



NTP
National Toxicology Program

Summary Minutes

NTP Board of Scientific Counselors

April 11, 2016

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I. Frequently Used Abbreviations and Acronyms

ACC	American Chemistry Council
ADME	absorption, distribution, metabolism, excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BDCM	bromodichloromethane
BSC	Board of Scientific Counselors
DNTP	Division of the NTP
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
HAAs	haloacetic acids
IARC	International Agency for Research on Cancer
ILS	Integrated Laboratory Services, Inc.
IRIS	Integrated Risk Information System
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute of Occupational Safety and Health
NTP	National Toxicology Program
ORoC	Office of the Report on Carcinogens
RoC	Report on Carcinogens

II. Attendees*

Members in Attendance (by videoconference):

Cynthia Afshari, Amgen
Norman Barlow, Johnson & Johnson
George Corcoran, Wayne State University (Chair)
Mary Beth Genter, University of Cincinnati
Daniel Kass, New York City Department of Health and Mental Hygiene
Steven Markowitz, City University of New York
Kenneth McMartin, Louisiana State University
James Stevens, Eli Lilly and Co.
Iris Udasin, Rutgers, University of Medicine and Dentistry of New Jersey

Members not in Attendance:

Lisa Peterson, University of Minnesota
Katrina Waters, Pacific Northwest National Laboratory

National Institute of Environmental Health Sciences (NIEHS) Staff:

Linda Birnbaum	Gloria Jahnke	Nigel Walker
John Bucher	Ruth Lunn	Lori White
Mike DeVito	Robin Mackar	Mary Wolfe
Robbin Guy	Kristina Thayer	

*The meeting was webcast. Individuals who viewed the webcast are not listed, except as noted.

Other Federal Agency Staff:

Paul Howard, U.S. Food and Drug Administration (FDA), BSC Liaison (by telephone)
Elizabeth Whelan, National Institute for Occupational Safety and Health (NIOSH), BSC Liaison (by telephone)

NIEHS Contractors:

Stan Atwood, Integrated Laboratory
Services, Inc. (ILS)
Sanford Garner, ILS

Ernie Hood, Bridport Services
Alton Peters, ILS
Pam Schwingl, ILS

Public:

Mary Ostrowski, American Chemistry Council (ACC, by telephone)

III. Introductions and Welcome

The National Toxicology Program (NTP) Board of Scientific Counselors (BSC) convened in public session April 11, 2016, at 3:30 PM in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC. The BSC members participated remotely by videoconference. Dr. George Corcoran served as chair, welcomed everyone to the meeting, and asked BSC members and other attendees to introduce themselves. Dr. Linda Birnbaum, Director of NIEHS and NTP, and NTP Associate Director Dr. John Bucher welcomed the BSC members and other attendees and thanked them for their participation. Dr. Lori White, BSC Designated Federal Official, read the conflict of interest policy statement.

IV. Introduction to Report on Carcinogens (RoC) Process and Concepts

Dr. Ruth Lunn, Office of the Report on Carcinogens (ORoC), reviewed the process involved in selecting candidate substances for inclusion in the Report on Carcinogens (RoC), which is a science-based public health document prepared by NTP for the Secretary of Health and Human Services. She provided an overview of the process from initial substance nomination to eventual publication in the RoC and provided more details on the process for selecting candidate substances.

The draft concepts for two substances were presented for BSC review at this meeting: *H. pylori*, (chronic infection), and di- and tri-haloacetic acids (HAAs) found as water disinfection by-products. NTP published requests for information in the **Federal Register**: *H. pylori* in 2012 and di- and tri-HAAs in 2015. BSC review is an early step in the candidate substance selection process, which also includes acquisition of scientific and public input. NTP considers comments on the draft concepts from the BSC and the public. The NTP Director selects the candidate substances for evaluation by ORoC. If a substance is selected, ORoC finalizes the concept document, establishes a webpage, posts relevant materials, and initiates protocol (if needed) and monograph development.

V. Draft Report on Carcinogens Concept: Di- and Tri-Haloacetic Acids Found as Water Disinfection By-Products

A. Presentation

Dr. Gloria Jahnke, ORoC, presented the draft RoC concept to the BSC. She provided background information about water disinfection by-products, of which more than 500 have been identified. She said over 48,000 public water systems in the United States provide disinfected water to more than 250 million people, with 98% of water treatment systems using some type of chlorine disinfection process. Ingestion is the major exposure route for HAAs, followed by inhalation and dermal exposures. Ten di- and tri-HAAs have been identified in water. Dr. Jahnke described current Environmental Protection Agency (EPA) regulations related to disinfection by-products, with expanded monitoring to take effect later in 2016.

