

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



**OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD**

1

2

3

4 The Honorable Stephen L. Johnson

5 Administrator

6 U.S. Environmental Protection Agency

7 1200 Pennsylvania Avenue, N.W.

8 Washington, D.C. 20460

9

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

12

13

14 Dear Administrator Johnson:

15

16 The Science Advisory Board (SAB) Ecological Processes and Effects Committee,
17 augmented with additional experts, reviewed the EPA White Paper titled *Aquatic Life*
18 *Criteria for Contaminants of Emerging Concern* (White Paper). EPA's 1985 *Guidelines*
19 *for Deriving Numerical National Water Quality Criteria for the Protection of Aquatic*
20 *Organisms and Their Uses* (Guidelines) specify procedural and data requirements for
21 deriving ambient water quality criteria for the protection of aquatic life (aquatic life
22 criteria). The Agency is faced with a number of technical issues and challenges in
23 deriving aquatic life criteria for contaminants of emerging concern (CECs) such as
24 pharmaceutical and personal care products that are commonly discharged at wastewater
25 treatment plants. To address these technical issues, the Office of Water and Office of
26 Research and Development have proposed recommendations for interpreting and/or
27 adapting principles in the 1985 Guidelines. EPA's White Paper describes the proposed
28 recommendations, focusing in particular on CECs that disrupt endocrine function in
29 animals. The White Paper also explores these recommendations in the context of a case
30 example CEC, ethynylestradiol, a synthetic pharmaceutical estrogen.

31

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

39

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

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 we
3 recommend that additional issues be considered. In particular, we urge EPA to create a
4 conceptual model to guide development of aquatic life criteria for CECs. Such a
5 conceptual model should include consideration of probable direct and/or indirect impacts
6 on food webs, ecological processes and services, and endangered or unique species of
7 special value or concern. We also recommend that EPA develop multiple lines of
8 evidence, consider uncertainty, and bolster consideration of mode of action in the criteria
9 development process. We suggest that mammalian pharmacology data available from the
10 drug discovery process, genomics / proteomics / metabolomics, and quantitative structure
11 activity relationships (QSAR) be used to screen CECs for modes of action and assess
12 potential multiple modes of action for individual CECs. To increase efficiency, parallel
13 processes could then be considered when developing aquatic life criteria for compounds
14 with similar modes of action.

15
16 The SAB generally supports EPA's proposed approaches for interpreting and / or
17 adapting principles in the Guidelines to address technical issues discussed in the White
18 Paper. However, we have noted specific concerns about these approaches and provide
19 recommendations to improve the White Paper. We emphasize that many CECs will
20 require special consideration because they do not fit the effect model discussed in the
21 White Paper (i.e., disruption of endocrine function), or may be not be well enough
22 understood to allow appropriate judgment of their mode of action. In addition, we note
23 that consideration of specific issues such as the potential for synergism among CECs in
24 mixtures and interactions with environmental variables is important to include in any
25 effort to derive aquatic life criteria.

26
27 The SAB finds that the ethynylestradiol illustrative example in the White Paper is a
28 well written and thorough review of the existing literature. It illustrates the complexities
29 inherent in generating aquatic life criteria for CECs. However, we do provide
30 recommendations to clarify the example and make it more useful.

31 The SAB also provides other suggestions to assist EPA in implementing the proposed
32 recommendations in the White Paper. These suggestions focus on: data collection and
33 research activities; incorporating ecological risk assessment principles into the criteria
34 derivation process; developing tissue residue-based criteria; developing exposure and
35 effect indicators that could be used in future derivation of criteria; special considerations
36 for endangered or commercially / recreationally important species; obtaining input from
37 private industry and state governments; and consideration of a mixture strategy for CECs.

-- Do not Cite or Quote --

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

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

3

4

Sincerely,

5

6

7

Dr. M. Granger Morgan, Chair
Science Advisory Board

8

9

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
46

**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, Department of Forest, Rangeland and Watershed, Stewardship, Colorado State University, Fort Collins, CO

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 and Associate Director, School of Aquatic and Fishery Sciences, 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
2
3

TABLE OF CONTENTS

4 **1. EXECUTIVE SUMMARY vii**

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 Paper6**

9

10 **4.1.1 Relevance of Acute Toxicity Effect Concentrations6**

11

12 **4.1.2 Defining Minimum Data Requirements Regarding Taxonomic Coverage9**

13

14 **4.1.3 Use of Non-resident Species in Criteria Development.....12**

15

16 **4.1.4 Defining Appropriate Chronic Toxicity Data15**

17

18 **4.1.5 Selection of Effect Endpoints for Criteria Developmen18**

19

20 **4.1.6 Involvement of an Expert Panel.....22**

21 **4.2 Charge Question 2. Comments on Technical Issues Addressed in the White Paper.....23**

22 **4.3 Charge Question 3. Comments on Part II of the White Paper.....27**

23 **4.4. Charge Question 4. Suggestions to Assist EPA inImplementing the Recommendations.....31**

24 **6. REFERENCES..... 38**

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.

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

The first part of EPA's White Paper (Part I), *General Challenges and Recommendations*, describes: 1) the technical challenges EPA faces in deriving aquatic life criteria for CECs; and 2) the proposed recommendations to address those challenges. The second part of the White Paper (Part II), *Illustration of Recommendations Using Data for 17 α -Ethinylestradiol (EE2)*, explores EPA's recommendations in the context of an example CEC, ethinylestradiol (EE2), which is a synthetic pharmaceutical estrogen. In its charge to the SAB, EPA requested

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

1 comments on the technical merit, practicality, and implementability of
2 recommendations in the White Paper to address: a) relevance of acute toxicity effect
3 concentrations in setting aquatic life criteria for CECs; b) defining minimum data
4 requirements regarding taxonomic coverage; c) use of non-resident species in criteria
5 development; d) defining appropriate chronic toxicity data; e) selection of effect
6 endpoints upon which to base criteria; and f) involvement of an expert panel in the
7 criteria development process. In addition, EPA asked the SAB to: comment on
8 whether the Agency has identified the appropriate issues to be addressed in deriving
9 aquatic life criteria for CECs; offer suggestions that may improve the utility of Part II
10 of the White Paper; and offer suggestions that would assist the Agency in
11 implementing proposed recommendations in the White Paper. In response to the
12 charge questions, the Committee has provided comments and recommendations to
13 improve the White Paper and assist EPA in deriving aquatic life criteria for
14 contaminants of emerging concern.

15

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

18

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

30

- 31 • Not enough is known about some classes of CECs (e.g., nanoparticles) to
32 determine whether acute toxicity needs to be taken into account in deriving
33 aquatic life criteria. Therefore, all available data on any new class of CECs
34 should be used in determining whether acute toxicity is likely to occur in
35 environmentally relevant settings.
- 36
- 37 • Some CECs appear to have differing modes of action for acute toxicity vs.
38 chronic toxicity. Lowest Observed Effect Concentrations (LOECs) and LC50s
39 (test concentrations that result in mortality to 50% of the test population) are
40 within one order of magnitude for some CECs, making acute toxicity relevant in
41 deriving aquatic life criteria. Therefore, “criteria maximum concentrations” to
42 protect against acute effects should be derived for compounds where LOECs are
43 found to be within one order of magnitude of LC50s, or where modes of action
44 for acute and chronic toxicity differ.

45

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

- 1 • Pulsed discharge of some CECs may result in exceedingly high concentrations of
2 CECs in specific circumstances such as natural disasters and spills. Because
3 acute toxicity may occur in these cases, available information should be used to
4 evaluate the likelihood that such discharges would require consideration of a
5 broad range of environmentally relevant concentrations.
6
- 7 • Mixtures of CECs with comparable modes of action may result in higher
8 environmental concentrations than would be expected for any single compound.
9 Therefore, research is needed to determine how aquatic life criteria for CECs can
10 take into account the fact that aquatic organisms are exposed to mixtures of
11 chemicals with similar modes of action.
12
- 13 • To maintain transparency in cases when criteria maximum concentrations are not
14 used in criteria development, a summary of all available data that provide
15 information on the relevance of acute toxicity should be included in any aquatic
16 life criteria document.
17

18 *Defining minimum data requirements regarding taxonomic coverage*
19

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

- 39 • EPA needs to define what constitutes a sufficiently robust set of chronic data for
40 criteria development. Although the example used in the White Paper generally
41 illustrates EPA's proposed process for making decisions concerning taxonomic
42 coverage, it would be helpful if EPA were more explicit in identifying what
43 constitutes a "sufficiently robust set of chronic data" and "a reasonable
44 understanding of the mode of action for the chemical that may allow inferences."
45

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

- 1 • The White Paper should place greater emphasis on information useful for
2 development of aquatic life criteria, rather than just toxicity requirements.
3 Incorporating effects on ecological processes (e.g., food webs, nutrient cycling,
4 primary production) rather than only target species would be valuable in criteria
5 development, and would follow more recent scientific thinking.
6
7 • As further discussed in Section 4.1.2 of this advisory report, EPA should consider
8 shifting from an approach requiring a minimum level of taxonomic coverage to
9 the approach of determining receptors of potential concern (ROPCs).
10
11 • Examples showing the unanticipated effects of CECs on non-target organisms
12 (e.g., the impact of antibiotics on plants and effect of atrazine on the quality of
13 algae available as food for other species) should be used in Part I of the White
14 Paper to help describe how the aquatic life criteria development process needs to
15 be more flexible depending on the compounds under evaluation.
16
17 • The discussion of taxonomic coverage in the White Paper should be expanded to
18 include specific recommendations concerning the marine environment.
19

20 *Use of non-resident species in criteria development*
21

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

- 32 • Because of the frequent use of non-resident species in toxicity testing, such
33 species could potentially be over-represented in aquatic life criteria databases.
34 Therefore, the proportion of the data set that should include resident species
35 should be carefully evaluated by an expert advisory panel assembled to review
36 each criterion.
37
38 • Although non-resident species can be used for criteria development, in no case
39 should a criterion be developed on the basis of non-resident species data alone.
40 Although the Guidelines have been designed to protect aquatic communities
41 (including endangered species), EPA should support research that addresses the
42 suitability of the use of surrogate species in assessing the responses of various
43 resident aquatic species (e.g., endangered or long-lived species and species with
44 varying life history strategies) to endocrine disrupting and other CECs.

