**Summary Minutes of the**
**U.S. Environmental Protection Agency (EPA)**
**Science Advisory Board (SAB)**
**Public Meeting**
**June 23-24, 2020**

Chartered Science Advisory Board Members:

Dr. Michael Honeycutt, Chair
Dr. Rodney Andrews
Dr. Hugh Barton
Dr. Deborah Bennett
Dr. Frederick Bernthal
Dr. Bob Blanz
Dr. Todd Brewer
Dr. Joel Burken
Dr. Janice Chambers
Dr. John Christy
Dr. Samuel Cohen
Dr. Tony Cox
Dr. Alison Cullen
Dr. Otto Doering
Dr. Susan Felter
Dr. Joseph Gardella
Dr. John Guckenheimer
Dr. Margaret MacDonell
Dr. Clyde Martin
Dr. Sue Marty
Mr. Robert Merritt
Dr. Larry Monroe
Dr. Thomas Parkerton
Dr. Robert Phalen
Dr. Kenneth Portier
Dr. Tara Sabo-Attwood
Dr. Mara Seeley
Dr. Anne Smith
Dr. Richard Smith
Dr. Jay Turner
Dr. Brant Ulsh
Dr. Donald van der Vaart
Ms. Carrie Vollmer-Sanders
Dr. Kimberly White
Dr. Mark Wiesner
Dr. Peter Wilcoxen
Dr. Richard Williams
Dr. Stanley Young

SAB Chemical Assessment Advisory Committee (CAAC) Members:

Dr. Richard Belzer
Dr. Tiffany Bredfeldt
Dr. Karen Chou
Dr. Harvey Clewell
Dr. Joanne English
Dr. David Hoel
Dr. Wayne Landis
Dr. Dennis Paustenbach
Dr. Isaac Pessah
Dr. Joann Brooks Powell
Dr. Thomas Rosol
Dr. Ted Simon
Dr. Eric Smith
Dr. Laura Vandenberg

Board Liaisons:

Dr. Paul Gilman, Chair, EPA Board of Scientific Counselors

SAB Staff Office:
Dr. Thomas Armitage, Designated Federal Officer (DFO) for Chartered SAB
Mr. Thomas Brennan, SAB Staff Office Director
Dr. Sue Shallal, Designated Federal Officer for the SAB CAAC

Other Attendees
See Attachment A.

**Meeting Summary:**

**Tuesday, June 23, 2020**

Convene the Meeting

Dr. Thomas Armitage, Designated Federal Officer (DFO) for the Chartered SAB convened the meeting and provided an opening statement. He explained the Zoom video logistics and how access was granted to both the public and public speakers. Dr. Armitage indicated that the Chartered SAB and CAAC were independent federal expert advisory committees chartered under the Federal Advisory Committee Act (FACA) and their meetings and deliberations complied with the requirements of FACA. Dr. Armitage noted that the SAB Staff Office had determined that members of the Chartered SAB and CAAC were in compliance with federal ethics laws. He noted that six individuals had registered to provide public comments during the public comment period on the agenda. Dr. Armitage indicated that all meeting materials were available on the SAB website. He noted that the meeting materials included Chartered SAB and SAB CAAC rosters,[1, 2] and meeting agenda.[3]
SAB Staff Office Director Thomas Brennan welcomed meeting participants and provided an overview of recent SAB activities. He noted that in the past year, the SAB had started fifteen new projects and completed nine of them. During that time, the SAB had improved the pace at which reports were generated by 40%. Mr. Brennan cited two reasons for this improvement: process improvements, and adopting a new report format.

Purpose of the Teleconference and Review of the Agenda

SAB Chair Dr. Michael Honeycutt reviewed the purpose of the meeting and the agenda. He indicated that: (1) the Chartered SAB would be conducting quality reviews of two reports that had been developed by SAB panels, a review of the All-Ages Lead (AALM) Model Panel's report,[4] and a review of the Computable General Equilibrium (CGE) Model Panel's report[5]; and (2) the Chartered SAB and the SAB CAAC would be conducting consultations on EPA's Consolidated Human Toxicity Assessment Guideline and EPA's New Approach Methods for Reducing the Use of Lab Animals for Chronic and Carcinogenicity Testing. Dr. Honeycutt noted that the quality reviews would be conducted by the Chartered SAB and therefore the SAB CAAC members attending the meeting did not have to vote on approval of the two draft reports. Dr. Honeycutt noted that for each of the consultations SAB and SAB CAAC members would

first hear presentations from EPA and would then discuss responses to the Agency's charge questions.

Public Comments

Dr. Honeycutt next called individuals on the list of public speakers[6] to provide oral comments. He asked each speaker to limit the comments to three minutes.

*Penelope Fenner-Crisp, Independent Consultant*

Dr. Fenner-Crisp provided comments for SAB consideration in its discussion of EPA's plans for reexamining its Human Toxicity Assessment Guidelines. Dr. Fenner-Crisp noted that at the Board's meeting a year ago she expressed concern about the hurried timing of EPA's plans to issue new guidelines for cancer and non-cancer risk assessment. Dr. Fenner-Crisp said she was pleased that the EPA now seemed to be committed to a more sensible timeline and process for stakeholder involvement. Dr. Fenner-Crisp commended the Agency for acknowledging the commonalities between cancer and non-cancer assessment and opting to develop consolidated guidelines to include assessment of all endpoints. She noted that the Integrated Risk Information System (IRIS) Handbook had not yet been released and the National Academy of Sciences (NAS) review of Toxic Substances Control Act (TSCA) guidance had recently resumed. She noted that proposed Modules 1 – 3 of the Human Toxicity Assessment Guidelines must serve as the Agency's approach to systematic review, thus resolving the current situation of two competing approaches. Dr. Fenner-Crisp said that in developing modules it would be appropriate to start with mutagenicity then go to immunotoxicity and epidemiology. She also suggested creating a module on endocrine disruption. Dr. Fenner-Crisp proposed development of a stand-alone document on cumulative risk assessment. She noted that with the emergence of COVID-19 intersecting environmental pollution, cumulative risk assessment had become an environmental justice issue.

*Patricia Bishop, Humane Society of the United States*

Ms. Patricia Bishop commended EPA for its ongoing efforts to end the use of animals for chemical and safety testing by 2035. Her comments focused on the EPA white paper describing "New Approach Methods and Reducing the Use of Laboratory Animals for Chronic and Carcinogenicity Testing." She noted that the mouse study had been identified as a superfluous test. She indicated that research conducted in the European Union (EU) showed the mouse test contributed little in risk assessment. She noted that while the 90-day mouse study was not a requirement under Part 158 Pesticide Assessment Guidelines, it was strongly encouraged by EPA but rarely used in any other capacity during risk assessment. Ms. Bishop urged the SAB to consider how the short-term repeat dose study in rodents could lead to a New Approach Method (NAM) that replaced animals altogether. She noted that, based on the Humane Society's review of pesticide human health risk assessments conducted by EPA over the past 20 years, these studies were rarely used in setting pesticide exposure limits. Ms. Bishop said she hoped EPA

could move away from the standard battery of tests and instead use animal tests only to answer specific questions and fulfill specific data needs.