Dr. Jahnke described scoping activities undertaken by ORoC to develop the concept, which included a review of NTP technical reports and RoC background documents and activities, as well as International Agency for Research on Cancer (IARC) monographs, Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profiles, EPA Integrated Risk Information System (IRIS) toxicological reviews, and preliminary literature reviews. The key issue emerging from this activity is whether some di- or tri-HAAs found in drinking water should be evaluated individually, some as a chemical class, or all as a chemical class. ORoC will address that question by developing an approach and rationale to evaluate some or all of the di- and tri-HAAs as a potential class. Input from an information group will be used to develop a protocol that outlines methods for the cancer evaluation. There is adequate human exposure to HAAs found as water disinfection by-products and there is an adequate cancer database of studies in experimental animals and studies on mechanisms of carcinogenicity. Dr. Jahnke said the rationale for the evaluation is to identify chemicals that may pose a cancer hazard to people living in the United States.

B. Public Comment

Dr. Corcoran noted that written comments were received from the American Chemistry Council (ACC) and distributed to the BSC before the meeting. Ms. Mary Ostrowski, representing the ACC, provided comments by telephone. She said EPA's 2006 Stage 2 rule regarding disinfection by-products effectively controls levels of four tri-halomethanes and five HAAs. She noted that controls are in place already to limit a wide range of disinfection by-products in drinking water, as mandated by EPA, and those controls will help to limit the formation of many other disinfection by-products. She said the question is whether there is public health value in spending public funds to evaluate further disinfection by-products, when control technology is capturing them and removing them from public exposure. In describing the history of ORoC's consideration of bromodichloromethane (BDCM), which is a disinfection by-product not part of the current concept, she noted that BDCM is currently listed in the RoC as *reasonably anticipated to be a human carcinogen*, based on a 1997 NTP bioassay; however, a 2006

bioassay found no evidence of carcinogenic activity. She asked whether NTP conclusions in updated NTP bioassays were used to modify RoC listings.

C. BSC Discussion

Dr. Mary Beth Genter, first BSC discussant, stated that with widespread exposure to by-products of chlorinated drinking water in the United States, the project would strengthen the science base in toxicology by bringing together and interpreting relevant studies on the topic. Based on the number of people exposed and the known biological activities of some of the drinking water disinfection by-products, she found the proposal meritorious and consistent with NTP's mission to strengthen the science base in toxicology regarding such compounds. She felt the clarity and validity of the rationale were well presented, but that it was unclear what strategy would be employed to fill significant data gaps if they are identified. She agreed that the project has high public health impact. She noted that some exposure data cited in the concept appeared to be different from those in the IARC report. She asked whether promotional activities in terms of the carcinogenic mechanism would be evaluated.

Dr. Norman Barlow, second BSC discussant, said the proposed project fits within the scope and goals of NTP. He noted that there is a very large number of people within the United States, Canada, and Europe who are potentially affected by exposure to water disinfection by-products. He said although there are EPA rules in place, as noted by the ACC's comments, it is unclear whether the 10 HAAs under consideration would actually be limited by those rules. He said given the large number of people potentially exposed, the varying concentrations of exposure, and the limited data on human exposure, further investigation is warranted.

Dr. Barlow said some of the compounds of concern already have animal data indicating potential cancer risk from exposure. The issue would potentially be whether the compounds could be lumped together as a class. He noted that it was not clear from the concept how determinations would be made to include compounds in a class or not, but assumed that that would likely not be fully elucidated until the full literature search is completed and there is a deeper understanding of the compounds' absorption, distribution, metabolism, excretion (ADME) properties. He felt the objectives and approach for the cancer evaluation were clearly articulated in the concept, and that the initial approach to the cancer evaluation was reasonable. He recommended evaluation of human data relating to exposure to drinking water, even if di- and tri-HAAs were not quantified. Given the number of people exposed and the uncertainty regarding class designation, he considered the evaluation to have high impact, unless epidemiologic studies show there is no cancer risk associated with exposure. He asked whether the literature search approach based on the 10 properties reported by Smith *et al.* (Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert P, Hecht SS, Bucher JR, Stewart BW, Baan R, Coglianò VJ, Straif K. 2015. Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis. *Environ Health Perspectives*) had been used previously. He recommended development of a plan regarding how compounds would be managed if they are found to be in different classes, or if there is insufficient information on individual compounds to put them into classes.