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

- 1 • Differences in strains, husbandry, health, and parasite and pathogen load (i.e.,
2 other stressors) contribute to variations in toxicity test response and thus should
3 be considered in the criteria development process.
4
- 5 • Issues to be considered in prioritizing species responses should include their
6 vulnerability, endangerment status, and recreational, commercial and ecological
7 value of the species.
8
- 9 • Non-resident and resident species data must meet test guidelines for data and
10 method validity.
11

12 *Defining appropriate chronic toxicity data*
13

14 In the White Paper, EPA recommends that the Guidelines requirements for chronic
15 toxicity test data be tightened by requiring at least one full life-cycle test for a fish
16 (life-cycle tests are already required for invertebrates) unless there is a compelling
17 body of information indicating that life processes outside the early life stage or partial
18 life-cycle exposure / observation window are not critical to capturing the biologically
19 important effects of chronic exposure to the chemical. The Committee strongly
20 supports EPA's proposed recommendation. We have provided additional
21 recommendations concerning the requirement for chronic toxicity data.
22

- 23 • EPA should critically review data dealing with transgenerational responses of
24 aquatic species and evaluate whether this additional testing would provide
25 significant new information to inform the criteria development process.
26
- 27 • Test guidelines should include flexibility to include assessment of key
28 developmental events, and professional judgment from an expert panel should be
29 used to evaluate the relevance of non-traditional endpoints such as immune
30 function and behavior. Behavioral endpoints related to population (e.g., predator-
31 prey interactions) and reproduction may hold some promise for criteria
32 development if the assays can be validated and variability can be understood.
33

34 *Selection of effect endpoints upon which to base criteria*
35

36 In the White Paper, EPA has identified a number of endpoints that could be
37 considered in developing aquatic life criteria for CECs. Moreover, the Agency
38 recommended more thorough exploration of the use of such endpoints in criteria
39 development. Generally, the Committee agrees that EPA should continue to explore
40 the possibility of using sublethal endpoints in helping to set aquatic life criteria.
41 However, we caution EPA that such "non-traditional" endpoints must ultimately be
42 linked to population endpoints (i.e., they must consider potential impacts to
43 populations not solely effects on individual organisms). We have provided a number
44 of recommendations concerning use of these endpoints:
45

- 1 • EPA should use “non-traditional measures” to develop an understanding of and
2 confirm mode of action.
3
- 4 • As further discussed in Section 4.1.5 of this advisory report, EPA should use
5 human health information and toxicology tools (genomics / physiologically based
6 pharmacokinetic models [PBPKs]) to reduce the uncertainty of aquatic life criteria
7 for CECs.
8
- 9 • EPA should consider the following key points concerning use of the non-
10 traditional endpoints discussed in the White Paper: 1) vitellogenin in males and
11 juveniles is an indicator of exposure to feminizing stressor, but its linkage to
12 population effects is limited; 2) strong correlations between vitellogenin and
13 fecundity have been observed in females, but this is not necessarily tied to altered
14 endocrine mode of action; 3) anomalous intersex can be indicative of exposure to
15 a feminizing stressor(s) but may not, at present, be directly tied to population
16 effects; and 4) gender ratio can be indicative of endocrine alteration, but baseline
17 information on appropriate life stages is necessary for this evaluation.
18

19 *Involvement of an Expert Panel*

20

21 Because the development of aquatic life criteria for CECs may be dependent on
22 technical interpretations of a wide range of toxicological information, EPA has
23 proposed that expert panels be used to provide professional judgment during criteria
24 development. The Committee strongly supports the use of panels comprised of
25 experts with a balanced range of perspectives to provide professional judgment
26 during the process of developing aquatic life criteria. However, we note that the use
27 of expert panels could lead to less consistency in how aquatic life criteria are
28 determined if the panels are not selected carefully. To help alleviate this potential
29 problem, we recommend that EPA develop specific guidance on the role of expert
30 panels in problem formulation, data evaluation, and generation of advice to support
31 criteria development. Specifically, we recommend that:
32

- 33 • The process for the use and selection of expert panels be described in detail and
34 that it be transparent.
35
- 36 • The panels be given a clear charge and understanding of their roles in the process.
37
- 38 • EPA take advantage of similar expert panel processes occurring in Europe and
39 Asia to the extent possible.
40

41 *Technical issues addressed in the White Paper*

42

43 The Committee was asked to comment on whether EPA has identified the
44 appropriate technical issues in the White Paper, and whether there are additional
45 important issues that the Agency has not identified. We find that EPA has identified
46 appropriate technical issues in the White Paper. However, as further discussed in

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

1 Section 4.1.6 of this advisory report, we recommend that the Agency address
2 additional issues to customize and update the 1985 Guidelines and thereby increase
3 the flexibility and specificity of the aquatic life criteria derivation process. The
4 following additional issues are of particular importance:
5

- 6 • In the White Paper, EPA should articulate principles that can be applied when
7 modifying the 1985 Guidelines to develop water quality criteria for CECs. In
8 particular, these principles should address: 1) obtaining a wide range of inputs
9 from diverse perspectives; 2) developing a robust conceptual model; and 3)
10 developing criteria for using multiple lines of evidence and identifying/including
11 uncertainties (quantitative and qualitative) associated with criteria development.
12
- 13 • It is particularly important that understanding and presenting uncertainty become
14 an intrinsic part of the aquatic life criteria development process. For example, the
15 uncertainties inherent in understanding modes of action, concentration-response
16 relationships, extrapolation of sensitivities, and derivation of ecological effects
17 should be quantified and / or described in a narrative sense.
18
- 19 • EPA should bolster the consideration of mode of action in the aquatic life criteria
20 derivation process. As stated previously, aquatic life criteria for CECs, should
21 take into account the fact that aquatic organisms are exposed to mixtures of these
22 chemicals. Understanding the mode of action of a compound is very important in
23 estimating mixture interactions. In fact, pharmacological mode of action is the
24 basis for evaluating multiple drug prescriptions in humans by pharmacists. EPA
25 should use mammalian pharmacology data available from the drug discovery
26 process, genomics / proteomics / metabolomics and quantitative structure activity
27 relationships (QSARs) to screen CECs for modes of action, identify CECs that
28 may act in an additive manner as mixtures, and assess potential multiple modes of
29 action for individual CECs. The Committee strongly recommends enhancing the
30 communication and data transfer capabilities between agencies such as the U.S.
31 Food and Drug Administration (FDA) and EPA to provide mode of action
32 information.
33
- 34 • In deriving aquatic life criteria for CECs, EPA should bolster consideration of
35 ecology and indirect ecological effects and also give special consideration to the
36 protection of threatened and endangered species.
37

38 *Part II of the white paper*

39
40 Part II of the White Paper uses ethynylestradiol (EE2) as a model chemical to
41 illustrate the technical issues presented and provide a basis for understanding the
42 recommendations in Part I. The Committee was asked to offer suggestions to
43 improve the utility of Part II. The Committee finds that Part II is a well-written and
44 thorough review of the existing literature on EE2. We agree that EE2 is an
45 appropriate initial focal CEC given the extensive data available relative to other CECs
46 and the ease with which it illustrates the complexities inherent in generating CEC-

1 specific water quality criteria. We have provided a number of specific
2 recommendations to improve Part II:
3

- 4 • EPA should explicitly recognize that EE2 is unique in being a data-rich CEC.
5 The White Paper should highlight the fact that the Agency's interest in CECs goes
6 beyond endocrine-active substances, and discuss how the example of EE2 might
7 be extrapolated to other substances, particularly those for which less data are
8 available and which have different modes of action.
9
- 10 • Parts I and II of the White Paper should be integrated. The Committee
11 appreciates the level of detail provided in Part II but we believe that the
12 illustrative pieces of Part II would be best presented in Part I in the form of
13 succinct text boxes illustrating key concepts derived from the various
14 recommendations (e.g., why certain steps in the Guidelines were included and
15 others were not). The most detailed components of Part II should be relegated to
16 appendices in Part I (which would become the sole document).
17
- 18 • Part II should discuss how the individual effects of EE2 on biota might be
19 changed by mixtures of compounds, especially those with similar modes of
20 action.
21
- 22 • As stated previously, a criterion should not be developed on the basis of non-
23 resident species data alone. Therefore, Part II should indicate that resident species
24 data, especially data from life-cycle tests using resident species, remain extremely
25 valuable and that results from non-resident species tests may not be generalized to
26 resident species without comparative sensitivity studies.
27
- 28 • The possibility of transgenerational effects should be explicitly addressed in Part
29 II.
30
- 31 • A broader array of endpoints should be included in Part II. For example, although
32 EE2 is a potent estrogen receptor agonist, it can also affect the central nervous
33 system (through steroid biotransformation), and an endpoint should be considered
34 to reflect this. Part II should also note that relevant and reproducible endpoints
35 indicative of adverse population level effects should be used.
36
- 37 • As further discussed in Section 4.3 of this advisory report, the use of weight of
38 evidence is implicit in the evaluation done in Part II, and should be explicitly
39 discussed. Furthermore, EC_x values (i.e., concentration causing an effect in x
40 percent of the test organisms) should be used in Part II instead of NOECs/LOECs
41 (i.e., no observed effects concentrations/lowest observed effects concentrations).
42 The Committee notes that if data are not be available to calculate an EC value,
43 EPA should recommend in Part II that such values be developed and used in
44 future criteria derivation.
45

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

- 1 • As further discussed in Section 4.3 of this report, the clarity and transparency of
2 Part II could be improved in a number of areas.
3

4 *Suggestions to assist EPA in implementing recommendations discussed in the White*
5 *Paper*
6

7 In Section 4.4 of this advisory report, the Committee has provided comments and
8 recommendations to assist EPA in implementing the approaches discussed in the
9 White Paper. The following key recommendations are provided:
10

- 11 • EPA should prioritize the list of CECs for which aquatic life criteria will be
12 developed. Data needs for these chemicals should be identified, and EPA should
13 fund the research and data collection activities necessary to support aquatic life
14 criteria development for CECs. In this regard, we recommend that EPA's Office
15 of Water and Office of Research and Development look for opportunities to
16 leverage EPA research with ongoing research in other federal agencies,
17 international agencies, and industry groups.
18
- 19 • The principles for conducting Ecological Risk Assessment should be explicitly
20 incorporated into the process of deriving aquatic life criteria for CECs. The
21 Committee recommends that EPA develop a separate process document that
22 discusses the intended application of aquatic life criteria for CECs. This process
23 document should establish linkages between the Guidelines, the EPA's Ecological
24 Risk Assessment Principles (U.S. EPA, 1992), and the White Paper.
25
- 26 • EPA should incorporate use of conceptual models and ecosystem-based criteria
27 into the process of deriving aquatic life criteria for CECs. The Committee notes
28 that EPA programs are moving toward developing more comprehensive
29 ecosystem-relevant criteria that take into consideration population-community
30 structure, ecosystem functions and processes, and ecosystem services. The data
31 available to develop criteria continuous concentrations are often derived from
32 "traditional" toxicity tests, which appear to be less relevant for CECs.
33 Accordingly, the Committee notes that it is important to develop the link between
34 the protected resource, the assessment endpoint, and the measurement endpoint
35 (i.e., not solely consider and use "traditional" toxicity tests).
36
- 37 • For bioaccumulative CECs where food chain transfer is a concern, EPA should
38 consider developing tissue-based criteria (i.e., expressing the criterion as a
39 concentration of the pollutant in fish tissue rather than a concentration in the
40 water). EPA should also consider expanding the definition of contaminants of
41 emerging concern to include chemicals and other substances of increasing
42 environmental concern due to anthropogenic activities and inadequate regulatory
43 approaches. The White Paper focuses on endocrine disrupting chemicals.
44 However, the Committee notes that some CECs do not fit the effect model of
45 endocrine disrupting chemicals, or are not well enough understood at this time to
46 allow a judgment of their mode of action. Nanoparticles are an example of such a

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

- 1 class of compounds. Additional work is needed to further develop
2 recommendations for deriving aquatic life water quality criteria for these other
3 kinds of chemicals.
4
- 5 • In Section 4.4 of this advisory report the Committee recommends additional
6 research to address important issues such as: the effects of mixtures of CECs,
7 interactions between CEC and other stressors, modes of action of CECs, and use
8 of field study results to inform the derivation of aquatic life criteria. The
9 Committee also recommends that the discussion of taxonomic coverage in the
10 White Paper be expanded to include specific recommendations concerning
11 derivation of criteria to protect marine organisms. We suggest that such guidance
12 may be best addressed by convening a “Pellston” type workshop that is comprised
13 of experts from multiple disciplines and types of organizations.
14

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 to aquatic organisms exposed to CECs during the early stages of life may
46 not be observed until adulthood. These chemicals may also have very specific modes

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

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

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

25 The Committee generally supports EPA's proposed approaches for interpreting
26 and/or adapting Guidelines principles to address the technical challenges discussed in
27 the White Paper. However in this advisory report we have recommended
28 improvements to the approaches proposed in the White Paper. In addition, we have
29 noted a number of specific technical and practical issues and caveats that should be
30 considered by EPA when implementing the proposed approaches. *In our responses*
31 *to each of the charge questions we have listed the key findings and comments as*
32 *bullets. These comments are followed by numbered lists of the key recommendations.*

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

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and 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; incorporation of ecological risk
6 assessment principles into the criteria derivation process; development of tissue
7 residue-based criteria (i.e., expressing the criterion as a concentration of the pollutant
8 in fish tissue rather than a concentration in the water) for bioaccumulative CECs
9 where food chain transfer is a concern; use of indicators for future development of
10 criteria; special considerations for endangered or commercially/recreationally
11 important species; obtaining input from private industry and state governments; and
12 consideration of a mixture strategy for CECs.

