<table>
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<tr>
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<th>Meeting Book Contents for review by all HAB members</th>
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<tbody>
<tr>
<td>1.</td>
<td>NSF Health Advisory Board</td>
</tr>
<tr>
<td>2.</td>
<td>Meeting Agenda – Fall 2020</td>
</tr>
<tr>
<td>3.</td>
<td>HAB Member Document Review Assignments Fall 2020</td>
</tr>
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<td>4.</td>
<td>Meeting Minutes – Spring 2020</td>
</tr>
<tr>
<td>5.</td>
<td>Fall 2020 Action Level Reconciliation Memo - Final</td>
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<td>6.</td>
<td>Chemical Reassessment Process Proposal (Memorandum)</td>
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<td>7.</td>
<td>NSF/ANSI/CAN 600 Qualitative Benchmarks (Memorandum)</td>
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<td>8.</td>
<td>Drinking Water Intake Rates Update (Memorandum)</td>
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<td>9.</td>
<td>STEL Derivation Review (Memorandum)</td>
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NSF International Health Advisory Board Fall 2020 Roster

NSF International Health Advisory Board Members/Affiliations:

Chair
Edward Ohanian, Ph.D.
Associate Director for Science
Office of Water
U.S. Environmental Protection Agency

Vice-Chair
Caroline English, Ph.D., DABT
Independent Consultant

Members

Steven Bursian, Ph.D.
Professor Emeritus
Michigan State University

Ms. Katherine Fallace, MPH, CPH,
Research Scientist
Health Risk Assessment Unit
Minnesota Department of Health

Elaine Z. Francis, Ph.D.
President
Sandcastle Toxicology Associates

Lynne Haber, Ph.D., DABT
Senior Toxicologist/Adjunct Associate Professor
Department of Environmental Health
College of Medicine
University of Cincinnati

Robert Hinderer, Ph.D.
Robert Hinderer Consulting, LLC

John C. Lipscomb, PhD, DABT, ATS
Toxicologist
U.S. Environmental Protection Agency (retired)

Paul A. White, Ph.D.
Leader, Genetic Toxicology Group
Environmental Health Science and Research
Bureau Health Canada
Adjunct Professor
Department of Biology
University of Ottawa

Dr. Douglas Wolf, D.V.M, PhD, FIATP, Fellow
ATS Senior Fellow, Product Safety
Syngenta Crop Protection, LLC
NSF INTERNATIONAL
HEALTH ADVISORY BOARD MEETING

Agenda for the Fall 2020 Meeting – November 2-3

November 2, 2020

9:00 Welcome and Opening Remarks Ed Ohanian (HAB Chair)
9:05 NSF International Welcome Kevan Lawlor (NSF CEO)
9:15 Approval of May 19-20, 2020 Meeting Minutes Ed Ohanian (HAB Chair)
Review of Meeting Agenda Ed Ohanian
Self-Introductions and Conflict of Interest Disclosures Ed Ohanian
Antitrust Statement & Updated HAB review process Kelly Magurany (HAB secretary)
9:40 Peer Review: Benzophenone (revised) Kelly Magurany (for NSF)
10:10 Peer Review: Chloroethane Brad Lampe (for NSF)
11:10 Break
11:15 Peer Review: Polymer (acrylate-phosphonate) Kasey Mohan (for NSF)
12:15 Get Your Lunch Break
12:30 Working Lunch
Selection of Meeting dates Ed Ohanian
HAB Member Updates HAB members
JPRSC Member Updates JPRSC members
Fun & Games Kevin Cox (for NSF)
1:45 JPRSC Update / Reconciled risk values Kristin Licko (WQA)
2:00 Peer Review: Ethyl butyrate Shannon Hamilton (for NSF)
3:00 Break
3:15 Peer Review: 3-MCPD Rebecca Adams (for NSF)
4:00 Summary of Action Items Ed Ohanian (HAB Chair)
Adjourn for the Day
<table>
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<tr>
<th>Time</th>
<th>Topic</th>
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<tr>
<td>9:00</td>
<td>Chemical Reassessment Process</td>
<td>Kelly Magurany (for NSF)</td>
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<td>9:45</td>
<td>Qualitative Paradigm</td>
<td>Kevin Cox (for NSF)</td>
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<td>10:45</td>
<td>Break</td>
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<td>11:00</td>
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<td>STEL</td>
<td>Brad Lampe (for NSF) Ed</td>
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<td>12:10</td>
<td>Summary of Action Items</td>
<td>Ohanian (HAB Chair)</td>
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<td>12:15</td>
<td>Get Your Lunch Break/ CLOSED SESSION</td>
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## Fall 2020 HAB Meeting Assignments*

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Document Name</th>
<th>Benzenophenone</th>
<th>Chloroethane</th>
<th>Acrylic Acid-Sodium Phosphinate Copolymer</th>
<th>Ethyl Butyrate</th>
<th>3-Monochloropropanediol</th>
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<td>Wolf</td>
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<td>All pathology sections</td>
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*As always, feel free to review documents that were not assigned to you as time permits.

**CHARGE QUESTIONS**

### Benzenophenone- REVISED

- Does the updated pathology interpretation for the liver and splenic endpoints substantiate the selection of the critical effect?
- Do you agree with the updated cancer weight of evidence conclusions regarding human relevance?
- Is the endocrine endpoint appropriately characterized in the updated text?

### Chloroethane

- Do you agree with the selection of the critical effect and proposed cancer classification?
- Do you agree with the dosimetric adjustment factor approach?
- Do you agree with the dose-response assessment and the use of bromoethane data to inform the potential dose-response curve?

### Acrylic Acid-Sodium Phosphinate Copolymer

- Do you agree with the selection of the critical effect of increased urinary phosphorus excretion?
- Does the mode of action discussion appropriately represent the observed effects?
- Are the approaches utilized for benchmark dose modeling appropriate?
- Do you agree with use of surrogate data and the associated uncertainty factor selection based on these data?
Ethyl Butyrate

- Are short-chain fatty acid ethyl esters appropriate surrogates for the assessment of ethyl n-butyrate?
- Do you agree with the selected key study and critical effects?
- Is the database uncertainty factor of 3x appropriate and adequately supported?

3-Monochloropropanediol

- Do you agree with the cancer weight of evidence characterization of "suggestive evidence of carcinogenicity?"
- Do you agree with the use of US EPA BMDS Bayesian modeling averaging for selection of the BMDL for derivation of the RfD?
- Do you agree with the key study selection and BMD modeling for the STEL?
NSF International Health Advisory Board  
May 19-20, 2020 Meeting (Virtual)

Draft Meeting Minutes

ATTENDANCE

HAB member Dr. Edward Ohanian (U.S. EPA, HAB Chair) chaired the meeting. Dr. Helen Goeden (Minnesota Department of Health, Vice Chair), Dr. David Blakey (Health Canada, retired), Dr. Steven Bursian (Michigan State University, retired), Dr. Caroline English (Consultant), Dr. Craig Farr (Consultant), Dr. Elaine Francis (Sandcastle Toxicology Assoc.), Dr. Lynne Haber (University of Cincinnati), Dr. Robert Hinderer (Consultant), Dr. John Lipscomb (U.S. EPA, retired), and Dr. Doug Wolf (Syngenta Crop Protection, LLC) were present. Dr. E. Gene McConnell (ToxPath Inc.) was absent from the meeting.

NSF staff present for the meeting included: Dr. Amanda Phelka (Director, Toxicology Services), Mr. Kevin Cox (Managing Toxicologist), Mr. Brad Lampe (Principal Toxicologist), Ms. Kelly Magurany (Principal Toxicologist), and Ms. Shannon Hamilton (Associate Toxicologist). Other NSF Toxicology Services and Water Program office technical staff members attended as observers for some of the individual chemical reviews and/or other topics for discussion.

Representatives of other certifying bodies present for the open session of the meeting included: Mr. Clif McLellan (ALS/TL), Mr. Javier Robles (ALS/TL), Mr. Brook Hatton (CSA), Ms. Shannon Etheridge (IAPMO), Ms. Ashli Henderson (UL), Ms. Kristin Licko (WQA) and Mr. Michael Spiering (WQA). Dr. Meg Whittaker, Dr. Bingxuan Wang, Dr. Zachary Guerette, Dr. Jennifer Rutkiewicz, and Ms. Nancy Linde (ToxServices, LLC) were present for portions of the open session as contract toxicologists.

OPENING REMARKS

Dr. Ohanian welcomed everyone and called the meeting to order.

Dr. Ohanian welcomed the HAB members. It was noted this was the 42nd meeting of the Health Advisory Board and the first-ever virtual meeting of the Board. She celebrated the enthusiasm and commitment of NSF staff leading into the meeting particularly given the new challenges faced with coordinating a virtual event. She thanked the HAB for their continued support and for contributing significantly to NSF and the other JPRSC member organizations success in staying true to their commitment to public health and safety, regardless of the challenges faced. She celebrated and thanked our retiring members, Drs. Goeden, Blakey, Farr, and McConnell, and welcomed Dr. Wolf to the HAB.

Dr. Ohanian thanked Mr. Kevin Cox (NSF), Ms. Kelly Magurany (NSF), Mr. Tyler Bagbey, Dr. Amanda Phelka (NSF), Dr. Helen Goeden (Minnesota Department of Health), and Ms. Megan Craig (NSF) for assisting with meeting preparations.
APPROVAL OF THE OCTOBER 22-23, 2019 MEETING MINUTES AND REVIEW OF THE AGENDA

The Chairman reviewed the minutes from the Fall 2019 meeting and asked members for any additions, deletions, or comments. Mr. Kevin Cox, interim-HAB Secretary, noted that comments received following circulation of the minutes were incorporated in the version included in the meeting packet.

- A motion was made to accept the minutes by acclamation.  
*The minutes were approved.*

Dr. Ohanian briefly reviewed the spring meeting agenda with the Board and noted it was again a full docket. No additional agenda items were added.

SELF-INTRODUCTIONS, CONFLICT OF INTEREST DISCLOSURES, AND THE ANTITRUST STATEMENT—MAY 19, 2020

- Drs. Ohanian, Goeden, Blakey, Bursian, English, Farr, Francis, Haber, Hinderer, Francis, Lipscomb, and Wolf reported no conflicts with the chemicals scheduled for review at this meeting.

- NSF staff, other JPRSC representatives, consultants, and observers present noted no conflicts.

- Dr. Doug Wolf provided a brief self-introduction.

Mr. Cox read the antitrust statement and all members present agreed to conform to its requirements.

PEER REVIEW: N-METHYL ANILINE—MAY 19, 2020

Dr. Bingxuan Wang (ToxServices) and Ms. Nancy Linde (ToxServices) presented the second review of the n-methyl aniline document and the following comments were offered:

- In the document, the results of the BMD modeling for the hematology parameters from the two-year study were not presented in the assessment because the BMD modeling results for the hematology parameters were higher than the spleen/hematopoietic effects. Which data were modeled, the 52- and 78-week time points or terminal 104-week time point? Decreases in erythrocytes and hematocrit were more pronounced during the interim sacrifices.  
*Only terminal incidence was modeled. Although the effects at interim sacrifice were noted by the authors, focus in the assessment was given to terminal animals, considering these animals had a greater chance of recovery.*

- As the hematology effects are more upstream and more relevant, it would be worth modeling the interim sacrifice hematology parameters, given the mode of action.
In comparing the LOAELs from short-term and chronic studies, the LOAELs were similar, and it appeared that exposure time did not significantly affect toxicity.

- The critical effect is methemoglobinemia and the resulting changes to erythrocytes and the spleen, as reflected in adverse effects on hematology parameters and spleen histopathology; however, it doesn’t appear that those specific effects were modeled. Those are upstream effects and may be more sensitive. Were these effects modeled, other than the histopathological effects?

  Modeling the hematology effects was considered, but in looking at the data, the terminal hematological effects (other than hemosiderosis) were reported at higher doses than the splenic effects.

  When modeling, was standard deviation, in addition to a 10% BMR, considered? EPA has evaluated other chemicals that cause methemoglobinemia, and both parameters are considered.

