

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



**OFFICE OF THE ADMINISTRATOR  
SCIENCE ADVISORY BOARD**

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38

Date to be inserted

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 Committee.

1 Overall, the SAB finds that, in the White Paper, EPA has identified appropriate  
2 technical issues to be considered in deriving aquatic life criteria for CECs. However,  
3 EPA was constrained by the 1985 Guidelines which, although excellent when developed,  
4 were never envisioned for use with the current CECs. The derivation of aquatic life  
5 criteria needs to be risk-based, using a transparent and consistent framework that  
6 provides necessary flexibility not presently possible within the algorithm approach of the  
7 1985 Guidelines. Hence, the SAB recommends that, to the extent practicable, the  
8 derivation of aquatic life criteria be risk-based using the principles defined in EPA's 1998  
9 *Guidelines for Ecological Risk Assessment*.

10  
11 Within the context of risk-based aquatic life criteria, we recommend that EPA  
12 consider issues in addition to those identified in the White Paper. In particular, we urge  
13 EPA to create a conceptual model to guide development of aquatic life criteria for CECs.  
14 Such a conceptual model should include consideration of probable direct and/or indirect  
15 impacts on food webs, ecological processes and services, and endangered or unique  
16 species of special value or concern. We also recommend that EPA develop multiple lines  
17 of evidence, consider uncertainty, and bolster consideration of mode of action in the  
18 criteria development process. We suggest that mammalian pharmacology data available  
19 from the drug discovery process, genomics/proteomics/metabolomics, and quantitative  
20 structure activity relationships (QSARs) be used to screen CECs for modes of action and  
21 assess potential multiple modes of action for individual CECs. To increase efficiency,  
22 parallel processes could then be considered when developing aquatic life criteria for  
23 compounds with similar modes of action.

24  
25 The SAB generally supports EPA's proposed approaches for interpreting and/or  
26 adapting principles in the Guidelines to address technical issues discussed in the White  
27 Paper. However, we have noted specific concerns about these approaches and provide  
28 recommendations to improve the White Paper. We emphasize that many CECs will  
29 require special consideration because they do not fit the effect model discussed in the  
30 White Paper (i.e., disruption of endocrine function), or may not be well enough  
31 understood to allow appropriate judgment of their mode of action. In addition, we note  
32 that specific issues such as the potential for joint interactions affecting toxicity exist for  
33 many CECs that may occur in mixtures in the environment and which may also interact  
34 with environmental variables such as temperature. Such possible interactions should be  
35 considered. As more information is developed on CECs, it is possible that water quality  
36 criteria may be revised up or down for individual CECs based upon data on joint  
37 interactions; use of such data would produce more risk-based criteria.

38  
39 The SAB finds that the ethynylestradiol illustrative example in the White Paper is a  
40 well written and thorough review of the existing literature. It illustrates the complexities  
41 inherent in generating aquatic life criteria for CECs. However, we do provide  
42 recommendations to clarify the example and make it more useful.

43 The SAB also provides other suggestions to assist EPA in implementing the proposed  
44 recommendations in the White Paper. These suggestions focus on: data collection and

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.

This report does not represent EPA policy.

1 research activities; developing tissue residue-based criteria; developing exposure and  
2 effect indicators that could be used in future derivation of criteria; special considerations  
3 for sensitive or commercially/recreationally important species; and obtaining input from  
4 private industry and state governments.  
5

6 Thank you for the opportunity to provide advice on this important topic. The SAB  
7 looks forward to receiving your response to this advisory.  
8

9 Sincerely,  
10

11  
12 Dr. Deborah Swackhamer, Chair  
13 Science Advisory Board  
14

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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45

**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**

**CHAIR**

**Dr. Judith L. Meyer**, Distinguished Research Professor Emeritus, Odum School of Ecology, University of Georgia, Athens, GA

**MEMBERS**

**Dr. Richelle Allen-King**, Professor and Chair, Department of Geology, University at Buffalo, Buffalo, NY

**Dr. Fred Benfield**, Professor of Ecology, Department of Biological Sciences, Virginia Tech, Blacksburg, VA

**Dr. Ingrid Burke**, Professor and Director, Haub School and Ruckelshaus Institute of Environment and Natural Resources, University of Wyoming, Laramie, WY

**Dr. G. Allen Burton**, Professor and Director, Cooperative Institute for Limnology and Ecosystems Research, School of Natural Resources and Environment, University of Michigan, Ann Arbor, MI

**Dr. Peter M. Chapman**, Principal and Senior Environmental Scientist, Environmental Sciences Group, Golder Associates Ltd, North Vancouver, British Columbia, Canada

**Dr. Loveday Conquest**, Professor, School of Aquatic and Fishery Sciences and Director, Quantitative Ecology and Resource Management Program, University of Washington, Seattle, WA

**Dr. Kenneth Dickson**, Regents Professor, Department of Biological Sciences, University of North Texas, Aubrey, TX

**Dr. Karen Kidd**, Canada Research Chair and Professor, Biology Department, University of New Brunswick, Saint John, New Brunswick, Canada

**Dr. Wayne Landis**, Professor and Director, Institute of Environmental Toxicology, Western Washington University, Bellingham, WA

**Dr. Ellen Mihaich**, President, Environmental and Regulatory Resources, LLC, Durham, NC

1

2 **Dr. Charles Rabeni**, Leader of Missouri Cooperative Fish and Wildlife Research Unit,  
3 U.S. Geological Survey, University of Missouri, Columbia, MO

4

5 **Dr. Amanda Rodewald**, Associate Professor of Wildlife Ecology, School of  
6 Environment and Natural Resources, The Ohio State University, Columbus, OH

7

8 **Dr. James Sanders**, Director and Professor, Skidaway Institute of Oceanography,  
9 Savannah, GA

10

11 **Dr. Daniel Schlenk**, Professor, Department of Environmental Sciences, University of  
12 California, Riverside, Riverside, CA

13

14 **Dr. Heiko Schoenfuss**, Professor of Aquatic Toxicology, Department of Biological  
15 Sciences, Aquatic Toxicology Laboratory, St. Cloud State University, St. Cloud, MN

16

17 **Dr. Geoffrey Scott**, Director, Center for Coastal Environmental Health and  
18 Biomolecular Research, National Ocean Services, National Oceanic and Atmospheric  
19 Administration, Charleston, SC

20

21 **Mr. Timothy Thompson**, Senior Environmental Scientist, Science, Engineering, and the  
22 Environment, LLC, Seattle, WA

23

24 **Dr. Glen Van Der Kraak**, Professor and Associate Dean, Integrative Biology, College  
25 of Biological Science, University of Guelph, Guelph, Ontario, Canada

26

27 **Dr. Ivor van Heerden**, Associate Professor and Director, Department of Civil and  
28 Environment Engineering, LSU Hurricane Public Health Research Center, Louisiana  
29 State University, Baton Rouge, LA

30

31 **SCIENCE ADVISORY BOARD STAFF**

32

33 **Dr. Thomas Armitage**, Designated Federal Officer, U.S. Environmental Protection  
34 Agency, Washington, DC

1 **U.S. Environmental Protection Agency**  
2 **Science Advisory Board**  
3 **BOARD**  
4

5  
6 **CHAIR**

7 **Dr. Deborah Swackhamer**, Professor of Environmental Health Sciences and Co-  
8 Director Water Resources Center, Water Resources Center, University of Minnesota, St.  
9 Paul, MN

10  
11 **SAB MEMBERS**

12 **Dr. David T. Allen**, Professor, Department of Chemical Engineering, University of  
13 Texas, Austin, TX

14  
15 **Dr. John Balbus**, Chief Health Scientist, Environmental Health Program, Environmental  
16 Defense Fund, Washington, DC

17  
18 **Dr. Gregory Biddinger**, Coordinator, Natural Land Management Programs, Toxicology  
19 and Environmental Sciences, ExxonMobil Biomedical Sciences, Inc., Houston, TX

20  
21 **Dr. Timothy Buckley**, Associate Professor and Chair, Division of Environmental Health  
22 Sciences, School of Public Health, The Ohio State University, Columbus, OH

23  
24 **Dr. Thomas Burke**, Professor, Department of Health Policy and Management, Johns  
25 Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

26  
27 **Dr. James Bus**, Director of External Technology, Toxicology and Environmental  
28 Research and Consulting, The Dow Chemical Company, Midland, MI

29  
30 **Dr. Deborah Cory-Slechta**, Professor, Department of Environmental Medicine, School  
31 of Medicine and Dentistry, University of Rochester, Rochester, NY

32  
33 **Dr. Terry Daniel**, Professor of Psychology and Natural Resources, Department of  
34 Psychology, School of Natural Resources, University of Arizona, Tucson, AZ

35  
36 **Dr. Otto C. Doering III**, Professor, Department of Agricultural Economics, Purdue  
37 University, W. Lafayette, IN

38  
39 **Dr. David A. Dzombak**, Walter J. Blenko Sr. Professor of Environmental Engineering,  
40 Department of Civil and Environmental Engineering, College of Engineering, Carnegie  
41 Mellon University, Pittsburgh, PA

42  
43 **Dr. T. Taylor Eighmy**, Interim Vice President for Research, Office of the Vice President  
44 for Research, University of New Hampshire, Durham, NH

45

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45

**Dr. Baruch Fischhoff**, Howard Heinz University Professor, Department of Social and Decision Sciences, Department of Engineering and Public Policy, Carnegie Mellon University, Pittsburgh, PA

**Dr. James Galloway**, Professor, Department of Environmental Sciences, University of Virginia, Charlottesville, VA

**Dr. John P. Giesy**, Professor, Department of Zoology, Michigan State University, East Lansing, MI

**Dr. James K. Hammitt**, Professor, Center for Risk Analysis, Harvard University, Boston, MA

**Dr. Rogene Henderson**, Senior Scientist Emeritus, Lovelace Respiratory Research Institute, Albuquerque, NM

**Dr. James H. Johnson**, Professor and Dean, College of Engineering, Architecture & Computer Sciences, Howard University, Washington, DC

**Dr. Bernd Kahn**, Professor Emeritus and Director, Environmental Radiation Center, Nuclear and Radiological Engineering Program, Georgia Institute of Technology, Atlanta, GA

**Dr. Agnes Kane**, Professor and Chair, Department of Pathology and Laboratory Medicine, Brown University, Providence, RI

**Dr. Meryl Karol**, Professor Emerita, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA

**Dr. Catherine Kling**, Professor, Department of Economics, Iowa State University, Ames, IA

**Dr. George Lambert**, Associate Professor of Pediatrics, Director, Center for Childhood Neurotoxicology, Robert Wood Johnson Medical School-UMDNJ, Belle Mead, NJ

**Dr. Jill Lipoti**, Director, Division of Environmental Safety and Health, New Jersey Department of Environmental Protection, Trenton, NJ

**Dr. Lee D. McMullen**, Water Resources Practice Leader, Snyder & Associates, Inc., Ankeny, IA

**Dr. Judith L. Meyer**, Distinguished Research Professor Emeritus, Odum School of Ecology, University of Georgia, Athens, GA

1 **Dr. Jana Milford**, Professor, Department of Mechanical Engineering, University of  
2 Colorado, Boulder, CO

3  
4 **Dr. Christine Moe**, Eugene J. Gangarosa Professor, Hubert Department of Global  
5 Health, Rollins School of Public Health, Emory University, Atlanta, GA

6  
7 **Dr. Duncan Patten**, Research Professor , Department of Land Resources and  
8 Environmental Sciences, Montana State University, Bozeman, MT, USA

9  
10 **Mr. David Rejeski**, Director, Foresight and Governance Project , Woodrow Wilson  
11 International Center for Scholars, Washington, DC

12  
13 **Dr. Stephen M. Roberts**, Professor, Department of Physiological Sciences, Director,  
14 Center for Environmental and Human Toxicology, University of Florida, Gainesville, FL

15  
16 **Dr. Joan B. Rose**, Professor and Homer Nowlin Chair for Water Research, Department  
17 of Fisheries and Wildlife, Michigan State University, East Lansing, MI

18  
19 **Dr. Jonathan M. Samet**, Professor and Chair , Department of Epidemiology, Bloomberg  
20 School of Public Health, Johns Hopkins University, Baltimore, MD

21  
22 **Dr. James Sanders**, Director and Professor, Skidaway Institute of Oceanography,  
23 Savannah, GA

24  
25 **Dr. Jerald Schnoor**, Allen S. Henry Chair Professor, Department of Civil and  
26 Environmental Engineering, Co-Director, Center for Global and Regional Environmental  
27 Research, University of Iowa, Iowa City, IA

28  
29 **Dr. Kathleen Segerson**, Professor, Department of Economics, University of  
30 Connecticut, Storrs, CT

31  
32 **Dr. Kristin Shrader-Frechette**, O'Neil Professor of Philosophy, Department of  
33 Biological Sciences and Philosophy Department, University of Notre Dame, Notre Dame,  
34 IN

35  
36 **Dr. V. Kerry Smith**, W.P. Carey Professor of Economics , Department of Economics ,  
37 W.P Carey School of Business , Arizona State University, Tempe, AZ

38  
39 **Dr. Thomas L. Theis**, Director, Institute for Environmental Science and Policy,  
40 University of Illinois at Chicago, Chicago, IL

41  
42 **Dr. Valerie Thomas**, Anderson Interface Associate Professor, School of Industrial and  
43 Systems Engineering, Georgia Institute of Technology, Atlanta, GA

1 **Dr. Barton H. (Buzz) Thompson, Jr.**, Robert E. Paradise Professor of Natural  
2 Resources Law at the Stanford Law School and Perry L. McCarty Director, Woods  
3 Institute for the Environment Director, Stanford University, Stanford, CA  
4

5 **Dr. Robert Twiss**, Professor Emeritus, University of California-Berkeley, Ross, CA  
6

7 **Dr. Thomas S. Wallsten**, Professor, Department of Psychology, University of Maryland,  
8 College Park, MD  
9

10 **Dr. Lauren Zeise**, Chief, Reproductive and Cancer Hazard Assessment Branch, Office  
11 of Environmental Health Hazard Assessment, California Environmental Protection  
12 Agency, Oakland, CA  
13

14 **SCIENCE ADVISORY BOARD STAFF**

15 **Mr. Thomas Miller**, Designated Federal Officer, U.S. Environmental Protection  
16 Agency, Washington, DC

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23

**NOTICE**

This report has been written as part of the activities of the EPA Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide balanced, expert assessment of scientific matters related to the problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use. Reports of the EPA Science Advisory Board are posted on the EPA website at <http://www.epa.gov/sab>.

1

2

3

**TABLE OF CONTENTS**

4

**1. EXECUTIVE SUMMARY ..... xii**

5

**2. INTRODUCTION..... 1**

6

**3. CHARGE TO THE COMMITTEE ..... 3**

7

**4. RESPONSE TO CHARGE QUESTIONS..... 6**

8

**4.1 Charge Question 1. Comments on Recommendations in the White Paper .....6**

9

**4.1.1 Relevance of Acute Toxicity Effect Concentrations .....6**

11

**4.1.2 Defining Minimum Data Requirements Regarding Taxonomic Coverage .....9**

13

**4.1.3 Use of Non-resident Species in Criteria Development.....13**

15

**4.1.4 Defining Appropriate Chronic Toxicity Data .....16**

17

**4.1.5 Selection of Effect Endpoints for Criteria Development.....19**

19

**4.1.6 Involvement of an Expert Panel.....23**

21

**4.2 Charge Question 2. Comments on Technical Issues Addressed in the White Paper.....24**

22

**4.3 Charge Question 3. Comments on Part II of the White Paper.....29**

23

**4.4. Charge Question 4. Suggestions to Assist EPA in Implementing the Recommendations .....33**

24

**6. REFERENCES..... 39**

25

## 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 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, 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*, within the framework of the 1985 Guidelines. Criteria derived within the risk assessment framework will provide additional consistency with other on-going work at EPA and will provide necessary flexibility not presently possible within the algorithm approach of the 1985 Guidelines.

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.