13

14 **3. CHARGE TO THE COMMITTEE**

15

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

23

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

29

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

31

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

41

42 *b. Defining Minimum Data Requirements Regarding Taxonomic Coverage:*

43

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

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and 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 no reason
23 to believe that they would misrepresent the sensitivity of comparable resident
24 species. Furthermore, the workgroup specifically suggest accepting data for
25 zebrafish (*Danio rerio*) and Japanese medaka (*Oryzias latipes*), to reflect
26 international 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_0 egg to F_1 offspring) or partial life-cycle (F_0
32 adult to F_1 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
46 stage or partial life-cycle exposure/observation window are not critical to

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

1 capturing the biologically important effects of chronic exposure to the chemical.
2 This amended requirement would include all chemicals, not just EDCs/CECs.
3

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

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

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

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

- 38 2. Please comment on whether EPA has identified the appropriate issues to be
39 addressed in deriving ALC for CECs. Are there additional important issues that
40 EPA has not identified?
41
- 42 3. Part II of this white paper was specifically developed as a companion to Part I and
43 focuses on the use of ethynylestradiol as a model chemical to illustrate the
44 technical issues presented by the workgroup, as well as providing a basis for
45 understanding the recommendations. Does the Committee have suggestions that

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

1 may improve the utility of Part II of this white paper for the purposes stated
2 above?

3
4 4. Does the Committee have suggestions that would assist EPA in implementing the
5 proposed recommendations discussed in the white paper, particularly with respect
6 to developing the necessary scientific data and information and/or providing
7 expert scientific input at the appropriate stages of the risk assessment process?
8

9 **4. RESPONSE TO CHARGE QUESTIONS**

10
11 **4.1 Charge Question 1. Please comment on the technical merit, practicality,**
12 **and implementability of recommendations addressing the following issues**
13 **as described in Parts I and II of EPA's white paper on Aquatic Life**
14 **Criteria for Contaminants of Emerging Concern: a) relevance of acute**
15 **toxicity effect concentrations in setting aquatic life criteria for**
16 **contaminants of emerging concern; b) defining minimum data**
17 **requirements regarding taxonomic coverage; c) use of non-resident**
18 **species in criteria development; d) defining appropriate chronic toxicity**
19 **data; e) selection of effect endpoints upon which to base criteria; and f)**
20 **involvement of an expert panel.**

21 22 **4.1.1 Relevance of Acute Toxicity Effect Concentrations**

23
24 As discussed in EPA's White Paper, aquatic life water quality criteria consist of a
25 Criterion Maximum Concentration (CMC) intended to protect against severe acute
26 effects of exposure to contaminants, and a Criterion Continuous Concentration (CCC)
27 intended to protect against the longer term effects of exposure on survival, growth,
28 and reproduction. EPA's Guidelines (Stephan et al., 1985) specify various data and
29 procedural recommendations for criteria derivation. The CMC is determined based
30 on available acute values (AVs). Acute values are median lethal concentrations or
31 median effect concentrations from aquatic animal acute toxicity tests (48 to 96 hours
32 long) meeting certain data quality requirements. The CCC is generally determined
33 based on available chronic values (CVs), which are either: a) the geometric mean of
34 the highest no-observed-effect concentration (NOEC) and the lowest observed effect
35 concentration (LOEC) for effects on survival, growth, or reproduction in aquatic
36 animal chronic tests; or b) in some recent criteria the EC₂₀ (the test concentration that
37 would cause a reduction in survival, growth, or reproduction in 20% of the test
38 population) based on concentration-effect regression analyses of the toxicity test data.
39 If chronic toxicity test data are not available for at least eight genera of aquatic
40 organisms with a specified taxonomic diversity, the CCC is derived on the basis of an
41 acute to chronic ratio (ACR) (i.e., the ratio of the AV to CV from parallel acute and
42 chronic tests for at least three species with a specified taxonomic diversity). EPA's
43 White Paper states that many CECs are physiologically active at concentrations
44 orders of magnitude lower than those causing acute lethality, and that concentrations
45 high enough to cause acute lethality may never occur in the environment. Therefore,
46 in the White Paper the Agency recommends that, when sufficient information

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

1 demonstrates a negligible risk of acute lethality for a CEC, the ALC for that
2 contaminant could consist of only a CCC.
3

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

14 *Caveats concerning use of the Criterion Continuous Concentration for aquatic life*
15 *water quality criteria*
16

17 Although the Committee generally supports EPA's recommendation to derive
18 aquatic life criteria for CECs directly from CCCs, we note that the following points
19 should be considered by the Agency when implementing this recommendation:
20

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

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

- 1 • Pulsed discharge may result in high ambient concentrations of CECs. The
2 Committee is concerned that the pulsed nature of some CEC releases (for
3 example: pulsed industrial discharge; tidal action in the marine environment; and
4 recurring natural events such as hurricanes that can cause flooding and release of
5 untreated sewage) may result in short-term concentrations of CECs that could
6 exceed what would generally be considered environmentally relevant
7 concentrations. Although CCCs may be applicable in these situations, the
8 Committee finds that acute toxicity should be considered to account for the effects
9 of compounds where extreme pulses may occur more frequently than the three-
10 year benchmark set by the Guidelines.
11
- 12 • Consideration of mixture effects is important. An additional concern of the
13 Committee is the need for the consideration of mixture effects in determining
14 whether acute toxicity could occur in natural settings. The White Paper explicitly
15 references common modes of action for multiple compounds (as in the examples
16 of EE2, estrone, and estradiol). The Committee feels strongly that mixture effects
17 of compounds with similar modes of action should be taken into account in
18 determining whether acute toxicity may occur in environmental situations. Thus a
19 mixtures strategy is needed to guide development and interpretation of aquatic life
20 criteria for CECs.

21
22 *Committee recommendations concerning the relevance of acute toxicity effect*
23 *concentrations*

24
25 As a consequence of the Committee's discussion and concerns listed above, we
26 provide the following recommendations to amend the White Paper text concerning
27 derivation of aquatic life criteria on the basis of the Criterion Continuous
28 Concentration:

- 29
- 30 1. Part 1 of EPA's White Paper contains a bulleted list (on page 28) identifying the
31 kinds of information that should be reviewed in order to determine whether the
32 differences between the CMCs and CCCs would be great enough to conclude that
33 the CMC is not needed to develop ALC. The Committee finds this list very helpful.
34 It addresses some of the concerns raised during the Committee's deliberation and it
35 may be particularly useful in providing lines of evidence to determine whether
36 acute toxicity data are needed. Therefore, we encourage expansion of this list in the
37 final White Paper to include additional information addressing the points mentioned
38 above.
39
 - 40 2. The Committee suggests that all available data on any new class of CECs should be
41 used in determining whether acute toxicity is likely to occur in environmentally
42 relevant settings. These data should be summarized to document when additional
43 data are needed, or when it is justifiable to move aquatic life criteria development
44 forward without the derivation of CMCs.
45

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

- 1 3. The Committee recommends that CMCs be derived for compounds where LOECs
2 are found to be within one order of magnitude of LC50s, or where different modes
3 of action occur for acute and chronic toxicity.
4
- 5 4. The Committee recommends that the likelihood of pulses of exposure to
6 contaminants be considered in determining the range of environmentally relevant
7 concentrations for criteria development.
8
- 9 5. The Committee suggests that EPA consider the mixture effects of compounds with
10 similar modes of action when determining the range of environmentally relevant
11 concentrations for criteria development.
12

13 The Committee finds that, together with those in the White Paper, these
14 considerations should allow a robust determination of whether CMCs are necessary
15 for derivation of ALC for CECs.
16

17 **4.1.2 Defining Minimum Data Requirements Regarding Taxonomic Coverage** 18

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

45 The Committee finds that the White Paper contains a comprehensive discussion of
46 the issue of taxonomic coverage for developing aquatic life criteria. EPA's 1985

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

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

16

17 *Concerns regarding taxonomic coverage for testing CECs*

18

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

28

- 29 • There is a need to maintain broad taxonomic coverage for development of aquatic
30 life criteria. The White Paper suggests that knowing certain modes of action
31 could potentially focus testing on a particular type of organisms (e.g., vertebrates
32 for “estrogenic” compounds). This suggestion is not wholly supported by the
33 Committee. As stated in the 1985 Guidelines, the procedure for estimating the 5th
34 percentile final chronic value is to use the four lowest values in the dataset. This
35 approach considers primarily vertebrates, and it is appropriate for EE2. However,
36 it is not always appropriate (e.g., in the case of the weak estrogenic compound
37 bisphenol A) to give primary consideration to vertebrates. Staples et al. (2008)
38 compared four species sensitivity distribution methods to develop a predicted no-
39 effect concentration for the aquatic environment for bisphenol A. Their study
40 indicated that when using the Guidelines approach, the four lowest predicted
41 values belonged to three invertebrates and one vertebrate. Clearly, this finding
42 suggests that there is a need to maintain a broad taxonomic coverage in the
43 development of aquatic life criteria.
- 44
- 45 • Little is known of chronic effects of CECs on “wild type” species. The
46 Committee is concerned that much of the toxicity testing for CECs has been done

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

1 on animals that are highly amenable to laboratory conditions and little is known
2 of chronic effects of chemicals on "wild types." There is also some probability
3 that criteria protecting "lab species" might not protect species of special concern
4 like the endangered short-nosed sturgeon, several species of Pacific salmon, or the
5 bull trout. Research is needed to evaluate the differences and similarities between
6 life-histories and sensitivities of endangered / threatened and standard laboratory
7 animals used for toxicity testing in order to have more confidence that surrogate
8 species will provide sufficient information to develop protective criteria.
9

- 10 • Modes of action are not known for some CECs. The Committee notes that it is
11 not safe to assume that a known mode of action is the only mode of action for a
12 CEC. Different organisms may be affected in different ways by the same
13 compound both as adults and at earlier stages of development. There is also the
14 potential for synergism among CECs in mixtures and in interactions with
15 environmental variables. It is the exception rather than the rule that modes of
16 action are known for CECs.
17

18 *Committee recommendations to improve the process of determining appropriate*
19 *taxonomic coverage*
20

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

- 36 1. EPA needs to define what constitutes a sufficiently robust set of chronic data.
37 Although the example used in the White Paper generally illustrates EPA's
38 proposed process for making decisions concerning taxonomic coverage, it would
39 be helpful to be more explicit in identifying what constitutes a "sufficiently robust
40 set of chronic data" and "a reasonable understanding of the mode of action for the
41 chemical that may allow inferences." The language in the White Paper introduces
42 uncertainty in both the general approach and in setting up specific test conditions.
43
- 44 2. EPA should consider emphasizing in the White Paper information necessary for
45 development of aquatic life criteria rather than just toxicity test requirements. To
46 that end, guidance on information needed to determine effects on ecological

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

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

43 **4.1.3 Use of Non-resident Species in Criteria Development**

44 EPA's Guidelines limit the data used for aquatic life criteria development to tests
45 with native species, while allowing use of non-resident species data to provide

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

1 additional, narrative evidence for criteria development. In its White Paper, EPA
2 suggests that excluding species from testing simply because they are not resident may
3 be unnecessarily restrictive for the purposes of deriving national criteria, and may
4 actually increase rather than decrease uncertainty. The White Paper recommends that
5 these “non-resident” species data be used in the aquatic life criteria derivation process
6 if the non-resident species data would enable better estimation of species sensitivity
7 distributions (SSDs). EPA recommends that criteria derivation calculations focus on
8 test data from species for which widely used and standardized test methods are
9 available, and for which there is no reason to believe that data would misrepresent the
10 sensitivity of comparable resident species. EPA specifically recommends accepting
11 data for zebrafish (*Danio rerio*) and Japanese medaka (*Oryzias latipes*), to reflect
12 international efforts toward data equivalency. As further discussed below, the
13 Committee agrees with this recommendation.