  Methemoglobinemia is the most appropriate effect to model. It is not appropriate to model congestion as it is an acute response at necropsy. The changes in hematology and clinical chemistry are consistent with methemoglobinemia.

  Use of the chronic study as the key study may be inappropriate. Methemoglobinemia is a persistent acute response while spleen effects observed after two years are the result of chronic oxidative stress, which is not what need to protect against.

  There is consistency with methemoglobinemia, and the associated clinical chemistry, across all studies. Instead of selecting a single study, it may be possible to combine the data from studies 52 weeks in duration and shorter for BMD modeling, thus creating a more powerful model.

  The database uncertainty factor seems unwarranted. In studies where you could see developmental toxicity, there is none. Therefore, not having a developmental toxicity study is not a deficiency. Is there an additional benefit from having the multigenerational study as compared to the single generation study?

  There is too much accuracy being ascribed to the modifying factor (1.6x to 4.3x). This should be captured in the uncertainty factors.

  The read-across justification in the document could be improved by more directly comparing the physical/chemical properties, key toxicokinetic parameters, and the results from the toxicity studies, in a table.

  The presentation of the cancer assessment could be improved in the document. Many facts are presented, but they are not pulled together with respect to the known mode of action. While it is helpful to identify other organizations that have applied a threshold approach,
application of the modified Hill criteria can be included. A more significant evaluation of
the Hill criteria within the document should be included to support the threshold approach.

- If the mode of action is understood sufficiently enough to adopt a non-linear approach, it
  signals that the toxicity is understood well enough such that a database uncertainty factor
  is generally not required.

- For the conversion between aniline and n-methylaniline, it appears that MAK utilized a
  straight conversion. The standard approach is to use a molar basis.

- For the BMD modeling, the use of restricted versus unrestricted models has been
  controversial. Historically, the US EPA has been uncomfortable with unrestricted models
  due to steeper slopes in the low dose region, whereas EFSA has been uncomfortable with
  restricted models due to uncertainty in the low dose region. Bayesian model averaging is
  supported because it considers the plausibility of different models and gives lower weight
  to poor models.

> There was hesitation in using Bayesian model averaging because the BMDL is so low.

- The low BMDL may not be an issue if focusing on methemoglobinemia. However, the
  rationale for throwing out individual models is problematic. This may be a reason to bound
  this at the LOAEL and divide by 10.

- What level of methemoglobinemia is biologically significant? For BMD modeling, a
  specified level of change that is adverse needs to be defined. In the US EPA nitrobenzene
  document, there is a short discussion regarding BMD modeling and a BMR of 10% was
  used. However, in an AEGL document, a methemoglobin level of around 2.8% in humans
  was considered non-adverse. This may be relevant to determining the BMR.

- Methemoglobinemia is not a desirable outcome, so it should be considered adverse. The
  key event is the methemoglobinemia and the other responses, such as the hematological
  changes, are secondary to the loss of red blood cells eliminated by spleen due to
  methemoglobinemia.

- Before combining datasets for BMD modeling purposes, ensure they have a similar dose
  response curve using statistics.

- The dataset used to derive the STEL is not appropriate for BMD modeling. There is great
  uncertainty between the control and the first non-zero dose.

- The critical effect for the STEL was closer to direct methemoglobinemia. Current NSF 600
  methods do not include calculating a short-term RfD equivalent. If calculated, it is lower
  than the chronic RfD.
• As a short-term effect methemoglobinemia is the most critical effect and the intake rate used in the STEL derivation represents a sensitive population (bottle-fed infant). This should be considered for establishing the TAC.

• In determining if there is a threshold in genetic toxicity studies one must consider the shape of the dose-response curves. Is it only the top dose that gives a positive response or is there a more gradual slope? More discussion should be added to the document regarding a threshold effect.

• The two-year study on dimethylaniline is not included in the tables (LOAEL). It is suggested to include this study in the tables for completeness.

• There appear to be math errors in the female LOAEL$^{HED}$ calculation for the 28-day GINC study.

• Because there is deposition of red cells in the spleen, along with other damage, there may be a disconnect between the later effects in spleen and early hematological effects. Even if BMD is higher with the hematology endpoints, that’s okay because there is no linearity between the up- and downstream actions of the chemical.

• There should be some uncertainty factor included to account for more rapid production of metabolite. The 3-fold factor included in UF calculation is acceptable.

• With respect to STEL, the dataset for spleen congestion does not meet requirements for BMD. Additionally, congestion is not appropriate to model from pathology standpoint.

• Mean corpuscular volume and mean corpuscular hemoglobin count are not appropriate endpoints to model as they are qualitative morphological effects on the red blood cells. There is a dose-related effect on hemoglobin in the female rats which should be modeled.

• Regarding the database uncertainty, the available studies were insufficient to address reproductive endpoints. For example, the males were not exposed prior to mating in order to address effects on spermatological parameters. The 3x database factor should be retained due to lack of reproductive toxicity data for either n-methylaniline or aniline.

• The database is lacking in studies for the target compound. The human variability factor should not specifically address the lack of target chemical data.

• If the aniline data are used, then we need to consider that the n-methylaniline has a lower point of departure (more toxic) than aniline and dimethylaniline. From a toxicity standpoint, dimethylaniline is a good surrogate for n-methylaniline.

• Several members noted that there were also editorial comments contained within their documents.
Action Items:

Members agreed that the document should be returned to HAB following incorporation of edits and comments.

RECOGNITION OF HAB MEMBERS – MAY 19, 2020

Dr. Ed Ohanian announced the retirement of four members, Dr. Helen Goeden, Dr. David Blakey, Dr. Craig Farr and Dr. Gene McConnell from the HAB.

- Dr. Ohanian noted that the board was losing four very significant contributors to the success of the HAB. The HAB has depended on each member for their important feedback in their areas of expertise. Dr. Ohanian noted that it has been an incredible experience as the HAB Chair, as he’s been very impressed by the contributions of all of the retiring members for their incredible feedback, attention, and willingness to help.

- The significant contributions from the retiring members were acknowledged with great appreciation by HAB membership and representatives of the JPRSC member organizations.

HAB MEMBERSHIP DISCUSSION– MAY 19, 2020

Mr. Kevin Cox (NSF) reviewed the information provided in the meeting packet regarding the membership policies of the HAB. He also discussed the rationale for seeking to fill two vacancies and the type of expertise that was being sought to selectively target expertise that was lost as a result of the retiring members. Mr. Cox then presented the names of the candidates for the two vacancies. Dr. Ed Ohanian then led the discussion of the candidates:

- As part of his presentation, Mr. Cox presented an overview of the status of current HAB membership. A request was also made to solicit volunteers for the Vice Chair position being vacated by Dr. Goeden.

- Nominating HAB members provided brief overviews of the candidates’ experience and expertise relevant to the genotoxicity expert vacancy: Dr. English spoke on behalf of Dr. David Eastmond, Dr. Lynne Haber spoke on behalf of Dr. Martha Moore, and Dr. David Blakey spoke on behalf of Dr. Paul White.

- The consensus among the HAB members indicated that all three genetic toxicity candidates are outstanding, and the HAB would be well-served by any of them. It was noted that the connection with Health Canada that Dr. David Blakey has brought to the board would be valuable to maintain through the addition of Dr. Paul White. It was also pointed out that Dr. Paul White has experience in developing new approach methodologies, which would bring value to the Board considering the importance of NAMs to the future of human health risk assessment. Based on a majority vote, Dr. Paul White was selected to fill the genotoxicity expert vacancy.
• Nominating HAB members provided brief overviews of the candidates’ experience and expertise relevant to the general risk assessment/state health agency vacancy: Dr. John Lipscomb spoke on behalf of Dr. Sabine Lange, and Dr. Helen Goeden spoke on behalf of Ms. Katherine Fallace.

• Discussion was primarily focused on the relevance of each candidate’s experience in terms of the HAB’s mission and charge. It was also noted that the connection with the Minnesota Department of Health (MDH) that Dr. Helen Goeden has brought to the Board would be valuable to maintain through Ms. Katherine Fallace, particularly the work of MDH in the area of drinking water contaminants. Based on a majority vote, Ms. Katherine Fallace was selected to fill the general risk assessment/state health agency vacancy.

• HAB members cast a private vote to select the HAB Vice Chair to replace Dr. Goeden. Nominees were Dr. Lynne Haber and Dr. Caroline English. Voting was conducted by private online messaging from the HAB membership to Mr. Cox. Dr. Caroline English was selected as the next HAB Vice Chair.

Selection of the Next Meeting Date:

• The initial choice presented for the Fall 2020 meeting was October 27-28; however, there were conflicts raised with this date and it was decided to send out an online survey to following the meeting to assist in the selection of the next meeting date. It was noted that the Fall meeting will likely be held as a virtual meeting.

• The first choice for the Spring 2021 meeting was identified as May 11-12.

Action Items:

• NSF will circulate a survey to determine if alternate dates would work for Fall 2020 meeting. NOTE – The results of this survey identified November 2-3 for the fall 2020 virtual meeting

Member Updates- May 19, 2020

HAB and JPRSC membership were provided opportunities to discuss their current activities outside of their HAB responsibilities:

• Dr. Goeden noted that she has been reassigned to COVID-19 activities. MDH has been working on a manganese manuscript that will be submitted soon. She also noted that PFAS remains an ongoing issue. Additionally, she pointed out that publication from NTP on boron should be coming out soon.

• Dr. Blakey noted that he has just been having a great time with his grandson.

• Dr. Bursian announced that he retired at the end of December and he has been working on an online toxicology course, as well as finishing up a PFAS manuscript.
• Dr. English commented on the activities of the U.S. EPA Science Advisory Board (SAB) for the upcoming fiscal year. Activities include IRIS assessments, consultation on the consolidation of toxicology assessment guidelines, and a consultation on alternative methods to chronic lab testing in animals. Additionally, the SAB established an ad-hoc COVID-19 review panel.

• Dr. Farr indicated that he has been spending time on local council and has been keeping busy with Zoom meetings for several organizations, as well as keeping in touch with his friends and family. He noted that he had to cancel a month-long trip to Ireland and Scotland due to COVID-19.

• Dr. Hinderer noted that he was keeping busy watching his new house being built in North Carolina.

• Dr. Haber indicated that she is finishing up a manuscript on relative potency factors for PAHs with Health Canada, as well as working on a peer-review related to PBPK models for manganese.

• Dr. Lipscomb announced that his daughter’s spring wedding was rescheduled due to COVID-19. He is currently planning a trip to Alaska and nearing completion on his workshop in his backyard. Additionally, he has completed an online risk assessment course for which he was the director, and an instructor, for the University of Louisville. He’s also produced his first manuscript, outside of federal overview, on protective risk assessments which was circulated to the HAB membership.

• Dr. Wolf did not have an update following his self-introduction provided in the morning.

• Dr. Ohanian noted that he was elected to the Toxicology Forum Board of Directors. He hopes to strengthen the bond between Toxicology Forum and federal agencies, as well as NGOs. U.S. EPA is co-sponsoring a workshop that will focus on problem formulation, mode of action, dose response, and new approach methodologies. Additionally, the U.S. EPA has an action plan for water reuse.

• Dr. Francis commented on the transition of two of her courses to online instruction. She has been helping homeschool her five-year-old grandson. Additionally, she is a member of the New Jersey Department of the Environment’s Science Advisory Board (SAB). The SAB has been meeting frequently on a project that should be completed within the next few months.

• Ms. Kristin Licko (WQA) announced she has been working with Dr. Bursian on a toxicology course and she has been appointed as an adjunct professor at Michigan State University.
• Mr. Brook Hatton (CSA) announced that CSA celebrated their 100th birthday last year and things are going well. On a personal note, balancing homeschooling and full-time job remotely has given him a greater appreciation for teachers.

• Ms. Ashli Henderson (UL) noted that not much has changed at UL aside from everyone working remotely due to COVID-19. She also noted she has been working with China more frequently and balancing 3 a.m. calls with young children’s sleeping schedules.

• Mr. Javier Robles (ALS/TL) noted that this was his first HAB meeting and that he was happy to be present.