*Tracey Woodruff, Professor and Director, Program on Reproductive Health and the Environment, University of California, San Francisco*

Dr. Tracey Woodruff's comments focused on EPA's human health toxicity guidelines. She agreed with Dr. Fenner-Crisp that a modular approach could act as a unifying approach and would allow for consistency across health endpoints. She commented that such an approach should be built on existing guidelines and should be consistent with recommendations from the National Academy of Sciences (NAS). Dr. Woodruff said there should be opportunities for public comments on scoping to ensure modules accounted for all necessary considerations. Dr. Woodruff recommended that EPA reconsider how it addressed human variability because standard default values (EPA's typical safety factor of 10) were inadequate. She commented that for cancer, the NAS had recommended a factor of 25 – 50 to account for variability between the median individual and those with more extreme responses. She indicated that the California-EPA (Cal-EPA) had incorporated differential susceptibility to carcinogens and non-carcinogens utilizing more recent science on increased susceptibility during the prenatal period and age-related susceptibility. Dr. Woodruff said EPA should start with Cal-EPA's life-stage derived adjustment values. She indicated that Cal EPA had also developed child-specific risk factors for chemicals and had addressed specific routes of exposure. She indicated that animal findings were relevant to humans unless there was scientific information to suggest otherwise. She recommended that the EPA adopt the NAS recommendation to assume risks at low doses unless shown otherwise, e.g. lead in particulate matter.

*Nicholas Chartres, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco (UCSF)*

Dr. Nicholas Chartres' comments focused on the SAB consultation on EPA's human health toxicity guidelines. With regard to charge question 2 to the SAB, Dr. Chartres said he wanted to focus on the use of systematic review methods. He commented that the Institute of Medicine (IOM) had twenty-one standards covering the entire systematic review process and defined a systematic review as a scientific investigation that focused on specific questions and used pre-specified scientific methods to identify, select, assess and summarize findings of similar but separate studies. He commented that if it was EPA's intent to incorporate the many recommendations submitted from the June 2019 SAB consultation which emphasized the need to update risk assessment guidelines, then EPA must implement a systematic review method that was compatible with empirically based existing methods using explicit pre-specified scientific methods. He commented that there were multiple well-developed science-based peer reviewed elements that EPA could readily apply, including the National Toxicology Program's method and the University of California San Francisco's navigation guide on systematic review methods. He remarked that the National Academy of Sciences had decided both of these approaches should be used. He noted that the World Health Organization was using the navigation guide to

conduct systematic reviews of occupational exposure. In response to charge question 4, he suggested that the EPA prioritize implementation of empirically based risk assessments before proceeding with development of the other modules. He commented that, without the development of these methods, risk assessments could be biased.

*Greylin Nielsen, Boston University School of Public Health*

Ms. Greylin Nielsen's comments focused on the SAB consultation on EPA's human toxicity assessment guidelines. She addressed the charge question on improving dose-response assessments. She commented on the importance of ensuring that all steps in developing consolidated guidelines proceed transparently and allowed opportunities for external peer review. She noted that the National Academy of Sciences (NAS) had already provided advice on topics under consideration in these modules and indicated that this advice should be incorporated while continuing to engage NAS. She commented on charge question number five and suggested that the SAB recommend methods for harmonizing cancer and non-cancer health effects be the highest priority. She said that the use of low-dose extrapolation approaches was closely tied to the issue of harmonizing cancer and non-cancer risk assessment and should be the second priority recommended by the SAB. Ms. Nielsen said that the lack of a defined threshold for non-cancer effects at the population level was part of the rationale for using low-dose extrapolation. She said that examples of this included the effects of $PM_{2.5}$ on cardiopulmonary mortality and arsenic on cardiovascular disease. She said that the use of various dose-response modeling approaches should be the third priority, followed by endogenous production of environmental contaminants. She noted that clear guidance was needed on how to incorporate probabilistic approaches into risk assessment.

SAB member Dr. Richard Smith asked Ms. Nielsen if she was advocating one particular approach to assessing the shape of the concentration-response curve at low doses. Ms. Nielsen responded that she recommended considering a range of approaches.

*Wendy Heiger-Bernays, Boston University School of Public Health*

Dr. Heiger-Bernays focused her comments on reducing the use of laboratory animals for chronic and carcinogenicity testing. She noted that the progress that made on new approach methodologies (NAMS) was impressive. She commented that the Toxicology in the 21st Century Program (Tox21) was a catalyst for moving these methods forward through collaboration among regulatory agencies, regulated entities, non-governmental organizations (NGOs) and academics. She noted a number of obstacles to developing new methodologies. She commented that budget restrictions on animal testing necessitated thoughtful data-driven methodologies. She commented that complex linkages of in vitro systems could not provide complete information about human populations. She commented on the challenges of modeling the susceptibility of humans who experienced complex disorders at different life stages with environmental chemical contributors. She noted that the NAS 2017 report *Using 21st Century Science to Improve Risk -Related Evaluations* warned against relying only on NAMS. Dr. Heiger-Bernays further commented on

the importance on relying on expert reviews, public comment and the work of NAS. She noted that the EPA needed to consider examples of chemicals where low dose effects may present challenges to predicting point of departure.

Dr. Honeycutt thanked the speakers for their comments and indicated that the Board would next conduct quality reviews of two SAB draft reports.

Quality Review of the Report Prepared by the SAB All Ages Lead Model Peer Review Panel

The Board discussed the draft report of the SAB All Ages Lead Model (AALM) Peer Review Panel. Dr. Honeycutt noted that quality review of SAB panel reports was a key function of the Chartered SAB. He noted that the Board must make a determination about the quality of all draft reports. Dr. Honeycutt then reviewed the agenda for the quality review. He indicated that Dr. Hugh Barton, Chair of the All Ages Lead Model Peer Review Panel, would present a summary of the draft report, the SAB would then hear comments from the lead SAB reviewers, Drs. Janice Chambers, Susan Felter, John Guckenheimer, and Sue Marty. He would then ask Dr. Barton to respond to the comments, ask for comments from other SAB members, and call for a vote on approval of the draft report.

*Comments from SAB lead reviewers*

Dr. Hugh Barton presented a summary of the Panel's review report. He thanked the Panel, the EPA SAB Staff Office, and Dr. James Brown of EPA's Office of Research and Development for the work completed during the review process. Dr. Barton indicated that members of the Panel had extensive modeling experience and were familiar with existing EPA lead models. He noted that some panelists had worked with the two major models discussed in lead modeling scientific literature, the Leggett and O'Flaherty models. Other members of the Panel had a wide range of model expertise that included work with pharmacokinetic models. He noted that members of the Panel were familiar with running the software. In addition, Dr. Barton noted that there was an independent model used for comparison to AALM under review by an expert panel member.

Dr. Barton indicated that the Panel was impressed with the new capabilities in the AALM but members thought there was a need for additional work. Dr. Barton indicated that the Panel had made concrete recommendations for short and long-term action, addressing all charge questions. Dr. Barton indicated that the Panel's overall perspective was presented in the draft letter to the Administrator in the report. He noted that the recommendations were grouped into three tiers or phases: Tier 1 recommendations focused on potential changes to AALM to clarify or correct model and/or documentation; Tier 2 recommendations focused on improvements to strengthen usability, especially with respect to risk assessment activities by multiple stakeholders; Tier 3 recommendations addressed biology, or other more complex issues. Dr. Barton noted that the Panel found it was important for the EPA to continue developing the AALM and to provide support and training, and turn the AALM into a model routinely applied in risk assessment. Dr. Honeycutt thanked Dr. Barton for his summary and asked for comments on the draft report from the lead SAB reviewers.