14 *Benefit of using non-resident species data*

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

27 The White Paper states that only “species with recognized international
28 equivalency [will] be included in criteria derivation with the full weight given to data
29 from resident species.” This approach supports international test harmonization
30 efforts. Specifically, the White Paper recommends use of zebra fish and Japanese
31 medaka. These two species have been largely used for EDC testing and have shown
32 sensitivity similar to native fathead minnows and other species. Tests conducted with
33 the zebra fish and Japanese medaka provide insight into the biochemical and
34 physiological mechanisms involved in the toxicity of CECs. More important is
35 matching the mode of action with the appropriate test species. The conservative
36 nature of the endocrine system, a target for most endocrine disrupting chemicals and
37 likely many CECs, renders the exclusion of non-resident species from aquatic life
38 criteria development biologically indefensible. Certainly the use of any test species
39 would be useful if it could aid in the interpretation of modes of action, relative taxa
40 tolerance, and endpoint sensitivity comparisons. For example, studies with surrogate
41 species have been conducted to demonstrate the toxicity of CECs to resident species,
42 such as the Rio Grande silvery Minnow and the North American Sturgeon, that are
43 too endangered for laboratory testing (Beyers, 1995; Dwyer et al., 2000). In such

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

1 cases test data from closely related non-resident species may provide laboratory
2 evidence useful in the development of protective aquatic life criteria for the
3 endangered resident species

4
5 *Concerns regarding the use of non-resident species data*

6 Although the Committee supports the use of non-resident species data for deriving
7 aquatic life criteria for CECs, we note the following concerns that should be
8 considered by EPA:
9

- 10 • Non-resident species are defined in different ways. The Committee notes that
11 EPA's Guidelines define "non-resident" species as those not native to the
12 continental United States and Canada. However, non-resident species have been
13 defined in other ways. At the federal level, they have been defined as species that
14 are not native to North America. Many states use the term non-resident species to
15 mean species not native to their specific region. Hence local criteria are
16 sometimes derived substituting species found locally. The definition of "non-
17 resident" (or non-native) and invasive species should be clearly stated in EPA's
18 White Paper. The White Paper should indicate whether organisms that have
19 migrated (or invaded or been stocked) are considered "resident."
20
- 21 • Non-resident species data may dominate the criteria derivation process. The
22 Committee is concerned that non-resident species and their large respective
23 databases could dominate the criteria derivation process. The recommendation to
24 use non-resident species data, as presented in the White Paper, is reasonable when
25 looking at criteria derivation from a continental perspective. However, including
26 non-resident species data in the criteria derivation process could lead to
27 inappropriately biased criteria development in certain sensitive geographic areas,
28 such as cold water and oligotrophic systems. More detailed information is needed
29 in the White Paper to address this concern.
30
- 31 • Variation in test organism response is often unknown. The Committee notes that
32 variation among the strains of test organisms used in laboratory studies is often
33 unknown. Therefore, it is difficult to understand whether the variation observed
34 between native and non-native species is within the uncertainty of the test data for
35 either species. Differences in husbandry, health, parasite and pathogen load (i.e.,
36 other stressors) may contribute to differences in test results between resident and
37 non-resident species. Within Pacific herring of Puget Sound there are apparent
38 stock differences in the frequency of malformations of new hatchlings that are not
39 related to spawning site. Differences in sensitivity have also been observed for
40 clones of *Daphnia magna*. While these issue of response variation should be
41 considered, many studies have shown parallel responses when fairly close
42 relatives are used.

43 *Committee recommendations regarding the use of non-resident species data*
44

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

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

- 11 1. As noted above, non-resident species could potentially be over-represented in
12 aquatic life criteria databases. The proportion of the data set that should include
13 resident species is a matter that should be carefully evaluated by the expert
14 advisory panel assembled to review each criterion.
15
- 16 2. In no case should a criterion be developed on the basis of non-resident species
17 data alone. Certainly if it is shown that resident species are ecologically relevant
18 and appropriately sensitive then they should be used for criteria derivation as long
19 as the studies meet appropriate quality criteria. Test species used in toxicity
20 testing tend to be easy to rear and test, and have appropriate sensitivity levels.
21 However, other factors should be considered when ample data are available for
22 prioritizing species responses for criteria development. These factors include
23 vulnerability, endangerment status, and recreational, commercial or ecological
24 value. In order to protect endangered species, studies should be completed to
25 compare toxicity test responses of common test species and endangered
26 organisms and thereby determine the relevance of surrogates in the criteria
27 development process.
28
- 29 3. The statement that criteria would be developed "...with full weight given to data
30 from resident species" should include a qualifier concerning the validity of the
31 data. An available resident species study with no obvious protocol, no
32 measurement of test concentrations, and no other protocol concerns should be
33 assigned a lower priority than a fully valid Organization for Economic
34 Cooperation and Development (OECD) / EPA guideline study with a "non-
35 resident" species. However, the Committee qualifies this recommendation by
36 emphasizing that all scientifically valid data should be used in setting criteria.
37
- 38 4. Differences in strains, husbandry, health, and parasite and pathogen load
39 contribute to response variation and should be considered in the aquatic life
40 criteria development process.
41
- 42 5. Non-resident species test data must meet Guidelines requirements for data and
43 method validity.
44

45 **4.1.4 Defining Appropriate Chronic Toxicity Data**

1
2 EPA's Guidelines state that acceptable chronic tests for derivation of aquatic life
3 criteria are full life-cycle exposures (F₀ egg to F₁ offspring) for vertebrates and
4 invertebrates, as well as partial life-cycle (adult to juvenile) and early life-stage (egg
5 to juvenile) tests for fish. EPA's White Paper states that some CECs may have potent
6 effects on life processes that lie outside the exposure period represented by early life
7 stage tests or effects may not be manifested until later in development. Thus, early
8 life stage tests might not be good predictors of chronic toxicity for these chemicals.
9 In the White Paper, EPA recommends that the Guidelines requirements for chronic
10 toxicity data be tightened by requiring at least one full life-cycle test for a fish (for
11 invertebrates, life-cycle tests are already required) unless there is a compelling body
12 of information indicating that life processes outside the early life stage or partial life-
13 cycle exposure/observation window are not critical to capturing the biologically
14 important effects of chronic exposure to the chemical.

15
16 The Committee strongly supports EPA's recommendation to amend the chronic
17 data acceptability requirements in the Guidelines. We also support extending this
18 requirement to all chemicals, not just endocrine disrupting chemicals and CECs. The
19 Committee finds that EPA's recommendation is justified based on evidence showing
20 that a number of chemicals may exert effects during the period of gonadal
21 differentiation, and that these effects may not be manifested until much later in life.
22 Including at least one full life cycle test in the test guidelines for fish ensures that
23 these types of effects are captured.

24
25 *Issues to be considered in defining appropriate chronic toxicity data*

26
27 Although the Committee supports EPA's recommendations concerning use of
28 chronic toxicity data for development of aquatic life criteria, we note the following
29 issues that should be addressed in defining appropriate chronic toxicity test data:

- 30
- 31 • Transgenerational effects of CECs are potentially important and should be
32 considered. There is evidence of transgenerational effects of some endocrine
33 disrupting chemicals, and the chronic test data recommendations in the White
34 Paper may need to be extended to include transgenerational tests when initial
35 results warrant this effort. Although we do not recommend adding a requirement
36 for transgenerational testing to the Guidelines, we suggest that EPA critically
37 review data dealing with transgenerational responses of aquatic species and
38 evaluate whether this additional testing provides significant new information that
39 informs the evaluation process. This critical review would indicate more
40 quantitatively the importance of requiring multi-generational studies.
 - 41
 - 42 • Flexibility in test guidelines is needed to include key developmental events. Test
43 guidelines must have the flexibility to include assessment of key developmental
44 events (e.g., metamorphosis in amphibians, acquisition of saltwater tolerance, or
45 smolting), particularly if these processes are identified in a ROPC.

46

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

- 1 • Test methods should include non-traditional measures that may be linked to
2 ecologically relevant endpoints. There is a need to ensure that the test methods
3 include provisions to consider non-traditional endpoints such as immune function
4 and behavior. These endpoints may directly impinge on ecologically-relevant
5 endpoints such as growth, reproduction and survival. In this case, professional
6 judgment from an expert panel is needed to determine the relevance of these non-
7 traditional endpoints.

8
9 The Committee also notes the following practical issues that should be addressed
10 if the chronic toxicity data recommendation in the White Paper is to be implemented:

- 11
12 • Surrogate test species may be needed. A key issue to be addressed is the
13 suitability of surrogate test species. Surrogates may be needed in the case of: 1)
14 long-lived species with delayed sexual maturity; 2) organisms of large size (which
15 precludes their suitability as a test species in the laboratory), 3) endangered
16 species, and 4) species for which there is little knowledge of the husbandry
17 conditions or background biology. There is also uncertainty in how differences in
18 the physiology and life history strategies (i.e., long-lived versus short-lived
19 species, differences in maternal-fetal transport of contaminants) may affect the
20 response of aquatic species to CECs and endocrine disrupters. Many of these
21 issues represent significant data gaps that need to be addressed. In these cases,
22 expert opinion may be needed to assist EPA in determining the suitability of
23 surrogate test species for use in criteria development.
- 24
25 • The Committee is divided in its assessment of the “guilty until proven innocent”
26 approach in the White Paper (p. 17). Some view it as extremely precautionary
27 while others view it as appropriate. The White Paper states that “...it is probably
28 wiser to require that the chronic toxicity data for fish include exposure and
29 observation over a full life-cycle unless there is an affirmative reason to believe
30 that it is not necessary.” The statement is used in the context of requiring a full
31 life cycle study instead of relying on an early life stage test for fish. Some
32 Committee members find that the statement does not appear to fit the process of
33 setting aquatic life criteria, whereas others find it to provide an important
34 perspective for establishing aquatic life criteria.

35
36 *Committee recommendations regarding the use of non-resident species data*

37
38 As mentioned above, the Committee strongly supports EPA’s recommendation
39 that at least one full life cycle test for a fish be included in the requirements for
40 testing all chemicals when deriving water quality criteria for the protection of aquatic
41 life in marine and freshwater environments. We provide the following
42 recommendations to implement the requirement for chronic toxicity data:

- 43
44 1. EPA should critically review data dealing with transgenerational responses of
45 aquatic species and evaluate whether or not this additional testing provides
46 significant new information that informs the evaluation process.

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
46

2. EPA should support research that addresses the suitability of the use of surrogate species in assessing the response of aquatic species (e.g., endangered or long lived species; species with varying life history strategies) to CECs.
3. Test guidelines should include flexibility to include assessment of key developmental events, and professional judgment from an expert panel should be used to evaluate the relevance of non-traditional endpoints such as immune function and 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 population-, not 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).

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

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

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

- 17
- 18 • Additional research is needed to link biomarkers to effects. The Committee notes
19 that the concept of using biological responses occurring prior to impacts on
20 growth, reproduction and survival has been proposed for more than 20 years as a
21 way to detect adverse effects in a population before the population is altered.
22 While there are examples of such “biomarkers of effect,” we find that the linkages
23 between biochemical, histological, and behavioral endpoints and reproduction,
24 growth, and survival are likely life-stage dependent and are difficult to validate,
25 particularly in the field. We note that “biomarkers of exposure” are available but
26 research is needed to interpret their significance.
27
 - 28 • Vitellogenin production is an excellent biomarker of exposure to feminizing
29 chemicals. One of the best examples of exposure biomarkers is the biological
30 response of vitellogenin production in male or juvenile animals. Vitellogenin is
31 an excellent *in vivo* biomarker for exposure to feminizing chemicals. If the
32 response is measured in the whole animal, it incorporates estrogenic as well as
33 anti-androgenic or other modes of action that can cause a feminized response
34 (production of an egg-yolk precursor). It is important to point out that this assay
35 is not identical to estrogen-receptor (ER) based *in vitro* bioassays. Some
36 compounds such as EE2 are very potent ER agonists but also have other modes of
37 action that may alter endocrine systems (Tabb and Blumberg, 2006) such as the
38 inhibition of several isoforms of cytochrome P450 (e.g., CYP3A), which are
39 important in the clearance of endogenous steroids (Parkinson, 2001).
40 Nonylphenols also have multiple modes of action other than direct binding to the
41 ER that lead to feminization [***DFO Note: Please provide reference***]. So the
42 observation of vitellogenin induction within an oviparous male or juvenile
43 organism does not indicate total specificity with regard to mode of action.
44 Anything that increases endogenous estrogen biosynthesis or diminishes clearance
45 would also provide this biological response. The Committee notes that the
46 reduction of vitellogenin in females may not indicate anti-estrogenic effects or

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

1 even alterations of endocrine activity, as basic hepatotoxicants in females can
2 elicit a similar effect. However, we point out that the correlations between
3 fecundity and vitellogenin in females have been observed to be strong even
4 though this may not indicate mode of action (see discussion below). Additional
5 studies are needed to examine hepatotoxicants or compounds with modes of
6 action exclusive of endocrine targets.

- 7
- 8 • The linkage of vitellogenin production to biological effects is limited. While the
9 linkage of vitellogenin to exposure is reasonably solid, linkages of vitellogenin in
10 males / juveniles to higher biological effects such as altered reproduction, survival
11 and growth are limited, even though the relationship may make intuitive sense.
12 Several studies have shown relationships between vitellogenin and reproduction
13 in the laboratory, often at concentrations beyond probable effect concentrations
14 (Thorpe et al., 2007), but few examples of population alterations have been noted
15 in the field. Even in the United Kingdom, where gender shifts to females were
16 originally noted and correlated with vitellogenin induction within males, intersex
17 individuals, and other histological anomalies, overall abundance declines within
18 the species of interest have not been reported. In fact, only one study (Kidd et al.,
19 2007) has linked population crash with vitellogenin or histopathological
20 alterations in fish. A similar occurrence has been noted in laboratory studies
21 where vitellogenin expression may or may not be linked to intersex (Grim et al.,
22 2007), which in turn may or may not lead to gender shifts. Even the relatively
23 clear signal of gender shift, while clearly impacting reproduction in laboratory
24 animals optimized to a specific gender ratio, may not significantly impact field
25 populations in an uncharacterized species (Munday et al., 2006). Clearly, a better
26 understanding of the population dynamics of a ROPC is needed to determine the
27 phenotypic plasticity of the gender ratio. Thus, gender shifts should be viewed
28 with caution, particularly in species that have not been well studied.

29
30 *Committee recommendations regarding selection of endpoints*

31
32 The Committee agrees that EPA should continue to explore the possibility of using
33 sublethal endpoints in helping to set aquatic life criteria. We provide the following
34 recommendations in this regard:

- 35
- 36 1. EPA should pursue the use of “non-traditional measures,” or endpoints for criteria
37 development, as discussed in the White Paper. The Agency should ensure that
38 such measures can be tied to impacts on populations or ecological processes, not
39 just to effects to individual organisms.
 - 40
41 2. EPA should use “non-traditional measures” when appropriate to develop an
42 understanding of and confirm mode of action.
 - 43
44 3. EPA should use human health information and toxicology tools (genomics/
45 PBPKs) when appropriate and available to reduce the uncertainty of aquatic life
46 criteria.

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

11
12 **4.1.6 Involvement of an Expert Panel**

13
14 Because development of aquatic life criteria for CECs may be dependent on
15 technical interpretations of a wide range of toxicological information, EPA has
16 proposed that expert panels be used to provide professional judgment during criteria
17 development. The Committee concurs that strong, active participation by a panel of
18 outside experts will be necessary to ensure that the approaches used (including the
19 designs for toxicity testing, the selected endpoints, and the necessary species and tests
20 to be used, i.e., the ROPCs) are the most appropriate for the compound under
21 scrutiny. As the EPA moves away from firm requirements for species and tests, it
22 will become increasingly important that expert panels comprising diverse expertise be
23 utilized to ensure that the best data are selected for necessary decisions. The National
24 Academy of Sciences and Society of Environmental Toxicology and Chemistry have
25 suggested similar approaches. In a recent report dealing with ecological risk
26 assessment in environmental decision making (U.S. EPA Science Advisory Board,
27 2007), the SAB strongly recommended that expert panels be used to provide
28 assistance to EPA during the problem formulation phase of ecological risk
29 assessments. The same recommendations are appropriate for development of aquatic
30 life criteria. Involving a suite of experts with a balanced range of perspectives during
31 the very early stages of problem formulation, and continuing their involvement as
32 external reviewers at strategic junctures throughout the process, will significantly
33 improve quality, utility, and defensibility of the criteria.

34
35 *Committee recommendations concerning the use of expert panels*

36
37 As stated above, the Committee concurs with the use of expert panels to provide
38 professional judgment during the process of developing aquatic life criteria. We offer
39 the following recommendations concerning the formation and use of expert panels:

- 40
41 1. The process for the use and selection of expert panels should be described in
42 detail and should be transparent. The process used to select and convene the
43 panels, the general attributes of panel composition, and methods used to address
44 issues such as identification and elimination of conflicts of interest must be
45 described (U.S. EPA, 2006). In this regard, one possible model to be considered
46 is the process used to select SAB committees and panels, where national and

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

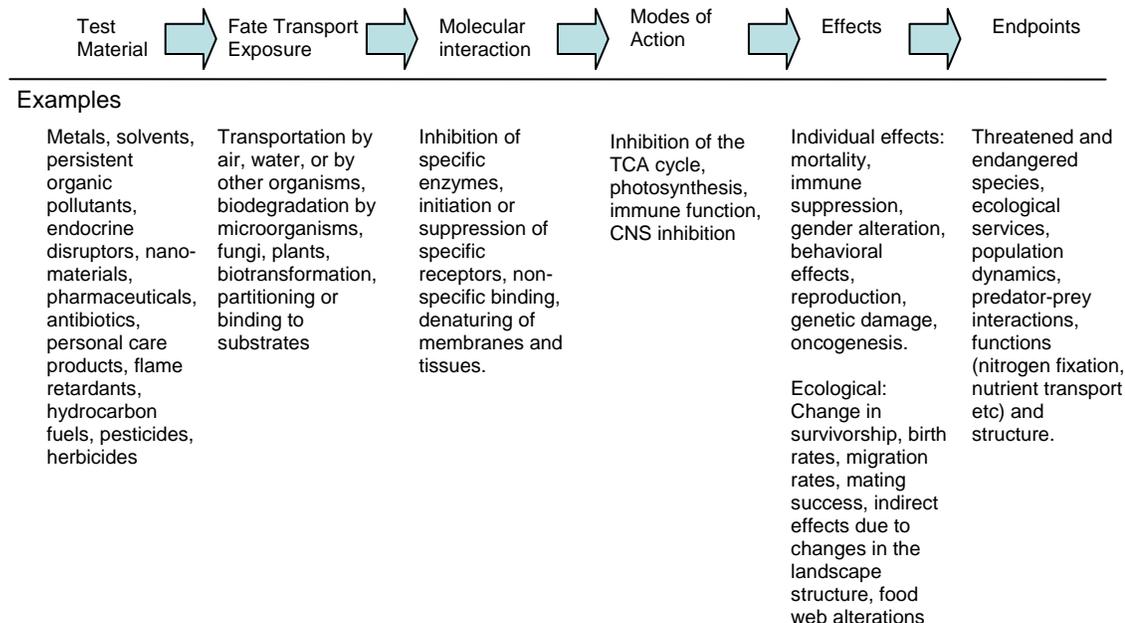
- 1 international experts are identified from multiple sectors representing broad
2 disciplinary expertise and professional affiliation (e.g., academic, appropriate
3 governmental agencies [such as FDA], non governmental organizations, and
4 private industry).
5
6 2. The charge to the panel and the expected end result must be clearly defined.
7
8 3. There are likely similar expert panel processes occurring elsewhere. The
9 Committee recommends that EPA determine whether similar processes are
10 underway in Europe and Asia, and if so, consider them as models to provide
11 additional insight and/or expertise.
12
13 4. The Committee is concerned that the use of expert panels could lead to less
14 consistency in how aquatic life criteria are determined. To help alleviate this
15 potential problem, we recommend that EPA develop specific guidance on the
16 roles of expert panels in problem formulation, data evaluation, and the generation
17 of recommendations leading to criteria derivation.

18
19 **4.2 Charge Question 2. Please comment on whether EPA has identified the**
20 **appropriate issues to be addressed in deriving ALC for CECs. Are there**
21 **additional important issues that EPA has not identified?**
22

23 As stated previously, EPA's White Paper identifies technical issues that need to
24 be addressed in deriving aquatic life criteria for CECs. The Committee was asked to
25 comment on whether the Agency has identified the appropriate issues in the White
26 Paper and whether there are additional important issues that EPA has not identified.
27 The Committee finds that appropriate technical issues have been identified in the
28 White Paper.
29

30 The Committee finds that EPA could clarify the process of developing aquatic life
31 criteria for CECs by articulating a set of principles that could be applied when
32 modifying the 1985 Guidelines to develop water quality criteria for such
33 contaminants. We also emphasize the importance of developing a conceptual model
34 to guide the process of developing aquatic life criteria for CECs. The conceptual
35 model should address more than the fate and direct effects of CECs. It should include
36 consideration of probable direct and or indirect impacts on food webs, ecological
37 processes and services, unique, endangered or keystone species or species of special
38 societal value or concern. The example provided in Figure 1 illustrates components
39 that could be included in such a conceptual model. Use of a conceptual model to
40 support criteria development would improve EPA's ability to address emerging
41 questions about unique mechanisms, fate processes, and effects endpoints. Use of the
42 conceptual model is further discussed below.
43

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

Figure 1. Example of a Generalized Conceptual Model for Deriving Aquatic Life Criteria

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 include the following: seek a wide range of inputs from diverse perspectives; determine appropriate ROPCs; develop a robust conceptual model; develop multiple lines of evidence; and identify uncertainties (quantitative and qualitative) associated with criteria development. Each of these principles is further discussed below:
 - Seek a wide range of inputs. EPA should seek input from a diversity of experts representing: Agency scientists, academic scientists, scientists in business and industry, state and tribal scientists, and the environmental community on the problem formulation, conceptual model development, modifications to the Guidelines dictated by the properties of a CEC, and the resulting recommendation for the aquatic life criterion. Adherence to this principle will ensure that the process stimulates a robust discussion and is

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

- 1 informed by and acceptable from a diversity of perspectives. This diversity
2 should include input from chemists, modelers, toxicologists, ecologists, and
3 risk assessors.
4
- 5 - Determine appropriate ROPCs. The process needs to clearly identify the need
6 to determine appropriate receptors of potential concern and not simply focus
7 on “traditional” test organisms.
8
 - 9 - Develop a robust conceptual model. At the start of the criterion development
10 process, the available data on fate and effects should be examined and used to
11 develop a conceptual model (e.g., Figure 1). Structure activity data and
12 modes of action of similar compounds/materials should be consulted to inform
13 model development. An expert panel should be convened to assist in the
14 problem formulation and conceptual model development step. Uncertainty
15 should be identified in the model and used to identify strategic efforts to
16 reduce uncertainty. The conceptual model should include more than fate and
17 effects data. It should include consideration of probable direct and or indirect
18 impacts on food webs, ecological processes and services, and unique,
19 endangered or keystone species or species of special societal value or concern
20 (charismatic species).
21
 - 22 - Develop multiple lines of evidence. The committee finds that a multiple line
23 of evidence approach has the potential to inform decision making and the
24 criterion recommendation. It also can serve to reduce uncertainty when the
25 lines converge and reinforce each other.
26
 - 27 - Identify uncertainties and conduct uncertainty analysis. As further discussed
28 below, EPA should identify the uncertainties associated with the criteria
29 developed for CECs. At all stages of criteria development, uncertainty should
30 be quantified and /or qualitatively discussed. Uncertainty should be used to
31 focus and prioritize data generation efforts.
32
- 33 2. EPA should develop an expert system or process to assist the development of
34 criteria for CECs. The expert system would establish a set of rules to enable
35 analysis of information supplied by the user and lead to recommendations
36 concerning one or more courses of user action. The Committee finds that such an
37 expert system would be an important tool for capturing and maintaining the state
38 of the art in aquatic life criteria development. It would serve as a vehicle for
39 connecting fate and effects assessment tools and capturing expert knowledge, and
40 it could serve as a platform for deriving priorities for future research in assessing
41 the risks of contaminants to aquatic life and ecosystems.
42
- 43 3. The Committee strongly recommends that understanding and presentation of
44 uncertainty become an intrinsic part of the aquatic life criteria development
45 process. The presentation of uncertainty needs to be an explicit and transparent
46 part of the analysis. For example, the uncertainties inherent in understanding

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

1 modes of action, determination of concentration-response relationships,
2 development of species sensitivity distributions, and derivation of ecological
3 effects should be quantified or described in a narrative sense. An important
4 aspect of this is developing an a priori understanding of the amount and types of
5 uncertainties that preclude the derivation of an aquatic life criterion. These
6 uncertainties can be classified into the categories listed below:

- 7
- 8 - Uncertainties that preclude the derivation of an aquatic life criterion.
 - 9
 - 10 - Areas in which uncertainties may be important and can be resolved with
11 additional modeling, research or a better understanding of the relationship of
12 the uncertainty to the standard setting process.
 - 13
 - 14 - Uncertainties that do not preclude the setting of an aquatic life criterion but
15 form the basis for future research programs.
 - 16

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

19

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

28

29 5. In the White Paper, EPA should discuss the importance of considering
30 environmental context (i.e., site specific considerations) in deriving aquatic life
31 criteria for CECs. These modifying factors should be mentioned in the CEC
32 criteria themselves. For example, characteristics of the receiving environment
33 affect bioavailability and toxicity to organisms (e.g., trophic status, dissolved
34 organic carbon, pH, and substrate types) as well as longevity of their exposure
35 due to impacts on the degradation and partitioning rates of these chemicals.
36 Several CECs have the potential, based on their physical-chemical properties, to
37 bioaccumulate and bioconcentrate, and this may result in diet-borne toxicity to a
38 predator. Degradation/biotransformation products of CECs should be considered
39 because there are instances where their toxicity is greater than the parent
40 compound. In addition, the Committee recommends considering analytical
41 chemistry because some aquatic life criteria have the potential to be set at
42 concentrations that are at or below current (widely available) abilities to easily
43 quantify CECs.

44

45 6. The Committee recommends that EPA keep abreast of the new science related to
46 CECs in order to ensure that the latest approaches for assessing the effects of

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

1 these chemicals are considered in criteria derivation. These types of effects may
2 include impacts on natural selection and genetic diversity, indirect effects through
3 changes in prey quality and quantity, and alteration of ecosystem function. We
4 also point out that effects of CECs may be non-linear, which would pose
5 challenges in derivation of aquatic life criteria. We note that consideration needs
6 to be given to the diversity of phylogenies, functions, and habitats represented in
7 the data used to establish an aquatic life criterion in order to ensure that the
8 overall goals of the process (adequate, appropriate level of population-level
9 protection) are met.

10

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

22

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

29

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

38

39 **4.3 Charge Question 3. Part II of this white paper was specifically developed**
40 **as a companion to Part I and focuses on the use of ethynylestradiol as a**
41 **model chemical to illustrate the technical issues presented by the**
42 **workgroup, as well as providing a basis for understanding the**
43 **recommendations. Does the *Committee* have suggestions that may**
44 **improve the utility of Part II of this white paper for the purposes stated**
45 **above?**

46

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

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

12

13 *Committee recommendations to improve the usefulness of the illustrative example*

14

- 15 1. In the White Paper, EPA should explicitly recognize that EE2 is unique in being a
16 data-rich CEC. The White Paper should highlight the fact that the Agency's
17 interest in CECs goes beyond endocrine-active substances, and discuss how the
18 example of EE2 might be extrapolated to other substances, particularly to data-
19 poor substances. EPA should consider conducting a similar assessment for a
20 compound with a minimal data set (in contrast to the maximal set of data
21 available for EE2) and evaluate the new approach accordingly.
22
- 23 2. Parts I and II of the White Paper should be integrated. While the Committee
24 appreciates the level of detail provided in Part II, we believe that the illustrative
25 pieces of Part II could be best presented in Part I in the form of succinct text
26 boxes illustrating key concepts derived from the various recommendations (e.g.,
27 why certain steps in the Guidelines were included and others were not), with the
28 more detailed components of Part II relegated to appendices in Part I (which
29 would become the sole document). Further, we suggest that the recommendations
30 could be best illustrated if the text boxes were not restricted to EE2 but rather
31 included other CECs (e.g., non-endocrine-active compounds, data-poor CECs).
32 In making these revisions, we urge the authors to ensure that the high level of
33 readability inherent in the present version of Part I is retained.
34
- 35 3. Regarding the scope of the material included in the EE2 example, we note that the
36 White Paper fails to address how the influence of EE2 might be affected by
37 mixtures of compounds, especially those with similar modes of action (e.g.,
38 estradiol, estrone), as well as environmental (e.g., temperature) and biological
39 (e.g., disease, starvation) modifying factors. Although the Committee recognizes
40 that various offices / groups within EPA are investigating mixtures of compounds,
41 and the White Paper cannot address all relevant issues in the development of
42 guidelines, the document needs to be explicit regarding the importance of
43 considering multiple stressors as well as synergies among CECs. For example,
44 the White Paper should, at the very least, state the rationale for not considering all
45 estrogens within a given body of water, and should provide examples of mixtures
46 and synergies that could affect the toxicity of EE2.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
4. Regarding choice of taxa for criteria derivation, the Committee agrees that, although use of non-resident species to assess EE2 effects appears to fit this case example, such may not always be the case. As such, the document should indicate that: 1) resident species data, especially life-cycle tests from resident species, remain extremely valuable, and 2) results from non-residents, while providing useful information, may not be generalized to resident species unless data are available to compare the sensitivities of the non-resident and resident species. We are also concerned that certain sensitive taxa such as amphibians were not included in Table 3.2, and that the key issue of development time to sexual maturity for long-lived, charismatic species, such as sturgeon, is not addressed in the document. Research should be conducted to develop comparisons between species that are long-lived and surrogate test species.
- 15
16
17
18
19
20
21
22
23
24
25
26
27
28
5. The Committee is concerned that transgenerational effects were not considered in Part II of the White Paper. On page 14 in Part II of the White Paper, EPA states that “it does not seem that the evidence for transgenerational effects is sufficient for requiring their inclusion in the definition of an acceptable chronic test.” Given EE2’s role as an endocrine disrupting chemical, it is surprising that transgenerational effects were not included in the treatment of EE2. Further, given the “guilty until proven innocent” rule mentioned previously, the Committee recommends that the possibility of transgenerational effects be explicitly addressed in this illustration. Although transgenerational effects may not be expected in the case of EE2, potential transgenerational consequences must be addressed in a clear and transparent manner to ensure the development of a process that can also be applied to substances for which transgenerational effects are expected.
- 29
30
31
32
33
34
35
36
37
38
39
40
6. The Committee recommends that a broader array of endpoints be included in Part II. For example, although EE2 is a potent estrogen receptor agonist, it also can affect the central nervous system through indirect effects (steroid biotransformation). Non-traditional endpoints such as genomic or physiologically based pharmacokinetic modeling (PBPK) studies might be considered. As noted previously, use of non-traditional endpoints requires an understanding of their relevance to the health of the organism and ultimately the population. The illustration in Part II needs to answer the question as to whether or not it is possible to calculate population-scale impacts with EE2 and, if not, how a criterion can be developed that will truly protect populations within a reasonable level of uncertainty (consistent with the intent of the Guidelines).
- 41
42
43
44
45
46
7. Two key recommendations regarding Part I of the White Paper are repeated here for the sake of consistency. First, the use of weight of evidence is implicit in the evaluation, but it needs to be explicit in the Part II of the document. Interactions between weight of evidence and the Precautionary Principle (i.e., appropriate levels of uncertainty) should be clarified. Second, when appropriate data are available, ECx values (i.e., the concentration causing an effect in x percent of the

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

- 1 test organisms) should be used rather than NOECs / LOECs (i.e., no observed
2 effects concentrations / lowest observed effects concentrations). Use of an
3 endpoint that reflects the concentration-response curve, not one that is based
4 solely on the concentrations tested, is the necessarily rigorous and technically
5 defensible approach.
6
- 7 8. If Part II of the White Paper is to remain as a separate document, the Committee
8 finds that its clarity and transparency could be improved in a number of areas. In
9 particular, the authors need to more explicitly describe how the illustration was
10 developed from the recommendations in Part I of the White Paper. Part II of the
11 White Paper also needs to be more explicit regarding how specific conclusions
12 and assessments derived from the data. The following specific revisions are
13 suggested:
14
- 15 - Data used to arrive at the values shown in Table 3.1 need to be provided in an
16 appendix.
17
 - 18 - Table 1 arguably includes chronic data (*Lytechinus* and *Strongylocentrotus*
19 echinoderm embryo development tests and the *Acartia* embryo test) that, not
20 surprisingly, provide the most sensitive responses. While the Committee
21 concurs that there is “ample evidence that a CMC is not needed and that it is
22 unnecessary to conduct further tests to meet the minimum data requirements,”
23 the differentiation between acute and chronic data needs to be more clear and
24 transparent along with the implications of including equivocal data.
25 Confusion between acute and chronic data can result in unnecessary levels of
26 uncertainty and variability in criteria development. We note that slide 11 of
27 the presentation provided by Dr. Russell Erickson of EPA ORD at the
28 Committee meeting on June 30 provides the requisite level of clarity and
29 transparency and could usefully be included in the document.
30
 - 31 - More explicit discussion of what constitutes “sufficient information” at
32 various decision points would be helpful.
33
 - 34 - The validity of using non-resident species is justified by text referring to
35 complex tables, which do not provide the level of clarity and transparency
36 necessary. Given the importance of validating the use of non-resident species,
37 a graphic representation of the data is required (e.g., SSDs or linear, horizontal
38 lines indicating ranges for survival, growth and reproduction showing where
39 the non-resident species fit).
40
 - 41 - If EPA decides not to integrate Parts I and II as recommended elsewhere in
42 our review, the Committee suggests that the authors add a concluding section
43 that summarizes the process used to assess how the process of developing an
44 aquatic life criterion for EE2 was modified by use of the new / revised
45 guidelines. Part II should in this case also provide an overview of how the
46 process is expected to ultimately influence the criteria derived (in other words,

1 what is the bottom line in terms of how the new recommendations changed
2 the final outcome?).

- 3
- 4 - The EE2 example in Part II relies on nominal concentrations in addition to
5 measured concentrations. The Committee assumes that criteria will not be
6 based on nominal concentrations. This needs to be made clear in the
7 document. Nominal concentrations would be acceptable if they were within
8 20% of concentrations measured during a test.
9
 - 10 - The first two paragraphs on page 13 of Part II would benefit from additional
11 information on the timing of exposures to clarify that a 16% reduction in
12 growth occurred after 28 days (paragraph 1, line 4), and the timing for lower
13 reproduction at 0.2 and 1 ng/L (paragraph 1, line 9). We have a similar
14 suggestion for effects on fertilization success (paragraph 2, lines 7-8).
15
 - 16 - EPA should include in the appendix the residency status of each species or
17 genus. The authors refer to residency in interpretations, but this information is
18 missing from the document.
19
 - 20 - A list of acronyms such as that provided for Part I also would be useful for
21 Part II if it remains as a separate document.
22
 - 23 - A few questions are raised regarding citations: (1) Wenzel et al. (2002) is
24 cited in the text (p. 14, paragraph 3, line 3) but not in the References, should
25 the date be 2001?; (2) Is the Kolpin et al. (2002) reference correct (both here
26 and in Part I) - it does not seem to apply as it is a 2-page response to a
27 comment, not a full paper?; (3) Lee and Choi (2006) is listed in the
28 References as "in press" but surely this is not still the case 2 years later?; and
29 (4) the reliance on McKim et al. (1978) is questioned regarding the assertion
30 that a "factor of 2 difference is generally found for other chemicals" (page 13,
31 incomplete paragraph beginning the page, last line). We note that the McKim
32 et al. (1978) paper only referred to one chemical, copper, and was published
33 thirty years ago in a journal that does not have a high level of peer review.
34

35 **4.4. Charge Question 4. Does the Committee have suggestions that would**
36 **assist EPA in implementing the proposed recommendations discussed in**
37 **the white paper, particularly with respect to developing the necessary**
38 **scientific data and information and/or providing expert scientific input at**
39 **the appropriate stages of the risk assessment process?**
40

41 The Committee has provided comments and recommendations to assist EPA in
42 implementing the proposed recommendations discussed in the White Paper. Many of
43 our comments focus on actions that would assist in implementation of the
44 recommendations in the White Paper. However, we have also provided broader
45 suggestions to facilitate future development of aquatic life criteria for CECs. Some of

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

1 our comments and recommendations elaborate upon points discussed in previous
2 sections of this advisory report.

3
4 *Points to be considered in implementing the proposed recommendations in the White*
5 *Paper*

- 6
7 • Developing new criteria for CECs will require intensive data collection /
8 generation activities by EPA. In an ideal world, it would be the Committee's
9 recommendation that the same level of effort required to register a new chemical
10 or pesticide also be required to develop aquatic life criteria for CECs. In that
11 case, EPA would have to provide the necessary research funds and personnel to
12 generate the data needed for developing relevant and defensible criteria.
13 Acknowledging that this may not be possible in a world of limited resources, it
14 will be important that OW / ORD prioritize the list of CECs for which aquatic life
15 criteria will be developed. EPA should also identify data needs for these
16 chemicals and leverage research development activities to develop the necessary
17 data. Prioritization of CECs and data needs is further discussed below. In
18 addition, EPA should conduct research to evaluate the sensitivity of test
19 organisms that could be used as surrogates for resident and endangered species.
20 Research should also compare the sensitivity of traditional and non-traditional test
21 endpoints.
22
- 23 • Leveraging research efforts of other agencies is essential. In a time of decreasing
24 research funds within the federal government, it is important that OW / ORD seek
25 opportunities to leverage research efforts of other government agencies (e.g.,
26 FDA, USDA, NOAA). The Committee was informed that EPA and the FDA are
27 coordinating data sharing. We recommend that this activity continue and further
28 that it be broadened to include other government agencies. We further support
29 international collaboration between EPA, the European Union, Environment
30 Canada and other appropriate non-US environmental agencies. In addition, it is
31 apparent that the regulated community, industries, animal husbandry
32 organizations (e.g., National Cattlemen's Beef Association) and Publicly Owned
33 Treatment Works, are actively engaged in independent evaluation of CECs.
34 Establishing a government/industry consortium may be a way of leveraging
35 limited funds for broader data development opportunities.
36
- 37 • Linkages between ecological risk assessment and development of aquatic life
38 criteria need to be articulated. The Committee finds that, in many ways, the 1985
39 Guidelines contain the same principles of evaluating ecological risk that were
40 subsequently incorporated into the 1989 *Risk Management Guidance for*
41 *Superfund, Volume 2: Environmental Evaluation Manual*, (U.S. EPA. 1989), and
42 in the 1992 *Framework for Ecological Risk Assessment* (U.S. EPA, 1992).
43 Furthermore, it was apparent from the presentations made by EPA to the
44 Committee that the ecological risk assessment principles have been considered by
45 OW and ORD in planning further development of aquatic life criteria for CECs.
46 However, the link between the 1989 Risk Management Guidelines and the aquatic

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

- 1 life criteria derivation process is not apparent. The white paper needs to explicitly
2 consider and illustrate risk assessment principles (e.g., identification of ROPCs,
3 development of a conceptual diagram as previously recommended by the
4 Committee).
- 5
- 6 • Tissue-based criteria should be considered for bioaccumulative CECs where food
7 chain transfer is a concern. As mentioned previously, EPA should consider
8 developing tissue-based criteria (i.e., expressing the criterion as a concentration of
9 the pollutant in fish tissue rather than a concentration in the water). Aquatic life
10 may be impaired directly by eating contaminated food, or indirectly by loss of
11 prey or other ecosystem alterations that could stem from CECs. EPA is
12 developing residue-based criteria for selenium (2002 and 2004 draft criteria
13 documents [U.S. EPA, 2007]). Arguably, selenium can be considered a
14 contaminant of emerging concern, but it does not fit the definition provided in
15 Section 1.1 of Part I of the White Paper. The Committee finds that it may be
16 useful to consider using selenium as an example for development of tissue-based
17 aquatic life criteria for CECs.
- 18
- 19 • Quantitative linkages are needed between mode of action indicators and
20 population-level endpoints. The proposed recommendations in the White Paper
21 are consistent with bettering the risk assessment process. However, it will be
22 important to set priorities for technical research that addresses significant gaps in
23 knowledge needed to develop: 1) new indicators; 2) modeling capabilities; and 3)
24 tools that provide integration and linkage of data sources. As mentioned
25 previously, one of the most important challenges facing EPA will be linking mode
26 of action indicators of exposure / effects to known population-level effects
27 measurement endpoints such as survival, growth, reproduction and development.
28 Developing conceptual models will guide criteria development but quantitative
29 linkages will be needed to discern how mode of action indicators connect with
30 population-level end points. The White Paper (p. 20, lines 21- 21) states that it is
31 important to have a clear linkage between mode of action indicators such as
32 histopathology and growth, reproduction and development. The Committee notes
33 that in some instances it may be possible to define scaled risk (e.g., level of
34 biological response in cell, tissue, etc.) and relative risk. This will make it
35 possible to develop mode of action fingerprints that may provide earlier warning
36 and greater sensitivity in predicting population-level effects.
- 37
- 38 • Additional factors may need to be considered to protect certain species. As noted
39 previously, development of aquatic life criteria to provide adequate levels of
40 protection for endangered, highly managed, protected and “charismatic” species
41 (e.g., marine mammals, eagles, polar bears, sturgeon) may require consideration
42 of additional factors. For example, in marine mammals a dive reflex can force
43 more contaminant into tissue due to pressure gradients. Endangered species may
44 have very different lag times for sexual differentiation and uptake characteristics
45 of CECs than the commonly used test species. For example, sturgeons are both
46 endangered and charismatic fishes, and they are known to readily accumulate

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

- 1 many CECs for an extended developmental period prior to reproduction. Given
2 their long lifespan, a life cycle chronic test to determine uptake would therefore
3 be impossible, and an early life cycle test would be inappropriate.
4
- 5 • There is a need to compile a list of priority CECs. To facilitate development of
6 aquatic life criteria, the Committee finds that it would be useful for federal
7 agencies working on CECs (e.g., EPA, the US Geological Survey, the US Food
8 and Drug Administration, the National Oceanic and Atmospheric Administration,
9 and others) to compile a list of priority CECs that may pose the greatest risks to
10 aquatic life – in other words, use a risk assessment approach in a problem
11 formulation exercise to determine contaminants of potential concern. Analytical
12 chemistry methods should be developed to measure levels of these contaminants
13 in aquatic environments. The Committee suggests that calculation of the ratios of
14 the Maximum Environmental Concentrations to meaningful measures of
15 biological effects (e.g., CCCs, or LC_xs from toxicity testing) could initially be
16 used to develop a list of high priority CECs. This kind of exercise would likely,
17 but not certainly, show that estrogens should be a top priority for aquatic life
18 criteria, as indicated in the White Paper.
19
 - 20 • There is a clear need for continued development of analytical capabilities to
21 measure levels of CECs in the aquatic environment. For example, the ability to
22 detect many of the CEC at appropriate concentrations in a controlled laboratory
23 setting may be entirely different from detecting those same low concentrations in
24 the aquatic environment. Addressing such issues will help current long term
25 monitoring programs (e.g., NOAA National Status and Trends and Mussel Watch
26 programs, US Geological Survey National Water Quality Assessment Program,
27 EPA Environmental Monitoring and Assessment Program) implement a
28 coordinated approach to better define CEC exposures in the environment. Efforts
29 to develop methodological approaches for lowering limits of detection and
30 standards for CECs should involve discussion among agencies as well as the
31 regulated community. It may be important to include the National Institute of
32 Standards and Technology in the development of environmental standards for
33 new CECs.
34
 - 35 • Input into the aquatic life criteria development process is needed from private
36 industry and state government. The perspective of these important stakeholders is
37 needed before finalizing the White Paper. These groups should be asked to
38 provide input on the science associated with the modifications of the Guidelines
39 related to CEC because aquatic life criteria will be used to develop state water
40 quality standards.
41
 - 42 • It would make sense to consider using parallel processes to develop aquatic life
43 criteria for compounds with similar modes of action (e.g. the estrogens, SSRIs).
44 For example, since estrone, estradiol and EE2 all act through the estrogen receptor
45 in the most sensitive taxa, fish, and there is growing evidence in the literature that
46 their effects are additive (Thorpe et al., 2007), it would make sense to develop

1 aquatic life criteria for the natural and synthetic estrogens using parallel
2 processes. Similar approaches may be possible for other CECs with highly
3 specific modes of action such as different classes of antibiotics, statin drugs and
4 other pharmaceuticals that are CECs.

- 5
- 6 • Further questions to consider. As EPA develops a research plan to support
7 derivation of aquatic life criteria for CECs, it may be useful to consider the
8 following questions mentioned previously: How can aquatic life criteria be
9 developed to take into account the fact that aquatic organisms are exposed to
10 mixtures of CECs and mixtures of CECs, known contaminants, and other
11 stressors? What are the likely modes of action of CECs that are known to be
12 present in the environment? How can field study results be used to inform the
13 derivation of an aquatic life criteria for a CEC?