• Ms. Shannon Ethridge (IAPMO) noted that IAPMO has been very busy and things are going well.

• NSF staff will present toxicology department updates during the closed session on day 2.

INTRODUCTION OF NEW HAB SECRETARY- MAY 19, 2020

Dr. Ed Ohanian (HAB Chair) announced that Ms. Kelly Magurany (NSF) will be next HAB Secretary. Ms. Magurany thanked Dr. Ohanian and the membership for the opportunity.

Dr. Lipscomb thanked Mr. Kevin Cox for his work as the interim-HAB secretary.

PEER REVIEW: OCTOXYNOL CBEL UPDATE – MAY 19, 2020

Dr. Zachary Guerrette (ToxServices) presented the first review of an expanded read-across for the Octoxynol CBEL and the following comments were offered:

• CAS numbers are helpful, but it is my understanding they are not unique. Is that an issue? Although an imperfect system, we’ve found CAS#s useful in determining which compounds to evaluate, and in data collection.

• The U.S. EPA Dashboard is also finding that CAS#s have limited use and are moving to using DTXSID as unique identifier.
  These compounds were detected in water samples and the mass spectrometry identified them as these CAS#s; therefore, a risk assessment was required to establish pass/fail criteria.

• Two different CAS#s and two different chemical names are being used to describe identical structures. Please clarify on why this needs to be addressed by the Health Advisory Board. Seeking HAB input on how to best identify substances in order to determine if criteria are available.

• What are the similarities between octylphenyl glycol ethers as compared to octylphenyl glycol ether ethoxylates? It isn’t clear why ethoxylates are being incorporated.
There are multiple names for the chemical class and can be referred to as ethers as well as ethoxylates.

- When defining a chemical class, one must consider whether it is focused on few chemicals or more encompassing. Chemical structure, physical/chemical properties, toxicokinetics, and available toxicity data must be considered.

- The category was clearly defined with the structural information available and the argument to support read-across was substantiated enough to indicate that it is appropriate to use this CBEL for these compounds.

- Reliance on CAS#s is turning out to be problematic. Minnesota Department of Health has started planning to include the CAS#, IUPAC name, and the DTXSID because it is a unique identifier for that chemical. Suggest including the DTXSID as a unique identifier, as this is a future direction in chemical identification.

- For ECHA, all the testing is driven by a CAS#. It may be difficult to get away from CAS#s because that is how data requests are driven. However, for complex mixtures, recognize that it may be difficult to identify if different formulations have similar chemistries due to confidential business information.

- Unique CAS#s included in a CBEL are listed as single line items in NSF/ANSI/CAN 600, with a note indicating that the compound is included in a CBEL.

- The work done regarding the additional substrates in this update is appropriate. In the original NSF CBEL document, there is reference to the database uncertainty factor being 10x in the response to the written comments at the end of the document. However, throughout the document itself, and in the executive summary, the database uncertainty factor is 3x. Please verify and correct in the NSF document.

- The database uncertainty factor of 10x should not be referred to as a “default.”

- Several members noted that there were also editorial comments contained within their documents.

**Action Items:**

Members agreed that the document can be accepted with proposed revisions and does not need to be returned.
JPRSC UPDATE / RECONCILED RISK VALUES – MAY 19, 2020

Ms. Kristin Licko (WQA) presented a brief JPRSC update including efforts to reconcile risk values among the JPRSC member organizations. Following the presentation, time was provided for the HAB members to ask questions and provide comments.

- In NSF/ANSI/CAN 600 (2019), the description for the cancer evaluation cites the 1996 guidance, not the 2005 guidance.
  NSF/ANSI/CAN 600 is a living document and can be updated to reflect the more appropriate 2005 guidance.

- If there are several recent assessments that are not consistent with each other, such as those published by different agencies like U.S. EPA, EFSA, etc., how is this handled?
  There is a tiered approach to establish preference, but then a weight-of-evidence approach is applied, and it is determined which agency follows the Section 3 guidelines most closely. NSF has coordinated efforts in the past between the EPA and Health Canada to identify the most appropriate criteria in instances where criteria have been derived by both agencies.

NSF/NIEHS COLLABORATION (QIVIVE) – MAY 19, 2020

Ms. Kelly Magurany (NSF) presented on the QIVIVE process that was incorporated into two revised risk assessments (t-butyl phenol and benzophenone) as part of a wider collaborative effort with NIEHS/NTP and the following comments relevant to the overall QIVIVE method were offered prior to review of the compound risk assessments:

- These assays were never intended for a use in quantitative risk assessment, but rather for screening for prioritization and for weight-of-evidence approaches. These assays are informative to understand the hazard potential and allow for greater confidence in negative data, but were never fit for purpose for quantitative risk assessment.

- An HAB member noted that Ms. Magurany provided a very nice overview of the approach, the evidence and the confounders. Overall, the presentation provided additional context that likely should be included in the document to provide more context on the objective of using the QIVIVE. It should be made clear within the documents on how the QIVIVE data are or are not integrated with the other lines of evidence. Are the QIVIVE data only for comparative purposes?

PEER REVIEW: T-BUTYL PHENOL – MAY 19, 2020

Ms. Kelly Magurany (NSF) presented the second review of the t-butyl phenol document (case study for NIEHS collaboration) and the following comments were offered:

- The adverse outcome pathway (AOP) refers to agonistic effects. However, it was described that tamoxifen can have both antagonistic effects and agonistic effects. It is recommended that these simply be referred to as “altered effects.”
It is hypothesized that the compound is acting as a selective estrogen receptor modulator.

- It seems it might be more appropriate to have a key event of altered organ weight without giving it a direction to account for agonism or antagonism.

- The application of database uncertainty factor should be more broadly considered. Lacking a specific study is a rather checkbox approach. Is there reason that the lack of a specific study type would be expected to impact the risk assessment?

- The use of the uterine weight changes and pup body weight changes is appropriate. To reiterate previous comments, the AOP should be more general to account for either increases or decreases in ovary or uterine weights. Locating other in vivo studies where mature females have been exposed to estrogenic compounds that resulted in decreased weights instead of increased weights could strengthen the overall argument.

- Page 18, line 11, indicates that the study was done according to OECD 422 and describes the dosing period for females was 54 days; however, it is unclear where 54 days was derived. When accounting for two weeks prior to mating, 21 days for gestation and 21 days during lactation, at a minimum the dosing period should be 56 days. Please clarify.

- Throughout the document, the units switch between ppm in diet and mg/kg-day. It would be beneficial to be more consistent with units throughout the document.

- Page 56, lines 14-15, provide the rationale for the selected critical effect for the STEL; however, the explanation was not clear. Please consider clarifying this statement. Both calculations should be presented so it is clear why the bottle-fed infant intake STEL value was lower.

Looking at an alternative endpoint of reduced uterine weight, this value was not as conservative as the value derived when looking at the pup body weights with the bottle-fed infant intake rate.

- The 3x database uncertainty factor was not just for the lack of a second developmental study, but also the lack of a 90-day study. Recognizing the lack of developmental effects from a second species in the present dataset, there is precedent in terms the EPA’s policy that developmental toxicity studies in two species are required for a database to be considered complete. This committee has used that precedent.

The two-generation study fulfills the 90-day study requirement and per the NSF/ANSI/CAN 600 standard a 90 day in two species is not a requirement. A developmental study in a second species is an NSF/ANSI/CAN 600 requirement and thus a 3x factor is applied.

- Do the available data provide a comprehensive view of potential endocrine effects?

No. The available assays aren’t comprehensive of all endocrine effects. Although an endocrine-mediated mode of action is plausible, the in vitro assays do not capture everything that a second species developmental study could provide.

- It is unclear how the human cell line assays relate to an entire in vivo human. Overall, the 3x database uncertainty factor is appropriate for both the TAC and the STEL.
• There is some concern about using decreased ovarian weight as the critical effect. The key study is dietary and decreased food consumption was observed. Was it considered that the changes in body weight and organ weight could be more a factor of decreased palatability than intrinsic toxicity? 

Ovary weight was evaluated relative to brain weight, so that would support changes in body weight as an intrinsic toxic effect. Additionally, there is supportive evidence that the mode of action is endocrine disruption and body weight changes in females were not statistically significant.

• Substantiate your rationale as to why palatability is not the driver of ovarian weight change.

• It appears the assessment artificially penalizes the STEL by superimposing a drinking water ingestion rate that is different from the one applied to the effects seen in the maternal animal. Does NSF 600 require, in all cases, that the higher ingestion rates be applied to developmental effects when we’re not using those effects to set a chronic oral RfD, but an excursion limit?

Current guidance says the default intake rate for STEL derivation is for the bottle-fed infant. This is an issue of standard STEL derivation practices that will be further discussed during the STEL case study presentation.

• It is recommended to have one table with BMD inputs in order to aid in the reproducibility of the modeling.

• To reiterate previous comments, the database uncertainty factor is not a check-box exercise. In general, the uncertainty factor value is appropriate, but not the rationale. The two-generation study cannot be used to fully address systemic toxicity as compared to the screening study. Developmental toxicity endpoints are data gaps due to lack of a second species as well as lack of histopathological data.

• Regarding the STEL, an additional explanation should be included as to why a bottle-fed infant rate was selected when the endpoint is more relevant to another susceptible population (pregnant women). It is not clear whether the appropriate intake is being used in the STEL calculation.

• Several members noted that there were also editorial comments contained within their documents.

**Action Items:**
Members agreed that the document can be accepted with proposed revisions and does not need to be returned to the full Board for further review. Dr. Hinderer and Dr. Haber offered to perform an abbreviated offline review following completion of proposed revisions.
Ms. Kelly Magurany (NSF) presented the second review of the benzophenone document (case study for NIEHS collaboration) on May 19, 2020. The following comments were offered during the open session on May 20, 2020:

- The use of the liver effects seems reasonable. However, it is difficult to follow the connection between bone marrow toxicity and the effects on the hematopoietic system. There is a section within the document that appears to discount the relationship of these effects. Please consider clarifying the text to make the argument stronger.

  The challenge was that there are not clinical data for the two-year study, so it is hard to interpret if the hematopoietic effects were a result of bone marrow toxicity or local toxicity to the spleen. The subchronic study effects suggest a potential effect, so we could not discount bone marrow toxicity. Even though it isn’t strong, we can’t discount hematopoietic toxicity; therefore, they are indicated in the assessment as being potentially related to bone marrow toxicity or a local effect, to be conservative.

- The selection of BMDL seems reasonable. Based on the table with all the comparative reference doses, there does not seem to be a lot of difference between them. Is it a possibility to use an RfD where the total uncertainty factor is less than 300x?

  Spleen endpoints in mouse have a total UF of 30x, so these were considered co-critical effects.

- The original document contained more emphasis on estrogenic effects while the revised document dismissed such effects. There should be a more balanced approach between dismissing such findings and overinterpreting results. The data are suggestive that benzophenone is a weak estrogenic compound.

  In the two-generation study, the anogenital distance (AGD) in females was shorter, but there was no effect in males. This finding was discounted citing Schwartz (2019). This finding should not be negated just because it is present in one sex and not the other. Overall, the document should provide more context and support for benzophenone being a weak estrogenic compound.

  Based on the weight-of-evidence, NSF agrees with this comment. AGD was difficult to interpret as the mode of action is not well understood, but it was not considered biologically relevant. However, if HAB disagrees, NSF would need to substantiate that argument because it would become the critical effect at the low dose.

- It is not recommended to use the two-generation study as the key study. Rather, address the issues of the two-generation study in the language that captures the database completeness. One of the challenges with the study was the number of animals used. Only ten animals were evaluated, and for some endpoints, only six animals were evaluated. This makes the power of this study not as great as typical two-generation studies.
Some parts of the document refer to the critical effect (multinucleated hepatocytes) as an early or precursor effect, while other parts refer to the critical effect as a regenerative effect. It is unlikely to be an early effect, please clarify within the document.

In selecting the critical effect, the first adverse effect or known precursor is determinative. There is clear liver and kidney toxicity in both rats and mice. In this case, it appears that the rat is a more sensitive species in the subchronic timeframe. Agree that the effects in the liver are adverse but question the choice of the critical effect given the uncertainty as to whether it is an early effect or a downstream effect. It is a precursor to cystic degeneration and is indicative of repair itself, so therefore, the most sensitive effect.