Dr. Janice Chambers commented that the draft report was clear and logical with consistency in presentation. She suggested including some longer explanations in text preceding recommendations and indicated her preference for a short, declarative/imperative style and recommendations throughout the report. Dr. Chambers indicated that she would have preferred to see an executive summary in the report but noted that elimination of the executive summary was a new format for SAB reports to streamline and eliminate repetition. Dr. Chambers suggested that the Board rethink this approach and indicated that she believes an executive summary is useful because it provides concise text presenting major recommendations. She recommended that an executive summary be created and indicated that suggested edits were included in her written comments.

Dr. Susan Felter commented that the draft report was well organized and all charge questions had been addressed. She provided a few editorial comments. Dr. Felter also asked questions about occupational exposures and indicated that it was not clear whether the AALM was intended to address occupational exposures. She encouraged the Agency to clarify this in the model documentation. Dr. Felter observed that the panel had asked EPA to make changes needed to facilitate use of the model, but she noted that the model was already available for use online. She noted that it was important to identify inappropriate outcomes that might be generated if the model was used prior to modification. Dr. Felter also noted that it would be helpful to readdress the meaning or definition of tier 2 recommendations. In addition, Dr. Felter commented on technical issues that were discussed in her written comments. She noted that some recommendations were not presented in the draft report as complete sentences and they should be expanded.

Dr. John Guckenheimer commented that he had looked back at foundational models that contributed to the AALM. He noted that he appeared to hold a more negative view of AALM than members of the Panel and others on the Board. Dr. Guckenheimer commented on the need for more experimental work to compare AALM model results. He noted concerns about the model software. The code was written in Fortran, translated to a proprietary language. He commented that the model had been given an excel overlay/interface and that special libraries were needed to let Excel interact with the Fortran substructure of the AALM. He indicated that it appeared few people could successfully run the AALM in this configuration and that it was difficult to reproduce results with necessary modifications.

Dr. Guckenheimer also commented that the scientific foundations of the AALM appeared to be weak. He noted that Leggett model at the core of AALM assumed the modeled biological system was linear. He noted that when data did not fit, it appeared the developers had used engineering approaches, adding more compartments to the model to fit the data. Dr. Guckenheimer further stated that biological systems were very nonlinear and that another foundational model (O'Flaherty) appeared to provide better fit in that regard. In addition, Dr. Guckenheimer commented that the numerical methods used in the AALM appeared to be weak. He noted that the AALM ignored almost entirely work done on numerical integration of differential equations and used ad hoc methods. Dr. Guckenheimer concluded the software did not appear to satisfy the

needs of the EPA. He indicated EPA should consider starting over using more modern software and software engineering capability than was used in the AALM.

Dr. Sue Marty commented that the AALM Panel had done an excellent job in reviewing the model. She offered suggestions on how to evaluate predicted accuracy and suggested improvements for user guide. Dr. Marty indicated she had tried downloading and using the AALM and had provided first hand feedback in her written comments. She indicated the panel had done a good job identifying errors in parameters. Her overall opinion was that the Panel had conducted an excellent review. Dr. Marty commented that three tier levels of recommendations were useful. She suggested putting more emphasis on the life stage part of the model and specifically recommended focusing on the pregnancy part of the model. She commented that the beginning of life was a critical place to start and noted that bone lead stores were mobilized into the body during pregnancy. She indicated that maternal age also was a factor because older women mobilized more lead stores. She also commented that higher lead, due to bone turnover, may be present in post-menopausal women and this should be considered by the modelers. Dr. Marty also commented that it was important to consider including lactation in the model.

Dr. Marty offered some editorial comments. She suggested including another acronym page for model variables and highlighting specific items in the letter to the Administrator. She also noted that the model's strength and limitations should be better described by EPA and that the SAB should recommend improving the supporting materials for the model. In addition, she indicated that the SAB should recommend that opportunities be developed for evaluating model parameters and values.

Dr. Barton responded to the comments from the lead SAB reviewers. He thanked the reviewers and noted that:

- Dr. Marty had provided useful suggestions for the letter to the Administrator.
- It would not be easy to incorporate the pregnancy model, substantial effort would be required and some intermediate discussion might be was warranted.
- Dr. Felter had raised a number of good issues.
- The panel had not included an executive summary and he suggested leaving this decision to the SAB Staff Office.
- He was happy to incorporate further edits or to include some things in an appendix.

D. Guckenheimer commented that there were never perfect software choices for modeling and that the user interface and documentation could use improvements. He suggested that the Board include his comments in an appendix for consideration by EPA.

*Comments from other SAB members*

Dr. Honeycutt thanked the lead reviewers and asked for comments from SAB and CAAC members.

A member commented that would be easy to start over in a new software environment. He supported including Dr. Guckenheimer's comments on the report. Another member commented that the draft report did not contain a reference to a recent NAS report on lead exposure. He suggested that it might be useful for the NAS to review what EPA had done.

Dr. Barton responded that the Panel had considered the NAS report and noted that three members of the AALM review panel served on the NAS committee. He noted that there was a paragraph in the SAB report that provided a link to the NAS activity being conducted at the same time as the SAB review.

A member commented that prenatal exposure may not be as important as suggested because of plasma volume increases. She noted that the impact on blood lead was minimal because bone turn-over was so large early in life. The member mentioned papers indicating that prenatal lead has very little association with IQ decrement. A member commented that for the model to be useful in risk management, there was a need to look at distributions of blood lead in approaches like use of the Shedds IUBK model. The member noted that EPA had recently used this model in the Agency's lead and copper rule and dust lead rule.
A member suggested conducting a sensitivity analysis for dermal exposure. She suggested EPA do a sensitivity analysis and consider fasting conditions. She commented that exposure impact of a meal lasted well beyond the meal for lead uptake. Therefore, a sensitivity analysis, more for occupational environment than childhood environments, with three meals provided, was warranted. She also suggested EPA consider oronasal as well as nasal inhalation for workers. In addition, the member indicated that one erroneous assumption may be included in the model regarding the decline of soil ingestion with age. She suggested that there was a more dramatic decline than assumed.

Another member commented that he supported Dr. Guckenheimer's opinions regarding the model structure and construction. He noted that Dr. Guckenheimer's comments about model should be included in a report appendix. He commented that the model was a step forward in understanding how biological systems handle lead. He noted that the occupational exposures discussion in draft report was excellent and that he did not think an executive summary was needed. A member commented that the AALM could help provide information to establish regulatory thresholds but there were other models with clearer formulations based on open source software. The member commented that modeling software should be easy to use and widely available. He indicated that the EPA should have a requirement for software format and availability.

Another member commented that that lead exposures during pregnancy and feeding were probably worth considering. She noted that bone deposition was important during development. A member responded that lead turnover in bone was rapid in young individuals. She indicated that the EPA should be commended for developing the model and noted that the Panel had done a good job reviewing it.

Dr. Barton commented on two lead models that had been discussed by the Panel, noting that the models of O'Flaherty and Leggett compared well when formulated with similar input. He noted that there were three members of the Panel who had reviewed both models. A member commented that if the model were to be used for regulation and it needed ad hoc adjustments the best course of action might be to initiate a new effort to develop the model.

Another member commented that AALM represented a step forward. He indicated that it would be helpful to make the model available and let people use it. He noted that it would be a good tool for developing estimates within its range of applicability and environmental exposures. He agreed with concerns with about prenatal exposure, but did not think this should delay model development. Another member commented on approaches to address programming issues. He noted that one could build an "R wrap around" to Fortran.