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 The first part of EPA's White Paper (Part I), *General Challenges and*  
2 *Recommendations*, describes: 1) the technical challenges EPA faces in deriving  
3 aquatic life criteria for CECs; and 2) the proposed recommendations to address those  
4 challenges. The second part of the White Paper (Part II), *Illustration of*  
5 *Recommendations Using Data for 17 $\alpha$ -Ethinylestradiol (EE2)*, explores EPA's  
6 recommendations in the context of an example CEC, ethinylestradiol (EE2), which is  
7 a synthetic pharmaceutical estrogen. In its charge to the SAB, EPA requested  
8 comments on the technical merit, practicality, and implementability of  
9 recommendations in the White Paper to address: a) relevance of acute toxicity effect  
10 concentrations in setting aquatic life criteria for CECs; b) defining minimum data  
11 requirements regarding taxonomic coverage in toxicity testing; c) use of non-resident  
12 species in criteria development; d) defining appropriate chronic toxicity data; e)  
13 selection of effect endpoints upon which to base criteria; and f) involvement of an  
14 expert panel in the criteria development process. In addition, EPA asked the SAB to:  
15 comment on whether the Agency has identified the appropriate issues to be addressed  
16 in deriving aquatic life criteria for CECs; offer suggestions that may improve the  
17 utility of Part II of the White Paper; and offer suggestions that would assist the  
18 Agency in implementing proposed recommendations in the White Paper. In response  
19 to the charge questions, the Committee has provided comments and recommendations  
20 to improve the White Paper and assist EPA in deriving aquatic life criteria for  
21 contaminants of emerging concern.

22  
23 *Relevance of acute toxicity effect concentrations in deriving aquatic life criteria for*  
24 *CECs*

25  
26 Many CECs are physiologically active at concentrations orders of magnitude  
27 lower than those causing acute lethality, and concentrations sufficient to cause  
28 lethality may never occur in the environment. Therefore, in the White Paper the  
29 Agency recommends that, when sufficient information demonstrates a negligible risk  
30 of acute lethality for a CEC, the "contaminant continuous concentration" (i.e., the  
31 concentration intended to protect against the longer term effects of exposure on  
32 survival, growth, and reproduction) be used to derive aquatic life criteria. In  
33 principle, the Committee supports EPA's suggestion to derive aquatic life criteria  
34 solely from criteria continuous concentrations for CECs when available information  
35 indicates that this is appropriate. However, we have recommended the following  
36 amendments in the White Paper:

- 37  
38 • Not enough is known about some classes of CECs (e.g., nanoparticles) to  
39 determine whether acute toxicity needs to be taken into account in deriving  
40 aquatic life criteria. Therefore, all available data on any new class of CECs  
41 should be used in determining whether acute toxicity is likely to occur in  
42 environmentally relevant settings.  
43  
44 • Some CECs appear to have differing modes of action for acute toxicity vs.  
45 chronic toxicity. Lowest Observed Effect Concentrations (LOECs) and LC50s

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 (test concentrations that result in mortality to 50% of the test population) are  
2 within one order of magnitude for some CECs, making acute toxicity relevant in  
3 deriving aquatic life criteria. Therefore, “criteria maximum concentrations” to  
4 protect against acute effects should be derived for compounds where LOECs are  
5 found to be within one order of magnitude of LC50s.  
6

- 7 • Pulsed discharges of CECs may occur during natural disasters and spills and  
8 result in atypically high concentrations in the environment. As further discussed  
9 in Section 4.1.1 of this report, aquatic life criteria derivations should consider  
10 whether concentrations capable of causing acute toxicity may occur during these  
11 pulsed discharges. Under this scenario, it may be important to use Criterion  
12 Maximum Concentrations (CMCs) in addition to Criterion Continuous  
13 Concentrations (CCCs) in the aquatic life criteria derivation process.  
14
- 15 • Mixtures of CECs with comparable modes of action may result in higher effective  
16 concentrations than would be expected based on the concentrations of any single  
17 compound. Therefore, research is needed to determine how aquatic life criteria for  
18 CECs can take into account the fact that aquatic organisms are exposed to  
19 mixtures of chemicals with similar modes of action.  
20
- 21 • To maintain transparency in cases when criteria maximum concentrations are not  
22 used in criteria development, a summary of all available data that provide  
23 information on the relevance of acute toxicity should be included in any aquatic  
24 life criteria document.  
25

26 *Defining minimum data requirements regarding taxonomic coverage in toxicity*  
27 *testing*  
28

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

1 have provided specific recommendations to improve the process of determining  
2 appropriate taxonomic coverage to develop aquatic life criteria for CECs:

- 3
- 4 • EPA needs to define what constitutes a sufficiently robust set of chronic data for  
5 criteria development. Although the example used in the White Paper generally  
6 illustrates EPA's proposed process for making decisions concerning taxonomic  
7 coverage, it would be helpful if EPA were more explicit in identifying what  
8 constitutes a "sufficiently robust set of chronic data" and "a reasonable  
9 understanding of the mode of action for the chemical that may allow inferences."  
10
  - 11 • The White Paper should place greater emphasis on information useful for  
12 development of aquatic life criteria, rather than just toxicity test requirements.  
13 Incorporating effects on ecological processes (e.g., food webs, nutrient cycling,  
14 primary production) rather than only target species would be valuable in criteria  
15 development, and would follow more recent scientific thinking.  
16
  - 17 • As further discussed in Section 4.1.2 of this advisory report, EPA should consider  
18 shifting from an approach requiring a minimum level of taxonomic coverage to  
19 the approach of determining receptors of potential concern (ROPCs).  
20
  - 21 • Examples showing the unanticipated effects of CECs on non-target organisms  
22 (e.g., the impact of antibiotics on plants and effect of atrazine on the quality of  
23 algae available as food for other species) should be used in Part I of the White  
24 Paper to help describe how the aquatic life criteria development process needs to  
25 be more flexible depending on the compounds under evaluation.  
26

### 27 *Use of non-resident species in criteria development*

28

29 Historically, EPA has not included data from toxicity testing with non-resident  
30 species in the actual criteria derivation process. In the White Paper, EPA  
31 recommends that "non-resident" species data be used in the aquatic life criteria  
32 derivation process if such data would enable a better estimation of species sensitivity  
33 distributions. The Committee agrees; we find that the exclusion of non-resident  
34 species data from criteria derivation is biologically and practically inconsistent with  
35 the intent of the Guidelines (i.e., providing an objective, internally consistent,  
36 appropriate, and feasible way of deriving national criteria). We have provided a  
37 number of specific recommendations concerning the use of non-resident species data:  
38

- 39 • Because of the frequent use of non-resident species in toxicity testing, such  
40 species could potentially be over-represented in aquatic life criteria databases.  
41 Therefore, the proportion of the data set that should include resident species  
42 should be carefully evaluated by an expert advisory panel assembled to review  
43 each criterion.  
44

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

- 1 • Although non-resident species can be used for criteria development, in no case  
2 should a criterion be developed on the basis of non-resident species data alone.  
3 Although the Guidelines have been designed to protect aquatic communities  
4 (including endangered species), EPA should support research that addresses the  
5 suitability of the use of surrogate species in assessing the responses of various  
6 resident aquatic species (e.g., endangered or long-lived species and species with  
7 varying life history strategies) to endocrine disrupting and other CECs.  
8
- 9 • Differences in strains, husbandry, health, and parasite and pathogen load (i.e.,  
10 other stressors) contribute to variations in toxicity test response and thus should  
11 be considered in the criteria development process.  
12
- 13 • Issues to be considered in prioritizing species responses should include their  
14 vulnerability, endangerment status, and recreational, commercial and ecological  
15 value.  
16
- 17 • Non-resident and resident species data must meet test guidelines for data and  
18 method validity.  
19

#### 20 *Defining appropriate chronic toxicity data*

21

22 In the White Paper, EPA recommends that the Guidelines requirements for chronic  
23 toxicity test data be tightened by requiring at least one full life-cycle test for a fish  
24 (life-cycle tests are already required for invertebrates) unless there is a compelling  
25 body of information indicating that life processes outside the early life stage or partial  
26 life-cycle exposure/observation window are not critical to capturing the biologically  
27 important effects of chronic exposure to the chemical. As further discussed in  
28 Section 4.1.4 of this report, the Committee strongly supports the use of fish full life-  
29 cycle test data in appropriate cases to develop aquatic life criteria. We find that it  
30 would be useful to develop a tiered testing approach to determine an appropriate  
31 rationale for use of data from fish full life-cycle, partial life-cycle, and possibly  
32 multigenerational testing to derive aquatic life criteria for CECs with parallel modes  
33 of action. We have provided additional recommendations concerning the requirement  
34 for chronic toxicity data.  
35

- 36 • EPA should critically review data dealing with transgenerational responses of  
37 aquatic species and evaluate whether this additional testing would provide  
38 significant new information to inform the criteria development process.  
39
- 40 • Test guidelines should include flexibility to include assessment of key  
41 developmental events, and professional judgment from an expert panel should be  
42 used to evaluate the relevance of non-traditional endpoints such as immune  
43 function and organism behavior. Behavioral endpoints (e.g., predator-prey  
44 interactions) may hold some promise for criteria development if the assays can be  
45 related to population-level responses and variability can be understood.

1

2 *Selection of effect endpoints upon which to base criteria*

3

4 In the White Paper, EPA has identified a number of endpoints that could be  
5 considered in developing aquatic life criteria for CECs. Moreover, the Agency has  
6 recommended more thorough exploration of the use of such endpoints in criteria  
7 development. Generally, the Committee agrees that EPA should continue to explore  
8 the possibility of using sublethal endpoints in helping to set aquatic life criteria.  
9 However, we caution EPA that such “non-traditional” endpoints must ultimately be  
10 linked to population endpoints (i.e., they must consider potential impacts to  
11 populations, not solely effects on individual organisms). We have provided a number  
12 of recommendations concerning use of these endpoints:

13

- 14 • EPA should use “non-traditional measures” to develop an understanding of and  
15 confirm mode of action of CECs.
- 16
- 17 • As further discussed in Section 4.1.5 of this advisory report, EPA should use  
18 human health information and toxicology tools (genomics/physiologically based  
19 pharmacokinetic models [PBPKs]) to reduce the uncertainty of aquatic life criteria  
20 for CECs.
- 21
- 22 • EPA should consider the following key points concerning use of the non-  
23 traditional endpoints discussed in the White Paper: 1) vitellogenin in males and  
24 juveniles is an indicator of exposure to feminizing stressor, but its linkage to  
25 population effects is limited; 2) strong correlations between vitellogenin and  
26 fecundity have been observed in females, but this is not necessarily tied to altered  
27 endocrine mode of action; 3) anomalous intersex can be indicative of exposure to  
28 a feminizing stressor(s) but may not, at present, be directly tied to population  
29 effects; and 4) gender ratio can be indicative of endocrine alteration, but baseline  
30 information on appropriate life stages is necessary for this evaluation.

31

32 *Involvement of an Expert Panel*

33

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

45

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

- 1 • The process for the use and selection of expert panels be described in detail and  
2 that it be transparent.  
3
- 4 • The panels be given clear charges and understanding of their roles in the process.  
5
- 6 • EPA take advantage of similar expert panel processes occurring in Europe and  
7 Asia to the extent possible.  
8

9 *Technical issues addressed in the White Paper*

10  
11 The Committee was asked to comment on whether EPA has identified the  
12 appropriate technical issues in the White Paper, and whether there are additional  
13 important issues that the Agency has not identified. We find that EPA has identified  
14 appropriate technical issues in the White Paper. However, as further discussed in  
15 Section 4.1.6 of this advisory report, we recommend that the Agency address  
16 additional issues to customize and update the 1985 Guidelines and thereby increase  
17 the flexibility and specificity of the aquatic life criteria derivation process. The  
18 following additional issues are of particular importance:

- 19  
20 • In the White Paper, EPA should articulate principles that can be applied when  
21 modifying the 1985 Guidelines to develop water quality criteria for CECs. In  
22 particular, these principles should address: 1) obtaining a wide range of inputs  
23 from diverse perspectives; 2) developing a robust conceptual model; 3)  
24 developing criteria for using multiple lines of evidence; and 4)  
25 identifying/including uncertainties (quantitative and qualitative) associated with  
26 criteria development.  
27
- 28 • It is particularly important that understanding and presenting uncertainty become  
29 an intrinsic part of the aquatic life criteria development process. For example, the  
30 uncertainties inherent in understanding modes of action, concentration-response  
31 relationships, extrapolation of sensitivities, and derivation of ecological effects  
32 should be quantified and/or described in a narrative sense.  
33
- 34 • EPA should bolster the consideration of mode of action in the aquatic life criteria  
35 derivation process. As stated previously, aquatic life criteria for CECs, should  
36 take into account the fact that aquatic organisms are exposed to mixtures of these  
37 chemicals. Understanding the mode of action of a compound is very important in  
38 estimating mixture interactions. In fact, pharmacological mode of action is the  
39 basis for evaluating multiple drug prescriptions in humans by pharmacists. EPA  
40 should use mammalian pharmacology data available from the drug discovery  
41 process, genomics/proteomics/metabolomics and quantitative structure activity  
42 relationships (QSARs) to screen CECs for modes of action, identify CECs that  
43 may act in an additive manner as mixtures, and assess potential multiple modes of  
44 action for individual CECs. The Committee strongly recommends enhancing the  
45 communication and data transfer capabilities between agencies such as the U.S.

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 Food and Drug Administration (FDA) and EPA to provide mode of action  
2 information.

3

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

7

### 8 *Part II of the White Paper*

9

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

19

- 20 • EPA should explicitly recognize that EE2 is unique in being a data-rich CEC.  
21 The White Paper should highlight the fact that the Agency's interest in CECs goes  
22 beyond endocrine-active substances, and discuss how the process outlined for  
23 EE2 might be applied to other substances, particularly those for which less data  
24 are available and which have different modes of action.
- 25
- 26 • The Committee suggests that some of the illustrative pieces of Part II could also  
27 be presented in Part I in the form of succinct text boxes illustrating key concepts  
28 derived from the various recommendations, and that the recommendations could  
29 be best illustrated if the text boxes were not restricted to EE2 but rather included  
30 other CECs.
- 31
- 32 • Part II should discuss how the individual effects of EE2 on biota might be  
33 changed by mixtures of compounds, especially those with similar modes of  
34 action.
- 35
- 36 • As stated previously, a criterion should not be developed on the basis of non-  
37 resident species data alone. Therefore, Part II should indicate that resident species  
38 data, especially data from life-cycle tests using resident species, remain extremely  
39 valuable and that results from non-resident species tests may not be generalized to  
40 resident species without comparative sensitivity studies.
- 41
- 42 • The possibility of transgenerational effects should be explicitly addressed in Part  
43 II.