14

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

17

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

- 22
- 23 1. EPA should develop a list of high priority CECs that may pose the greatest risks
24 to aquatic life. Additional work should then be completed to further assess the
25 potential risks posed by these chemicals and fund the research and data collection
26 activities needed to support future development of aquatic life criteria. In this
27 regard, we recommend that EPA's Office of Water and Office of Research and
28 Development look for opportunities to leverage existing research with those on-
29 going in other federal programs, similar programs with international agencies, and
30 industry groups, to gather the data needed to develop the aquatic life criteria.
31 The Agency should also work with other federal agencies to develop analytical
32 chemistry detection methods and standards for these chemicals.
33
 - 34
 - 35 2. EPA should explicitly incorporate the principles for conducting Ecological Risk
36 Assessment into the process of deriving aquatic life criteria for CECs. The
37 Committee recommends that the EPA develop a separate process document that
38 discusses the intended application of aquatic life criteria for CECs, and cross-links
39 the 1985 Guidelines, the EPA's 1992 Ecological Risk Assessment Principles, and
40 the 2008 aquatic life CEC criteria White Paper. This cross-link document should
41 also incorporate relevant ecological risk principles from other similar documents
42 developed for FDA, TSCA, or FIFRA. The document should not only outline the
43 process of aquatic life criteria development, but address elements such as
44 contaminant exposure through food uptake, Water Effects Ratios, Whole Effluent
45 Testing, mixtures of compounds with similar modes of action, and application of
46 aquatic life criteria for CECs in sediment management programs. The Committee

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

- 1 is not recommending the development of a large, comprehensive document, rather
2 something short and concise similar to the Eco Update Bulletins that have been
3 published by EPA's Office of Solid Waste and Emergency Response (OSWER).
4
- 5 3. As previously discussed, the Committee recommends that EPA incorporate the
6 use of conceptual site models and ecosystem-based criteria into the process of
7 deriving aquatic life criteria for CECs. We note that EPA programs are moving
8 toward developing more comprehensive ecosystem-relevant criteria that take into
9 consideration population-community structure, ecosystem functions-processes,
10 and ecosystem services. The data available to develop CCCs are often
11 "traditional" toxicity test data. It is important to develop the link between the
12 protected resource, the assessment endpoint, and the measurement endpoint. An
13 appropriate conceptual model for deriving aquatic life criteria for a CEC (see
14 Figure 1) may be used to develop the fate and effects data and data quality
15 objectives needed to support the aquatic life criterion.
16
- 17 4. As previously discussed, EPA should consider (where appropriate) developing
18 tissue residue-based aquatic life criteria for CECs. The Agency should consider
19 developing tissue-based criteria using the selenium example and expanding the
20 definition of contaminants of emerging concern to include "chemicals and other
21 substances of increasing environmental concern due to anthropogenic activities
22 and for which current regulatory approaches are inadequate." Tissue residue-
23 based criteria should be considered for CECs that have potential to bioaccumulate
24 (e.g., carbamazepine) and bioconcentrate (e.g., flame retardants). At a minimum,
25 the conceptual model could be used to help determine how to evaluate the
26 available environmental data and models to assess the main routes of exposure for
27 aquatic organisms.
28
- 29 5. EPA should use a "mode of action" approach to develop more effective aquatic
30 life criteria not only for CECs, but also for legacy contaminants and mixtures.
31 Additional studies in genomic and toxicodynamics processes would provide
32 necessary data for the identification of "mode of action" fingerprints and aid in
33 this process, particularly in the problem formulation stage of risk assessment.
34 This should help guide regulators to carry out the most efficient bioassays which
35 will be used in setting thresholds or criteria.
36
- 37 6. The Committee recommends that EPA appropriately use novel environmental
38 indicators (molecular, genomics, proteomics) developed at other agencies,
39 industry, and by academia in future development of criteria. For example, NOAA
40 has developed a robust health effects assessment for bottle nosed dolphins that
41 addresses many CECs including flame retardants and antibiotic resistance
42 (National Oceanic and Atmospheric Administration, 2008). The assessment
43 involved analysis of the immune function data and other health information on the
44 animals such as clinical evaluation, blood chemistries, contaminants and
45 hormones. Since dolphins are apex predators that breathe the air, swim in the
46 water and constantly eat seafood, they provide a most exposed individual model.

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

- 1 This type of insight may be pivotal in enhancing what EPA can do using the
2 approach outlined in Part I of the White Paper.
3
- 4 7. EPA should take into consideration appropriate additional factors to ensure that
5 aquatic life criteria are protective of endangered and protected species and
6 commercially / recreationally important species. These species are protected by
7 additional laws (e.g., Magnuson Stephens, Marine Mammal Protection Act) and
8 this may invoke other special considerations when developing aquatic life criteria.
9
- 10 8. EPA should obtain input from private industry and state government on the
11 Agency's proposed approaches for developing aquatic life criteria for CECs
12 before finalizing the White Paper.
13
- 14 9. EPA should consider developing a mixture strategy to develop aquatic life criteria
15 for classes of compounds with similar modes of action. As previously mentioned
16 parallel processes could be used to develop aquatic life criteria for broad classes
17 of CECs with similar modes of action (e.g., the estrogens, SSRIs).
18
19

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 Beyers, D.W. 1995. Acute toxicity of Rodeo herbicide to Rio Grande silvery minnow
8 as estimated by surrogate species: plains minnow and fathead minnow. *Archives of*
9 *Environmental Contamination and Toxicology*, 29:24-26.
10
11 Brain, R.A, M.L. Hanson, K.R. Solomon, and B.W. Brooks. 2007. Targets, effects
12 and risks in aquatic plants exposed to pharmaceuticals. *Reviews of Environmental*
13 *Contamination and Toxicology*, 192:67-115.
14
15 Chandler, G.T., T.L. Cary, A.C. Bejarano, J. Pender, and J.L. Ferry. 2004.
16 Population consequences of fipronil and degradates to copepods at field
17 concentrations: An integration of life cycle testing with Leslie matrix population
18 modeling. *Environmental Science and Technology*, 38:6407-6414.
19
20 Chapman, P.M., McDonald, B. Kickham, P.E., McKinnon, S. 2006. Global
21 geographic differences in marine metals toxicity. *Marine Pollution Bulletin*, 52:
22 1081-1084.
23
24 Dwyer, F.J., D.K. Hardesty, C.G. Ingersoll, J.K. Kunz, and D.W. Whites. 2000.
25 *Assessing Contaminant Sensitivity of American Shad, Atlantic Sturgeon, and*
26 *Shortnose Sturgeon. Final Report, February 2000.* U.S, Geological Survey,
27 Columbia Environmental Research Center, Columbia, MO [Available at:
28 <http://www.cerc.usgs.gov/pubs/center/pdfDocs/91008.pdf>]
29
30 European Commission. 2008. *The EU Water Framework Directive – Integrated*
31 *River Basin Management for Europe.* [http://ec.europa.eu/environment/water/water-](http://ec.europa.eu/environment/water/water-framework/index_en.html)
32 [framework/index_en.html](http://ec.europa.eu/environment/water/water-framework/index_en.html) . [Accessed September 2, 2008]
33
34 Filby, A.L., T. Neuparth, K.L. Thorpe, R. Owen, T.S. Galloway, and C.R. Tyler
35 2007. Health impacts of estrogens in the environment, considering complex mixture
36 effects. *Environmental Health Perspectives*, 115 : 1704-1710.
37
38 Grim, K.C., M. Wolfe, W. Hawkins, R. Johnson, and J. Wolf. 2007. Intersex in
39 Japanese medaka (*Oryzias latipes*) used as negative controls in toxicologic bioassays:
40 A review of 54 cases from 41 studies. *Environmental Toxicology and Chemistry*,
41 26:1636-1643.
42
43 Kidd, K.A., P.J. Blanchfield, K.H. Mills, V.P. Palace, R.E. Evans, J.M. Lazorchak,
44 and R.W. Flick 2007. Collapse of a fish population after exposure to a synthetic
45 estrogen. *Proceedings of the National Academy of Sciences of the United States of*
46 *America*, 104: 8897-8901.

- 1
2 Lawton, J.C., P.L. Pennington, K.W. Chung, and G.I. Scott. 2006. Toxicity of
3 atrazine to the juvenile hard clam, *Mercenaria mercenaria*. *Ecotoxicology and*
4 *Environmental Safety*, 65(3): 388-394.
5
6 Mount, D.R., P.V. Hodson, G. Ankley, K. Brix, W. Clements, G. Dixon, A.R.J.
7 Erickson, A. Fairbrother, C. Hickey, R. Lanno, C.Lee, W. Munns, R. Ringer, J.
8 Stavely, and C. Wood. 2003. Effects Assessment. In: Reiley et al. (ed.), *Water*
9 *Quality Criteria Development: Comparing Current Approaches*. SETAC Press,
10 Pensacola, FL, 53-118.
11
12 Munday, P.L., P.M. Bustion, and R.R. Warne. 2006. Diversity and flexibility of sex-
13 change strategies in animals. *Trends in Ecology and Evolution*, 21:89-95.
14
15 National Oceanic and Atmospheric Administration. 2008. *Health and Risk*
16 *Assessment of Bottlenose Dolphin Populations, 2008*.
17 <http://www8.nos.noaa.gov/nccos/npe/projectdetail.aspx?id=53&fy=2008> [Accessed
18 August 29, 2008]
19
20 Parkinson, A. . 2001. Biotransformation of xenobiotics, In: *Casarett & Doull's*
21 *Toxicology: The Basic Science of Poisons* (C. Klaasen Ed). McMillan Publishers,
22 New York, NY.
23
24 Pennington, P. L., J.W. Daugomah, A.C. Colbert, M H. Fulton, P.B. Key, B C.
25 Thompson, E D. Strozier and G.I. Scott. 2001. Analysis of pesticide runoff from
26 mid-Texas estuaries and risk assessment implications for marine phytoplankton.
27 *Journal of Environmental Science and Health*, 36(1): 1-14.
28
29 Pennington, P.L. and G.I. Scott. 2001. The toxicity of atrazine to the estuarine
30 phytoplankter *Pavlova* Sp. (Prymnesiophyceae): increased sensitivity after chronic
31 exposure. *Environmental Toxicology and Chemistry*, 20 (10): 2237-2242.
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.
46

This draft is a work in progress, does not reflect consensus advice or recommendations, has not been reviewed or approved by the Chartered SAB, and does not represent EPA Policy

- 1 Thorpe, K.L., R. Benstead, T.H. Hutchinson, and C.R. Tyler 2007. Associations
2 between altered vitellogenin concentrations and adverse health effects in fathead
3 minnow (*Pimephales promelas*). *Aquatic Toxicology*, 85:176-183.
4
- 5 U.S. EPA. 1989. *Risk Assessment Guidance for Superfund, Part A*. EPA/540/1-
6 89/002. Office of Emergency and Remedial Response. U.S. Environmental
7 Protection Agency, Washington, D.C.
8
- 9 U.S. EPA. 1992. *Framework for Ecological Risk Assessment*. EPA/600/R-92-001.
10 U.S. Environmental Protection Agency Risk Assessment Forum, Washington, D.C.
11 [Available at: <http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=30759>]
12
- 13 U.S. EPA. 2006. *Peer Review Program*. <http://epa.gov/peerreview/> [Accessed
14 August 22, 2008]
15
- 16 U.S. EPA 2007. Selenium Aquatic Life Criterion – draft.
17 <http://www.epa.gov/waterscience/criteria/selenium/> [Accessed August 22, 2008]
18
- 19 U.S. EPA Science Advisory Board. 2007. *Advice to EPA on Advancing the Science
20 and Application of Ecological Risk Assessment in Environmental Decision Making: A
21 Report of the U.S. EPA Science Advisory Board*. EPA-SAB-08-003. U.S.
22 Environmental Protection Agency, Washington, D.C. [Available at:
23 [http://yosemite.epa.gov/sab/sabproduct.nsf/WebReportsbyYearBOARD!OpenView&
24 Start=1&Count=800&Expand=1#1](http://yosemite.epa.gov/sab/sabproduct.nsf/WebReportsbyYearBOARD!OpenView&Start=1&Count=800&Expand=1#1)]
25