Dr. Honeycutt indicated that the Board needed to come to agreement on disposition of the report. He reviewed the options that had been discussed. He suggested that additional clarification and incorporation of comments be sufficient to finalize the report. He also indicated that Dr. Guckenheimer's opinion could be included in an appendix .

Several members agreed that the Drs. Barton and Honeycutt should incorporate edits and finalize the report on behalf of the Board. Other members supported incorporation of Dr. Guckenheimer's comments in an appendix. Dr. Guckenheimer agreed with this suggestion.

A motion was made to have Dr. Barton work with Dr. Honeycutt to revise and finalize the report taking into account the quality review comments and incorporating Dr. Guckenheimer's comments as an appendix. The motion was seconded and unanimously approved by voice vote. Dr. Honeycutt thanked the members for reviewing the report.

<u>Quality Review of the SAB Draft Report on EPA's Computable General Equilibrium Model, SAGE</u>

After a break, the Board discussed the SAB draft report on EPA's Computable General Equilibrium (CGE) Model, SAGE. Dr. Honeycutt reviewed the four quality review questions: (1) whether the original charge questions were adequately addressed; (2) whether there were any technical omissions or errors; (3) whether the report is clear and logical; and (4) whether conclusions are supported by the body of the report. He then asked Dr. Wilcoxen, Chair of the CGE Model Review Panel, to provide an overview of the report.

Dr. Wilcoxen noted that the CGE model review followed a previous SAB review of economy-wide modeling which resulted in a September 2017 SAB report recommending the use of economy-wide models as a supplement to EPA's analytical tools. He indicated that CGE models could capture interactions between markets and pick up important aspects of social costs, benefits and impacts of regulation. Dr. Wilcoxen indicated that the SAB's 2017 economy-wide modeling report recommended that EPA move forward with an open source approach and

develop its own internal modeling capacity. He noted that in response to that recommendation, the Agency's National Center for Environmental Economics (NCEE) had developed a new model, SAGE, which was the subject of the SAB report being discussed. Dr. Wilcoxen indicated that SAGE was a CGE model designed to be used for regulatory analysis. Dr. Wilcoxen indicated that the NCEE had asked the SAB to conduct the initial review of SAGE based on ten charge questions addressing: (1) documentation; (2) structure and assumptions; (3) inputs; (4) plausibility of results; (5) verification tests; (6) whether the agency provided adequate hooks for modeling compliance; (7) versioning; (8) future peer reviews; (9) updates; and (10) near term updates.

Dr. Wilcoxen summarized the report. He noted that, on the whole, the Panel was very impressed by how much NCEE had achieved in the time they had been working on this model. The Panel found good documentation and reasonable assumptions. Nonetheless, the Panel produced seventy-two different recommendations scattered across the ten charge questions. The Panel divided its recommendations into three tiers with Tier 1 denoting those recommendations that should be adopted before regulatory analysis, Tier 2 for recommendations that could benefit the model in the near-term and Tier 3 recommendations for long-term improvements. The letter to the Administrator listed the top three Tier 1 recommendations: (1) improving the baseline over the current "balanced growth baseline;" (2) improving the way consumer decisions are modelled to take account of the shares of good changing with income; and (3) improving the current assumption that the U.S is a small open economy, meaning U.S. actions have no impact on world markets. Dr. Honeycutt thanked Dr. Wilcoxen and asked for quality review comments from the three lead reviewers, Drs. Otto Doering, Anne Smith, and Richard Williams.

*Comments from SAB lead reviewers*

Dr. Doering commented that the panel's report provided an excellent and constructive review that should be valuable to EPA. Dr. Doering indicated that the charge questions had been adequately addressed by the Panel. He noted that EPA staff had provided excellent charge questions that were relevant and allowed the Panel to review the model. He indicated that he had not found important technical errors or omissions. He indicated that he had found the draft report to be both clear and logical. Dr. Doering noted that prioritization of recommendations under various topics had added to the clarity and logic of the review and should aid EPA in directing its resources in improving the model. Dr. Doering further commented that the recommendations and priority given to the recommendations were well targeted. Dr. Doering noted that the recommendation CQ10-9 on p. 23 about allowing imperfect competition should be elevated to Tier 1 status. He also commented that the assumption of perfect competition was often violated and the suggested that a sensitivity analysis be conducted.

Dr. Anne Smith expressed general agreement with Dr. Doering's comments. She said that the review provided guidance to EPA about where it could make the most valuable improvements to this model. She said that the Panel had provided comments on how to make the documentation more accessible to a range of readers. She commented that when the Panel provided

recommendations to enhance the complexity of the model, the guidance was provided in a way that would make the changes more tractable.

Dr. Smith indicated that she did not see any major technical errors but provided a number of suggestions to improve the report. She noted that recommendation CQ10-1 on p. 21 of the panel's report called for adding emissions of key pollutants to the model with $CO_2$ as the first key pollutant. However, it was not clear why $CO_2$ would be the first pollutant to add given that the goal was to model non-carbon pollution. Dr. Smith indicated that adding conventional pollutants would not be a natural extension of the model architecture. Pointing to recommendation CQ10-6 on p. 23 of the panel's report which focused on the partial putty-clay assumption in SAGE, Dr. Smith commented that the partial putty-clay formulation had a long history in CGE modelling. Dr. Smith noted that, with respect to recommendation CQ10-7, the Panel had recommended developing a tool to more flexibly expand and collapse the industry detail. She commented that this recommendation seemed only to apply to industry detail but noted that it would also be important to have regional detail. Dr. Anne Smith suggested that the report mention regional detail or, at least, explain why it is not as important as industry detail. Dr. Smith also commented that recommendation CQ10-7 should be given a higher priority (presently given a Tier 3 rating).

Dr. Smith also suggested rearranging recommendations so they flowed from Tier 1 to Tier 3 within each question. She indicated that this would allow the reader to see them in the order of priority. Dr. Smith noted that only three of the Tier 1 recommendations were mentioned in the letter among the many Tier 1 recommendations. She commented that it was not clear how these three recommendations were chosen among Tier 1 recommendations. She suggested that the top three Tier 1 recommendations be denoted differently (e.g., Tier 1*) to provide emphasis. Dr. Smith commented that, for a tool that would be used to look at sector-specific regulations, the Panel's third recommendation (to relax the assumption of a small open-economy model) may not be critical.

Dr. Smith called for other clarifications. She commented that recommendation CQ1-7, simplification of the section on the solution method, was not well justified. She noted that the recommendation referred to a certain solution method but it described an optimization method (GAMS code) to solve the model. She indicated that this seemed to confuse the function of the GAMS code in SAGE model. She noted that in recommendation CQ1-9, the last sentence said that "the wealth accumulation equation should also be provided …," seeming to imply that capital gains were part of wealth accumulation. Dr. Smith recommended that the report clarify why this equation was requested. Dr. Smith noted that recommendation CQ2-1 had to do with shifting modeling of the transition path to the steady state but it seemed to be recommending obliquely against using the Congressional Budget Office (CBO) 30-year projection. Dr. Smith recommended that there be a clear indication of whether the Panel was recommending not using CBO projections. Dr. Smith also noted that recommendations CQ2-10 and CQ2-14 referenced a myopic version of SAGE. She commented that it was not immediately clear that Panel was recommending that NCEE develop a myopic version of SAGE in the future. She also

commented that recommendation CQ3-5, calling for clarification of the intertemporal calibration, might belong in charge question 1 rather than charge question 3. She noted that if it belonged in charge question 3, more should be said about input. Dr. Smith noted that, in general, the conclusions and recommendations in the report were well supported.