44

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

- 1 • A broader array of endpoints should be included in Part II. For example, although  
2 EE2 is a potent estrogen receptor agonist, it can also affect the central nervous  
3 system (through steroid biotransformation), and an endpoint should be considered  
4 to reflect this. Part II should also note that relevant and reproducible endpoints  
5 indicative of adverse population level effects need to be used.  
6
- 7 • As further discussed in Section 4.3 of this advisory report, the use of weight of  
8 evidence is implicit in the evaluation done in Part II, and should be explicitly  
9 discussed. Furthermore, when appropriate data are available, EC<sub>x</sub> values (i.e.,  
10 concentration causing an effect in x percent of the test organisms) should be used  
11 in Part II instead of NOECs/LOECs (i.e., no observed effects  
12 concentrations/lowest observed effects concentrations). The use of the EC<sub>x</sub>  
13 values takes advantage of more of the information from a toxicity test, and  
14 confidence intervals can be generated. The raw data from most toxicity tests can  
15 be used to calculate an EC<sub>x</sub> value. The selection of a specific EC<sub>x</sub> value for  
16 derivation of an aquatic life criterion depends upon the level of protection or  
17 effect that decision-makers are willing to accept or detect in the field. However,  
18 an EC<sub>20</sub> has been used for most species and an EC<sub>10</sub> has been used for threatened  
19 and endangered species. The Committee notes that if data are not available to  
20 calculate an EC value, EPA should recommend in Part II that such values be  
21 developed and used in future criteria derivation. Published data sets are available  
22 for much of the fathead minnow and other species toxicity tests conducted at  
23 EPA's Duluth Laboratory and other laboratories. If the data are available then the  
24 regression should be calculated. The Committee also notes that if the data are not  
25 available then the value of the NOEL/LOEL should be carefully evaluated.  
26 Without information on the variability of the test results, and consequently the  
27 statistical power, it is not clear what the values represent.  
28
- 29 • As further discussed in Section 4.3 of this report, the clarity and transparency of  
30 Part II could be improved in a number of areas.  
31

32 *Suggestions to assist EPA in implementing recommendations discussed in the White*  
33 *Paper*  
34

35 In Section 4.4 of this advisory report, the Committee has provided comments and  
36 recommendations to assist EPA in implementing the approaches discussed in the  
37 White Paper. The following key recommendations are provided:  
38

- 39 • As noted at the beginning of this Executive Summary, the principles for  
40 conducting Ecological Risk Assessment should be incorporated into the process  
41 of deriving aquatic life criteria for CECs. The Committee recommends that,  
42 pending revision of the 1985 Guidelines, EPA develop a separate process  
43 document that discusses the intended application of aquatic life criteria for CECs.  
44 This process document should establish linkages between the Guidelines, EPA's

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

- 1 Ecological Risk Assessment Principles (U.S. EPA, 1993, 1998), and the White  
2 Paper.  
3
- 4 • EPA should prioritize the list of CECs for which aquatic life criteria will be  
5 developed. Data needs for these chemicals should be identified, and EPA should  
6 fund the research and data collection activities necessary to support aquatic life  
7 criteria development for CECs. In this regard, the Committee recommends that  
8 EPA's Office of Water and Office of Research and Development look for  
9 opportunities to leverage EPA research with ongoing research in other federal  
10 agencies, international agencies, and industry groups.  
11
  - 12 • EPA should incorporate use of conceptual models and ecosystem-based criteria  
13 into the process of deriving aquatic life criteria for CECs. The Committee notes  
14 that EPA programs are moving toward developing more comprehensive  
15 ecosystem-relevant criteria that take into consideration population-community  
16 structure, ecosystem functions and processes, and ecosystem services.  
17 Accordingly, the Committee notes that it is important to develop the link between  
18 the protected resource, the assessment endpoint, and the measurement endpoint.  
19
  - 20 • For bioaccumulative CECs where food chain transfer is a concern, EPA should  
21 consider developing tissue-based criteria (i.e., expressing the criterion as a  
22 concentration of the pollutant in fish tissue rather than a concentration in the  
23 water).  
24
  - 25 • EPA should also consider expanding the definition of contaminants of emerging  
26 concern to include chemicals and other substances of increasing environmental  
27 concern due to anthropogenic activities and inadequate regulatory approaches.  
28 The White Paper focuses on endocrine disrupting chemicals. However, the  
29 Committee notes that some CECs do not fit the effect model of endocrine  
30 disrupting chemicals, or are not well enough understood at this time to allow a  
31 judgment of their mode of action. Nanoparticles are an example of such a class of  
32 compounds. Additional work is needed to further develop recommendations for  
33 deriving aquatic life water quality criteria for these other kinds of chemicals.  
34
  - 35 • In Section 4.4 of this advisory report the Committee recommends additional  
36 research to address important issues such as: the effects of mixtures of CECs,  
37 interactions between CEC and other stressors, modes of action of CECs,  
38 comparative sensitivities of resident and non-resident species, and use of field  
39 study results to inform the derivation of aquatic life criteria. The Committee also  
40 recommends that the discussion of taxonomic coverage in the White Paper be  
41 expanded to include specific recommendations concerning derivation of criteria to  
42 protect marine organisms. EPA's 1985 Guidelines call for assessment of marine  
43 organisms in the same manner as freshwater organisms. However, due to specific  
44 issues unique to marine organisms, such as physiological requirements (e.g.,  
45 maintenance of salt balance) and life-history strategies (e.g., reproduction tied to

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.

This report does not represent EPA policy.

1 tidal cycles), more specific guidance for CECs is likely needed. We suggest that  
2 such guidance may be best addressed by convening a “Pellston” type workshop  
3 (Society of Environmental Toxicology and Chemistry, 2008) that is comprised of  
4 experts from multiple disciplines and types of organizations.

1

2     **2.     INTRODUCTION**

3

4     EPA's Office of Water (OW) requested that the Science Advisory Board (SAB)  
5 provide advice on the Agency's proposed recommendations pertaining to derivation  
6 of water quality criteria for the protection of aquatic life (aquatic life criteria) for  
7 contaminants of emerging concern (CECs) such as pharmaceuticals and personal care  
8 products that are commonly discharged in municipal wastewaters. EPA's proposed  
9 recommendations are provided in a white paper titled *Aquatic Life Criteria for*  
10 *Contaminants of Emerging Concern* (White Paper). The White Paper, prepared by  
11 the EPA Office of Water and Office of Research and Development Emerging  
12 Contaminants Workgroup, was reviewed by the SAB Ecological Processes and  
13 Effects Committee (Committee). To augment the expertise on the Committee for this  
14 advisory activity, several environmental toxicologists with specific knowledge of the  
15 effects of endocrine disrupting chemicals also participated in the review.

16

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

33

34     The term CEC has been used by EPA to identify a variety of chemical compounds  
35 that have no regulatory standard, have been recently discovered in the natural  
36 environment because of improved analytical chemistry detection levels, and  
37 potentially cause deleterious effects to aquatic life at environmentally relevant  
38 concentrations. The Agency has indicated that it is particularly concerned about  
39 pharmacologically active chemical compounds and personal care products that are  
40 commonly discharged at wastewater treatment plants and may stimulate physiological  
41 responses in humans, plants, and animals. Many of these compounds are known to  
42 disrupt endocrine function in animals, and are thus referred to as endocrine disrupting  
43 chemicals. These chemicals may demonstrate low acute toxicity but cause significant  
44 reproductive effects at very low levels of exposure. In addition, the effects of  
45 exposure of aquatic organisms to CECs during the early stages of life may not be

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 observed until adulthood. These chemicals may also have very specific modes of  
2 action that affect only certain types of aquatic animals (e.g., vertebrates such as fish).  
3 Therefore, EPA has suggested that traditional chronic toxicity test endpoints specified  
4 in the Guidelines may not be sufficiently comprehensive, and Guidelines  
5 requirements for taxonomic coverage in toxicity testing may not be appropriate to  
6 derive aquatic life criteria for these chemicals. The White Paper focuses on  
7 recommendations to derive aquatic life criteria for endocrine disrupting chemicals.

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

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

32 The Committee finds that, in the White Paper, EPA has identified appropriate  
33 technical issues and challenges to developing aquatic life criteria for CECs.  
34 However, we recommend that the Agency address additional issues to customize and  
35 update the Guidelines and thereby increase the flexibility and specificity of the  
36 aquatic life criteria derivation process. We find that EPA could clarify the process of  
37 developing aquatic life criteria for CECs by articulating a clear set of principles that  
38 could be applied when modifying the Guidelines. We also emphasize the importance  
39 of developing a conceptual model to guide the process of developing aquatic life  
40 criteria for CECs. The Committee finds that Part II of the White Paper is a well  
41 written and thorough review of the existing literature on EE2 that illustrates the  
42 complexities inherent in generating aquatic life criteria for CECs. However, we have  
43 provided recommendations to improve the usefulness of this case example. In

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 particular we suggest that EPA more explicitly describe how the illustration in Part II  
2 was developed from the recommendations in Part I of the White Paper.

3 The Committee has also provided other suggestions to assist EPA in implementing  
4 the proposed recommendations in the White Paper. These suggestions focus on:  
5 improved data collection and research activities; development of tissue residue-based  
6 criteria (i.e., expressing the criterion as a concentration of the pollutant in fish tissue  
7 rather than a concentration in the water) for bioaccumulative CECs where food chain  
8 transfer is a concern; use of indicators for future development of criteria; special  
9 considerations for endangered or commercially/recreationally important species;  
10 obtaining input from private industry and state governments; and consideration of a  
11 mixture strategy for CECs.

### 12 13 **3. CHARGE TO THE COMMITTEE**

14  
15 EPA's Offices of Water (OW) and Research and Development (ORD) sought  
16 advice from the Science Advisory Board on the scientific and technical merit of a  
17 draft white paper on aquatic life water quality criteria (ALC) for contaminants of  
18 emerging concern (CEC). The white paper developed by the EPA Emerging  
19 Contaminants Workgroup describes how the Agency intends to address the  
20 challenges it faces in developing ALC for CECs. The specific charge questions  
21 below were provided to the Committee:

- 22  
23 1. The following recommendations have been developed to address important  
24 technical challenges and issues in deriving water quality criteria for CECs. Please  
25 comment on the technical merit, practicality, and implementability of the  
26 recommendations addressing the following issues as described in Part I of the  
27 white paper and the ethynylestradiol (EE2) case study in Part II.

28  
29 *a. Relevance of Acute Toxicity Effect Concentrations in Setting ALC for CECs:*

30  
31 Criteria consist of a Criterion Maximum Concentration (CMC), intended to  
32 address acute lethality and a Criterion Continuous Concentration (CCC), intended  
33 to address effects of chronic exposures on survival, growth, and reproduction.  
34 Many CECs are physiologically active at concentrations orders of magnitude  
35 lower than those causing acute lethality, and the high concentrations sufficient to  
36 cause lethality may never occur in the environment. Rather than rotely requiring  
37 a robust acute toxicity data set for such chemicals, the workgroup recommends  
38 that aquatic life criteria consist of only a CCC and that no CMC be derived, when  
39 sufficient information demonstrates risks of acute lethality are negligible.

40  
41 *b. Defining Minimum Data Requirements Regarding Taxonomic Coverage:*

42  
43 If an acute criterion is not calculated, then the CCC cannot be calculated using the  
44 acute to chronic ratio (ACR) approach and must be instead calculated directly  
45 from chronic toxicity data. Procedures for this are included in the Guidelines

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 (pages 40-42), but they require that acceptable chronic toxicity tests be conducted  
2 for a broad range of taxonomic groups. In the case of many CECs, toxicological  
3 research tends to focus on organisms for which the mode of action is most  
4 relevant (e.g., vertebrates for estrogen mimics) and may have limited data  
5 coverage for other taxonomic groups that will likely be less sensitive. To avoid  
6 generation of resource-intensive chronic toxicity data for insensitive species that  
7 will have little impact on the final criterion, the workgroup recommends  
8 interpreting the minimum data requirements for taxonomic coverage as  
9 information requirements instead of toxicity test requirements. By this we mean  
10 that, rather than requiring a specific chronic toxicity test, the data requirement for  
11 certain taxonomic group expected to be insensitive might be met by a body of  
12 information demonstrating insensitivity of the taxon to the CEC.

13

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

15

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

27

28 *d. Defining Appropriate Chronic Toxicity Data:*

29

30 For fish, the Guidelines allow the use of early life stage (ELS; egg to juvenile)  
31 exposures in lieu of full life-cycle (F<sub>0</sub> egg to F<sub>1</sub> offspring) or partial life-cycle (F<sub>0</sub>  
32 adult to F<sub>1</sub> juvenile) exposures for determining chronic toxicity of chemicals,  
33 unless there is reason to believe this is inappropriate. Current understanding of  
34 many CECs, particularly endocrine disrupting compounds (EDCs), is that  
35 important effects of these chemicals may not occur, or at least not be expressed,  
36 until after the ELS exposure window; in fact, partial life-cycle exposures may also  
37 miss important effects, such as those on sexual development. For such chemicals,  
38 it is clear that the definition of an acceptable chronic test must include  
39 consideration of key windows of exposure and effect (e.g., to include sexual  
40 development and reproduction in assessments of steroid hormone  
41 agonists/antagonists). However, even more broadly, the workgroup recommends  
42 that the Office of Water consider amending the chronic data acceptability  
43 requirements in the Guidelines to require at least one full life-cycle test for a fish  
44 (for invertebrates, life-cycle tests are already required) unless there is a  
45 compelling body of information indicating that life processes outside the early life

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 stage or partial life-cycle exposure/observation window are not critical to  
2 capturing the biologically important effects of chronic exposure to the chemical.  
3 This amended requirement would include all chemicals, not just EDCs/CECs.  
4

5 *e. Selection of Effect Endpoints upon Which to Base Criteria*  
6

7 Aquatic life criteria typically are based on direct measures of survival, growth,  
8 and reproduction; other measures of response are generally not included unless  
9 they can be shown to be closely linked to expected changes in population  
10 dynamics. The workgroup supports this existing guidance, but recognizes that  
11 many CECs, particularly those with very specific modes of action like steroid  
12 hormone agonists/antagonists, will have data for a wide variety of histological,  
13 biochemical, physiological, or behavioral endpoints that may warrant  
14 consideration as measures of biologically important effects. The degree to which  
15 such measures can be used to infer population level effects is likely endpoint-,  
16 chemical-, and/or organism-specific, and developing a universal list of  
17 recommended endpoints is therefore beyond the scope of the workgroup's  
18 activities. Rather, the recommendation here is simply that criteria development  
19 more thoroughly explores such possibilities.  
20

21 *f. Involvement of an Expert Panel:*  
22

23 While not addressed explicitly in the Guidelines, the complexities involved in the  
24 assessment of many CECs, and the reliance on professional judgment in making  
25 some of the determinations required under the workgroup's recommendations,  
26 make clear the need to bring the best scientific knowledge to bear in the  
27 development of criteria for CECs, as well as other chemicals. The workgroup  
28 supports the recommendation from a Society of Environmental Toxicology and  
29 Chemistry (SETAC) Pellston workshop held in 2003 (Mount et al., 2003)  
30 indicating that criteria development should involve recruitment of an expert panel  
31 early in the process to insure that all relevant issues are considered during initial  
32 development of the criterion and to provide scientific perspective on decisions  
33 that are made as part of the process. Such a panel would not undermine the  
34 authority of the Agency to make policy decisions regarding criteria, but would  
35 ensure that such policy decisions are made from the best possible technical  
36 foundation. It is envisioned that expert panels would be formed around specific  
37 chemicals, or perhaps groups of chemicals with chemical or toxicological  
38 similarities (e.g., same mode of action).  
39

- 40 2. Please comment on whether EPA has identified the appropriate issues to be  
41 addressed in deriving ALC for CECs. Are there additional important issues that  
42 EPA has not identified?  
43
- 44 3. Part II of this white paper was specifically developed as a companion to Part I and  
45 focuses on the use of ethynylestradiol as a model chemical to illustrate the

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 technical issues presented by the workgroup, as well as providing a basis for  
2 understanding the recommendations. Does the Committee have suggestions that  
3 may improve the utility of Part II of this white paper for the purposes stated  
4 above?

5

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

10

#### 11 **4. RESPONSE TO CHARGE QUESTIONS**

12

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

16

17 **4.1 Charge Question 1. Please comment on the technical merit, practicality,  
18 and implementability of recommendations addressing the following issues  
19 as described in Parts I and II of EPA's white paper on Aquatic Life  
20 Criteria for Contaminants of Emerging Concern: a) relevance of acute  
21 toxicity effect concentrations in setting aquatic life criteria for  
22 contaminants of emerging concern; b) defining minimum data  
23 requirements regarding taxonomic coverage; c) use of non-resident  
24 species in criteria development; d) defining appropriate chronic toxicity  
25 data; e) selection of effect endpoints upon which to base criteria; and f)  
26 involvement of an expert panel.**

27

##### 28 **4.1.1 Relevance of Acute Toxicity Effect Concentrations**

29

30 As discussed in EPA's White Paper, aquatic life water quality criteria consist of a  
31 Criterion Maximum Concentration (CMC) intended to protect against severe acute  
32 effects of exposure to contaminants, and a Criterion Continuous Concentration (CCC)  
33 intended to protect against the longer term effects of exposure on survival, growth,  
34 and reproduction. EPA's Guidelines (Stephan et al., 1985) specify various data and  
35 procedural recommendations for criteria derivation. The CMC is determined based  
36 on available acute values (AVs). Acute values are median lethal concentrations or  
37 median effect concentrations from aquatic animal acute toxicity tests (48 to 96 hours  
38 long) meeting certain data quality requirements. The CCC is generally determined  
39 based on available chronic values (CVs), which are either: a) the geometric mean of  
40 the highest no-observed-effect concentration (NOEC) and the lowest observed effect  
41 concentration (LOEC) for effects on survival, growth, or reproduction in aquatic  
42 animal chronic tests; or b) in some recent criteria the EC<sub>20</sub> (the test concentration that  
43 would cause a reduction in survival, growth, or reproduction in 20% of the test  
44 population) based on concentration-effect regression analyses of the toxicity test data.  
45 If chronic toxicity test data are not available for at least eight genera of aquatic

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 organisms with a specified taxonomic diversity, the CCC is derived on the basis of an  
2 acute to chronic ratio (ACR) (i.e., the ratio of the AV to CV from parallel acute and  
3 chronic tests for at least three species with a specified taxonomic diversity). EPA's  
4 White Paper states that many CECs are physiologically active at concentrations  
5 orders of magnitude lower than those causing acute lethality, and that concentrations  
6 high enough to cause acute lethality may never occur in the environment. Therefore,  
7 in the White Paper the Agency recommends that, when sufficient information  
8 demonstrates a negligible risk of acute lethality for a CEC, the ALC for that  
9 contaminant could consist of only a CCC.

