National Institute of Standards and Technology in the development of environmental standards for new CECs.

- Input into the aquatic life criteria development process is needed from private industry and state government. The perspective of these important stakeholders is needed before finalizing the White Paper. These groups should be asked to provide input on the science

associated with the modifications of the Guidelines related to CECs because aquatic life criteria will be used to develop state water quality standards.

- It would make sense to consider using parallel processes to develop aquatic life criteria for compounds with similar modes of action (e.g., the estrogens, SSRIs). Since estrone, estradiol and EE2 all act through the estrogen receptor in the most sensitive taxa, fish, and there is growing evidence in the literature that their effects are additive (Thorpe et al., 2003), it would make sense to develop aquatic life criteria for the natural and synthetic estrogens using parallel processes. Similar approaches may be possible for other CECs with highly specific modes of action such as different classes of antibiotics, statin drugs, and other pharmaceuticals that are CECs.

- Further questions to consider. As EPA develops a research plan to support derivation of aquatic life criteria for CECs, it may be useful to consider the following questions mentioned previously: How can aquatic life criteria be developed to take into account the fact that aquatic organisms are exposed to mixtures of CECs and mixtures of CECs, known contaminants, and other stressors? What are the likely modes of action of CECs that are known to be present in the environment? How can field study results be used to inform the derivation of an aquatic life criterion for a CEC?

Committee recommendations to assist EPA in implementing proposed approaches to developing aquatic life criteria for contaminants of emerging concern

The Committee provides the following specific recommendations to assist EPA in implementing the Agency's proposed approaches to developing aquatic life criteria for CECs. Some of these recommendations have been discussed in the context of responses to the other charge questions in this report.

1. EPA should develop a list of high priority CECs that may pose the greatest risks to aquatic life. Additional work should then be completed to further assess the potential risks posed by these chemicals and fund the research and data collection activities needed to support future development of aquatic life criteria. In this regard, we recommend that EPA's Office of Water and Office of Research and Development look for opportunities to leverage existing research with those ongoing in other federal programs, similar programs in international agencies, and industry groups, to gather the data needed to develop the aquatic life criteria. In particular, aquatic life criteria derivation for CECs should be conducted with knowledge of data provided by the Toxic Substances Control Act new product review process. The Agency should also work with other federal agencies to develop analytical chemistry detection methods and standards for these chemicals.

2. EPA should explicitly incorporate the principles for conducting Ecological Risk Assessment into the process of deriving aquatic life criteria for CECs. The Committee recommends that the EPA develop a separate process document that discusses the intended application of aquatic life criteria for CECs, and cross-links the 1985 Guidelines, EPA's 1992 Ecological Risk Assessment Principles, and the 2008 aquatic life CEC criteria White Paper. This cross-link document should also incorporate relevant ecological risk principles from other similar

documents developed for FDA, the Toxic Substances Control Act, or the Federal Insecticide, Fungicide, and Rodenticide Act. The document should not only outline the process of aquatic life criteria development, but address elements such as contaminant exposure through food uptake, Water Effects Ratios, Whole Effluent Testing, mixtures of compounds with similar modes of action, and application of aquatic life criteria for CECs in sediment management programs. The Committee is not recommending the development of a large, comprehensive document, rather something short and concise similar to the Eco Update Bulletins that have been published by EPA's Office of Solid Waste and Emergency Response (OSWER).

3. As previously discussed, the Committee recommends that EPA incorporate the use of conceptual models and ecosystem-based criteria into the process of deriving aquatic life criteria for CECs. We note that EPA programs are moving toward developing more comprehensive ecosystem-relevant criteria that take into consideration population-community structure, ecosystem functions-processes, and ecosystem services. The data available to develop CCCs are often "traditional" toxicity test data. It is important to develop the link between the protected resource, the assessment endpoint, and the measurement endpoint. An appropriate conceptual model for deriving aquatic life criteria for a CEC (see Figure 1) may be used to develop the fate and effects data and data quality objectives needed to support the aquatic life criterion.

4. As previously discussed, EPA should consider (where appropriate) developing tissue residue-based aquatic life criteria for CECs. The Agency should consider developing tissue-based criteria using the selenium example and expanding the definition of contaminants of emerging concern to include "chemicals and other substances of increasing environmental concern due to anthropogenic activities and for which current regulatory approaches are inadequate." Tissue residue-based criteria should be considered for CECs that have potential to bioaccumulate (e.g., carbamazepine) and bioconcentrate (e.g., flame retardants). At a minimum, the conceptual model could be used to help determine how to evaluate the available environmental data and models to assess the main routes of exposure for aquatic organisms.

5. EPA should use a "mode of action" approach to develop more effective aquatic life criteria not only for CECs, but also for legacy contaminants and mixtures. Additional studies in genomic and toxicodynamics processes would provide necessary data for the identification of "mode of action" fingerprints and aid in this process, particularly in the problem formulation stage of risk assessment. This should help guide regulators to carry out the most efficient bioassays which will be used in setting thresholds or criteria.

6. The Committee recommends that EPA appropriately use novel environmental indicators (molecular, genomics, proteomics) developed by other agencies, industry, and academia in future development of criteria. For example, NOAA has developed a robust health effects assessment for bottle nosed dolphins that addresses many CECs including flame retardants and antibiotic resistance (Fair et al., 2006; Goldstein et al., 2006; Houde et al., 2006; National Oceanic and Atmospheric Administration, 2008; Reif et al., 2006). This assessment involved analysis of immune function data and other animal health information such as

clinical evaluation, blood chemistry, contaminant and hormone data. Since dolphins are apex predators that breathe the air, swim in the water and constantly eat seafood, they provide a most exposed individual model. This type of insight may be pivotal in enhancing what EPA can do using the approach outlined in Part I of the White Paper.

7. EPA should take into consideration appropriate additional factors to ensure that aquatic life criteria are protective of sensitive and commercially/recreationally important species. These species are protected by additional laws (e.g., Magnuson Stevens Fishery Conservation and Management Act, Marine Mammal Protection Act) and this may invoke other special considerations when developing aquatic life criteria.

8. Before finalizing the White Paper, EPA should obtain input from private industry and state government on the Agency's proposed approaches for developing aquatic life criteria for CECs .

9. EPA should consider developing a mixture strategy to develop aquatic life criteria for classes of compounds with similar modes of action. As previously mentioned parallel processes could be used to develop aquatic life criteria for broad classes of CECs with similar modes of action (e.g., the estrogens, SSRIs).

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