A point of departure with a lower level of uncertainty is preferable where supported (UF of 30x as compared to 300x).

Regarding the clarity of the relationship between bone marrow toxicity and spleen effects—the level of connection here ultimately affects the selection of the critical effect. The biggest question here is whether to treat this as an entire sequela of insult or as individual observations. Concur with collectively looking at these effects.

From a pathology perspective, a member disagreed with the suggested cytotoxic mode of action. The multinucleated cells in the mouse liver are a common finding in older mice as they frequently occur as mice age. These would also be enhanced by exposure to xenobiotics. It is unusual that none were identified in 80-week old mice. However, the only evidence of cell death in the hepatocytes was at a two-year timepoint. A regenerative mode of action would be determined by shorter term studies versus a chronic study. In the short-term studies, we do not see hepatocyte toxicity or cell death, but nuclear receptor agonism and hypertrophy suggesting that it is not a cytotoxic mode of action. In long-term studies in mice, multinucleated giant cells are an effect of xenobiotic exposure and cells not dividing following exposure. The giant cells should not be used as an indicator of adversity at two years, shorter term time points should be considered instead.

A member agreed with interpretation of renal toxicity. The reported renal tubule regeneration; although not potent, is sufficient to advance chronic progressive nephropathy (CPN) with the rat being a more sensitive species. Enhanced tumor development in the kidney is a secondary effect to CPN. CPN itself is not relevant to humans.

There is some indication that high-dose female animals have mild bone marrow atrophy but would not call it bone marrow toxicity. Reticulocytes have less hemoglobin so MCH will be decreased. The decreased longevity of RBCs and regenerative anemia can be considered adverse if it persists.

It is not appropriate to develop a mode of action using a two-year time point for this chemical as hepatocyte necrosis is not observed in short-term exposures.
• It is unclear why the study authors didn’t identify multinucleated hepatocytes in controls animals; however, some pathologists will normalize to zero. Cytotoxicity (necrosis) was not observed at any early timepoints.

• With prominent enzyme induction, we see an increase in hormone metabolism and corresponding decrease in hormone-related tumors (e.g. fibroadenomas).

• Was other ToxCast data evaluated? The focus here is on the endocrine system. Other liver parameters should be on ToxCast as well, including metabolizing enzymes across enzyme systems. Other ToxCast assays were not explored. This assessment primarily focused on mature assays per the recommendation of NIEHS. This evaluation could be done as a follow-up.

• In the 10-day intraperitoneal (IP) study, liver toxicity was reported as unspecified “degenerative histopathology”. Degenerative histopathology could be vacuolation, not cytotoxicity/necrosis. Necrosis is necessary to support the cytotoxic mode of action.

• Provide more clarity regarding the described degeneration in bone marrow as there are several cell types. It may be regenerative anemia (bone marrow is response).

• Extramedullary hematopoiesis is very common in the mouse. While it may not lead to adversity, it is present and indicative of an effect (although it is observed in the controls as well). It is slightly increased in the treated animals due to the response to regenerative anemia and an insufficient response from the bone marrow, therefore using the spleen as a compensatory response. Overall, you cannot rule out the potential adversity of the splenic effects.

• Be careful of terminology, degeneration and damage doesn’t necessarily mean necrosis. Those effects are not suggestive of a cytotoxic mode of action. This is an enzyme induction/nuclear receptor agonism mode of action.

• Interpret the whole of the study. It would not be unexpected to see hepatocyte necrosis in a mouse liver in a chronic study; however, there is no dose-dependent increase in severity. Using the end of a study to determine the mode of action is not how the mode of action human relevance framework should be applied.

• Please provide a more rigorous cancer weight of evidence assessment using the modified Hill criteria.

• Considering the pathology-focused comments, the order of doses will be relevant in the context of the STEL. Based on mode of action, effects may be occurring earlier during exposure.
• For the BMD modeling, be clear when you talk about 10% (BMDL_{10}) for continuous data. Be explicit if it is a 10% change in mean or other measure. Constant or modeled variance should also be noted.

• The primary rationale for updating the risk assessment should be provided within the document. What has changed since the original 2010 risk assessment that warranted the update? More value would be added to the updated risk assessment by incorporating more substantiation and conversation around the changes from the 2010 risk assessment.

Changes include a progression in our understanding of the endpoints, new in vitro data, and an EFSA evaluation in which the liver effects were dismissed (the dismissal was unsubstantiated).

• Several members noted that there were also editorial comments contained within their documents.

**Action Items:**
Members agreed that the document should be returned to HAB following incorporation of requested edits/comments. Dr. Wolf offered to provide a reference regarding proliferative and non-proliferative lesions of the liver to assist the document author in addressing HAB comments. Additionally, Dr. Wolf offered to perform an abbreviated offline review following completion of proposed revisions.

**Adjournment**
Meeting adjourned for the day at approximately 5:00 pm.
HAB OPEN SESSION – DAY 2 (MAY 20, 2020)

CHEMICAL PRIORITIZATION UPDATE – MAY 20, 2019

Ms. Kelly Magurany’s (NSF) presentation update on the proposed prioritization process being developed by NSF in order to maintain the scientific integrity of the drinking water criteria database was postponed to accommodate discussion of benzophenone due to late adjournment of the open session on May 19, 2020. It was suggested that a short teleconference outside the regular meeting be scheduled to cover the chemical prioritization update.

Action Items:

Members agreed that a separate time for this presentation should be scheduled. Ms. Kelly Magurany will schedule the presentation at a later date based on the availability of the HAB membership. (Following the meeting a date of July 14th, 11-12pm was identified).

STANDARD 600 QUALITATIVE BENCHMARKS – MAY 20, 2019

Mr. Kevin Cox’s (NSF) presentation update on the proposed incorporation of TTC concepts into NSF 600 was postponed to accommodate discussion of benzophenone due to late adjournment of the open session on May 19, 2020. It was suggested that a sub-group of HAB members work with the JPRSC membership outside the regular meeting to review the Standard 600 Qualitative Benchmarks update.

Action Items:

Members agreed that the document related to TTC incorporation in NSF/ANSI/CAN 600 will be re-presented to the full HAB following an offline sub-panel workgroup with Dr. Bursian, Dr. Hinderer, Dr. Lipscomb, and Dr. Meg Whittaker. (Dates of workgroup meetings to be determined).

STANDARD STEL DERIVATION DISCUSSION – MAY 20, 2019

Mr. Kevin Cox (NSF) presented several risk assessment case studies where there is a lack of clarity in applying the revised STEL procedure recently adopted into NSF/ANSI/CAN 600. The following comments were offered:

- This issue has come up more often than expected after adopting multi-generation assessments at MDH. There are layers of issues within this topic. MDH has published on this experience and has shared the publication with NSF.

- There must be consistency in focusing the selection of studies for value derivation as to the intended purpose of the value. For short-term values, use short-term data and uncertainty factor rationale appropriate for short-term values.
Action Items:
Members agreed that the document related to STEL derivation language in NSF/ANSI/CAN 600 will be re-presented to the full HAB following an offline sub-panel workgroup with Dr. English, Dr. Haber, Dr. Lipscomb, and Dr. Goeden, with Ms. Katherine Fallace. (Dates of workgroup meetings to be determined).
Previously, action levels for unregulated chemicals established by different certification bodies have varied resulting in inconsistencies in the product certification process. Effective April 17, 2013, CSA Group, NSF International, IAPMO, UL and the Water Quality Association established the Joint Peer Review Steering Committee (JPRSC). The purpose of this committee is to consolidate efforts among ANSI accredited product certification bodies with drinking water accredited scopes, to nominate/prioritize chemical risk assessment documents for review by the NSF Health Advisory Board (HAB), to assist with the maintenance of NSF/ANSI/CAN 600, to reduce duplication in risk assessment efforts, and to harmonize risk assessment methods and values used to evaluate compliance of products to NSF/ANSI drinking water standards. This committee may also nominate new board members when openings are identified. In 2018 ALS Global joined the committee to support its mission.

With the assistance of the NSF International Health Advisory Board (HAB), the certifying organizations are working together to consolidate more than 400 previously established action levels and to harmonize the external peer review process for all future risk assessments. The attached document "Decision Process for Reconciling Action Levels" defines a process and decision diagram for reconciling legacy actions levels among the certifying organizations. This process was initially presented to the HAB at the April 17, 2013 HAB meeting. Following feedback from the HAB regarding the decision process, requests for additional documentation and the rationale for the proposed final Action Levels for the first 10 chemicals, the process was accepted.

This memo documents another set of chemicals reviewed according to the approved process. Proposed action levels, their basis, and supporting information are documented in the following tables. Action levels needing a more thorough evaluation by the HAB have been identified. Per the peer review requirements in NSF/ANSI/CAN 600, there are several exceptions where risk assessments are not required to undergo external peer review by the HAB. These documents are reviewed and accepted by the JPRSC through a consensus process and are presented below as a notification to the HAB. Supportive documentation for any risk assessment is available upon request from the JPRSC.
Decision Process for Reconciling Action Levels

Start:
- Action levels based on Authoritative Body peer reviewed assessment?
  - Yes: Is a more recent peer reviewed risk assessment available?
    - Yes: Group 1: Certifiers adopt Authoritative Body values (FYI to HAB)
    - No: Group 2: Certifiers adopt NSF action levels
  - No: Is there an NSF risk assessment approved by the HAB?
    - Yes: Is new information the basis for an OC risk assessment?
      - Yes: Group 5: FYI to HAB
      - No: Is an OC expert panel-approved risk assessment available?
        - Yes: Unanimous agreement on action levels by JPRSC?
          - Yes: Group 3: Certifiers adopt action levels reconciled by HAB
          - No: Group 4: New document(s) presented to HAB
        - No: Group 2: Certifiers adopt NSF action levels

Key:
OC = Other Certifiers; JPRSC = Joint Peer Review Steering Committee
HAB = NSF Health Advisory Board
<table>
<thead>
<tr>
<th>Substance</th>
<th>Current Action Levels (mg/L)</th>
<th>Proposed Action Levels (mg/L)</th>
<th>Basis</th>
<th>Comments</th>
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<tbody>
<tr>
<td></td>
<td>TAC SPAC</td>
<td>TAC SPAC</td>
<td>Minimum data requirements for a qualitative paradigm according to Section 3 of NSF/ANSI/CAN 600 were met through an evaluation of the weight of evidence that suggests that the substance is neither mutagenic nor clastogenic. An Ames assay, a gene mutation assay, and an <em>in vitro</em> micronucleus test were consistently negative. A comparative TAC based on a rat NOAEL of 25 mg/kg-day was also calculated at 10 μg/L. The overall weight of evidence for genotoxicity indicates that this substance is unlikely to exhibit mutagenic or clastogenic effects based on absence of effect in <em>in vitro</em> studies and supports clearing the compound to a TAC and SPAC of 10 μg/L.</td>
<td>This is qualitative assessment from NSF. There was unanimous agreement by the JPRSC to accept the action levels on 5/6/2020.</td>
</tr>
<tr>
<td>Phenylethanal</td>
<td>0.003 0.0003</td>
<td>0.01 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAS # 122-78-1</td>
<td>TOE Entry</td>
<td>3/20/2020</td>
<td>Minimum data requirements for a qualitative paradigm according to Section 3 of NSF/ANSI/CAN 600 were met through an evaluation of the weight of evidence that suggests that the substance is neither mutagenic nor clastogenic. As there was insufficient data for 1,4-diacetylbenzene, a CBEL approach was taken according to Section 3.8.1.1. A negative reverse mutation assay from analogue acetophenone (CAS # 98-86-2) is used to address genotoxicity. A positive <em>in vitro</em> CHO assay for analogue acetophenone (CAS # 98-86-2) was mitigated by lack of evidence of a carcinogenic effect in a chronic study. A negative <em>in vivo</em> micronucleus test for analogue 4-hydroxyacetophenone (CAS # 99-93-4) was used to address clastogenicity. The overall weight of evidence for genotoxicity indicates that this substance is unlikely to exhibit mutagenic or clastogenic effects based on absence of effect in both <em>in vitro</em> and <em>in vivo</em> studies for two surrogate compounds and supports clearing the compound to a TAC and SPAC of 10 μg/L.</td>
<td>This is qualitative assessment from NSF. There was unanimous agreement by the JPRSC to accept the action levels on 5/6/2020.</td>
</tr>
<tr>
<td>1,4-diacetylbenzene</td>
<td>0.003 0.0003</td>
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<td></td>
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Threshold of evaluation (TOE) Risk Assessments: FYI to NSF HAB
Associated Action Levels: TAC = 3 ppb, SPAC = 0.3 ppb, and STEL = 10 ppb