Dr. Richard Williams expressed support for the Panel's report. He noted that, since he was not an expert in CGE modeling, his comments addressed how the model would be used in regulatory analysis. Dr. Williams noted that stakeholders and the general public would have to rely on results of a complex model. Therefore, the model should be validated and EPA should plan for a retrospective review of the model. Dr. Williams emphasized the need for uncertainty analysis (as reflected in lines 4 – 6 on p. 22 of the panel's report). Dr. Williams advised caution using the Congressional Budget Office (CBO) projections (p. 7, line 34 – 36) since the CBO may be using unrealistic assumptions. Dr. Williams asked who the "the less technical users" referred to on p. 2, line 12 were. Dr. Williams also questioned how much confidence could be attached to any forty year model projections.

Dr. Wilcoxen responded to the comments from lead reviewers. He noted that that additional work was needed to introduce imperfect competition to CGE models. He noted that his preference would be to move recommendation CQ10-9 (to allow imperfect competition) to Tier 2 rather than Tier 1. With respect to a query as to why the panel was recommending incorporation of $CO_2$ emissions, Dr. Wilcoxen said the panel wanted EPA to have $CO_2$ in the model to study price-based mechanisms but he agreed that the recommendation could be demoted. With respect to the literature on the putty-clay method, Dr. Wilcoxen asked Dr. Smith to send a reference from the literature. With respect to a point about recommending regional detail as an important tool under recommendation CQ10-7, Dr. Wilcoxen indicated that regional detail could be included and noted that the Panel had listed this recommendation as Tier 3 because the Panel wanted the Agency to focus on econometric estimation. He offered to add in regional detail and list the recommendation as Tier 2. He indicated that a comment about how the panel had selected the top 3 recommendations was correct. He agreed that a Tier 0 or Tier* level could be added unless others object to having 4 levels. Dr. Wilcoxen explained that the transition path from the CBO projections, mentioned by Dr. Williams, could be revised but it was in the report because the Panel was concerned about not projecting deficits. Dr. Wilcoxen agreed with the suggestion to "do validation down the road" and conduct a "retrospective review of how the model had performed." Dr. Wilcoxen also said he could clarify issues about existing diagnostics. He explained that the Panel wanted the Agency to move toward custom econometric estimation. Dr. Wilcoxen said he would take the SAB reviewers' into consideration and address them in revising the report.

*Comments from other SAB members*

Dr. Honeycutt thanked Dr. Wilcoxen and asked other SAB members for their comments. A member commented on the effects of job loss on health status and crime and questioned a sentence from the SAB's 2017 report on economy-wide modeling which said that the "effect is likely to be small." A member responded that there were countervailing impacts as shown by

national mortality data. A member commented that COVID-19 would underscore the recommendation to not use a balanced growth baseline and not assume the economy was at full employment. A member suggested that Dr. Wilcoxen strengthen the report language recommending that EPA econometrically estimate parameters in order to be able to do probabilistic uncertainty analysis. A member commented on the relationship between mortality and air pollution. A member recommended adding a line to the report to call for graphics in the recommendation concerning a section for non-modelers. He noted that graphics in the user guide would help non-modelers understand the model. Another member noted that there was an ongoing SAB effort to look at cost-benefit analyses.

Dr. Honeycutt thanked SAB members for their comments and called for a motion on disposition of the report. A motion was made to revise the report and send it to a selected group of SAB members for approval after which it would be sent to all members for SAB for e-mail concurrence. The motion was approved by voice vote.

Consultation on Activities to Re-examine and Consolidate EPA's Human Toxicity Assessment Guidelines

Dr. Honeycutt indicated that the next item on the agenda was a consultation with EPA on the Agency's activities to re-examine and consolidate the Human Toxicity Assessment Guidelines. Dr. Honeycutt reviewed the agenda. He noted that members would hear remarks from EPA and then discuss responses to the Agency's charge questions.[7]

*EPA remarks*

Dr. Honeycutt introduced the first EPA speaker, Mr. David Dunlap, Deputy Assistant Administrator for Science Policy, EPA Office of Research and Development. Mr. Dunlap thanked the SAB for its work on a number of reviews. He noted that SAB reviews had addressed COVID-19 research needs, the EPA's Lead and Copper rule, the Safer Affordable Fuel Efficient (SAFE) Vehicles Rule, the Science and Transparency Rule, the Mercury and Air Toxics Rule (MATS), Navigable Waters Protection Rule, the Scientific and Technological Achievement Awards (STAA), All-Ages Lead Model, and would address the Multi-Agency Radiation Survey and Site Investigation Manual (MARSSIM), reduced form tools for estimating air quality benefits, and revised guidelines for preparing economic analysis. Mr. Dunlap said that in the coming months, the SAB would also be asked to look at a biosolids risk assessment model, viability testing for ballast water, evaluating exposure potential for trespassers on hazardous waste sites, and Integrated Risk Information System (IRIS) assessments. Mr. Dunlap remarked on environmental progress that had been made by the Agency on its 50th anniversary. He said over 90% of water systems in the U.S. met all health-based standards. He noted that from 1970 – 2019, the six criteria air pollutants had been reduced by 76%. He remarked that since 1983, the SAB had produced over 761 reports and over 30 original studies. With respect to the EPA Office of Research and Development's (ORD) request for the SAB's involvement in consolidating human toxicity guidelines, Mr. Dunlap said some of the guidelines were over 30 years old and guidelines were missing for some important topics like immunotoxicity. Mr. Dunlap asked the

SAB to take up the challenge with some urgency and asked that the SAB commit to regular and in-depth engagement until the completion of this project.

Dr. David Bussard, Chair of EPA's Risk Assessment Forum, presented the slides posted at the meeting webpage[8]. Dr. Bussard first reminded the audience that the SAB had already given ORD over 160 pages of written comments in June 2019 and over 240 unique comments. He noted the range of comments on issues ranging from characterizing uncertainty, variability and dose-response to suggestions for a more unified approach across cancer and non-cancer assessment endpoints. Dr. Bussard also noted that EPA had considered prior National Academy of Sciences reviews. He noted that the EPA was planning to update and consolidate its guidelines on assessing the toxicity and dose-response for human health effects of chemicals (to be chaired by Dr. Michael Firestone in the Office of Children's Health Protection) and start review of key dose-response issues (to be chaired by Dr. Lynn Flowers of ORD).

Dr. Michael Firestone, Senior Science Advisory in EPA's Office of Children's Health Protection, presented the two-phase approach shown in Slide 6 of EPA's presentation. He noted that Phase 1 involved developing the guideline blueprint; Phase 2 involved drafting the guidelines. He noted that modules fell into two types, common elements and modules for specific endpoints. He indicated that common element modules described how to set up the process of risk assessment. Endpoint-specific modules were the modules that would replace existing EPA guidance. Dr. Firestone reminded SAB members that they were being asked to comment on the proposed approach, as shown in charge question 1.

Dr. Firestone indicated that proposed common element modules included planning and scoping a human toxicity assessment, identifying and evaluating toxicity studies, hazard identification and dose-response assessment. Dr. Firestone then reviewed charge question 2 which asked the SAB to comment on the scientific adequacy of EPA's common element modules. Dr. Firestone identified endpoint specific modules that included developmental toxicity, reproductive toxicity, immunotoxicity, carcinogenicity, mutagenicity, and neurotoxicity. Dr. Firestone noted that EPA already had guidelines for most of these topics but they needed updating. Dr. Firestone indicted that charge question 3 asked the SAB to comment on the proposed endpoint-specific modules. Dr. Firestone said the SAB's comments on EPA's priorities would be most welcome. In particular for charge question 5, Dr. Firestone noted that SAB members would be asked to prioritize various dose-response issues that needed attention.