10  
11 In principle, the Committee supports EPA's recommendation to derive aquatic life  
12 criteria directly from CCCs thus forgoing CMCs and ACRs. The Committee  
13 recognizes that, for many CECs, acute toxicity may only occur at concentrations  
14 several orders of magnitude greater than those likely to occur in the aquatic  
15 environment. The Committee also recognizes that the suggestion to forgo derivation  
16 of CMCs is not designed to truncate the aquatic life criteria development process, but  
17 rather is designed to allocate resources to areas most likely to affect the final aquatic  
18 life criteria and to avoid delaying implementation of aquatic life criteria due to a lack  
19 of data for species that are not likely to be sensitive.

20  
21 *Caveats concerning use of the Criterion Continuous Concentration for aquatic life*  
22 *water quality criteria*

23  
24 Although the Committee generally supports EPA's recommendation to derive  
25 aquatic life criteria for CECs directly from CCCs, we note that the following points  
26 should be considered by the Agency when implementing this recommendation:

- 27
- 28 • Some CECs do not fit the effect model of endocrine disrupting chemicals.  
29 Foremost on the Committee's list of concerns is that some CECs do not fit the  
30 effect model of endocrine disrupting chemicals (EDCs), or are not well enough  
31 understood at this time to allow a judgment of their mode of action.  
32 Nanoparticles are an example of such a class of compounds. Additional work is  
33 needed to further develop recommendations for deriving aquatic life water quality  
34 criteria for these other kinds of chemicals. EPA's White Paper focuses in  
35 particular on CECs that disrupt endocrine function in animals. Thus, many of the  
36 Committee's comments address deriving ALCs for CECs with modes of action  
37 similar to those of EDCs.  
38
  - 39 • For some CECs, acute toxicity may occur in environmental settings. The  
40 Committee notes that for some CECs, the LOECs and LC50s (test concentrations  
41 that result in mortality to 50% of the test population) are within one order of  
42 magnitude of each other, indicating that acute toxicity may occur in  
43 environmental settings. For these chemicals derivation of a CMC may be  
44 appropriate. Examples of such chemicals include fluoxetine (a selective serotonin  
45 reuptake inhibitor or SSRI) and gemfibrozil (a blood cholesterol regulator).

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1

- 2 • Some compounds have differing modes of action for acute and chronic toxicity.

3

4

5

6

7

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

18

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

28

29 *Committee recommendations concerning the relevance of acute toxicity effect*  
30 *concentrations*

31

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

36

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

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1

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

7

8 3. The Committee recommends that CMCs be derived for compounds where LOECs  
9 are found to be within one order of magnitude of LC50s.

10

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

14

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

18

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

22

#### 23 **4.1.2 Defining Minimum Data Requirements Regarding Taxonomic Coverage**

24

25 EPA's draft White Paper states that a consequence of dropping acute toxicity  
26 testing requirements for deriving aquatic life criteria for CECs is the inability to  
27 calculate a CCC using the ACR approach. The Committee notes that CCCs could,  
28 however, be developed directly from sufficiently robust sets of chronic data using  
29 procedures in the Agency's Guidelines (Stephan et al., 1985, pages 40-42). These  
30 procedures require that acceptable chronic toxicity tests be conducted for a broad  
31 range of taxonomic groups. EPA has suggested that, if insufficient data from actual  
32 toxicity tests are available to fulfill the minimum data requirements for CECs, a  
33 reasonable understanding of the toxicological mode of action for a chemical may  
34 allow inferences as to what taxa (and endpoints) are most likely to be insensitive, and  
35 measured chronic values for those taxa might not be needed. Thus, in the White  
36 Paper, EPA has recommended that, for CECs without complete chronic toxicity data  
37 sets to fulfill minimum data requirements, there be an evaluation of whether sufficient  
38 information exists to conclude that certain taxa would not be sensitive to the  
39 chemical. To accomplish this, EPA recommends interpreting the minimum data  
40 requirements for taxonomic coverage as "information requirements" instead of  
41 "toxicity test requirements." EPA notes that this would avoid generation of resource-  
42 intensive chronic toxicity data for insensitive species that would have little impact on  
43 the final criterion. The Committee agrees with EPA's recommendation. However, as  
44 further discussed below, the Agency needs to define: 1) what constitutes a sufficiently  
45 robust set of chronic data for criteria derivation, and 2) what constitutes a reasonable

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 understanding of the mode of action for the chemical that may allow inferences  
2 concerning the insensitivity of particular taxa. In addition, the Committee has noted a  
3 number of concerns that should be addressed by EPA as it implements the proposed  
4 approach.

5  
6 The Committee finds that the White Paper contains a comprehensive discussion of  
7 the issue of taxonomic coverage for developing aquatic life criteria. EPA's 1985  
8 Guidelines require that data be available for the following organisms: a salmonid in  
9 the class Osteichthyes, a second family in the class Osteichthyes, a third family in the  
10 phylum Chordata, a planktonic crustacean, a benthic crustacean, an insect, a family in  
11 a phylum other than Arthropoda or Chordata, and a family in any order of insect or  
12 other phylum not already represented. This requirement is the same for freshwater as  
13 well as marine organisms. In the White Paper, EPA notes these taxonomic coverage  
14 requirements but recommends movement to a more "expert judgment" approach that  
15 is logical and should address some of the unique properties of CECs. The Committee  
16 understands and appreciates the desirability of avoiding the extra work required to  
17 develop chronic data for species that are unlikely to be sensitive to certain CECs. On  
18 the other hand, we emphasize that it is equally important to perform adequate testing  
19 to ensure protection of aquatic life. Therefore it is important to define what  
20 constitutes a sufficiently robust set of chronic data for criteria derivation and also to  
21 provide additional guidance concerning the data needed to infer that various taxa are  
22 insensitive to chemicals with specific modes of action.

#### 23 *Concerns regarding taxonomic coverage for testing CECs*

24  
25  
26 The Committee emphasizes that there are instances in which CECs have been  
27 shown to have unanticipated effects on non-target organisms. Examples include the  
28 impact of antibiotics on plants (Brain et al., 2008) and atrazine effects on the quality  
29 of algae (Pennington and Scott, 2001). These types of examples should be used in  
30 Part I of the White Paper to help describe how the aquatic life criteria development  
31 process might need to be more flexible depending on the compounds under  
32 evaluation. In addition, we note the following important points to be considered  
33 concerning appropriate taxonomic coverage for deriving aquatic life criteria for  
34 CECs:

- 35  
36 • There is a need to maintain broad taxonomic coverage for development of aquatic  
37 life criteria. The White Paper suggests that knowing certain modes of action  
38 could potentially focus testing on a particular type of organisms (e.g., vertebrates  
39 for "estrogenic" compounds). This suggestion is not wholly supported by the  
40 Committee. As stated in the 1985 Guidelines, the procedure for estimating the 5<sup>th</sup>  
41 percentile final chronic value is to use the four lowest values in the data set. This  
42 approach considers primarily vertebrates, and it is appropriate for EE2. However,  
43 it is not always appropriate (e.g., in the case of the weak estrogenic compound  
44 bisphenol A) to give primary consideration to vertebrates. Staples et al. (2008)  
45 compared four species sensitivity distribution methods to develop a predicted no-

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 effect concentration for the aquatic environment for bisphenol A. Their study  
2 indicated that when using the Guidelines approach, the four lowest predicted  
3 values belonged to three invertebrates and one vertebrate. Clearly, this finding  
4 suggests that there is a need to maintain a broad taxonomic coverage in the  
5 development of aquatic life criteria.  
6

- 7 • Little is known of chronic effects of CECs on “wild type” species. The  
8 Committee is concerned that much of the toxicity testing for CECs has been done  
9 on animals that are highly amenable to laboratory conditions and little is known  
10 of chronic effects of chemicals on "wild types." There is also some probability  
11 that criteria protecting "lab species" might not protect species of special concern  
12 like the endangered short-nosed sturgeon, several species of Pacific salmon, or the  
13 bull trout. Research is needed to evaluate the differences and similarities between  
14 life-histories and sensitivities of endangered/threatened and standard laboratory  
15 animals used for toxicity testing in order to have more confidence that surrogate  
16 species will provide sufficient information to develop protective criteria.  
17
- 18 • Modes of action are not known for some CECs. The Committee notes that it is  
19 not safe to assume that a known mode of action is the only mode of action for a  
20 CEC. Different organisms may be affected in different ways by the same  
21 compound both as adults and at earlier stages of development. There is also the  
22 potential for synergism among CECs in mixtures and in interactions with  
23 environmental variables. It is the exception rather than the rule that modes of  
24 action are known for CECs.  
25

26 *Committee recommendations to improve the process of determining appropriate*  
27 *taxonomic coverage*  
28

29 Although the example used in Part II of EPA’s White Paper to illustrate derivation  
30 of aquatic life criterion for an endocrine disrupting chemical is data rich, the  
31 Committee notes that the same cannot be said for all or even most CECs. As EPA  
32 correctly states in the White Paper, in many cases non-traditional endpoints (i.e.,  
33 endpoints not traditionally measured in toxicity testing) will almost certainly need to  
34 be considered for CECs. However, the use of non-traditional endpoints requires an  
35 understanding of their relevance to the health of the organism, and ultimately the  
36 population, and also an understanding of the variability inherent in the measure. The  
37 key to determining appropriate taxonomic coverage and endpoints is ecological  
38 relevance. These considerations call for keeping the taxonomic coverage as broad as  
39 possible, considering the trophic position of the test organisms, and establishing a  
40 clear process or set of guidelines to determine the "insensitivity" of taxa. The  
41 Committee provides the following recommendations to improve the process of  
42 determining appropriate taxonomic coverage for criteria development:  
43

- 44 1. EPA needs to define what constitutes a sufficiently robust set of chronic data.  
45 Although the example used in the White Paper generally illustrates EPA’s

- 1 proposed process for making decisions concerning taxonomic coverage, it would  
2 be helpful to be more explicit in identifying what constitutes a "sufficiently robust  
3 set of chronic data" and "a reasonable understanding of the mode of action for the  
4 chemical that may allow inferences." The language in the White Paper introduces  
5 uncertainty in both the general approach and in setting up specific test conditions.  
6
- 7 2. EPA should consider emphasizing in the White Paper information necessary for  
8 development of aquatic life criteria rather than just toxicity test requirements. To  
9 that end, guidance on information needed to determine effects on ecological  
10 processes (e.g., food webs, nutrient cycling, and primary production) rather than  
11 only target species would be valuable in criteria development, and would follow  
12 more recent scientific thinking. In addition, there is a need for consideration of  
13 appropriate conceptual models that include fate pathways and exposure to the  
14 CECs. An understanding of exposure pathways could help direct testing toward  
15 more relevant species.  
16
- 17 3. An approach that might be considered by EPA would be to shift from a minimum  
18 level of required taxonomic coverage toward determining receptors of potential  
19 concern (ROPCs). EPA acknowledges in the White Paper example illustrating  
20 development of an aquatic life criterion for EE2 that certain types of organisms  
21 might be differentially sensitive or impacted by a compound. The Committee  
22 notes that, if sufficient information exists on sensitivity, then expert judgment  
23 concerning data development should prevail. This would result in a more focused  
24 approach to data development keeping in mind a weight of evidence rather than a  
25 broad requirement for testing all eight taxa specified in the Guidelines. This  
26 would be a more flexible risk-based rather than set approach and would be  
27 consistent with the risk-assessment terminology used throughout Part I of the  
28 White Paper.  
29
- 30 4. Examples showing the unanticipated effects of CECs on non-target organisms  
31 (e.g., the impact of antibiotics on plants and atrazine effects on the quality of  
32 algae) should be used in Part I of the White Paper to help describe how the  
33 aquatic life criteria development process might need to be more flexible  
34 depending on the compounds under evaluation.  
35
- 36 5. The Committee recommends that the discussion of taxonomic coverage in the  
37 White Paper be expanded to include specific recommendations concerning the  
38 marine environment. EPA's 1985 Guidelines call for assessment of marine  
39 organisms in the same manner as freshwater organisms. However, a discussion of  
40 testing marine organisms was omitted from EPA's White Paper. We note that  
41 including consideration of testing marine organisms would be consistent with the  
42 approach taken by the European Union as it developed its Water Framework  
43 Directive (European Commission, 2008). Due to specific issues unique to marine  
44 organisms, such as physiological requirements (e.g., maintenance of salt balance)  
45 and life-history strategies (e.g., reproduction tied to tidal cycles), more specific

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 guidance for CECs is likely needed. The Committee suggests that this guidance  
2 may be best addressed by convening a “Pellston” type workshop (Society of  
3 Environmental Toxicology and Chemistry, 2008) that is comprised of experts  
4 from multiple disciplines and types of organizations. Since testing requirements  
5 for marine organisms are already being considered by EPA, this should be stated  
6 in the White Paper.

#### 8 **4.1.3 Use of Non-resident Species in Criteria Development**

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

#### 24 *Benefit of using non-resident species data*

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

37 The White Paper states that only “species with recognized international  
38 equivalency [will] be included in criteria derivation with the full weight given to data  
39 from resident species.” This approach supports international test harmonization  
40 efforts. Specifically, the White Paper recommends use of zebrafish and Japanese  
41 medaka. These two species have been largely used for EDC testing and have shown

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 sensitivity similar to native fathead minnows and other species. Tests conducted with  
2 the zebrafish and Japanese medaka provide insight into the biochemical and  
3 physiological mechanisms involved in the toxicity of CECs. More important is  
4 matching the mode of action with the appropriate test species. The conservative  
5 nature of the endocrine system, a target for most endocrine disrupting chemicals and  
6 likely many CECs, renders the exclusion of non-resident species from aquatic life  
7 criteria development biologically indefensible. Certainly the use of any test species  
8 would be useful if it could aid in the interpretation of modes of action, relative taxa  
9 tolerance, and endpoint sensitivity comparisons. For example, studies with surrogate  
10 species have been conducted to demonstrate the toxicity of CECs to resident species,  
11 such as the Rio Grande silvery Minnow and the North American Sturgeon, that are  
12 too endangered for laboratory testing (Beyers, 1995; Dwyer et al., 2000). Additional  
13 studies of the sensitivity of marine and freshwater test species are cited in the  
14 recommendations below. In such cases test data from closely related non-resident  
15 species may provide laboratory evidence useful in the development of protective  
16 aquatic life criteria for the endangered resident species

17  
18 *Concerns regarding the use of non-resident species data*

19 Although the Committee supports the use of non-resident species data for deriving  
20 aquatic life criteria for CECs, we note the following concerns that should be  
21 considered by EPA:  
22

- 23 • Non-resident species are defined in different ways. The Committee notes that  
24 EPA's Guidelines define "non-resident" species as those not native to the  
25 continental United States and Canada. However, non-resident species have been  
26 defined in other ways. At the federal level, they have been defined as species that  
27 are not native to North America. Many states use the term non-resident species to  
28 mean species not native to their specific region. Hence local criteria are  
29 sometimes derived substituting species found locally. The definition of "non-  
30 resident" (or non-native) and invasive species should be clearly stated in EPA's  
31 White Paper. The White Paper should indicate whether organisms that have  
32 migrated (or invaded or been stocked) are considered "resident."  
33
- 34 • Non-resident species data may dominate the criteria derivation process. The  
35 Committee is concerned that non-resident species and their large respective  
36 databases could dominate the criteria derivation process. The recommendation to  
37 use non-resident species data, as presented in the White Paper, is reasonable when  
38 looking at criteria derivation from a continental perspective. However, including  
39 non-resident species data in the criteria derivation process could lead to  
40 inappropriately biased criteria development in certain sensitive geographic areas,  
41 such as cold water and oligotrophic systems. More detailed information is needed  
42 in the White Paper to address this concern.  
43

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

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

13 *Committee recommendations regarding the use of non-resident species data*

14

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

- 25 1. As noted above, non-resident species could potentially be over-represented in  
26 aquatic life criteria databases. The proportion of the data set that should include  
27 resident species is a matter that should be carefully evaluated by the expert  
28 advisory panel assembled to review each criterion.  
29
- 30 2. In no case should a criterion be developed on the basis of non-resident species  
31 data alone. Certainly if it is shown that non-resident species are ecologically  
32 relevant and appropriately sensitive then they should be used for criteria  
33 derivation as long as the studies meet appropriate quality criteria. Test species  
34 used in toxicity testing tend to be easy to rear and test, and have appropriate  
35 sensitivity levels. However, other factors should be considered when ample data  
36 are available for prioritizing species responses for criteria development. These  
37 factors include vulnerability, endangerment status, and recreational, commercial  
38 or ecological value. In order to protect endangered species, studies should be  
39 completed to compare toxicity test responses of common test species and  
40 endangered organisms and thereby determine the relevance of surrogates in the  
41 criteria development process. Previously EPA and the U.S. Fish and Wildlife  
42 Service (Besser et al., 2005; Dwyer et al., 1999, 2005; and Sappington et al.,  
43 2001) compared the sensitivity of common freshwater and marine testing species