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<th>Chemical Name</th>
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<tr>
<td>2-Ethylphenol</td>
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<td>3-Ethylphenol</td>
<td>620-17-7</td>
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<td>Acrylate phosphinate-sulphonate copolymer</td>
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<td>CI Acid Blue 9</td>
<td>2650-18-2</td>
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<td>Distillates (petroleum), catalytic reformer fractionator residue, low-boiling, sulfonated, sodium salts</td>
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<td>Erythrosine</td>
<td>16423-68-0</td>
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<td>Ethanol, 2,2'-(((methyl-1H-benzotriazol-1-yl)methyl)imino)bis-</td>
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<td>Ethylphenol</td>
<td>25429-37-2</td>
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<tr>
<td>Hydroxystearic acid</td>
<td>106-14-9</td>
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<td>Methylbenzamide</td>
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<td>Polyamino polyether methylene phosphonate, sodium salt</td>
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<td>Sodium polynaphthalenesulfonate</td>
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<tr>
<td>Tricaprylin</td>
<td>538-23-8</td>
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</table>
MEMORANDUM: CHEMICAL PRIORITIZATION PROCESS REVIEW

TO: NSF HEALTH ADVISORY BOARD (HAB)
CC: JOINT PEER REVIEW STEERING COMMITTEE (JPRSC)
FROM: KELLY MAGURANY, M.SC, DABT
      PRINCIPAL TOXICOLOGIST
SUBJECT: CHEMICAL REASSESSMENT PROCESS REVIEW
DATE: SEPTEMBER 18, 2020

Fall 2020 HAB Meeting Objectives:

1) Present the proposed reassessment process for reevaluating prioritized chemicals;
2) Present approval pathways of reassessment that require HAB review and those that may be reviewed by the JPRSC;
3) Present the ongoing monitoring process;
4) Seek Health Advisory Board (HAB) input on the reassessment and monitoring processes and reassessment approval pathways.

Background:

NSF’s mission is to ensure public health protection and in so doing needs to ensure that the chemical acceptance criteria that have been determined are consistent with the currently available safety data, scientific knowledge, and risk assessment methodologies. In the Spring 2020 HAB supplemental meeting, the Health Advisory Board reviewed NSF International’s chemical prioritization process proposal. This process was accepted and has been given preliminary adoption within the Joint Peer Review Steering Committee contingent upon development of a standard operating procedure and NSF/ANSI/CAN 600 standard language, if applicable, for further review. Subsequent to the implementation of a prioritization process, a reassessment process needs also to be developed to ensure efficiency in chemical reviews by considering only those substantive changes for review by the Health Advisory Board.

In addition, NSF has in place a monitoring program for new safety data and the opportunity to utilize this information going forward to maintain chemical risk assessments with the most current science. New data identified within this monitoring program may result in chemical reprioritization as new data may identify novel hazards that would require review.

Overall, the goal of this work is to establish formal processes for maintaining chemical acceptance criteria with the latest science. NSF International appreciates HAB member input on our proposed approach. As a primer for discussions, please see Appendix A for the proposed reassessment process, Appendix B for additional granularity associated with reassessment pathways and Appendix C the proposed process for reaction to the NSF monitoring program.
Appendix A: Chemical Reassessment Process

1 The compound status “TBD” should be added to the TED Prioritization spreadsheet pending the release of the draft assessment. Details of the authority review, applicability to drinking water criteria and the timeline should be noted.

2 The data introduce novel toxicity at less than the current point of departure, provide evidence for higher potency or refute or negate the current interpretations for mode of action or human relevance

3 Current risk assessment methods include use of the human equivalent dose, current intake rates, benchmark dose modeling, etc.
Appendix B: Reassessment Process Pathways

Evaluation of an authority risk assessment (NSF/ANSI/CAN 600 Sections 3.2 and 3.3)

Considerations include:

- Source
- Relevance to the drinking water route of exposure
- Data quality (in comparison with current guidelines)
- Data interpretation (e.g. human relevance, mode of action, adaptive vs adverse responses)
- Dose-response methods
- Uncertainty Factor Selection

What if:

- The RfD is derived consistent with NSF/ANSI/CAN 600, but the uncertainty factor selection is not → Seek HAB Review if data interpretation is required to identify uncertainty factors (e.g. 3x for LOAEL to NOAEL, when using a LOAEL; 1x or 3x for database where not all five core studies are available; 1x or 3x for subchronic to chronic without chronic data)
- The assessment is consistent with NSF/ANSI/CAN 600 but the key study is not of high quality or the endpoint or mode of action is controversial and warrants careful interpretation → Update Assessment → Seek HAB Review
- Data suggests the endpoints identified as the critical effect by the published risk assessment may not be human relevant based on current science → Update Assessment → Seek HAB Review
- The assessment is consistent with NSF/ANSI/CAN 600 except an lifestage adjustment (for a mutagenic mode of action) or a dosimetric adjustment factor (HED) was not applied → Update; adjust UF → JPRSC Review
- The assessment is consistent with NSF/ANSI/CAN 600 except BMD modeling was not used → Update → JPRSC Review
- Other scenarios not identified here may be suggested by the HAB or JPRSC to be discussed and a pathway defined for the Fall 2020 HAB live meeting.

Use of Read Across (NSF/ANSI/CAN Section 3.8)

It is recommended that documentation supporting class-based evaluation criteria be subject to the external peer-review. Exceptions to this include:

- The chemical is subject of a class-based published peer-review assessment meeting NSF/ANSI/CAN 600 standards → JPRSC Review
- The chemical has been well established as part of a chemical category by a competent authority (e.g. by the US EPA) → JPRSC Review
Appendix C: Monitoring Program for New Data
MEMORANDUM: NSF/ANSI/CAN 600 QUALITATIVE BENCHMARKS

TO: NSF HEALTH ADVISORY BOARD (HAB)
CC: JOINT PEER REVIEW STEERING COMMITTEE (JPRSC)
FROM: KEVIN COX MPH, JD
MANAGING TOXICOLOGIST
SUBJECT: STANDARD 600 QUALITATIVE BENCHMARKS
DATE: NOVEMBER 3, 2020

Spring 2020 HAB Meeting Objectives:

1) Briefly review current qualitative benchmarks as well as the Threshold of Toxicology Concern (TTC);
2) Discuss results from HAB subpanel discussion on proposed incorporation of current state TTC into NSF/ANSI/CAN 600;
3) Discussion of key points raised by HAB subpanel including use of qualitative approaches for chemical with sufficient toxicity data as well as applicability of the default 10x factor to derive a Single Product Allowable Concentration (SPAC)
4) Seek input from the HAB on the proposed approach to inform efforts of the HAB subpanel to draft language for incorporation into NSF/ANSI/CAN 600 to be presented at the Spring 2021 HAB meeting.

Background:

The current qualitative paradigms within NSF/ANSI/CAN 600 Section 3 have been unchanged since the prior Annex A was first established in the late 1990s. With the widespread adoption among authoritative bodies of the Threshold of Toxicology Concern (TTC), incorporation of the TTC into NSF/ANSI/CAN 600 would allow for modernization of existing paradigms and greater flexibility in assigning criteria to chemicals for which existing risk values are not available.

A TTC-style approach was originally applied by the U.S. FDA as the Threshold of Regulation (TOR) as a way to manage the safety evaluation of compounds, without mutagenic structural alerts, migrating to food at very low concentration from food contact materials. The TOR (stipulated under 21 CFR §170.39) has a value of 1.5 µg/person/day, or 0.025 µg/kg-day for a 60 kg person. The TOR approach was later expanded based on compound Cramer classifications and rebranded to the TTC being applied also to food flavoring components, other food additives contaminants or impurities, and drugs impurities (Munro et al., 1996; Kroes et al. 2004; Munro et al., 2008). Since its development, the TTC has been utilized as a pragmatic risk assessment tool in the regulatory community, including U.S. FDA (food contact materials, pharmaceutical impurities), JECFA (food flavoring agents), EFSA (food additives and impurities), and EMEA (pharmaceutical impurities) (EFSA, 2016).

At the Spring 2020 meeting, NSF briefly presented on the topic of incorporation of TTC into NSF/ANSI/CAN 600 but due to time constraints, the discussion was halted but several HAB
members volunteered to meet as a subpanel to discuss and refine a potential process to incorporate TTC into NSF/ANSI/CAN 600 for additional discussion at the Fall 2020 meeting.

**Current Qualitative Paradigms:**

The NSF qualitative assessment paradigms for substances with limited datasets were adopted in 1987 and revised in 1999 by the Health Advisory Board (HAB). The current paradigm allows for assigning a Total Allowable Concentration (TAC) and Single Product Allowable Concentration (SPAC) using a tiered approach when there are limited data available for a substance. The criteria for the various tiers are described below:

**Tier I data**

TAC = 10 µg/L Mutagenicity and clastogenicity data are available and provide clear evidence of non-genotoxicity (see NSF/ANSI/CAN 600 Section 3.9.15). The weight of evidence from all other relevant data concludes that the substance is not a hazard at exposures of 10 µg/L or less.

**Tier II data**

TAC = 50 µg/L A repeated-dose study of less than 90 days is also available, and the weight of evidence from the required genotoxicity studies (i.e., mutagenicity and clastogenicity) and all other relevant data concludes that the substance is not genotoxic and not a human health hazard at exposures of 50 µg/L or less.

These qualitative thresholds may not be appropriate and/or additional studies or review are required when:

1) The weight of evidence from the required genotoxicity studies and/or other relevant data concludes that the data are insufficient to assess potential mutagenicity and/or clastogenicity (i.e. mixed or equivocal results require peer-review).

2) The weight of evidence from the required genotoxicity studies and/or other relevant data concludes that the substance is likely to be mutagenic and/or clastogenic and/or there are potential health risks at exposures of 10 µg/L or less (or 50 µg/L or less, depending on the relevant Tier).

When there are insufficient data for a qualitative risk assessment as described above, the substance is evaluated using the Threshold of Evaluation (TOE) policy in which the TAC is 3 µg/L and the SPAC is 0.3 µg/L. The available evidence (e.g., structure activity relationships) must conclude that the substance is not altering for mutagenic carcinogenicity and/or for other human health hazards at exposures of 3 µg/L or less.

**TTC Overview:**

The TTC is intended to establish levels of human exposure that would not represent a safety concern using toxicology data from other chemicals sharing some structural similarities (EFSA,
Munro et al. (1996) gathered a data set of 613 chemicals covering industrial chemicals, agrochemicals, food chemicals and consumer chemicals. These chemicals were categorized by Cramer structural class (137 class I, 28 class II, 448 class III). The lowest NOEL for each chemical was plotted and the 5th percentile NOEL values were used as the criteria for each TTC level (2941 NOELs were identified from the 613 chemicals). See Figure 1 below:

The TTC was further refined to address chemicals with structural alerts DNA-reactive mutagenicity as well as organophosphates by Kroes et al. (2004) with TTC values of 0.0025 µg/kg-day and 0.3 µg/kg-day, respectively. Additionally, Kroes et al. (2004) clarified chemicals that should be excluded from application of the TTC. See Table 1 below:
Table 1: Tiered TTC values from Kroes et al. (2004), adapted from Kosemund, Eurotox 2015

<table>
<thead>
<tr>
<th>Tier</th>
<th>Exposure Limit (µg/day)</th>
<th>Exposure Limit (µg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusions (e.g. metals, proteins, bioaccumulation potential; very high potency carcinogens)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical with Structural Alerts</td>
<td>0.15</td>
<td>0.0025</td>
</tr>
<tr>
<td>No structural alerts (FDA ToR)</td>
<td>1.5</td>
<td>0.025</td>
</tr>
<tr>
<td>Organophosphates</td>
<td>18</td>
<td>0.3</td>
</tr>
<tr>
<td>Cramer Class III</td>
<td>90</td>
<td>1.5</td>
</tr>
<tr>
<td>Cramer Class II</td>
<td>540</td>
<td>9</td>
</tr>
<tr>
<td>Cramer Class I</td>
<td>1800</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 2 below provides the derivation of the drinking water TAC and SPAC values following the current TTC approach for substances that have structural alerts for DNA reactivity or those without, including NSF’s existing Threshold of Evaluation process, or TOE (based on US FDA TOR), and those evaluated based on the Cramer classification. The TAC and SPAC criteria identified in Table 1 would only be utilized once a chemical has been evaluated to the proposed process for implementing the TTC within NSF/ANSI/CAN 600.