*SAB discussion of responses to the charge questions*

SAB members discussed responses to the charge questions. A member suggested that EPA should consider a fifth stage to look back at the process retrospectively.

A member commented that he didn't see anything in EPA's plans about scientists interacting with each other. He warned against the temptation to fix poor experimental design with data analysis. In response, Dr. Firestone said a lot of those things were being considered in planning and scoping. In response to a question Dr. Bussard said EPA leadership would need to consider budget options on how the project moved forward.

A member said he thought the Agency should include economists in their risk assessments. Another SAB member urged EPA to take a broad approach to the dose-response questions, looking at non-parametric versus parametric statistical methods, causal analysis, machine learning, etc.

An SAB member asked EPA about SAB's role and CASAC's role in developing the guidelines. EPA Staff responded that it would be helpful to hear whether there were other modules that EPA should develop. A member spoke about the "fit for purpose" areas that should include detailed information. The member noted that, given the multiple systematic review approaches being used at EPA, some information was needed about how the consolidated Module 1 and Module 2 would work to marry those approaches as well as the move away from animal testing.

In response to a question from an SAB member about whether exposure guidelines would be included in the revision, Dr. Firestone said EPA had recently developed exposure assessment guidelines (in December 2019). Dr. Firestone said the pieces should fit together (exposure assessment, risk characterization and consolidated guidelines).

A member warned against the sequential nature of EPA's approach noting that, in reality, many efforts happened simultaneously. He noted that the Adverse Outcome Pathways (AOP) and Mode of Action (MOA) discussion would likely take place between Module 1 and Module 2 when more detail about health effects was examined. EPA staff described the iterative nature of risk assessment and indicated that the underlying biology had to be embedded into each part of the assessment.

A member spoke about the importance of systems biology and model de-averaging to capture the idea of individual susceptibility. The member called attention to the emerging science on the biology of chronic inflammation. Another member emphasized why she wanted to see exposure explicitly included in the common element modules. She also recommended that Mode of Action be explicitly identified.

A member emphasized the importance of including systematic review in the common modules so that the ability to evaluate study quality was addressed. A member questioned how the modular framework was going to address cumulative risk assessment and whether low dose effects shown by the epidemiological literature would be included. Another member questioned whether there was any plan to collaborate with the Organization for Economic Cooperation and Development (OECD).

Another member raised the issue of whether an SAB panel should be convened to support EPA's re-examination of their human toxicity guidelines. Dr. Honeycutt and Mr. Brennan said they would look into the possibility of forming such a panel composed of CAAC and chartered SAB members.

A member commented that immunotoxicology guidelines would be very helpful, especially when focused on providing a clear understanding of human relevance of various indicators. She also noted that an effort to harmonize cancer and non-cancer dose-response would be helpful, particularly for non-mutagenic carcinogens.

A member commented on the importance of mode of action and the need to use mode of action to drive the whole risk assessment process. Another member noted that there was a commonality across the modules. He also commented on the high probability of seeing associations due to chance alone in epidemiological studies. A member commented that providing case study examples would be very important.

Dr. Honeycutt thanked EPA staff and SAB members for participating in the consultation and asked SAB members to send their individual written comments in response to the charge question to the DFO by July 10, 2020. The DFO then stated that the meeting would recess for the day and reconvene at 12:30 p.m. (Eastern Time) the following day.

**Wednesday, June 24, 2020**

Dr. Thomas Armitage, DFO for the Science Advisory Board, reconvened the meeting at12:30 p.m. (Eastern Time) and indicated that the Chartered Science Advisory Board (SAB) and the SAB Chemical Assessment Advisory Committee (CAAC) were continuing the SAB meeting that had begun the previous day.

Review of Agenda for the Day

Dr. Michael Honeycutt welcomed Chartered SAB members, SAB CAAC members, and EPA staff to the meeting and reviewed the agenda for the day. He indicated that the sole agenda item for the afternoon was to conduct a consultation with EPA on new methods for reducing the use of laboratory animals for chronic and carcinogenicity testing. Dr. Honeycutt noted that the Board would hear presentations from EPA staff and others. He noted that the speakers' presentation slides[9] were posted on the SAB meeting webpage. After each presentation Board members would ask questions and discuss the presentation topics and responses to the charge questions.[10] Dr. Honeycutt also announced that there would be an opportunity for members of the public to provide brief clarifying oral comments before the meeting adjourned. He indicated that members of the public wishing to provide comments should send an email to the DFO, Dr. Armitage by 3:00 p.m. (Eastern Time). Dr. Honeycutt then announced the list of speakers shown on the Agenda and asked members whether they had questions. There were no questions so he introduced the first speaker, Dr. Anna Lowit, Senior Science Advisor for EPA's Office of Pesticide Programs (OPP).

Consultation on New Approach Methods for Reducing the Use of Laboratory Animals for Chronic and Carcinogenicity Toxicity Testing

Presentations and SAB Discussion

*Dr. Anna Lowit, Senior Science Advisor for EPA's Office of Pesticide Programs (OPP)*

Dr. Anna Lowit of EPA's Office of Pesticide Programs indicated that the Agency had begun research in 2006 on methods that could be used to move away from animal testing. She summarized guiding principles for data needed to test pesticides for registration. She indicated

that the Agency wanted to ensure there was sufficient information to reliably support registration decisions that were protective of public health and the environment while avoiding the generation and evaluation of data that did not materially influence the scientific certainty of a regulatory decision. She noted that the toxicity evaluations used by EPA had saved 200,000 lab animals. Dr. Lowit then summarized OPP's guidances and policies for waiver of toxicity tests. She summarized EPA's "6-pack initiative" which used QSARs and in vitro testing to replace the use of tests with laboratory animal. She noted that the Office of Pesticide Programs had successfully used these methods to replace use of laboratory animals. Dr. Lowit then introduced six scientists who would describe their work to reduce and replace the use of laboratory animals in chronic and carcinogenicity testing. She asked SAB members if they had questions. Several members asked questions

A member asked Dr. Lowit to describe implementation of EPA's test replacement strategy. Dr. Lowit indicated that the Agency first wanted to remove tests that were not used. She noted that an Ecotox workgroup was beginning a review of options.

A member commented that he was uncomfortable with eliminating animal tests that addressed learning. He also noted that in nature, rodents had inherently short-lives and that when used for laboratory testing, they were meaningful lives. Dr. Lowit clarified that in her remarks she was referring to reducing the use of laboratory animals in testing required by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

A member questioned whether the uncertainty in extrapolating from cells or animals to humans would be discussed in another presentation. Dr. Lowit responded that EPA was working with other organizations to address this issue. A member asked Dr. Lowit how the Agency would take into consideration the Integrated Risk Information System (IRIS) definition of an adverse effect (i.e., on an "intact animal"). Dr. Lowit acknowledged that there were challenges in attempting a complete replacement of animal testing.

*Dr. Gina Hilton, People for the Ethical Treatment of Animals; Dr. Gregory Akerman, EPA*

Dr. Gina Hilton of People for the Ethical Treatment of Animals was joined by Dr. Gregory Akerman of EPA. They presented information on EPA's "guiding principles for data requirements." They also discussed an international weight of evidence based approach for carcinogenicity assessment and described EPA's "Rethinking Carcinogenicity Assessment for Agrochemicals Project" (ReCAAP). They noted that a goal of the project was to move away from a checkbox approach to a weight of evidence approach for carcinogenicity assessment using information that was already being collected. They summarized the group's strategy of applying this process to seek waivers of requirements for rat or mouse testing. There were no questions so Dr. Honeycutt thanked the speakers and called for the next presentation.

*Dr. Warren Casey, Division of the National Toxicology Program National Institute of Environmental Health Sciences*

Dr. Warren Casey of the National Institute for Environmental Health Sciences described a carcinogenicity assessment program developed by the National Toxicology Program. He indicated that this was a disease-focused method, rather than an agent-focused method, to make testing more relevant to humans. He noted that ongoing work addressed cardiovascular health, carcinogenesis, and neurotoxicity, with a toolbox built for each. He indicated that this assessment program had better relevance to human exposures and could better synthesize testing. He commented that he was not against animal testing but indicated that it should have better application to humans. He noted that the program was the beginning of a long-process, now at formulation stage, and was a collaboration among the National Institutes of Health, the National Cancer Institute, the EPA, The Food and Drug Administration other agencies. There were no questions so Dr. Honeycutt thanked the speaker and called for the next presentation.

*Dr. Jessica LaRocca, Corteva Agriscience*

Dr. Jessica LaRocca of Corteva Agriscience provided information on the molecular point of departure project of the Health and Environmental Sciences Institute (HESI) safety assessment program. She indicated that a molecular point of departure Team was drawing from many general mammalian toxicology studies, to create "point-of-departure number," not a specific numerical value. She indicated that the goal was to reduce use of animal testing, decrease time required for an assessment, and increase throughput, while still protecting human health. She indicated that this method used toxicogenomics. She described software that had been developed and presented data from short-term study. Dr. LaRocca noted that it was necessary to develop consensus on what represented an appropriate biological response, the reproducibility of a result, the overall study design (e.g., number of studies, what surrogate organs to use), and what duration of exposure was required but the goal was to use short-term rodent studies and integrated transcriptomics to develop a "point of departure value."

SAB members discussed the usefulness of the method and asked questions. A member asked whether the software was helpful in evaluating hormesis. Dr. LaRocca responded that the goal was to derive the point of departure not the mechanism itself.

A member referred to a slide showing a log-based relationship noting that he had many questions about the analysis. He cautioned against using the analysis for prediction, noting that, once the probability component was removed, there was no longer an estimate of uncertainty needed for risk assessment. He also noted that the confidence interval in the example was for the regression line and was not relevant to existing or new data points. He asked that these issues be addressed. A member commented that the presentation was interesting. He noted that the method had useful aspects but did not yield a risk value. A member questioned what doses and time courses were used in the method. Dr. LaRocca indicated that a wide dose range was needed and that the results

of 5, 14, and 90-day studies did not vary much. A member noted that chemicals had a "potency" only in relation to a defined endpoint or biological outcome. The member questioned whether the method was dependent upon adverse outcome pathways (AOPs). Dr. LaRocca responded indicating that the method was not tied to specific AOPs. A member commented that, although the method was not designed to identify hormesis, this could theoretically be done if enough data were available.

Another member commented that genomic transcriptomics data varied greatly and this affected its usefulness for risk assessment. Members posed questions about dose-extrapolation issues. Dr. LaRocca indicated that work was underway to define optimal study design based on physiologically based kinetic methods. A member commented that it was important to compare risk in a way that was relevant to humans. Another member commented that the method did not appear to be a risk assessment but rather a safety assessment. It could not be used to predict or compare risk. A member commented that the method could be used to compare similar risks.

A member commented that it was important to consider techniques to "look across organs." Dr. LaRocca responded, indicating that the liver was a promising organ for identification of biological stress, even if it was not the most sensitive organ. A member commented that, to be useful, risk assessment methods should include modern data analysis and provide information needed to answer both toxicological and economic questions. He noted that risk assessment was not a point estimate. He noted a point estimate was a hazard estimate and did not include uncertainty.

A member noted that the new approach methods being discussed could drive numbers to very low levels, for sake of saving animals without economic analysis. Dr. Lowit noted that the EPA conducted many analyses to assess exposure and risk. She indicated that the volume of work was very large and mechanistic studies were needed. She indicated that EPA had been moving away from animal studies a considerable period of time. A member asked EPA to describe success in developing new approach methods over the next one or two years. EPA staff responded that long term success might equate to developing a useful data package that used fewer animal studies and incorporated transcriptomics

*Dr. Chris Corton, EPA Center for Computational Toxicology and Exposure*

Dr. Corton described how EPA was evaluating pesticides using liver tumor modes of action. He indicated that the Agency was identifying gene expression biomarkers to predict liver tumors. He described the accuracy of six biomarkers for gene expression to predict liver tumors. He indicated that this approach had worked well and the Agency hoped to identify more biomarkers that could be used in the future.

Members discussed the method and asked questions. A member asked whether EPA had used whole animal data or just in vitro studies. Dr. Corton responded that the data had come from many studies of male rats and that the goal was to predict biomarkers for mode of action that the

Office of Pesticide Programs could use in assessments. A member suggested that the Agency increase emphasis on relevance to humans. Another member questioned how reproducible genomic methods were cross labs. Dr. Corton indicated that they were reproducible.

*Dr. Celia Tan, EPA Office of Pesticide Programs*

Dr. Celia Tan of EPA's Office of Pesticide Programs discussed the use of kinetically-derived maximum (KMD) doses in risk assessment. She described the Office of Pesticide Program's work to use kinetically-derived maximum doses to eliminate duplicative testing or unnecessary studies, lessen animal suffering by not testing at doses that cause overt toxicity, quantify and reduce uncertainty in risk assessment, evaluate consistency with mode of action hypothesis, and extrapolate points of departure across species, routes and life-stages.

Members discussed the usefulness of this approach and asked questions. A member commented that the approach was promising and asked whether EPA had developed guidance. Dr. Tan indicated that the Agency was working on guidance. Some members expressed reservations about the KMD approach. A member commented that in the case example presented, the mode of action was glutathione depletion which was difficult to extrapolate. Another member expressed support for EPA's method. She noted that testing the very highest dose an organism can tolerate leads to saturation and did not provide data relevant to lower human exposure. She recommended that the EPA examine data about human exposures. A member suggested examining predictability across rodent data. A member commented that KMD could be used as triage for in-vitro analyses.

*Additional comments from SAB members*

Dr. Honeycutt thanked the speakers for their presentations and called for further comments from SAB members about the EPA's proposed new approach methods. A member commented that he had found the information presented to be useful but he was not sure how decisions would be made. He questioned whether long term results could be predicted from shorter term studies. Members questioned how the methods were being validated and noted that most of the modes of action discussed were not applicable to humans.

A member commented that it was important to consider timing of exposure and dynamics that occurred at multiple time scales (i.e., short duration and long duration of exposure must also be considered). A member commented that it was important to consider procedures needed to implement alternatives to animal tests. EPA staff noted that the Agency had discretion to grant waivers and was currently working on guidance for waivers. EPA staff noted that a number of companies were currently working on side-by-side comparisons of data sets needed for these approaches and considering how to implement alternatives to animal testing.

A member questioned whether EPA could make corrections after a waiver had been granted. EPA staff responded that the Agency could re-evaluate requirements under FIFRA if new data provided new information.