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

- 1 with protected/endangered fish species and found that these surrogate test species  
2 (e.g., rainbow trout) may equally protect endangered species. However, these  
3 surrogate fish species do not necessarily provide protection for other threatened  
4 and endangered non-fish species such as marine mammals, wildlife and birds that  
5 reside and feed in aquatic ecosystems and utilize ecosystem goods and services.  
6 Additional consideration of these other non-fish protected species is required in  
7 developing risk-based approaches for CECs that fully protect all threatened and  
8 endangered species.  
9
- 10 3. The statement that criteria would be developed "...with full weight given to data  
11 from resident species" should include a qualifier concerning the validity of the  
12 data. An available resident species study with no obvious protocol, no  
13 measurement of test concentrations, or other protocol concerns should be assigned  
14 a lower priority than a fully valid Organization for Economic Cooperation and  
15 Development (OECD)/EPA guideline study with a "non-resident" species.  
16 However, the Committee qualifies this recommendation by emphasizing that all  
17 scientifically valid data should be used in setting criteria.  
18
- 19 4. Differences in strains, husbandry, health, and parasite and pathogen load  
20 contribute to response variation and should be considered in the aquatic life  
21 criteria development process.  
22
- 23 5. Non-resident as well as resident species test data must meet Guidelines  
24 requirements for data and method validity.  
25

#### 26 **4.1.4 Defining Appropriate Chronic Toxicity Data** 27

28 EPA's Guidelines state that acceptable chronic tests for derivation of aquatic life  
29 criteria are full life-cycle exposures ( $F_0$  egg to  $F_1$  offspring) for vertebrates and  
30 invertebrates, as well as partial life-cycle (adult to juvenile) and early life-stage (egg  
31 to juvenile) tests for fish. EPA's White Paper states that some CECs may have potent  
32 effects on life processes that lie outside the exposure period represented by early life  
33 stage tests or effects may not be manifested until later in development. Thus, early  
34 life stage tests might not be good predictors of chronic toxicity for these chemicals.  
35 In the White Paper, EPA recommends that the Guidelines requirements for chronic  
36 toxicity data be tightened by requiring at least one full life-cycle test for a fish (for  
37 invertebrates, life-cycle tests are already required) unless there is a compelling body  
38 of information indicating that life processes outside the early life stage or partial life-  
39 cycle exposure/observation window are not critical to capturing the biologically  
40 important effects of chronic exposure to the chemical.  
41

42 The Committee strongly supports EPA's recommendation to amend the chronic  
43 data acceptability requirements in the Guidelines. However, we are divided in our  
44 assessment of the "guilty until proven innocent" approach in the White Paper (page  
45 17). Some Committee members view it as appropriate while others view it as

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 extremely precautionary. The White Paper states that "...it is probably wiser to  
2 require that the chronic toxicity data for fish include exposure and observation over a  
3 full life-cycle unless there is an affirmative reason to believe that it is not necessary."  
4 The statement is used in the context of requiring a full life cycle study instead of  
5 relying on an early life stage test for fish. Some Committee members find that the  
6 statement does not appear to fit the process of setting aquatic life criteria, whereas  
7 others find it to provide an important perspective for establishing aquatic life criteria.  
8

9 The Committee also supports extending the recommendation to amend the chronic  
10 data acceptability requirement to all chemicals, not just endocrine disrupting  
11 chemicals and CECs. The Committee finds that EPA's recommendation is justified  
12 based on evidence showing that a number of chemicals may exert effects during the  
13 period of gonadal differentiation, and that these effects may not be manifested until  
14 much later in life. Including at least one full life cycle test in the test guidelines for  
15 fish ensures that these types of effects are captured.  
16

17 *Issues to be considered in defining appropriate chronic toxicity data*  
18

19 Although the Committee supports EPA's recommendations concerning use of  
20 chronic toxicity data for development of aquatic life criteria, we note the following  
21 issues that should be addressed in defining appropriate chronic toxicity test data:  
22

- 23 • Transgenerational effects of CECs are potentially important and should be  
24 considered. There is evidence for some chemicals that exposure in one generation  
25 creates effects in a later generation that were not observed in prior generations  
26 even in the same life stage. Accordingly, the chronic toxicity data requirements  
27 include a full life-cycle test to be conducted for at least one species of fish. There  
28 is still some uncertainty as to whether a full life-cycle test might underestimate  
29 the chronic effects that would be seen in exposures extending over more than two  
30 generations (multigenerational testing). We do not recommend adding a  
31 requirement for multigenerational testing to the Guidelines, but suggest that EPA  
32 critically review data dealing with transgenerational responses of aquatic species  
33 and evaluate whether this additional testing provides significant new information  
34 that informs the evaluation process. This critical review should examine the  
35 utility of multigenerational tests relative to proposed fish full life-cycle (FFLC)  
36 tests as well as partial life-cycle (PLC) tests and early life-stage studies. The  
37 intent of this recommendation is to ensure that a full range of development (e.g.,  
38 early life stage to adult) is evaluated sufficiently to assure adequate aquatic life  
39 protection. The Committee generally supports the concept of fish full life-cycle  
40 testing because it spans the entire exposure window in the early life-cycle to  
41 adults. The Committee also supports further development of a tiered testing  
42 approach to derive an appropriate rationale for the use of FFLC, PLC, and  
43 possibly multigenerational testing for chemicals with parallel modes of action.  
44

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

- 1 • Flexibility in test guidelines is needed to include key developmental events. Test  
2 guidelines must have the flexibility to include assessment of key developmental  
3 events (e.g., metamorphosis in amphibians, acquisition of saltwater tolerance),  
4 particularly if these processes are identified in a ROPC.  
5
- 6 • Test methods should include non-traditional measures that may be linked to  
7 ecologically relevant endpoints. There is a need to ensure that the test methods  
8 include provisions to consider non-traditional endpoints such as immune function  
9 and organism behavior. These endpoints may directly impinge on ecologically-  
10 relevant endpoints such as growth, reproduction and survival. In this case,  
11 professional judgment from an expert panel is needed to determine the relevance  
12 of these non-traditional endpoints.  
13

14 The Committee also notes the following practical issues that should be addressed  
15 if the chronic toxicity data recommendation in the White Paper is to be implemented:  
16

- 17 • Surrogate test species may be needed. A key issue to be addressed is the  
18 suitability of surrogate test species. Surrogates may be needed in the case of: 1)  
19 long-lived species with delayed sexual maturity; 2) organisms of large size (which  
20 precludes their suitability as a test species in the laboratory), 3) endangered  
21 species, and 4) species for which there is little knowledge of the husbandry  
22 conditions or background biology. There is also uncertainty in how differences in  
23 the physiology and life history strategies (i.e., long-lived versus short-lived  
24 species, differences in maternal-fetal transport of contaminants) may affect the  
25 response of aquatic species to CECs and endocrine disrupters. Many of these  
26 issues represent significant data gaps that need to be addressed. In these cases,  
27 expert opinion may be needed to assist EPA in determining the suitability of  
28 surrogate test species for use in criteria development.  
29

30 *Committee recommendations regarding defining appropriate chronic toxicity data*  
31

32 As discussed above, the Committee strongly supports EPA's recommendation  
33 concerning the use of at least one full life cycle test for a fish in appropriate cases for  
34 testing all kinds of chemicals when deriving water quality criteria for the protection  
35 of aquatic life in marine and freshwater environments. We provide the following  
36 recommendations to implement the requirement for chronic toxicity data:  
37

- 38 1. As discussed above, EPA should critically review data dealing with  
39 transgenerational responses of aquatic species and evaluate whether or not this  
40 additional testing provides significant new information that informs the evaluation  
41 process.  
42
- 43 2. EPA should support research that addresses the suitability of the use of surrogate  
44 species in assessing the response of aquatic species (e.g., endangered or long lived  
45 species; species with varying life history strategies) to CECs.

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44

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, 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).

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

- 1 • Activational biological effects can provide useful information. CECs often  
2 induce changes in behaviors, secondary sexual characteristics, or levels of  
3 hormones or hormone-induced products. Many of these responses are transitory  
4 or may revert to their prior or normal condition with cessation of exposure.  
5 Accordingly, it is often difficult to interpret these activational responses in  
6 relation to higher level biological effects. Nevertheless, these endpoints do  
7 provide useful information, particularly regarding mode of action. Consideration  
8 of such effects would certainly help reduce uncertainty in a risk assessment  
9 paradigm. While it is clear that these endpoints alone could not be utilized to set  
10 criteria, the Committee notes that sublethal endpoints integrated with  
11 toxicodynamic and kinetic factors could provide useful data in a problem  
12 formulation step related to some CEC, and could also help identify data gaps that  
13 may help reduce uncertainty and aid in criteria development.  
14
- 15 • Use of non-traditional sublethal endpoints holds promise but further validation of  
16 such endpoints is needed. Behavioral endpoints related to population (e.g.,  
17 predator-prey interactions) and reproduction may hold some promise for criteria  
18 development if the assays can be validated and variability can be understood.  
19 Immune function and genetic variation are also endpoints that should be explored  
20 (Filby et al., 2007). In addition, models capable of extrapolating laboratory  
21 endpoints to the population level should be targeted for development (Ankley et  
22 al., 2008; Chandler et al., 2004). Exploration of endpoints related to ecological  
23 processes (e.g., primary productivity, decomposition rate) is also warranted.  
24
- 25 • Research is needed to determine how aquatic life criteria for CECs can take into  
26 account the fact that aquatic organisms are exposed to mixtures of these  
27 chemicals. As noted previously, in developing aquatic life criteria for CECs it  
28 will be particularly important to consider the effects of mixtures. The Committee  
29 provides a number of comments in this regard. We note that understanding the  
30 mode of action of a compound is extremely important in estimating mixture  
31 interactions. Mixtures of CECs with comparable modes of action may result in  
32 higher environmental concentrations than would be expected for any single  
33 compound. In fact, pharmacological mode of action is the basis for evaluating  
34 multiple drug prescriptions in humans by pharmacists. For example, if it is  
35 known that a vertebrate is exposed to aryl hydrocarbon receptor (AhR) agonists  
36 and estrogen receptor (ER) agonists, it is likely that antagonism of each effect  
37 could occur. Information regarding mode of action should be made available to  
38 EPA from manufacturers or other governmental agencies (e.g., available from the  
39 U.S. Food and Drug Administration [FDA] or from testing under the requirements  
40 of the Federal Insecticide, Fungicide, and Rodenticide Act [FIFRA]). It is  
41 through use of this information that non-traditional measures can confirm similar  
42 or different modes of action in targeted ROPCs. The Committee strongly  
43 recommends enhancing the communication and data transfer capabilities between  
44 agencies such as FDA and EPA to provide these data.  
45

- 1 • Mode of action fingerprints developed by evaluating combined sublethal  
2 endpoints should be linked to *in vivo* species testing. The Committee notes that  
3 much of the toxicity testing for compounds such as pharmaceuticals and personal  
4 care products has been conducted using mammals and other vertebrates.  
5 Additional data are needed for other “keystone” species. We suggest that the  
6 choice of species, critical life stages and complicating stressors (i.e., salinity and  
7 temperature) could be potentially identified in a problem formulation/conceptual  
8 model stage of a risk assessment paradigm. If these data are not available,  
9 research and development could be undertaken to obtain mode of action  
10 “fingerprints” for a CEC or any other compound through combined sublethal  
11 endpoints (i.e., genomic-transcriptomic, proteomic, metabolomic) and  
12 toxicodynamic/kinetic feature evaluations within sentinel species (to cover  
13 taxonomic issues). It is likely that, through this process, additional “side-effects,”  
14 or species-specific modes of action, can be obtained. These data could be  
15 integrated with “fingerprints” of other compounds with different modes of action  
16 and utilized to help address mixture issues or potential indirect effects. The  
17 toxicity to a particular species at a particular trophic position could then be  
18 modeled to assess indirect impacts on other populations.  
19
- 20 • Additional research is needed to link biomarkers to effects. The Committee notes  
21 that the concept of using biological responses occurring prior to impacts on  
22 growth, reproduction and survival has been proposed for more than 20 years as a  
23 way to detect adverse effects in a population before the population is altered.  
24 While there are examples of such “biomarkers of effect,” we find that the linkages  
25 between biochemical, histological, and behavioral endpoints and reproduction,  
26 growth, and survival are likely life-stage dependent and are difficult to validate,  
27 particularly in the field. We note that “biomarkers of exposure” are available but  
28 research is needed to interpret their significance.  
29
- 30 • Vitellogenin production is an excellent biomarker of exposure to feminizing  
31 chemicals. One of the best examples of exposure biomarkers is the biological  
32 response of vitellogenin production in male or juvenile animals. Vitellogenin is  
33 an excellent *in vivo* biomarker for exposure to feminizing chemicals. If the  
34 response is measured in the whole animal, it incorporates estrogenic as well as  
35 anti-androgenic or other modes of action that can cause a feminized response  
36 (production of an egg-yolk precursor). It is important to point out that this assay  
37 is not identical to estrogen-receptor (ER) based *in vitro* bioassays. Some  
38 compounds such as EE2 are very potent ER agonists but also have other modes of  
39 action that may alter endocrine systems (Tabb and Blumberg, 2006) such as the  
40 inhibition of several isoforms of cytochrome P450 (e.g., CYP3A), which are  
41 important in the clearance of endogenous steroids (Parkinson, 2001).  
42 Nonylphenols also have multiple modes of action other than direct binding to the  
43 ER that lead to enhanced estradiol synthesis (Harris et. al, 2001; Kazeto et al.,  
44 2004; Martin-Skilton et al., 2006; Meucci et al., 2006; Thibaut and Porte, 2004).  
45 So the observation of vitellogenin induction within an oviparous male or juvenile

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 organism does not indicate total specificity with regard to mode of action.  
2 Anything that increases endogenous estrogen biosynthesis or diminishes clearance  
3 would also provide this biological response. The Committee notes that the  
4 reduction of vitellogenin in females may not indicate anti-estrogenic effects or  
5 even alterations of endocrine activity, as basic hepatotoxicants in females can  
6 elicit a similar effect. However, we point out that the correlations between  
7 fecundity and vitellogenin in females have been observed to be strong even  
8 though this may not indicate mode of action (Miller et al, 2007) (see discussion  
9 below). Additional studies are needed to examine hepatotoxicants or compounds  
10 with modes of action exclusive of endocrine targets.  
11

12 • The linkage of vitellogenin production to biological effects is limited. While the  
13 linkage of vitellogenin to exposure is reasonably solid, linkages of vitellogenin in  
14 males/juveniles to higher biological effects such as altered reproduction, survival  
15 and growth are limited, even though the relationship may make intuitive sense.  
16 Several studies have shown relationships between vitellogenin and reproduction  
17 in the laboratory, often at concentrations beyond probable effect concentrations  
18 (Thorpe et al., 2007), but few examples of population alterations have been noted  
19 in the field. Even in the United Kingdom, where gender shifts to females were  
20 originally noted and correlated with vitellogenin induction within males, intersex  
21 individuals, and other histological anomalies, overall abundance declines within  
22 the species of interest have not been reported. In fact, only one study (Kidd et al.,  
23 2007) has linked population crash with vitellogenin or histopathological  
24 alterations in fish. A similar occurrence has been noted in laboratory studies  
25 where vitellogenin expression may or may not be linked to intersex (Grim et al.,  
26 2007), which in turn may or may not lead to gender shifts. Even the relatively  
27 clear signal of gender shift, while clearly impacting reproduction in laboratory  
28 animals optimized to a specific gender ratio, may not significantly impact field  
29 populations in an uncharacterized species (Munday et al., 2006). Clearly, a better  
30 understanding of the population dynamics of a ROPC is needed to determine the  
31 phenotypic plasticity of the gender ratio. Thus, gender shifts should be viewed  
32 with caution, particularly in species that have not been well studied.  
33

#### 34 *Committee recommendations regarding selection of endpoints*

35

36 The Committee agrees that EPA should continue to explore the possibility of using  
37 sublethal endpoints in helping to set aquatic life criteria. We provide the following  
38 recommendations in this regard:  
39

40 1. EPA should pursue the use of “non-traditional measures,” or endpoints for criteria  
41 development, as discussed in the White Paper. The Agency should ensure that  
42 such measures can be tied to impacts on populations or ecological processes, not  
43 just to effects to individual organisms.  
44