Table 2: TAC and SPAC values based on TTC approach

<table>
<thead>
<tr>
<th>Classification</th>
<th>TTC (µg/kg/day)</th>
<th>TAC (µg/L)</th>
<th>SPAC (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotoxicity Structural Alert (highest concern)</td>
<td>0.0025(1)</td>
<td>0.2(2)</td>
<td>0.02(2)</td>
</tr>
<tr>
<td>Threshold of evaluation (not structurally alerting, low toxicity)</td>
<td>0.025</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>Cramer Class III (high concern)</td>
<td>1.5</td>
<td>9</td>
<td>0.9</td>
</tr>
<tr>
<td>Cramer Class II (intermediate concern)</td>
<td>9</td>
<td>56 (60 rounded)</td>
<td>5.6 (6 rounded)</td>
</tr>
<tr>
<td>Cramer Class I (low concern)</td>
<td>30</td>
<td>188 (200 rounded)</td>
<td>18.8 (20 rounded)</td>
</tr>
</tbody>
</table>

1 10^-6 risk level
2 TAC = 10^-3 risk level without life stage adjustment for mutagenic mode of action assuming 0.032 L/kg
3 TAC with life-stage adjustment (default 2.54 factor) for mutagenic mode of action

TAC (no genotoxicity alerts) = TTC x 20% relative source contribution/0.032 L/kg. SPAC = TAC/10

Discussion and Revised Proposal:

Following discussions with the HAB subpanel, it was helpful to the group to compare how the criteria were derived (particularly the uncertainty factors used in each approach). Figure 2 below is intended to provide a side-by-side comparisons between quantitative approaches and TTC.
Figure 2: Comparison of TTC approach with Non-Cancer Quantitative Paradigmss

As the above demonstrates, uncertainties are not equally reflected between TTC and the current quantitative approach for non-cancer endpoints; however, the lack of a database factor within the TTC approach can be partially accounted for in the method used to determine the POD NOEL as the 5% percentile NOEL value within the Munro Cramer category. A review by EFSA and WHO (2016) concluded that TTC is a valid screening tool to assess low dose chemical exposures and to distinguish those for which further data are required to assess human health risk. A proposal to incorporate TTC into the current NSF/ANSI/CAN 600 process is presented in Figure 3 below:
Figure 3: Comparison of Current and Proposed Qualitative Approaches

**CURRENT APPROACH**

New Chemical

- Detection < 3 or 0.3 ppb

TOE Assessment

- Detection < 10 ppb

Qualitative Assessment

- Detection > 10 ppb

Quantitative Assessment

- Ingestion 0.032 L/kg

TAC

- Divide by 10

SPAC

- RSC 0.2

**PROPOSED APPROACH**

New Chemical

- Detection < 3 or 0.3 ppb

TOE Assessment

- Detection > 3 or < TTC

TTC Assessment

- Detection > TTC or WOE

Quantitative Assessment

- Ingestion 0.032 L/kg

TAC

- Divide by 10

SPAC

- RSC 0.2

**TTC PARADIGM (non-Cancer)**

- Used Munro dataset (613 substances, 2941 NOAELs)
- Key Study (chronic, subchronic, repro, dev)
- Point of Departure
  - NOAEL based on fifth percentile of chemical class from Munro dataset
  - If subchronic, 3x factor applied
- UF Values
  - Human Extrapolation (UFA/UFH) = 100x
  - Database not applied
- POD / 100 = Oral Reference Dose
  - Cramer III = 1.5 μg/kg-day
  - Cramer II = 9 μg/kg-day
  - Cramer I = 30 μg/kg-day
- Application of 0.032 L/kg-day ingestion rate
- Use of 0.2 RSC
- TAC = SPAC?
- Non-Cancer TTC may pose potential risk with probability estimated between 0-5%
- Weight of evidence approach must be applied for any chemicals with toxicity data to verify appropriateness of TTC category approach
- EFSA 2018 Review – TTC fit for purpose

**QUANTITATIVE PARADIGM (non-Cancer)**

- Key Study (chronic, subchronic, repro, dev)
- Point of Departure
  - NOAEL
  - LOAEL / (3 or 10)
  - BMDL
- UF Values
  - Human Extrapolation
    - UFA
    - Default dosimetry
    - Advanced dosimetry
  - UFH
    - Default dosimetry
    - Advanced dosimetry
  - Subchronic to chronic (3x or 10x)
  - Database (3x of 10x)
  - POD / UF = Oral Reference Dose
It should be acknowledged that the above proposal is for non-cancer endpoints and is presented to help inform the upcoming discussion at the Fall 2020 meeting. One of the key items in the proposal is the use of the TTC where the chemical does have toxicity data as a fit-for-purpose approach so long as there is a weight of evidence review that such TTC is protective. This does not depart significantly from how the TOE as well as current qualitative paradigm has been applied by certifying organizations historically. Anther unresolved issue is reconciling the current qualitative paradigm approach of setting the TAC equal to the SPAC should be retained in the new TTC paradigm. This issue also led to a discussion by the HAB subpanel of the necessity of the SPAC overall within the Standard.

It was also recognized by the HAB subpanel that the FDA is currently considering updates to the current TTC; however, it was recognized that there are benefits of updating NSF/ANSI/CAN 600 using the current approach and consider additional changes to the TTC as they become more widely adopted accepted.

OUTSTANDING QUESTIONS:

1) Can the TTC be applied for chemicals with toxicology data so long as a weight-of-evidence review indicates the TTC is sufficiently protective (fit for purpose)?

2) Should current qualitative approach of TAC=SPAC be retained in the application of TTC to NSF/ANSI/CAN 600?

References:


MEMORANDUM: DRINKING WATER INTAKE RATES

TO: NSF HEALTH ADVISORY BOARD (HAB)
CC: JOINT PEER REVIEW STEERING COMMITTEE (JPRSC)
FROM: KELLY MAGURANY, M.SC, DABT
PRINCIPAL TOXICOLOGIST
SUBJECT: DRINKING WATER INTAKE (DWI) RATES
DATE: SEPTEMBER 18, 2020

Fall 2020 HAB Meeting Objectives:

1) Present the current state of DWI rates in the NSF/ANSI/CAN 600 standard;
2) Present the DWI rates used by drinking water regulators at Health Canada and U.S. EPA
3) Seek Health Advisory Board (HAB) input on the most appropriate use of DWI rates for
   the NSF/ANSI/CAN 600 while considering consistency with authoritative bodies.

Background:

NSF’s mission is to ensure public health protection and in so doing needs to ensure that the
chemical acceptance criteria that have been determined are consistent with the currently
available safety data, scientific knowledge, and risk assessment methodologies. A key
component of our acceptance criteria derivation is the application of the most current
knowledge on drinking water intake rates for adults and sensitive subpopulations such as infants,
pregnant women and children. Recent updates to the U.S. EPA Exposure Factors Handbook
(2019)\(^1\) presented new data on ingestion of drinking water that presents an opportunity to
review NSF/ANSI/CAN 600 current DWI rates.

The goal of this review is to identify the most appropriate data to be used to derive drinking water
acceptance criteria consistent with drinking water regulatory authorities. The following
data present the current state of NSF/ANSI/CAN 600 DWI rates, the U.S. EPA DWI rates for
water regulations, Health Canada’s approach and the recommended NSF/ANSI/CAN 600
approach relative to these data for HAB review.

\(^{1}\) U.S. Exposure Factors Handbook, 2011 (EFH, 2011) Chapter 3 Ingestion of Water and Other Select Liquids
Current NSF/ANSI/CAN 600 DWI

<table>
<thead>
<tr>
<th>Population</th>
<th>L/kg/day</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (1-3 months)</td>
<td>0.228</td>
<td>EFH, 2011: 90th% intake, consumers only, community water; 1994-1996, 1998 CSFII data; Table 3-19</td>
</tr>
<tr>
<td>Children (1-2 year)</td>
<td>0.056</td>
<td>EFH, 2011: 90th% intake, per capita consumption, all water sources; 1994-1996, 1998 CSFII data; Table 3-75</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>0.039</td>
<td>Human Health Ambient Water Quality Criteria, 2015 : EFH, 2011: 90th% intake, per capita, community water; NHANES 2003-06; BW: 80 kg DWI: 2.4 L (0.030 L/kg)</td>
</tr>
<tr>
<td>Adults</td>
<td>0.032</td>
<td>EFH = Exposure Factors Handbook</td>
</tr>
</tbody>
</table>

U.S. EPA

- **Safe Drinking Water Act** (relevant to the regulation of drinking water contaminants)
  - Reference [US EPA 2002 guideline](#):
    - Adults: BW: 70 kg; DWI: 2 L/day (0.029 L/kg)
    - Child: BW: 10 kg; DWI 1 L/day (0.1 L/kg)
    - 90th%, consumers only, community water
  - Nothing new has been regulated since 2006. As such, SDWA has not updated DWI/BW values.

- **Clean Water Act**
  - [Human Health Ambient Water Quality Criteria](#)
  - 90th %, per capita, community water
  - Adults: BW: 80 kg; DWI: 2.4 L/day (0.030 L/kg) (EFH 2011; NHANES 2003-2006)

- **US EPA Pesticide Benchmarks** for drinking water
  - 90th %, community water, consumers only
  - Referenced values for 2017 benchmark updates; EPA EFH, 2011:
    - Adults: BW: 80 kg; DWI: 2.5 L/d (0.031 L/kg) (NHANES 1999-2006)
    - Females of repro. Age: BW: 69 kg; DWI: 2.5 L/d (0.036 L/kg) (NHANES 1999-2006)
    - Children (using infant data 0-1 yr): 0.15 L/kg-day (CSFII 1994-1996, 1998; Table 3-19)

- **Recent U.S. EPA Health Advisories for PFOA & PFOS for drinking water**
  - Guideline:
    - Infant/child = 0-12 months DWI (not specified) and 10 kg
    - Adult = 80 kg (DWI not specified)
  - Compound specific: EPA selected lactating women as the most sensitive subpopulation
    - DWI/bw = 0.054 L/kg-day; 90th percentile consumers only estimate of combined direct and indirect community water ingestion for lactating women (see Table 3-81 in USEPA 2011b; CSFII 1994–1996 and 1998).
> Other EPA considerations


### Health Canada DWI Rates

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Body Weight (kg)*</th>
<th>Water Intake (L)*</th>
<th>Water Intake Rate (L/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 months (breast fed)</td>
<td>6.3</td>
<td>0.744 (breast milk)</td>
<td>0.118</td>
</tr>
<tr>
<td>0-5 months (formula fed)</td>
<td>6.3</td>
<td>0.826</td>
<td>0.131</td>
</tr>
<tr>
<td>6-11 months (breast fed)</td>
<td>9.1</td>
<td>0.632 (breast milk)</td>
<td>0.069</td>
</tr>
<tr>
<td>6-11 months (formula)</td>
<td>9.1</td>
<td>0.764</td>
<td>0.084</td>
</tr>
<tr>
<td>1 year</td>
<td>11.0</td>
<td>0.36</td>
<td>0.033</td>
</tr>
<tr>
<td>2-3 years</td>
<td>15</td>
<td>0.43</td>
<td>0.029</td>
</tr>
<tr>
<td>4-8 years</td>
<td>23</td>
<td>0.53</td>
<td>0.023</td>
</tr>
<tr>
<td>9-13 years</td>
<td>42</td>
<td>0.74</td>
<td>0.018</td>
</tr>
<tr>
<td>14-18 years</td>
<td>62</td>
<td>1.09</td>
<td>0.018</td>
</tr>
<tr>
<td>19+ years</td>
<td>74</td>
<td>1.53</td>
<td>0.021</td>
</tr>
</tbody>
</table>