Mr. Daniel Kass, third BSC discussant, concurred that the proposal is worthy of investigation by virtue of the extent of exposure. He would have liked more data on levels of HAAs in water supplies in New York City and their disinfection practices. He assessed the overall significance as modest, but worthy of investigation.

Dr. Jahnke responded to the questions about class by mentioning ORoC's recent consideration of cobalt, where the classes of cobalt compounds issue had arisen. The classification of carcinogens approach is new for ORoC and Dr. Jahnke described the challenge of searching based on mechanism, when the mechanism is not known. She said human data are being considered, but human cancer data related to di- and tri-HAAs were not located. Regarding data gaps, she acknowledged that a learning process would be involved, with help in-house from the NTP Laboratory. She said promotion activity in terms of characteristics of carcinogenicity would be assessed.

Dr. Corcoran summarized the discussion, stating that two BSC members placed a high priority on the project, with a third thinking it was perhaps not as high a priority in terms of the potential for finding a major health impact, but that it is nonetheless a worthwhile effort. He added that he would be particularly interested in the effects of exposure to these compounds in early development.

VI. Draft Report on Carcinogens Concept: *Helicobacter Pylori* (Chronic Infection)

A. Presentation

Dr. Lunn presented the draft RoC concept to the BSC. She described *H. pylori*, which colonizes the stomach and causes peptic ulcers. It is a gram negative bacteria that is primarily spread by human contact. She discussed the risk factors for infection and routes of transmission, and noted that *H. pylori* prevalence increases with age, varies geographically, and is related to economic status. It is a common infection that disproportionately infects certain immigrant groups and minorities in the United States. IARC concluded that chronic infection with *H. pylori* is carcinogenic to humans. It contributes 6.2% of the global cancer burden and is a major risk factor for gastric cancer, which is the third-leading cause of cancer mortality worldwide.

Dr. Lunn said the current question is not whether *H. pylori* causes cancer, but how to prevent *H. pylori*-related cancer deaths. Strategies to prevent gastric cancer have focused on eradication of *H. pylori*. Treatment of *H. pylori* has been shown to reduce cancer risk by 35%; screening and treatment programs have been shown to be cost-effective in both low-risk and high-risk countries.

ORoC's scoping activities have documented exposure to *H. pylori* in the United States. No new studies or information were identified that are inconsistent with the IARC review, but interest in cancer prevention was identified. The proposed objective and approach would build on the recent IARC assessments to develop a monograph with a cancer hazard evaluation component, a substance profile, and an appendix. The appendix would be developed with the assistance of subject matter experts, if needed, and would summarize information on prevention strategies and supplement the document with new studies or policies. *H. pylori* should be evaluated for the

RoC because of public health and environmental justice concerns, since the bacterium is a major contributor to the global burden of cancer, especially for low-income countries and subpopulations in the United States. Dr. Lunn said a goal of the RoC evaluation would be to help increase awareness of ongoing cancer prevention activities.

B. BSC Questions and Discussion

Dr. James Stevens asked whether underlying disease state, presence of disease, and inflammation correlated, or whether the incidence is only correlated with rates of *H. pylori* infection absent symptoms of other gastrointestinal distress or disease. He asked if there was any association between occurrence of ulcers, regardless of cause, and gastric cancer. Dr. Lunn said she was unsure whether any studies to address those questions had been done, but it is likely that more people get ulcers than cancer. She noted that although many people are infected with *H. pylori*, the rate of gastric cancer is low. The risk factor is similar to that of other biological agents that have been listed in the RoC for cancer. She emphasized that the risk factor is not *H. pylori* itself, but chronic infection with *H. pylori*, similarly to the association of viruses and cancer. Dr. Stevens said it is likely there are many more people with *H. pylori* than have ulcers, and many more people with ulcers than people with gastric cancer, but if there is an association, the question is whether it is more important to treat ulcers than *H. pylori* infection, and whether that would serve to mitigate some of the gastric cancer risk. He commented that treating drinking water is a way to eliminate infection in developing countries; however, water chlorination may lead to some risk, as seen in the HAAs presentation. In this case a reasonable mitigation strategy may be to treat water rather than individuals. He asked whether water decontamination might be a reasonable strategy. Dr. Lunn replied that drinking water is just one of the routes of exposure, but water decontamination could be one strategy among many to decrease gastric cancer due to chronic *H. pylori* infection.