A member questioned whether statistical learning theory had been used to look for correlations among effects within the body. He also noted that many biological processes had thresholds. He questioned whether these thresholds were considered in EPA's analysis or genetic screening. EPA staff responded that research on the heart and spleen had been built on phenotypic anchoring.

A member commented that the U.S. Food and Drug Administration (FDA) insisted on receiving the datasets used by the epidemiologists. He noted that analysis of epidemiological data showed that these studies often could not be replicated. He suggested that the SAB form a small group to look at the use of epidemiology studies in general. He also recommended that the EPA use the same approach as FDA. Another member noted that it was difficult to replicate basic science studies, not just epidemiological studies. He indicated that animal studies should be examined for relevance to humans. He expressed concern about going only to in-vitro studies, which could use doses that would kill outright, let alone cause cancer. A member indicated he was skeptical of eliminating animal studies. Another member commented that he was concerned about the lack of sophistication in some of the statistical analyses.

Dr. Honeycutt asked member if there were further comments from SAB members or clarifying comments from members of the public. There were no further comments from SAB members. The DFO indicated that no members of the public had requested time to provide clarifying comments.

Closing Remarks

Dr. Honeycutt thanked members of the chartered SAB and SAB Chemical Assessment Advisory Committee for participating in the meeting. He indicated that he would work with the Chairs of the SAB panels that had developed the reports on the All Ages Lead Model and the CGE SAGE model to move the reports forward in accordance with the decisions made at the meeting. He also indicated that he would work the DFO to develop letters to EPA transmitting comments on the two consultations that had been conducted. He asked SAB members to send their final written comments in response to the charge questions for the consultations to the DFO by July 10th so they could be included in attachments to the letters.

Meeting Adjourned

Dr. Armitage thanked members for their participation and adjourned the meeting at approximately 5 pm (Eastern Time).

Respectfully Submitted:

/s/

Dr. Thomas Armitage
Designated Federal Officer

Certified as Accurate:

/s/

Dr. Michael Honeycutt
Chartered SAB Chair

November 23, 2020
Date

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by committee members during the course of deliberations within the meeting. Such ideas, suggestions, and deliberations do not necessarily reflect definitive consensus advice from the panel members. The reader is cautioned to not rely on the minutes to represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final advisories, commentaries, letters, or reports prepared and transmitted to the EPA Administrator following the public meetings.

**Appendix A: Additional meeting participants who requested the meeting call-in number.**

| Name | Affiliation |
|---|---|
| Gregory Akerman | EPA |
| Satheesh Anand | Boeringer Ingelheim Animal Health |
| Scott Auerbach | NIEHS |
| Maksat Babayev | |
| Michael Bartels | ToxMetrics, LLC |
| Michael Battaloria | FMC Agricultural Solutions |
| Richard Becker | American Chemistry Council |
| Patricia Bishop | The Humane Society of the United States |
| Todd Blessinger | EPA |
| Bryan Bloomer | EPA |
| Michael Broder | EPA |
| David Bussard | EPA |
| Warren Casey | NIH |
| Nicholas Chartres | University of California San Francisco Program on Reproductive Health and the Environment |
| Amy Clippinger | PETA International Science Consortium |
| Chris Corton | EPA |
| James Couch | NIOSH |
| Allison Crimmins | EPA |
| Michael Devito | EPA |
| Maria Doa | EPA |
| Jeanne Domoradski | Corteva |
| Jeffrey Driver | Risk Sciences, LLC |
| David Dunlap | EPA |
| Rebecca Dzubow | EPA |
| Michelle Embry | HESI |
| David Evans | EPA |
| Penelope Fenner-Crisp | |
| Zaida Figueroa | EPA |
| Michael Firestone | EPA |
| Lynn Flowers | EPA |
| Amber Goetz | Syngenta |
| Iris Goodman | EPA |
| Phillip Goodrum | GSI Environmental |
| Stephen Graham | EPA |
| Maureen Gwinn | EPA |
| Alison Harrill | NIEHS |
| Maria Hegstad | Inside EPA |
| Wendy Heiger-Bernays | Boston University School of Public Health |

| Name | Affiliation |
|---|---|
| Gina Hilton | PETA International Science Consortium Ltd. |
| Joseph Hubbard | EPA |
| Sid Hunter | EPA |
| Khanna Johnston | EPA |
| Daland Juberg | Juberg Toxicology Consulting |
| Carolyn Kilgore | EPA |
| Nicole Kleinstreuer | NIH |
| Andrew Kraft | EPA |
| Jessica LaRocca | Corteva |
| Ryan Liu | EPA |
| Caleb Lord | Syngenta |
| Anna Lowit | EPA |
| Michelle Mabson | Earthjustice |
| Susan Makris | EPA |
| Mario Mangino | EPA |
| Carl Mazza | EPA |
| Roger Miksad | Battery Council International |
| Connie Mitchell | HESI |
| Greylin Nielson | Boston University School of Public Health |
| Doug Obey | IWP News |
| Edward Ohanian | EPA |
| Beth Owens | EPA |
| Doritza Pagan-Rodreguez | EPA |
| Syril Pettit | HESI |
| Solomon Pollard | EPA |
| Kathleen Raffaele | EPA |
| Deborah Ramsingh | Health Canada |
| Swati Rayasam | University of California San Francisco |
| Brandy Riffle | BASF |
| Thomas Russell | EPA |
| Satinder Sarang | Shell |
| Manthan Shah | EPA |
| Sue Shallal | EPA |
| Robert Skoglnd | Covestro, LLC |
| Holly Stallworth | EPA |
| Greg Susanke | EPA |
| Celia Tan | EPA |
| Russell Thomas | EPA |
| John Vandenberg | EPA |
| Julia Varshavsky | California OEHHA |
| Nicolo Visconti | |
| Kathleen Vork | California OEHHA |

| Name | Affiliation |
|---|---|
| Kevin Wheeler | EPA |
| Cris Williams | ILA |
| Douglas Wolf | Syngenta |
| Ann Wolverton | EPA |
| Diana Wong | EPA |
| Tracey Woodruff | University of California San Francisco Program on Reproductive Health and the Environment |
| June Yan | Corteva Agriscience |
| Suzanne Yohannan | IWP News |

**Materials Cited:**

All meeting materials are available on the SAB website (http://www.epa.gov/sab) at the page for the June 23-24, 2020 meeting. The direct web link is: https://yosemite.epa.gov/sab/sabproduct.nsf/a84bfee16cc358ad85256ccd006b0b4b/2c671de30d06e7d7852585750056209a!OpenDocument&Date=2020-06-24

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[1] SAB Roster

[2] SAB Chemical Assessment Advisory Committee Roster

[3] Agenda

[4] Review of the All Ages Lead Model External Review Draft 2.0

[5] SAB Technical Review of EPA's Computable General Equilibrium Model, SAGE

[6] Registered Public Speakers

[7] Charge for Consolidated Human Toxicity Assessment Guideline Design and Development

[8] EPA Presentation - Update and Consolidation of EPA Human Toxicity Assessment Guidelines. Mr. David Dunlap, Dr. David Bussard, and Dr. Michael Firestone

[9] Presentations for the Consultation on New Approach Methods and Reducing the Use of Laboratory Animals for Chronic and Carcinogenicity Testing

[10] Charge for New Approach Methods and Reducing the Use of Laboratory Animals for Chronic and Carcinogenicity Testing