* The % of intake was not reported

---

2 References:


American Academy of Pediatrics

“On average, your baby should take in about 2½ ounces (75 mL) of formula a day for every pound (453 g) of body weight,” or 0.166 L/kg.

https://www.healthychildren.org/English/ages-stages/baby/formula-feeding/Pages/Amount-and-Schedule-of-Formula-Feedings.aspx

Other References to Consider


Recommended NSF Standard DWI

<table>
<thead>
<tr>
<th>Population</th>
<th>L/kg/day</th>
<th>Details*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child (0-12 months)¹</td>
<td>0.140</td>
<td>90th% intake, consumers only, community water; 1994-1996, 1998 CSFII**; Table 3-19</td>
</tr>
<tr>
<td>Pregnant women²</td>
<td>0.033</td>
<td>90th% intake, consumers only, community water; 1994-1996, 1998 CSFII**, Table 3-75</td>
</tr>
<tr>
<td>Lactating</td>
<td>0.054</td>
<td>90th% intake, consumers only, community water; 1994-1996, 1998 CSFII**; Table 3-75</td>
</tr>
<tr>
<td>Child-bearing age</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>Adults³</td>
<td>0.034</td>
<td>EFH, 2019: 90th% intake, consumers only, community water; NHANES 2005-2010; Table 3-21</td>
</tr>
</tbody>
</table>

¹ To remain consistent with U.S. EPA SDWA standards. This value also aligns well with Health Canada.
² Consumers only, community water exposure was selected to remain consistent with U.S. EPA SDWA standards. In addition, consumers only exposure represents the more conservative and relevant population for drinking water ingestion as opposed to per capita exposure.
³ Consumers only, community water exposure was selected to remain consistent with U.S. EPA SDWA standards. In addition, consumers only exposure represents the more conservative and relevant population for drinking water ingestion as opposed to per capita exposure.
* See Appendix for references
** Still considered the most reliable data for this population per EFH, 2019
HAB Charge Questions

1) Do you agree with the NSF recommended changes?

2) Any concerns with the approach?

3) Are there any data that we should be aware of that may further inform our decision making?
Appendix

From EFH, 2011:

Table 3-19. Consumer-Only Estimates of Direct and Indirect Water Ingestion Based on 1994-1996, 1998 CSFII: Community Water (mL/kg-day)

<table>
<thead>
<tr>
<th>Age</th>
<th>Sample Size</th>
<th>Mean</th>
<th>10</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>90</th>
<th>95</th>
<th>99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to ≈1 month</td>
<td>37</td>
<td>137*</td>
<td>11*</td>
<td>65*</td>
<td>138*</td>
<td>197*</td>
<td>235*</td>
<td>238*</td>
<td>263*</td>
</tr>
<tr>
<td>1 to ≈3 months</td>
<td>108</td>
<td>119*</td>
<td>12*</td>
<td>71</td>
<td>107</td>
<td>151</td>
<td>228*</td>
<td>285*</td>
<td>345*</td>
</tr>
<tr>
<td>3 to ≈6 months</td>
<td>269</td>
<td>80</td>
<td>7</td>
<td>27</td>
<td>77</td>
<td>118</td>
<td>148</td>
<td>173*</td>
<td>222*</td>
</tr>
<tr>
<td>6 to ≈12 months</td>
<td>534</td>
<td>53</td>
<td>5</td>
<td>12</td>
<td>47</td>
<td>81</td>
<td>112</td>
<td>129</td>
<td>186*</td>
</tr>
<tr>
<td>1 to ≈2 years</td>
<td>880</td>
<td>27</td>
<td>4</td>
<td>9</td>
<td>20</td>
<td>36</td>
<td>56</td>
<td>75</td>
<td>109*</td>
</tr>
<tr>
<td>2 to ≈3 years</td>
<td>879</td>
<td>26</td>
<td>4</td>
<td>9</td>
<td>21</td>
<td>36</td>
<td>52</td>
<td>62</td>
<td>121*</td>
</tr>
<tr>
<td>3 to ≈6 years</td>
<td>3,703</td>
<td>24</td>
<td>4</td>
<td>9</td>
<td>19</td>
<td>23</td>
<td>26</td>
<td>34</td>
<td>54*</td>
</tr>
<tr>
<td>6 to ≈11 years</td>
<td>1,439</td>
<td>12</td>
<td>3</td>
<td>7</td>
<td>13</td>
<td>20</td>
<td>27</td>
<td>36</td>
<td>67*</td>
</tr>
<tr>
<td>11 to ≈16 years</td>
<td>911</td>
<td>13</td>
<td>2</td>
<td>5</td>
<td>15</td>
<td>17</td>
<td>23</td>
<td>29</td>
<td>43*</td>
</tr>
<tr>
<td>16 to ≈18 years</td>
<td>339</td>
<td>12</td>
<td>2</td>
<td>5</td>
<td>16</td>
<td>18</td>
<td>24</td>
<td>30</td>
<td>52*</td>
</tr>
<tr>
<td>18 to ≈21 years</td>
<td>361</td>
<td>13</td>
<td>2</td>
<td>5</td>
<td>16</td>
<td>17</td>
<td>23</td>
<td>32</td>
<td>53*</td>
</tr>
<tr>
<td>21 to ≈25 years</td>
<td>8,355</td>
<td>17</td>
<td>3</td>
<td>7</td>
<td>13</td>
<td>22</td>
<td>33</td>
<td>44</td>
<td>77*</td>
</tr>
<tr>
<td>25 to ≈65 years</td>
<td>1,927</td>
<td>18</td>
<td>5</td>
<td>10</td>
<td>16</td>
<td>24</td>
<td>32</td>
<td>37</td>
<td>73*</td>
</tr>
<tr>
<td>All ages</td>
<td>17,815</td>
<td>17</td>
<td>3</td>
<td>7</td>
<td>13</td>
<td>22</td>
<td>33</td>
<td>44</td>
<td>77*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>90th % Intake (L/kg-day) weighted to sample size</th>
<th>90th % Intake (L/kg-day) (0-12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>0.235</td>
<td>8.695</td>
</tr>
<tr>
<td>108</td>
<td>0.228</td>
<td>24.624</td>
</tr>
<tr>
<td>269</td>
<td>0.148</td>
<td>39.812</td>
</tr>
<tr>
<td>534</td>
<td>0.112</td>
<td>59.808</td>
</tr>
<tr>
<td>948</td>
<td>0.112</td>
<td>132.939</td>
</tr>
</tbody>
</table>

The sample size does not meet minimum requirements as described in the Third Report on Nutrition Monitoring in the United States (FASEB/LSRO, 1995).
From EFH, 2019:

Chapter 3—Ingestion of Water and Other Select Liquids

Table 3.21. Two-Day Average® Consumer-Only® Estimates of Combined Direct and Indirect® Water Ingestion Based on National Health and Nutrition Examination Survey (NHANES) 2005–2010: Community Water (mL/kg-day)

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Sample Size</th>
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<th>95th</th>
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<td>18.5</td>
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<td>1.4</td>
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<td>18.5</td>
<td>28.7</td>
<td>48.7</td>
<td>57.3</td>
<td>84.5</td>
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</tr>
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<td>38.8</td>
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</tr>
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<td>4 to &lt;6 years</td>
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<td>23.0</td>
<td>63.9</td>
<td>96.2</td>
<td>113.3</td>
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<td>167.0</td>
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</tr>
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<td>0.9</td>
<td>2.8</td>
<td>6.6</td>
<td>14.9</td>
<td>24.6</td>
<td>31.1</td>
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<td>1.1</td>
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<td>6.1</td>
<td>15.1</td>
<td>26.5</td>
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<td>0.9</td>
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<td>4.3</td>
<td>8.2</td>
<td>17.4</td>
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<td>9.1</td>
<td>17.2</td>
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<td>9.1</td>
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<td>60.9</td>
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<td>5.7</td>
<td>11.0</td>
<td>18.7</td>
<td>27.0</td>
<td>36.3</td>
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<td>80+ years</td>
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<td>0.5</td>
<td>0.4</td>
<td>1.0</td>
<td>2.2</td>
<td>5.7</td>
<td>11.0</td>
<td>18.7</td>
<td>27.0</td>
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<td>59.4</td>
<td>99.8</td>
</tr>
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<td>Birth to &lt;2 years</td>
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<td>33.5</td>
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<td>6.3</td>
<td>12.9</td>
<td>22.3</td>
<td>33.5</td>
<td>42.5</td>
<td>64.1</td>
<td>120.7</td>
</tr>
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<td>60+ years</td>
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<td>0.2</td>
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<td>4.4</td>
<td>8.1</td>
<td>14.7</td>
<td>22.8</td>
<td>32.5</td>
<td>39.6</td>
<td>58.0</td>
<td>120.7</td>
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<td>Mexican American</td>
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<td>13.8</td>
<td>0.5</td>
<td>0.1</td>
<td>1.2</td>
<td>2.1</td>
<td>4.5</td>
<td>9.4</td>
<td>17.4</td>
<td>28.7</td>
<td>38.9</td>
<td>73.1</td>
<td>244.4</td>
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<tr>
<td>Non-Hispanic white</td>
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<td>0.1</td>
<td>0.6</td>
<td>1.5</td>
<td>3.7</td>
<td>8.3</td>
<td>15.5</td>
<td>25.8</td>
<td>33.3</td>
<td>61.0</td>
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<tr>
<td>Non-Hispanic black</td>
<td>6,098</td>
<td>17.0</td>
<td>0.4</td>
<td>0.3</td>
<td>1.5</td>
<td>3.0</td>
<td>7.2</td>
<td>14.2</td>
<td>23.7</td>
<td>35.1</td>
<td>45.1</td>
<td>69.8</td>
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<td>0.1</td>
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<td>5.0</td>
<td>8.6</td>
<td>14.4</td>
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<td>68.8</td>
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<td>Other race—including multiple</td>
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<td>0.3</td>
<td>1.8</td>
<td>3.5</td>
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<td>14.7</td>
<td>24.5</td>
<td>38.0</td>
<td>51.3</td>
<td>84.7</td>
<td>227.1</td>
</tr>
</tbody>
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Table 3.81. Consumers-Only Estimated Direct and Indirect Community Water Ingestion by Pregnant, Lactating, and Child-Bearing Age Women (mL/kg-day)

<table>
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<tr>
<th>Women Categories</th>
<th>Sample Size</th>
<th>Mean</th>
<th>90th Percentile</th>
<th>95th Percentile</th>
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</thead>
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<tr>
<td>Pregnant</td>
<td>65</td>
<td>14*</td>
<td>12*</td>
<td>15*</td>
</tr>
<tr>
<td>Lactating</td>
<td>33</td>
<td>26*</td>
<td>18*</td>
<td>18*</td>
</tr>
<tr>
<td>Nonpregnant, nonlactating ages 15 to 44 years</td>
<td>2,028</td>
<td>15</td>
<td>14</td>
<td>16</td>
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</tbody>
</table>
MEMORANDUM: STEL DERIVATION REVIEW

TO: NSF HEALTH ADVISORY BOARD (HAB)
CC: JOINT PEER REVIEW STEERING COMMITTEE (JPRSC)
FROM: BRADLEY J. LAMPE, MPH
PRINCIPAL TOXICOLOGIST
SUBJECT: STEL DERIVATION REVIEW
DATE: SEPTEMBER 24, 2020

Fall 2020 HAB Meeting Objectives:

1) Present the problem formulation and background on issues to be addressed;
   a. Course of action to take when STEL < TAC
   b. Revisit type(s) of studies appropriate for STEL derivation
   c. Selection of appropriate population for drinking water intake rate for the STEL
   d. Identify appropriate database requirements for the STEL calculation
2) Summarize input from HAB and JPRSC members regarding the STEL derivation and above issues;
3) Propose new language in NSF/ANSI/CAN 600 that would provide specific guidance related to these issues;
4) Seek HAB feedback on proposed language.

Background:

According to NSF/ANSI/CAN 600 – Health Effects Evaluation and Criteria for Chemicals in Drinking Water (referred to as the “Standard” in the remainder of this memorandum), the default drinking water consumption rate for the short-term exposure level (STEL) calculation shall reflect that of a bottle-fed infant, in the absence of data suggesting that other populations are more sensitive. In the 2019 publication of the Standard, the STEL derivation was revised by updating the bottle-fed infant intake rate from 0.1 L/kg-day to 0.228 L/kg-day. In addition, the revision to the Standard included recommendations for other populations of interest, including 0.056 L/kg-d for a 1 to < 2-year-old child, 0.039 L/kg-d for a pregnant woman, and 0.032 L/kg-d for an adult. The revised drinking water intake rate for bottle-fed infants recommended by the 2019 publication of the Standard exceeds the corresponding adult drinking water intake rate by a factor of seven. Consequently, the use of the new intake values has led to several instances where the STEL value is less (more conservative) than the calculated long-term total allowable concentration (TAC) value. Four examples of recent NSF drinking water risk assessments in which this situation has arisen are briefly summarized in Table 1.
As illustrated in Table 1, there are several factors besides the seven-fold difference in the default drinking water intake that also contribute to an increased likelihood of the calculated STEL being less than the TAC. These factors include:

- Use of longer-term studies (i.e. 90 days) for both the TAC and STEL derivation: Although the STEL is expected to be greater (or less conservative) than the TAC due in part to the general assumption that a shorter-duration exposure would be associated with less toxicity than a corresponding longer-duration exposure (dependent on the nature of the critical effect), since the same key study (and therefore, exposure duration) is often used for both the TAC and STEL calculations, this assumption is often not reflected in the final action levels. In two of the four case studies shown in Table 1, the key studies for the TAC and STEL derivations were the same. In the other two case studies (MTBE and cyclopentanone), the studies used in the TAC derivation were longer in duration that those used in the STEL derivation, but the studies used to derive the STEL were longer-term studies of 90 days and 25 weeks in duration. Although these studies were associated with points of departure that were slightly greater than the corresponding points of departure
MEMORANDUM: STEL DERIVATION REVIEW

associated with the TAC calculation, these differences in points of departure were not significant enough to offset the larger disparities in the drinking water intake rates.

- Lack of a duration-based uncertainty factor: As the TAC is intended to represent a potential of lifetime exposure to a contaminant, it is typically subject to a duration-based uncertainty factor if the key study is not reflective of a lifetime duration of exposure, such as a 90-day subchronic study. Conversely, a duration-based uncertainty factor is not applied to the STEL. Thus, in cases where the key study used to identify the TAC is a chronic study or multi-generation reproduction study which results in no duration-based uncertainty factor being applied, the TAC is less likely to be more conservative than the STEL. This was the case in three of the four case studies shown in Table 1.

- Unclear database requirements for the STEL: Although the TAC and the STEL address different durations of exposure and would therefore be expected to have different criteria for database requirements, in practice the Standard makes no provisions for proposing a separate database requirement factor for the STEL derivation. As shown in all four examples illustrated in Table 1, the database uncertainty factor for the TAC and SPAC was the same.

- Unclear guidance on selecting the appropriate population for identifying the drinking water intake rate: Although the Standard identifies drinking water intake rates for both the “default” bottle-fed infant population as well as other populations of interest, NSF has consistently applied the most conservative drinking water intake specific to bottle-fed infants in the STEL derivation, regardless of the critical effect. For example, the key study used for the STEL derivation in the tetrahydrofuran risk assessment was a multi-generation reproduction study, in which the population of interest may be pregnant women rather than bottle-fed infants.

Additionally, in three of the four cases shown in Table 1 for which the action levels were finalized, the final criteria for the STEL value was increased to the TAC. However, there are no provisions in the Standard that recommend this course of action. Moreover, increasing the STEL value to the TAC when the calculated STEL was lower is not health-protective, and is not consistent with approaches used by other public health agencies, such as the Minnesota Department of Health. Despite these concerns, NSF has provided rationale to support this course of action in the relevant risk assessment documents, which include:

- A high-dose NOAEL was used to derive the STEL; therefore, the STEL is inherently overly-conservative.
- The available repeated-dose studies did not provide any evidence of adverse acute effects associated with the chemical of interest.
- The magnitude of the critical effect associated with the STEL was considered of marginal toxicological significance and/or was observed at or near the recommended limit dose (1000 mg/kg-day).
The key study used to derive the STEL had an exposure period of 90 days or more, which is longer than a “typical” short-term duration.

These issues were discussed in two separate (virtual) meetings of the STEL task group which were held on July 27, 2020 and August 25, 2020, which were attended by the following HAB and JPRSC members:

- Kevin Cox, MPH, JD, Managing Toxicologist, NSF International
- J. Caroline English, Ph.D., DABT (Vice Chair, NSF Health Advisory Board), Independent Consultant
- Shannon Ethridge, M.S., DABT, Toxicologist, IAPMO
- Katie Fallace, MPH, CPH, Research Scientist, Health Risk Assessment Unit, Minnesota Department of Health
- Helen Goeden, Ph. D., Senior Toxicologist/Risk Assessor, Health Risk Assessment Unit, Minnesota Department of Health
- Lynne Haber, Ph.D., DABT, Senior Toxicologist/Adjunct Associate Professor, Department of Environmental Health, College of Medicine, University of Cincinnati
- Ashli Henderson, Project Chemist, Underwriters Laboratories
- Bradley J. Lampe, MPH. Principal Toxicologist, NSF International
- John Lipscomb, Ph.D. U.S. EPA (Retired)
- Kelly Magurany, M.S., DABT, Principal Toxicologist, NSF International (HAB Secretary)
- Clif McLellan, Vice President, ALS/Truesdale

During these two meetings, the following observations and recommendations were made:

- If short-term studies (e.g. 28-day studies) are available in the dataset, then these should be considered in the STEL derivation as opposed to using 90-day studies. The shorter-term animal studies are adequately representative of the 90 days of human exposure that is associated with the STEL for water extractives testing.
- The long-term study almost always results in a lower value, except for developmental toxicants. Thus, 90-day studies are not typically applied in an evaluation for short-term effects.
- In many cases, if the key study used in the STEL derivation is a development study, then the drinking water intake rate for pregnant women could be considered. However, there could be developmental effects that impact the infant. The same issue applied for reproductive effects which could be relevant to infants. Therefore, the selection of the appropriate population for the intake rate depends on the specific endpoint of interest that should be critically evaluated as part of the assessment as opposed to using default approaches.
MEMORANDUM: STEL DERIVATION REVIEW

- In cases where you have a study driving a lower action level that is short-term in duration, then that study should also drive the TAC.
- The database requirements associated with the STEL derivation should be different than the database requirements for the chronic value (TAC).
- If the database allows, then the use of a study of less-than-subchronic in duration should be prioritized for the STEL derivation.
- A database uncertainty factor is relevant to the short-term action level derivation, but not necessarily due to lack of longer-term studies.
- Regarding the database uncertainty factor for the short-term value, the most common database issue is the lack of a multigeneration reproduction study or extended one-generation reproduction study. Any evidence of immunotoxicity or neurotoxicity also contributes to this factor. Data gaps for longer duration studies are not considered.
- When considering the database uncertainty factor, conceptually one should be using weight-of-evidence thinking rather than “check box” thinking. The author of the document should think about the mode of action as it relates to the relevant toxicological endpoints.
- Although setting the long-term value to the short-term value is generally preferred if the latter is less than the shorter, the use of the term “default approach” should be avoided.
- For the database requirements for the STEL, the revised Standard could specify two systemic bioassays, rather than chronic or subchronic assays.
- If the short-term value is less than the calculated long-term value, then setting the long-term value to the level of the short-term value is the typical approach. However, there is no “default” approach. The nature of the endpoint, duration of exposure, and other factors should be considered to determine the appropriate approach.
- If a long-term study is used to derive a short-term value, then we would not use the infant drinking water intake rate.
- If the calculated STEL is lower the than the calculated TAC, the author of the risk assessment document should determine if it is due to the short-term reference dose being more conservative or is it due to the difference in intake rates?
- The author of the risk assessment document should also consider whether differences in dose spacing between the studies used to derive the STEL and the TAC, and whether bolus dosing effects of gavage exposure versus more gradual dosing associated with drinking water or dietary administration contribute to differences between the two action levels. These could be factors that imply that the difference might not be “real.”
- Trying to find a balance between two disparate risk values presents a significant challenge. When comparing values difficult to compare whether they should be the same. There could be a different suite of studies that address short-term vs long-term that impact the point of departure selection.
MEMORANDUM: STEL DERIVATION REVIEW

Recommendations:

As seen in the above case studies, the change to using a more conservative bottle-fed infant intake rate (0.228 L/kg-day) as the default intake rate for the STEL derivation has resulted in STEL values that are more conservative than TAC values. This occurrence is not consistent with the intent of the Standard, in which the STEL is intended to address short-term exposures and short-term exceedances of the TAC and should therefore be less conservative (higher) than the TAC; however, dependent on the relevance of the observed critical effect to short-term exposures. Although the large discrepancy in the adult versus the bottle-fed infant drinking water intake rates is the main contributor to this occurrence, several other factors contribute as well, including: use of longer-than-short-term studies to derive the STEL, including studies of 90 days or more in duration, application of the same database requirements for the STEL derivation as the TAC derivation, and unclear guidance on selecting the population of interest when identifying the appropriate drinking water intake rate for the STEL derivation.

New language in the Standard will be proposed to provide additional clarity on how these issues that affect the STEL derivation can be addressed. The proposed language is shown below:

Additional language in section 3.7:

Since the STEL is intended to address short-term exceedances of the TAC in an extraction test, the STEL cannot be less than the TAC. If the calculated STEL is less than the calculated TAC, then the TAC shall be reduced from its calculated value to the value of the calculated STEL. Deviations from this action may be considered with professional judgment on a case-by-case basis, particularly when differences between the STEL and TAC can be shown to be attributable to non-biological phenomena, such as differences in dose spacing between the key studies or use of a high-dose NOAEL to derive the STEL.

Additional language in section 3.4:

If the dataset includes at least one short-term toxicity study and at least one subchronic 90-day study, the use of data from the terminal evaluation of a short-term toxicity study, or the use of data from an interim evaluation in a subchronic or long-term study (for example, at 14 or 28 days) shall be preferred over using data from the terminal evaluation of the subchronic study when deriving the STEL, provided that the critical effect is not related to developmental and reproductive toxicity.

Additional language in section 3.4:

When evaluating the quality and completeness of the database when deriving the STEL, consideration shall be given as to whether the dataset adequately addresses reproductive and developmental toxicity endpoints, as well as potential immunological and neurotoxicological effects that could result from acute exposure to large doses. Any additional data gaps related to the known or presumed mode of action shall also be considered. The lack of subchronic or long-
term studies in multiple test species shall not be considered a critical data gap for the derivation of the STEL.

**Additional language in section 3.4:**

*When selecting the population-specific drinking water intake rate used in the STEL derivation, consideration shall be given to intraspecies sensitivity to the critical effect (i.e. which age group or population is anticipated to be the most sensitive) and mode of action. For example, if the critical effect is related to developmental or reproductive toxicity, and if the mode of action has been shown or is presumed to target the maternal animal, then the drinking water intake rate for pregnant women shall be used in the STEL derivation rather than the default bottle-fed infant drinking water intake rate. Additionally, if adults are known or presumed to be more sensitive to the critical effect than infants, then the drinking water intake rate for adults shall be used in the STEL derivation rather than the default bottle-fed infant drinking water intake rate.*