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

- 1 2. EPA should use “non-traditional measures” when appropriate to develop an  
2 understanding of and confirm mode of action.  
3
- 4 3. EPA should use human health information and toxicology tools (genomics/  
5 PBPKs) when appropriate and available to reduce the uncertainty of aquatic life  
6 criteria.  
7
- 8 4. EPA should consider the following key points concerning use of the non-  
9 traditional endpoints discussed in the White Paper: 1) vitellogenin in males and  
10 juveniles is an indicator of exposure to a feminizing stressor(s), but its linkage to  
11 population effects is limited; 2) strong correlations between vitellogenin and  
12 fecundity have been observed in females, but this is not necessarily tied to altered  
13 endocrine mode of action; 3) Anomalous intersex is indicative of a gender  
14 stressor(s), but has not been strongly tied to population effects; and 4) gender ratio  
15 can be indicative of endocrine alteration, but baseline information on appropriate  
16 life history is necessary for this evaluation.  
17

#### 18 **4.1.6 Involvement of an Expert Panel**

19

20 Because development of aquatic life criteria for CECs may be dependent on  
21 technical interpretations of a wide range of toxicological information, EPA has  
22 proposed that expert panels be used to provide professional judgment during criteria  
23 development. The Committee concurs that strong, active participation by a panel of  
24 outside experts will be necessary to ensure that the approaches used (including the  
25 designs for toxicity testing, the selected endpoints, and the necessary species and tests  
26 to be used, i.e., the ROPCs) are the most appropriate for the compound under  
27 scrutiny. As the EPA moves away from firm requirements for species and tests, it  
28 will become increasingly important that expert panels comprising diverse expertise be  
29 utilized to ensure that the best data are selected for necessary decisions. The National  
30 Academy of Sciences and Society of Environmental Toxicology and Chemistry have  
31 suggested similar approaches. In a recent report dealing with ecological risk  
32 assessment in environmental decision making (U.S. EPA Science Advisory Board,  
33 2007), the SAB strongly recommended that expert panels be used to provide  
34 assistance to EPA during the problem formulation phase of ecological risk  
35 assessments. The same recommendations are appropriate for development of aquatic  
36 life criteria. Involving a suite of experts with a balanced range of perspectives during  
37 the very early stages of problem formulation, and continuing their involvement as  
38 external reviewers at strategic junctures throughout the process, will significantly  
39 improve quality, utility, and defensibility of the criteria.  
40

#### 41 *Committee recommendations concerning the use of expert panels*

42

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

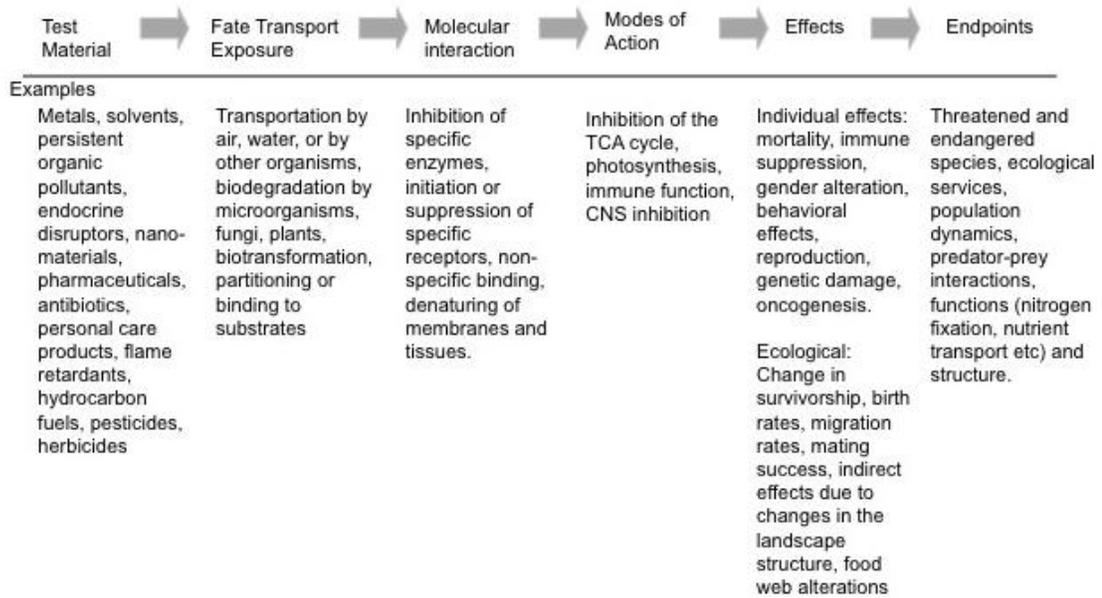
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45

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, where 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

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30

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 following additional issues in order to customize and update the 1985 Guidelines and thereby increase the flexibility and specificity of the aquatic life criteria derivation process:

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.
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

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 model; develop multiple lines of evidence; and identify uncertainties (quantitative  
2 and qualitative) associated with criteria development. Each of these risk  
3 assessment-based principles is further discussed below:

- 4
- 5 - Seek a wide range of inputs. EPA should seek input from a diversity of  
6 experts representing: Agency scientists, academic scientists, scientists in  
7 business and industry, state and tribal scientists, and the environmental  
8 community on the problem formulation, conceptual model development,  
9 modifications to the Guidelines dictated by the properties of a CEC, and the  
10 resulting recommendation for the aquatic life criterion. Adherence to this  
11 principle will ensure that the process stimulates a robust discussion and is  
12 informed by and acceptable from a diversity of perspectives. This diversity  
13 should include input from chemists, modelers, toxicologists, ecologists, and  
14 risk assessors.
  - 15
  - 16 - Determine appropriate ROPCs. The process needs to clearly identify the need  
17 to determine appropriate receptors of potential concern and not simply focus  
18 on “traditional” test organisms.
  - 19
  - 20 - Develop a robust conceptual model. At the start of the criterion development  
21 process, the available data on fate and effects should be examined and used to  
22 develop a conceptual model (e.g., Figure 1). Structure activity data and  
23 modes of action of similar compounds/materials should be consulted to inform  
24 model development. An expert panel should be convened to assist in the  
25 problem formulation and conceptual model development step. Uncertainty  
26 should be identified in the model and used to identify strategic efforts to  
27 reduce uncertainty. The conceptual model should include more than fate and  
28 effects data. It should include consideration of probable direct and or indirect  
29 impacts on food webs, ecological processes and services, and unique,  
30 endangered or keystone species or species of special societal value or concern  
31 (charismatic species).
  - 32
  - 33 - Develop multiple lines of evidence. The committee finds that a multiple line  
34 of evidence approach has the potential to inform decision making and the  
35 criterion recommendation. It also can serve to reduce uncertainty when the  
36 lines converge and reinforce each other.
  - 37
  - 38 - Identify uncertainties and conduct uncertainty analysis. As further discussed  
39 below, EPA should identify the uncertainties associated with the criteria  
40 developed for CECs. At all stages of criteria development, uncertainty should  
41 be quantified and/or qualitatively discussed. Uncertainty should be used to  
42 focus and prioritize data generation efforts.
  - 43
  - 44 3. EPA should develop a system or process to assist the development of criteria for  
45 CECs. The system would establish a set of rules to enable analysis of information

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 supplied by the user and lead to recommendations concerning one or more  
2 courses of user action. The Committee finds that such a system would be an  
3 important tool for capturing and maintaining the state of the art in aquatic life  
4 criteria development. It would serve as a vehicle for connecting fate and effects  
5 assessment tools and capturing expert knowledge, and it could serve as a platform  
6 for deriving priorities for future research in assessing the risks of contaminants to  
7 aquatic life and ecosystems.  
8

9 4. The Committee strongly recommends that understanding and presentation of  
10 uncertainty become an intrinsic part of the aquatic life criteria development  
11 process. The presentation of uncertainty needs to be an explicit and transparent  
12 part of the analysis. For example, the uncertainties inherent in understanding  
13 modes of action, determination of concentration-response relationships,  
14 development of species sensitivity distributions, and derivation of ecological  
15 effects should be quantified or described in a narrative sense. An important  
16 aspect of this is developing an a priori understanding of the amount and types of  
17 uncertainties that preclude the derivation of an aquatic life criterion. These  
18 uncertainties can be classified into the categories listed below:  
19

- 20 - Uncertainties that preclude the derivation of an aquatic life criterion.
- 21
- 22 - Areas in which uncertainties may be important and can be resolved with  
23 additional modeling, research or a better understanding of the relationship of  
24 the uncertainty to the standard setting process.  
25
- 26 - Uncertainties that do not preclude the setting of an aquatic life criterion but  
27 form the basis for future research programs.  
28

29 Identification of uncertainties in these categories can be addressed in derivation of  
30 the conceptual model in consultation with the expert panel.  
31

32 5. EPA should bolster the consideration of mode of action and ecology in the aquatic  
33 life criteria derivation process. A better understanding of the molecular  
34 interactions and modes of action will reduce uncertainty in that aspect of the  
35 conceptual model. A better understanding of the ecological effects and context  
36 will allow more specific and flexible predictions of risks to individuals,  
37 populations and ecological structure and function. This will reduce predictive  
38 uncertainty. The Committee encourages the developers of the aquatic life criteria  
39 to further integrate these advances into the criteria derivation process.  
40

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

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

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

11

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

23

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

35

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

42

43 10. In developing aquatic life criteria for CECs, EPA should give special  
44 consideration to the protection of threatened and endangered species. Unlike  
45 other species, threatened and endangered species are managed so that effects on

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 individuals, not populations, are avoided. Specific mortality of threatened and  
2 endangered individuals, along with the contribution of each to the survival of the  
3 population, are parameters requiring accuracy with a minimum of uncertainty. In  
4 certain cases specific populations or evolutionarily significant units are the  
5 assessment endpoints to be considered.  
6

7 **4.3 Charge Question 3. Part II of this white paper was specifically developed**  
8 **as a companion to Part I and focuses on the use of ethynylestradiol as a**  
9 **model chemical to illustrate the technical issues presented by the**  
10 **workgroup, as well as providing a basis for understanding the**  
11 **recommendations. Does the *Committee* have suggestions that may**  
12 **improve the utility of Part II of this white paper for the purposes stated**  
13 **above?**  
14

15 The Committee finds that Part II of EPA's white paper, which is intended to  
16 illustrate application of EPA's recommendations concerning aquatic life criteria for  
17 CECs (rather than serve as a comprehensive case-study) is a generally well-written  
18 and thorough review of the existing literature on EE2; however, some improvements  
19 are recommended to enhance clarity. The Committee agrees that EE2 is an  
20 appropriate initial focal CEC given: 1) the extensive data available relative to other  
21 CECs; and 2) the ease with which it illustrates the complexities inherent in generating  
22 CEC-specific water quality criteria to protect aquatic life. Nevertheless, there may be  
23 limitations as to how readily the insights gained from the EE2 illustration can be  
24 applied to other CECs. The following recommendations are provided to improve the  
25 usefulness of the EE2 example.  
26

27 *Committee recommendations to improve the usefulness of the illustrative example*  
28

- 29 1. In the White Paper, EPA should explicitly recognize that EE2 is unique in being a  
30 data-rich CEC. The White Paper should highlight the fact that the Agency's  
31 interest in CECs goes beyond endocrine-active substances, and discuss how the  
32 example of EE2 might be extrapolated to other substances, particularly to data-  
33 poor substances. EPA should consider conducting a similar assessment for a  
34 compound with a minimal data set (in contrast to the maximal set of data  
35 available for EE2) and evaluate the new approach accordingly.  
36
- 37 2. The Committee suggests that some of the illustrative pieces of Part II could also  
38 be included in Part I in the form of succinct text boxes illustrating key concepts  
39 derived from the various recommendations (e.g., why certain steps in the  
40 Guidelines were included and others were not). Further, we suggest that the  
41 recommendations could be best illustrated if the text boxes were not restricted to  
42 EE2 but rather included other CECs (e.g., non-endocrine-active compounds, data-  
43 poor CECs). In making these revisions, we urge the authors to ensure that the  
44 high level of readability inherent in the present version of Part I is retained.  
45

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

- 1 3. Regarding the scope of the material included in the EE2 example, we note that the  
2 White Paper fails to address how the influence of EE2 might be affected by  
3 mixtures of compounds, especially those with similar modes of action (e.g.,  
4 estradiol, estrone), as well as environmental (e.g., temperature) and biological  
5 (e.g., disease, starvation) modifying factors. Although the Committee recognizes  
6 that various offices/groups within EPA are investigating mixtures of compounds,  
7 and the White Paper cannot address all relevant issues in the development of  
8 guidelines, the document needs to be explicit regarding the importance of  
9 considering multiple stressors as well as synergies among CECs. For example,  
10 the White Paper should, at the very least, state the rationale for not considering all  
11 estrogens within a given body of water, and should provide examples of mixtures  
12 and synergies that could affect the toxicity of EE2.  
13
- 14 4. Regarding choice of taxa for criteria derivation, the Committee agrees that,  
15 although use of non-resident species to assess EE2 effects appears to fit this case  
16 example, such may not always be the case. As such, the document should  
17 indicate that: 1) resident species data, especially life-cycle tests from resident  
18 species, remain extremely valuable, and 2) results from non-residents, while  
19 providing useful information, may not be generalized to resident species unless  
20 data are available to compare the sensitivities of the non-resident and resident  
21 species. We are also concerned that certain sensitive taxa such as amphibians  
22 were not included in Table 3.2, and that the key issue of development time to  
23 sexual maturity for long-lived, charismatic species, such as sturgeon, is not  
24 addressed in the document. Research should be conducted to develop  
25 comparisons between species that are long-lived and surrogate test species.  
26
- 27 5. The Committee is concerned that transgenerational effects were not considered in  
28 Part II of the White Paper. On page 14 in Part II of the White Paper, EPA states  
29 that “it does not seem that the evidence for transgenerational effects is sufficient  
30 for requiring their inclusion in the definition of an acceptable chronic test.” Given  
31 EE2’s role as an endocrine disrupting chemical, it is surprising that  
32 transgenerational effects were not included in the treatment of EE2. Further,  
33 given the “guilty until proven innocent” rule mentioned previously, the  
34 Committee recommends that the possibility of transgenerational effects be  
35 explicitly addressed in this illustration. Although transgenerational effects may  
36 not be expected in the case of EE2, potential transgenerational consequences must  
37 be addressed in a clear and transparent manner to ensure the development of a  
38 process that can also be applied to substances for which transgenerational effects  
39 are expected.  
40
- 41 6. The Committee recommends that a broader array of endpoints be included in Part  
42 II. For example, although EE2 is a potent estrogen receptor agonist, it also can  
43 affect the central nervous system through indirect effects (steroid  
44 biotransformation). Non-traditional endpoints such as genomic or physiologically  
45 based pharmacokinetic modeling (PBPK) studies might be considered. As noted

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

- 1 previously, use of non-traditional endpoints requires an understanding of their  
2 relevance to the health of the organism and ultimately the population. The  
3 illustration in Part II needs to answer the question as to whether or not it is  
4 possible to calculate population-scale impacts with EE2 and, if not, how a  
5 criterion can be developed that will truly protect populations within a reasonable  
6 level of uncertainty (consistent with the intent of the Guidelines).  
7
- 8 7. Two key recommendations regarding Part I of the White Paper are repeated here  
9 for the sake of consistency. First, the use of weight of evidence is implicit in the  
10 evaluation, but it needs to be explicit in the Part II of the document. Interactions  
11 between weight of evidence and the Precautionary Principle (i.e., appropriate  
12 levels of uncertainty) should be clarified. Second, when appropriate data are  
13 available, EC<sub>x</sub> values (i.e., the concentration causing an effect in x percent of the  
14 test organisms) should be used rather than NOECs/LOECs (i.e., no observed  
15 effects concentrations/lowest observed effects concentrations). The EC<sub>x</sub> value  
16 reflects the information in the entire concentration-response curve and confidence  
17 intervals can be calculated as part of the curve fitting process. In contrast, the use  
18 of NOECs or LOECs by hypothesis tests are dependent upon the test  
19 concentrations that are used, the variability of the experimental technique, and the  
20 power of the statistical test. It is also not possible to generate confidence intervals  
21 for the NOEC/LOEC determinations. When available, the data used in a  
22 NOEC/LOEC determination should be used to calculate the EC<sub>x</sub> value. Curve  
23 fitting, which uses more of the information contained in a data set and enables  
24 derivation of confidence intervals in the estimation of the EC<sub>x</sub>, is the preferred  
25 method for representing dose (concentration)-response information.  
26
- 27 8. The Committee finds that the clarity and transparency could be improved in  
28 several areas. In particular, the authors need to more explicitly describe how the  
29 illustration was developed from the recommendations in Part I. Part II also needs  
30 to be more explicit regarding how specific conclusions and assessments derived  
31 from the data. The following specific revisions are suggested:  
32
- 33 - Data used to arrive at the values shown in Table 3.1 need to be provided in an  
34 appendix.
  - 35 - Table 1 arguably includes chronic data (*Lytechinus* and *Strongylocentrotus*  
36 echinoderm embryo development tests and the *Acartia* embryo test) that, not  
37 surprisingly, provide the most sensitive responses. While the Committee  
38 concurs that there is “ample evidence that a CMC is not needed and that it is  
39 unnecessary to conduct further tests to meet the minimum data requirements,”  
40 the differentiation between acute and chronic data needs to be more clear and  
41 transparent along with the implications of including equivocal data.  
42 Confusion between acute and chronic data can result in unnecessary levels of  
43 uncertainty and variability in criteria development. We note that slide 11 of  
44 the presentation provided by Dr. Russell Erickson of EPA ORD at the  
45

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

- 1 Committee meeting on June 30 provides the requisite level of clarity and  
2 transparency and could usefully be included in the document.  
3
- 4 - More explicit discussion of what constitutes “sufficient information” at  
5 various decision points would be helpful.  
6
  - 7 - The validity of using non-resident species is justified by text referring to  
8 complex tables, which do not provide the level of clarity and transparency  
9 necessary. Given the importance of validating the use of non-resident species,  
10 a graphic representation of the data is required (e.g., SSDs or linear, horizontal  
11 lines indicating ranges for survival, growth and reproduction showing where  
12 the non-resident species fit).  
13
  - 14 - The Committee suggests that the authors add a concluding section that  
15 summarizes the process used to assess how the process of developing an  
16 aquatic life criterion for EE2 was modified by use of the new/updated  
17 guidelines. Part II should also provide an overview of how the process is  
18 expected to ultimately influence the criteria derived (in other words, what is  
19 the bottom line in terms of how the new recommendations changed the final  
20 outcome?).  
21
  - 22 - The EE2 example in Part II relies on nominal concentrations in addition to  
23 measured concentrations. The Committee assumes that criteria will not be  
24 based on nominal concentrations. However, it is acknowledged that as long as  
25 measured concentrations are within 20% of the nominal concentrations  
26 employed in a study, the concentrations reported could be the nominal  
27 concentrations. This needs to be made clear in the document.  
28
  - 29 - The first two paragraphs on page 13 of Part II would benefit from additional  
30 information on the timing of exposures to clarify that a 16% reduction in  
31 growth occurred after 28 days (paragraph 1, line 4), and the timing for lower  
32 reproduction at 0.2 and 1 ng/L (paragraph 1, line 9). We have a similar  
33 suggestion for effects on fertilization success (paragraph 2, lines 7-8).  
34
  - 35 - EPA should include in the appendix the residency status of each species or  
36 genus. The authors refer to residency in interpretations, but this information is  
37 missing from the document.  
38
  - 39 - A list of acronyms such as that provided for Part I also would be useful for  
40 Part II.  
41
  - 42 - A few questions are raised regarding citations: (1) Wenzel et al. (2002) is  
43 cited in the text (p. 14, paragraph 3, line 3) but not in the References; should  
44 the date of the reference be 2001?; (2) Is the Kolpin et al. (2002) reference  
45 correct (both here and in Part I) - it does not seem to apply as it is a 2-page

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 response to a comment, not a full paper?; (3) Lee and Choi (2006) is listed in  
2 the References as “in press” but surely this is not still the case 2 years later?;  
3 and (4) the reliance on McKim et al. (1978) is questioned regarding the  
4 assertion that a “factor of 2 difference is generally found for other chemicals”  
5 (page 13, incomplete paragraph beginning the page, last line). We note that  
6 the McKim et al. (1978) paper only referred to one chemical, copper, and was  
7 published thirty years ago in a journal that does not have a high level of peer  
8 review.  
9

10 **4.4. Charge Question 4. Does the Committee have suggestions that would**  
11 **assist EPA in implementing the proposed recommendations discussed in**  
12 **the white paper, particularly with respect to developing the necessary**  
13 **scientific data and information and/or providing expert scientific input at**  
14 **the appropriate stages of the risk assessment process?**  
15

16 The Committee has provided comments and recommendations to assist EPA in  
17 implementing the proposed recommendations discussed in the White Paper. Many of  
18 our comments focus on actions that would assist in implementation of the  
19 recommendations in the White Paper. However, we have also provided broader  
20 suggestions to facilitate future development of aquatic life criteria for CECs. Some of  
21 our comments and recommendations elaborate upon points discussed in previous  
22 sections of this advisory report.  
23

24 *Points to be considered in implementing the proposed recommendations in the White*  
25 *Paper*  
26

- 27 • Developing new criteria for CECs will require intensive data collection /  
28 generation activities. In an ideal world, it would be the Committee’s  
29 recommendation that the same level of effort required to register a new chemical  
30 or pesticide also be required to develop aquatic life criteria for CECs.  
31 Acknowledging that this may not be possible in a world of limited resources, it  
32 will be important that OW/ORD prioritize the list of CECs for which aquatic life  
33 criteria will be developed. EPA should also identify data needs for these  
34 chemicals and leverage research development activities to develop the necessary  
35 data. Prioritization of CECs and data needs is further discussed below. In  
36 addition, EPA should conduct research to evaluate the sensitivity of test  
37 organisms that could be used as surrogates for resident and endangered species.  
38 Research should also compare the sensitivity of traditional and non-traditional test  
39 endpoints.  
40
- 41 • Leveraging research efforts of other agencies is essential. In a time of decreasing  
42 research funds within the federal government, it is important that OW/ORD seek  
43 opportunities to leverage research efforts of other government agencies (e.g.,  
44 FDA, U.S. Department of Agriculture [USDA], National Oceanic and  
45 Atmospheric Administration [NOAA]). The Committee was informed that EPA

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 and the FDA are coordinating data sharing. We recommend that this activity  
2 continue and further that it be broadened to include other government agencies.  
3 We further support international collaboration between EPA, the European Union,  
4 Environment Canada and other appropriate non-U.S. environmental agencies. In  
5 addition, it is apparent that the regulated community, industries, animal husbandry  
6 organizations (e.g., National Cattlemen’s Beef Association) and Publicly Owned  
7 Treatment Works, are actively engaged in independent evaluation of CECs.  
8 Establishing a government/industry consortium may be a way of leveraging  
9 limited funds for broader data development opportunities.

10

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

25

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

38

39 • Quantitative linkages are needed between mode of action indicators and  
40 population-level endpoints. The proposed recommendations in the White Paper  
41 are consistent with bettering the risk assessment process. However, it will be  
42 important to set priorities for technical research that addresses significant gaps in  
43 knowledge needed to develop: 1) new indicators; 2) modeling capabilities; and 3)  
44 tools that provide integration and linkage of data sources. As mentioned  
45 previously, one of the most important challenges facing EPA will be linking mode

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 of action indicators of exposure/effects to known population-level effects  
2 measurement endpoints such as survival, growth, reproduction and development.  
3 Developing conceptual models will guide criteria development but quantitative  
4 linkages will be needed to discern how mode of action indicators connect with  
5 population-level end points. The White Paper (p. 20, lines 21- 21) states that it is  
6 important to have a clear linkage between mode of action indicators such as  
7 histopathology and growth, reproduction and development. The Committee notes  
8 that in some instances it may be possible to define scaled risk (e.g., level of  
9 biological response in cell, tissue, etc.) and relative risk. This will make it  
10 possible to develop mode of action fingerprints that may provide earlier warning  
11 and greater sensitivity in predicting population-level effects.  
12

13 • Additional factors may need to be considered to protect certain species. As noted  
14 previously, development of aquatic life criteria to provide adequate levels of  
15 protection for endangered, highly managed, protected and “charismatic” species  
16 (e.g., marine mammals, eagles, polar bears, sturgeon) may require consideration  
17 of additional factors. For example, in marine mammals a dive reflex can force  
18 more contaminant into tissue due to pressure gradients. Endangered species may  
19 have very different lag times for sexual differentiation and uptake characteristics  
20 of CECs than the commonly used test species. For example, sturgeons are both  
21 endangered and charismatic fishes, and they are known to readily accumulate  
22 many CECs for an extended developmental period prior to reproduction. Given  
23 their long lifespan, a life cycle chronic test to determine uptake would be  
24 impossible, and an early life cycle test would be inappropriate.  
25

26 • There is a need to compile a list of priority CECs. To facilitate development of  
27 aquatic life criteria, the Committee finds that it would be useful for federal  
28 agencies working on CECs (e.g., EPA, the U.S. Geological Survey, the U.S. Food  
29 and Drug Administration, the National Oceanic and Atmospheric Administration,  
30 and others) to compile a list of priority CECs that may pose the greatest risks to  
31 aquatic life – in other words, use a risk assessment approach in a problem  
32 formulation exercise to determine contaminants of potential concern. Analytical  
33 chemistry methods should be developed for CECs that are not already being  
34 measured in aquatic environments. The Committee suggests that calculation of  
35 the ratios of the Maximum Environmental Concentrations to meaningful measures  
36 of biological effects (e.g., CCCs, or LC<sub>x</sub>s from toxicity testing) could initially be  
37 used to develop a list of high priority CECs. This kind of exercise would likely,  
38 but not certainly, show that estrogens should be a top priority for aquatic life  
39 criteria, as indicated in the White Paper.  
40

41 • There is a clear need for continued development of analytical capabilities to  
42 measure levels of CECs in the aquatic environment. The ability to detect many of  
43 the CECs at appropriate concentrations in a controlled laboratory setting may be  
44 entirely different from detecting those same low concentrations in the aquatic  
45 environment. Addressing such issues will help current long term monitoring

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

1 programs (e.g., NOAA National Status and Trends and Mussel Watch programs,  
2 U.S. Geological Survey National Water Quality Assessment Program, EPA  
3 Environmental Monitoring and Assessment Program) implement a coordinated  
4 approach to better define CEC exposures in the environment. Efforts to develop  
5 methodological approaches for lowering limits of detection and standards for  
6 CECs should involve discussion among agencies as well as the regulated  
7 community. It may be important to include the National Institute of Standards  
8 and Technology in the development of environmental standards for new CECs.  
9

- 10 • Input into the aquatic life criteria development process is needed from private  
11 industry and state government. The perspective of these important stakeholders is  
12 needed before finalizing the White Paper. These groups should be asked to  
13 provide input on the science associated with the modifications of the Guidelines  
14 related to CECs because aquatic life criteria will be used to develop state water  
15 quality standards.  
16
- 17 • It would make sense to consider using parallel processes to develop aquatic life  
18 criteria for compounds with similar modes of action (e.g., the estrogens, SSRIs).  
19 Since estrone, estradiol and EE2 all act through the estrogen receptor in the most  
20 sensitive taxa, fish, and there is growing evidence in the literature that their  
21 effects are additive (Thorpe et al., 2003), it would make sense to develop aquatic  
22 life criteria for the natural and synthetic estrogens using parallel processes.  
23 Similar approaches may be possible for other CECs with highly specific modes of  
24 action such as different classes of antibiotics, statin drugs and other  
25 pharmaceuticals that are CECs.  
26
- 27 • Further questions to consider. As EPA develops a research plan to support  
28 derivation of aquatic life criteria for CECs, it may be useful to consider the  
29 following questions mentioned previously: How can aquatic life criteria be  
30 developed to take into account the fact that aquatic organisms are exposed to  
31 mixtures of CECs and mixtures of CECs, known contaminants, and other  
32 stressors? What are the likely modes of action of CECs that are known to be  
33 present in the environment? How can field study results be used to inform the  
34 derivation of an aquatic life criteria for a CEC?  
35

36 *Committee recommendations to assist EPA in implementing proposed approaches to*  
37 *developing aquatic life criteria for contaminants of emerging concern*  
38

39 The Committee provides the following specific recommendations to assist EPA in  
40 implementing the Agency's proposed approaches to developing aquatic life criteria  
41 for CECs. Some of these recommendations have been discussed in the context of  
42 responses to the other charge questions in this report.  
43

- 44 1. EPA should develop a list of high priority CECs that may pose the greatest risks  
45 to aquatic life. Additional work should then be completed to further assess the

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

- 1 potential risks posed by these chemicals and fund the research and data collection  
2 activities needed to support future development of aquatic life criteria. In this  
3 regard, we recommend that EPA's Office of Water and Office of Research and  
4 Development look for opportunities to leverage existing research with those on-  
5 going in other federal programs, similar programs with international agencies, and  
6 industry groups, to gather the data needed to develop the aquatic life criteria.  
7 The Agency should also work with other federal agencies to develop analytical  
8 chemistry detection methods and standards for these chemicals.  
9
- 10 2. EPA should explicitly incorporate the principles for conducting Ecological Risk  
11 Assessment into the process of deriving aquatic life criteria for CECs. The  
12 Committee recommends that the EPA develop a separate process document that  
13 discusses the intended application of aquatic life criteria for CECs, and cross-links  
14 the 1985 Guidelines, the EPA's 1992 Ecological Risk Assessment Principles, and  
15 the 2008 aquatic life CEC criteria White Paper. This cross-link document should  
16 also incorporate relevant ecological risk principles from other similar documents  
17 developed for FDA, the Toxic Substances Control Act, or the Federal Insecticide,  
18 Fungicide, and Rodenticide Act. The document should not only outline the  
19 process of aquatic life criteria development, but address elements such as  
20 contaminant exposure through food uptake, Water Effects Ratios, Whole Effluent  
21 Testing, mixtures of compounds with similar modes of action, and application of  
22 aquatic life criteria for CECs in sediment management programs. The Committee  
23 is not recommending the development of a large, comprehensive document, rather  
24 something short and concise similar to the Eco Update Bulletins that have been  
25 published by EPA's Office of Solid Waste and Emergency Response (OSWER).  
26
- 27 3. As previously discussed, the Committee recommends that EPA incorporate the  
28 use of conceptual site models and ecosystem-based criteria into the process of  
29 deriving aquatic life criteria for CECs. We note that EPA programs are moving  
30 toward developing more comprehensive ecosystem-relevant criteria that take into  
31 consideration population-community structure, ecosystem functions-processes,  
32 and ecosystem services. The data available to develop CCCs are often  
33 "traditional" toxicity test data. It is important to develop the link between the  
34 protected resource, the assessment endpoint, and the measurement endpoint. An  
35 appropriate conceptual model for deriving aquatic life criteria for a CEC (see  
36 Figure 1) may be used to develop the fate and effects data and data quality  
37 objectives needed to support the aquatic life criterion.  
38
- 39 4. As previously discussed, EPA should consider (where appropriate) developing  
40 tissue residue-based aquatic life criteria for CECs. The Agency should consider  
41 developing tissue-based criteria using the selenium example and expanding the  
42 definition of contaminants of emerging concern to include "chemicals and other  
43 substances of increasing environmental concern due to anthropogenic activities  
44 and for which current regulatory approaches are inadequate." Tissue residue-  
45 based criteria should be considered for CECs that have potential to bioaccumulate

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.

This report does not represent EPA policy.

- 1 (e.g., carbamazepine) and bioconcentrate (e.g., flame retardants). At a minimum,  
2 the conceptual model could be used to help determine how to evaluate the  
3 available environmental data and models to assess the main routes of exposure for  
4 aquatic organisms.  
5
- 6 5. EPA should use a “mode of action” approach to develop more effective aquatic  
7 life criteria not only for CECs, but also for legacy contaminants and mixtures.  
8 Additional studies in genomic and toxicodynamics processes would provide  
9 necessary data for the identification of “mode of action” fingerprints and aid in  
10 this process, particularly in the problem formulation stage of risk assessment.  
11 This should help guide regulators to carry out the most efficient bioassays which  
12 will be used in setting thresholds or criteria.  
13
- 14 6. The Committee recommends that EPA appropriately use novel environmental  
15 indicators (molecular, genomics, proteomics) developed at other agencies,  
16 industry, and by academia in future development of criteria. For example, NOAA  
17 has developed a robust health effects assessment for bottle nosed dolphins that  
18 addresses many CECs including flame retardants and antibiotic resistance (Fair et  
19 al., 2006; Goldstein et al., 2006; Houde et al., 2006; National Oceanic and  
20 Atmospheric Administration, 2008; Reif et al., 2006). The assessment involved  
21 analysis of the immune function data and other health information on the animals  
22 such as clinical evaluation, blood chemistries, contaminants and hormones. Since  
23 dolphins are apex predators that breathe the air, swim in the water and constantly  
24 eat seafood, they provide a most exposed individual model. This type of insight  
25 may be pivotal in enhancing what EPA can do using the approach outlined in Part  
26 I of the White Paper.  
27
- 28 7. EPA should take into consideration appropriate additional factors to ensure that  
29 aquatic life criteria are protective of sensitive and commercially/recreationally  
30 important species. These species are protected by additional laws (e.g.,  
31 Magnuson Stephens, Marine Mammal Protection Act) and this may invoke other  
32 special considerations when developing aquatic life criteria.  
33
- 34 8. EPA should obtain input from private industry and state government on the  
35 Agency’s proposed approaches for developing aquatic life criteria for CECs  
36 before finalizing the White Paper.  
37
- 38 9. EPA should consider developing a mixture strategy to develop aquatic life criteria  
39 for classes of compounds with similar modes of action. As previously mentioned  
40 parallel processes could be used to develop aquatic life criteria for broad classes  
41 of CECs with similar modes of action (e.g., the estrogens, SSRIs).  
42  
43

## 6. REFERENCES

- 1  
2  
3 Ankley, G.T., Miller, D.H., Jensen, K.M., Villeneuve, D.L., Marinovic, D. 2008.  
4 Relationship of plasma sex steroid concentrations in female fathead minnows to  
5 reproductive success and population status. *Aquatic Toxicology*, 88:69-74.  
6  
7 Baird, D.J., I Barber, P. and P. Calow. 1990. Clonal variation in general responses of  
8 *Daphnia magna* Straus to toxic stress. 1. Chronic life-history effects. *Functional*  
9 *Ecology*, 4:399-407.  
10  
11 Besser, J.M., N. Wang, F.J. Dwyer, F.L. Mayer, and C.G. Ingersoll. 2005. Assessing  
12 contaminant sensitivity of endangered and threatened aquatic species: Part II.  
13 Chronic toxicity of copper and pentachlorophenol to two endangered species and two  
14 surrogate species. *Archives of Environmental Contamination and Toxicology*, 48:155-  
15 165.  
16  
17 Beyers, D.W. 1995. Acute toxicity of Rodeo herbicide to Rio Grande silvery minnow  
18 as estimated by surrogate species: plains minnow and fathead minnow. *Archives of*  
19 *Environmental Contamination and Toxicology*, 29:24-26.  
20  
21 Brain, R.A., M.L. Hanson, K.R. Solomon, and B.W. Brooks. 2007. Targets, effects  
22 and risks in aquatic plants exposed to pharmaceuticals. *Reviews of Environmental*  
23 *Contamination and Toxicology*, 192:67-115.  
24  
25 Chandler, G.T., T.L. Cary, A.C. Bejarano, J. Pender, and J.L. Ferry. 2004.  
26 Population consequences of fipronil and degradates to copepods at field  
27 concentrations: An integration of life cycle testing with Leslie matrix population  
28 modeling. *Environmental Science and Technology*, 38:6407-6414.  
29  
30 Chapman, P.M., McDonald, B. Kickham, P.E., McKinnon, S. 2006. Global  
31 geographic differences in marine metals toxicity. *Marine Pollution Bulletin*, 52:  
32 1081-1084.  
33  
34 Dwyer, F.J., D.K. Hardesty, C.E. Henke, C.G. Ingersoll, D.W. Whites, D.R. Mount,  
35 and C.M. Bridges. 1999. *Assessing contaminant sensitivity of endangered and*  
36 *threatened species: Effluent toxicity tests*. EPA/600/R-99/098. U.S. Environmental  
37 Protection Agency, Washington, D.C.  
38  
39 Dwyer, F.J., D.K. Hardesty, C.G. Ingersoll, J.K. Kunz, and D.W. Whites. 2000.  
40 *Assessing Contaminant Sensitivity of American Shad, Atlantic Sturgeon, and*  
41 *Shortnose Sturgeon. Final Report, February 2000*. U.S. Geological Survey,  
42 Columbia Environmental Research Center, Columbia, MO [Available at:  
43 <http://www.cerc.usgs.gov/pubs/center/pdfDocs/91008.pdf>]  
44  
45

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

- 1 Dwyer, F.J., L.C. Sappington, D.R. Buckler, C.M. Bridges, I.E. Greer, D.K. Hardesty,  
2 C.E. Henke, C.G. Ingersoll, J.L. Kunz, D.W. Whites, J. Ausperger, D.R. Mount, K,  
3 Haffala, and G.N. Neuderfer. 2005. Assessing contaminant sensitivity of endangered  
4 and threatened aquatic species: Part I. Acute toxicity of five chemicals. *Archives of*  
5 *Environmental Contamination and Toxicology*, 48:143-154.  
6
- 7 Dwyer, F.J., L.C. Sappington, D.R. Buckler, and S.B. Jones. 1995. *Use of surrogate*  
8 *species in assessing contaminant risk to endangered and threatened fishes.*  
9 EPA/600/R-96/029. U.S. Environmental Protection Agency, Gulf Breeze, FL.  
10
- 11 European Commission. 2008. *The EU Water Framework Directive – Integrated*  
12 *River Basin Management for Europe.* [http://ec.europa.eu/environment/water/water-](http://ec.europa.eu/environment/water/water-framework/index_en.html)  
13 [framework/index\\_en.html](http://ec.europa.eu/environment/water/water-framework/index_en.html) . [Accessed September 2, 2008]  
14
- 15 Fair, P.A., T.C. Hulsey, R.A. Varela, J.D. Goldstein, J. Adams, E.S. Zolman, G.D.  
16 Bossart. 2006. Hematology, serum chemistry, and cytology findings from apparently  
17 healthy Atlantic bottlenose dolphins (*Tursiops truncatus*) inhabiting the estuarine  
18 waters of Charleston, South Carolina. *Aquatic Mammals*, 32(2):182-195.  
19
- 20 Filby, A.L., T. Neuparth, K.L. Thorpe, R. Owen, T.S. Galloway, and C.R. Tyler  
21 2007. Health impacts of estrogens in the environment, considering complex mixture  
22 effects. *Environmental Health Perspectives*, 115:1704-1710.  
23
- 24 Goldstein, J.D., E. Reese, J.S. Reif, R.A. Varela, S.D. McCulloch, R.H. Defran, P.A.  
25 Fair, and G.D. Bossart. 2006. Hematologic, biochemical, and cytologic findings  
26 from apparently healthy Atlantic bottlenose dolphins (*Tursiops truncatus*) inhabiting  
27 the Indian River Lagoon, Florida, USA. *Journal of Wildlife Diseases* 42(2):447-454.  
28
- 29 Grim, K.C., M. Wolfe, W. Hawkins, R. Johnson, and J. Wolf. 2007. Intersex in  
30 Japanese medaka (*Oryzias latipes*) used as negative controls in toxicologic bioassays:  
31 A review of 54 cases from 41 studies. *Environmental Toxicology and Chemistry*,  
32 26:1636-1643.  
33
- 34 Harris, C.C., E.M. Santos, A. Janbakhsh, T.G. Pottinger, C.R. Tyler, and J.P.  
35 Sumpter. 2001. Nonylphenol affects gonadotropin levels in the pituitary gland and  
36 plasma of female rainbow trout. *Environmental Science and Technology*, 35:2909-  
37 2916.  
38
- 39 Hershberger, P.K., N.E. Elder, J. Wittouck, K. Stick, and R.M. Kocan. 2005.  
40 Abnormalities in larvae from the once-largest Pacific herring population in  
41 Washington State result primarily from factors independent of spawning location.  
42 *Transactions of the American Fisheries Society*, 142:326-337.  
43  
44  
45

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

- 1 Houde, M., T.A.D. Bujas, J. Small, R.S. Wells, P.A. Fair, G.D. Bossart, K.R.  
2 Solomon, and D.C.G, Muir. 2006. Biomagnification of perfluoroalkyl compounds in  
3 the bottlenose dolphin (*Tursiops truncatus*) food web. *Environmental Science and*  
4 *Technology*, 40(13):4138-4144.  
5
- 6 Kazeto. Y., A.R. Place, and J.M. Trant. 2004. Effects of endocrine disrupting  
7 chemicals on the expression of CYP19 genes in zebrafish (*Danio rerio*) juveniles.  
8 *Aquatic Toxicology*, 69:25-34.  
9
- 10 Kidd, K.A., P.J. Blanchfield, K.H. Mills, V.P. Palace, R.E. Evans, J.M. Lazorchak,  
11 and R.W. Flick 2007. Collapse of a fish population after exposure to a synthetic  
12 estrogen. *Proceedings of the National Academy of Sciences of the United States of*  
13 *America*, 104: 8897-8901.  
14
- 15 Lawton, J.C., P.L. Pennington, K.W. Chung, and G.I. Scott. 2006. Toxicity of  
16 atrazine to the juvenile hard clam, *Mercenaria mercenaria*. *Ecotoxicology and*  
17 *Environmental Safety*, 65(3): 388-394.  
18
- 19 Martin-Skilton, R., M.W.H. Coughtrie, and C. Porte. 2006. Sulfotransferase  
20 activities towards xenobiotics and estradiol in two marine fish species (*Mullus*  
21 *barbatus* and *Lepidorhombus boscii*): characterization and inhibition by endocrine  
22 disrupters. *Aquatic Toxicology*, 79:24-30.  
23
- 24 Meucci, V, and A. Arukwe. 2006. Transcriptional modulation of brain and hepatic  
25 estrogen receptor and P450arom isotypes in juvenile Atlantic salmon (*Salmo salar*)  
26 after waterborne exposure to xenoestrogen, 4-nonylphenol. *Aquatic Toxicology*,  
27 77:167-177.  
28
- 29 Miller, D.H., K.M. Jensen, D.L. Villeneuve, M.D. Kahl, E.A. Makynen, E.J. Durhan,  
30 and G.T. Ankley. 2007. Linkage of biochemical responses to population-level  
31 effects: a case study with vitellogenin in the fathead minnow (*Pimephales promelas*).  
32 *Environmental Toxicology and Chemistry*, 26:521-527.  
33
- 34 Mount, D.R., P.V. Hodson, G. Ankley, K. Brix, W. Clements, G. Dixon, A.R.J.  
35 Erickson, A. Fairbrother, C. Hickey, R. Lanno, C.Lee, W. Munns, R. Ringer, J.  
36 Stavely, and C. Wood. 2003. Effects Assessment. In: Reiley et al. (ed.), *Water*  
37 *Quality Criteria Development: Comparing Current Approaches*. SETAC Press,  
38 Pensacola, FL, 53-118.  
39
- 40 Munday, P.L., P.M. Bustion, and R.R. Warne. 2006. Diversity and flexibility of sex-  
41 change strategies in animals. *Trends in Ecology and Evolution*, 21:89-95.  
42  
43  
44  
45

- 1  
2 National Oceanic and Atmospheric Administration. 2008. *Health and Risk*  
3 *Assessment of Bottlenose Dolphin Populations, 2008.*  
4 <http://www8.nos.noaa.gov/nccos/npe/projectdetail.aspx?id=53&fy=2008> [Accessed  
5 August 29, 2008]  
6  
7 Parkinson, A. 2001. Biotransformation of xenobiotics, In: *Casarett & Doull's*  
8 *Toxicology: The Basic Science of Poisons* (C. Klaasen Ed). McMillan Publishers,  
9 New York, NY.  
10  
11 Pennington, P. L., J.W. Daugomah, A.C. Colbert, M H. Fulton, P.B. Key, B C.  
12 Thompson, E D. Strozier and G.I. Scott. 2001. Analysis of pesticide runoff from  
13 mid-Texas estuaries and risk assessment implications for marine phytoplankton.  
14 *Journal of Environmental Science and Health*, 36(1): 1-14.  
15  
16 Pennington, P.L. and G.I. Scott. 2001. The toxicity of atrazine to the estuarine  
17 phytoplankter *Pavlova* Sp. (Prymnesiophyceae): increased sensitivity after chronic  
18 exposure. *Environmental Toxicology and Chemistry*, 20 (10): 2237-2242.  
19  
20 Reif, J.S., M.S. Mazzoil, S.D. McCulloch, R.A. Varela, J.D. Goldstein, P.A. Fair, and  
21 G.D. Bossart. 2006. Lobomycosis in Atlantic bottlenose dolphins from the Indian  
22 River Lagoon, Florida. *Journal of the American Veterinary Medical Association*,  
23 228(1):104-108.  
24  
25 Sappington, L.C., F.L. Mayer, F.J. Dwyer, D.R. Buckler, J.R. Jones, and M.R.  
26 Ellersieck. 2001. Contaminant sensitivity of threatened and endangered fishes  
27 compared to standard surrogate species. *Environmental Toxicology and Chemistry*,  
28 20:2869-2876.  
29  
30 Society of Environmental Toxicology and Chemistry. 2008. *SETAC Completed*  
31 *Workshops*.<http://www.setac.org/node/104> [Accessed September 26, 2008]  
32  
33 Staples, CA, K.B. Woodburn, G.M. Klecka, E.M. Mihaich, A.T. Hall, L. Ortego, N.  
34 Caspers, and S.G. Hentges. 2008. Comparison of four species sensitivity distribution  
35 methods to calculate predicted no effect concentrations for bisphenol A. *Human and*  
36 *Ecological Risk Assessment*, 14:455-478.  
37  
38 Stephan, C.E., D.I. Mount, D.J. Hansen, J.H. Gentile, G.A. Chapman, and W.A.  
39 Brungs. 1985. *Guidelines for Deriving Numerical national Water Quality Criteria*  
40 *for the Protection of Aquatic Organisms and Their Uses*. PB85-227049. National  
41 Technical Information Service, Springfield, VA. [available at:  
42 <http://www.epa.gov/waterscience/criteria/library/85guidelines.pdf>]  
43  
44 Tabb, M.M. and B. Blumberg. 2006. New modes of action for endocrine-disrupting  
45 chemicals. *Molecular Endocrinology*, 20:475-482.

This draft SAB Committee report has been prepared for quality review and approval of the chartered SAB.  
This report does not represent EPA policy.

- 1  
2 Thibaut, R., and C. Porte. 2004. Effects of endocrine disrupters on sex steroid  
3 synthesis and metabolism pathways in fish. *Journal of Steroid Biochemistry and*  
4 *Molecular Biology*, 92:485-494.  
5  
6 Thorpe, K.L., R. Benstead, T.H. Hutchinson, and C.R. Tyler. 2007. Associations  
7 between altered vitellogenin concentrations and adverse health effects in fathead  
8 minnow (*Pimephales promelas*). *Aquatic Toxicology*, 85:176-183.  
9  
10 Thorpe, K.L., R.I. Cummings, T.H. Hutchinson, M. Scholze, G. Brighty, JH.P.  
11 Sumpter, and C.R. Tyler. 2003. Relative potencies and combination effects of  
12 steroidal estrogens in fish. *Environmental Science and Technology*, 37:1142-1149.  
13  
14 U.S. EPA. 1989. *Risk Assessment Guidance for Superfund, Part A*. EPA/540/1-  
15 89/002. Office of Emergency and Remedial Response. U.S. Environmental  
16 Protection Agency, Washington, D.C.  
17  
18 U.S. EPA. 1992. *Framework for Ecological Risk Assessment*. EPA/600/R-92-001.  
19 U.S. Environmental Protection Agency Risk Assessment Forum, Washington, D.C.  
20 [Available at: <http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=30759>]  
21  
22 U.S. EPA. 2006. *Peer Review Program*. <http://epa.gov/peerreview/> [Accessed  
23 August 22, 2008]  
24  
25 U.S. EPA 2007. Selenium Aquatic Life Criterion – draft.  
26 <http://www.epa.gov/waterscience/criteria/selenium/> [Accessed August 22, 2008]  
27  
28 U.S. EPA Science Advisory Board. 2007. *Advice to EPA on Advancing the Science*  
29 *and Application of Ecological Risk Assessment in Environmental Decision Making: A*  
30 *Report of the U.S. EPA Science Advisory Board*. EPA-SAB-08-003. U.S.  
31 Environmental Protection Agency, Washington, D.C. [Available at:  
32 [http://yosemite.epa.gov/sab/sabproduct.nsf/WebReportsbyYearBOARD!OpenView&](http://yosemite.epa.gov/sab/sabproduct.nsf/WebReportsbyYearBOARD!OpenView&Start=1&Count=800&Expand=1#1)  
33 [Start=1&Count=800&Expand=1#1](http://yosemite.epa.gov/sab/sabproduct.nsf/WebReportsbyYearBOARD!OpenView&Start=1&Count=800&Expand=1#1)]  
34