Dr. Iris Udasin, first BSC discussant, said there is inherent value in treating gastrointestinal symptoms, but it is unclear whether treating symptoms reduces cancer; there is not sufficient literature on that issue. She noted that although gastric cancer is uncommon in the United States, it is still relatively common globally. She found the project to be of very high merit and priority, although different from the usual RoC goals, in that the focus is on prevention rather than ascertaining whether or not *H. pylori* is a carcinogen. She said well water and agriculture are among the largest sources of exposure, and so prevention strategies should focus there. She felt the clarity of the presentation and rationale for the proposed evaluation were excellent. She called for improvement in exposure assessment and prevention, as well as development of improved diagnostic modalities. She expressed interest in exploring whether treating the condition could make other issues worse, such as adversely affecting the gut microflora. She cited the example of unintended consequences of treatment with proton pump inhibitors.

Dr. Steven Markowitz, second BSC discussant, echoed Dr. Udasin's positive comments about the concept. He was glad to hear Dr. Lunn characterize *H. pylori* infection as an environmental justice issue. He noted that upon reading the concept, he wondered what NTP could contribute above and beyond what IARC had done recently, but was convinced by the rationale for the proposed evaluation. He approved of the concept's emphasis on raising awareness. Prevention

and intervention strategies are not normally components of RoC evaluations, and he wondered whether putting those topics in the monograph's appendix might de-emphasize them. He suggested they might go in the main body of the monograph instead. He linked intervention and prevention research to etiology, because prevention of gastric cancer through interruption of infection would serve as further proof that *H. pylori* is an etiologic agent. He noted that another aspect of prevention/intervention research would be attention on virulence factors. He characterized the project as having reasonably high impact.

Dr. Lunn clarified that the primary goal of the project is still to evaluate the carcinogenicity of *H. pylori* for listing in the RoC. Given the IARC work and other studies, ORoC could take advantage and not utilize a great deal of additional resources for the evaluation. She acknowledged the unique opportunity in this evaluation to explore prevention and intervention strategies, allowing the inclusion of helpful information beyond simply listing the substance as *known or reasonably anticipated to be a human carcinogen*. She said Dr. Markowitz's recommendation for moving the prevention/intervention information into the main document would be considered.

Dr. Barlow said he considered the concept more acceptable given that it would use a limited amount of resources. He wondered if it was worthwhile to put effort into an evaluation when conclusions were already reached by IARC. He questioned whether pursuing a prevention strategy fits with NTP's mandate. Dr. Lunn said the RoC evaluation would update and add to existing information.

Dr. Kenneth McMartin discussed the contrast between exposure and prevalence, which alludes to people who have already been infected. He asked how an actual exposure assessment would be done in this case. Dr. Lunn said ORoC would not actually conduct an exposure assessment; prevalence would be used to document whether a significant number of people in the United States are exposed to *H. pylori*.

Dr. Corcoran summarized the discussion, noting that there were differences of opinion as to whether the proposed project was within the mission and goals of the NTP. He said the BSC agreed that the clarity and validity of the rationale were very clear, as were the proposed approach and stated objectives. He said two of the discussants rated the proposal as having high priority, noting the potential for worldwide impact and environmental justice.

VII. Adjournment

Dr. Bucher thanked Dr. Corcoran for chairing the meeting and the BSC members for their comments. Dr. Birnbaum added her thanks. Dr. Corcoran thanked the presenters and the BSC members for their participation, particularly the four BSC members attending for the first time (Drs. Afshari, McMartin, Stevens, and Kass). He thanked Dr. White, Ms. Robbin Guy, and the NIEHS Audio/Visual staff for their contributions to organizing and conducting the remote meeting.

Dr. Corcoran adjourned the meeting at 5:00 PM, April 11, 2016.

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NTP Board of Scientific Counselors

Dr. George Corcoran

Chair, NTP Board of Scientific Counselors

[Redacted]

Date:

