

**Summary Minutes of the
U.S. Environmental Protection Agency (EPA)
Science Advisory Board (SAB)
Polycyclic Aromatic Hydrocarbon (PAH) Mixtures Review Panel
Public Meeting of June 21-23, 2010**

Date and Time: Monday, June 21, 2010, 9:00 AM – 5:00 PM ET; Tuesday, June 22, 2010, 9:00 AM – 3:45 PM; Wednesday, June 23, 2010, 8:30 AM – 2:00 PM

Location: Washington Marriott at Metro Center, 775 12th Street, N.W., Washington, D.C. 20005

Purpose: The purpose of the meeting was to conduct a review of EPA's draft technical document, *Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures*.

Participants: PAH Mixtures Review Panel (for full roster, see Attachment A)

Dr. Nancy Kim, Chair
Dr. Shantu Amin
Dr. Frederick Beland
Dr. James Chen
Dr. John DiGiovanni
Dr. Marilie Gammon
Dr. David Gaylor
Dr. Nicholas Geacintov
Dr. Chris Gennings
Dr. Joshua Hamilton
Dr. Edmond LaVoie
Dr. Aramandla Ramesh
Dr. Benjamin Rybicki
Dr. Paul Strickland
Dr. Emanuela Taioli

Mr. Aaron Yeow, Designated Federal Officer (DFO)
Dr. Vanessa Vu, Director, EPA Science Advisory Board Staff Office
Ms. Becki Clark, EPA Office of Research and Development (ORD)
Dr. Lynn Flowers, EPA Office of Research and Development (ORD)
Dr. Stephen Nesnow, EPA Office of Research and Development (ORD)
Other Attendees (See Attachment B)

Monday, June 21, 2010

Opening Remarks

Mr. Aaron Yeow, the DFO for the PAH Mixtures Review Panel, opened the meeting. He noted that as required under the Federal Advisory Committee Act (FACA), the Committee's deliberations are held in public with advanced notice given in the Federal Register¹, and the meeting minutes will be made publicly available after the meeting. He noted that the Panel received four requests from the public to present oral comments. In addition, there were two separate mechanisms for providing written public comments – submissions to the EPA public docket and submissions directly to the SAB Staff Office. The Panel members have been provided with the written public comments submitted to EPA's public docket as well as the written public comments submitted directly to the SAB Staff Office. These are also available on the SAB website. He also noted that the Panel members are all subject to federal ethics regulations and conflict-of-interest laws that pertain to them. He then turned the meeting over to Dr. Vanessa Vu, the Director of the SAB Staff Office and then to Dr. Nancy Kim, Chair of the PAH Mixtures Review Panel.

Dr. Vanessa Vu welcomed everyone to the public meeting of the SAB PAH Mixtures Review Panel. She thanked the members of the Panel for their participation in this meeting and for their public service. She stated that she is looking forward to the discussions and deliberations over the next few days. She then turned the meeting over to Dr. Nancy Kim.

Dr. Nancy Kim, Chair of the PAH Mixtures Review Panel, welcomed everyone and indicated that the purpose of the meeting was to provide advice on the Agency's draft technical document, *Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures*. She reviewed the Agenda for the meeting², and had the members of the Panel introduce themselves. She then introduced Ms. Becki Clark from EPA's Office of Research and Development for her opening remarks.

Ms. Becki Clark, Acting Director of EPA's National Center for Environmental Assessment (NCEA) stressed the importance of PAHs due to their widespread existence and widespread exposures to them. She indicated that the draft technical document under review is an update to the currently used approach, which was developed in 1993. She noted that the Integrated Risk Information System (IRIS) reassessment for benzo[a]pyrene (BaP) is ongoing and is on a parallel track to this draft technical document. She stated that external peer review is important to EPA and that she is looking forward to the Panel's review.

Public Comments

Dr. Annette Rohr, from the Electric Power Research Institute (EPRI), was on the phone and provided her oral statement³. She indicated that EPRI has also submitted written comments to the Panel and that she hoped that the Panel had a chance to review them. She indicated that EPRI had concerns with the weight of evidence evaluation performed in the document, that EPA has derived RPFs for many PAHs based on an outdated cancer slope factor (CSF) for BaP, that

EPA had not validated any of the RPFs, and that EPA did not adequately assess the data quality of the studies used in the RPF derivation. The Panel did not have any questions for Dr. Rohr.

Dr. Anne LeHuray, from the Pavement Coatings Technology Council, presented her oral comments with slides⁴, and stressed that the draft document did not provide sufficient scientific data or quantitative data to support the hypothesis of similar modes of action of the PAHs, that all studies with pertinent PAH toxicological data should be included, and that RPFs from non-cancer endpoints should not be calculated. The Panel did not have any questions for Dr. LeHuray.

Dr. Kimberly Wise, from the American Petroleum Institute (API), presented her oral comments with slides⁵, and stressed that EPA did not perform a weight of evidence evaluation as called for in EPA's 2005 Cancer Guidelines, that the scientific evidence did not support that all PAHs act via a mutagenic mode of action, and that EPA provided little information in support of the dose additivity assumption. The Panel did not have any questions for Dr. Wise.

Mr. Matthew Forister, from the Association of American Railroads (AAR) presented his oral comments with slides⁶, and stressed that EPA should derive RPFs separately for each route of exposure, that the RPF approach should not use the highest average RPFs from multiple target organs, that the approach did not provide criteria for defining a "good fit" of the data, and that RPFs for any PAH that received a low confidence or very low confidence rating should not be finalized. The Panel did not have any questions for Mr. Forister.

With no further questions from the Panel for the public commenters, Dr. Kim proceeded with asking certain panel members to lead the discussion of responding to the charge to the Panel⁷.

Charge Questions 2 and 3 – Rationale for Recommending an RPF Approach and Previous RPF Approaches

There was general agreement among the Panel members that BaP was the most appropriate PAH to use as an index chemical for the RPF approach. There was also general agreement that EPA's two assumptions underpinning the RPF approach, that the PAHs had a similar mode of action and that interactions did not occur, were not adequately justified. The Panel members overall did not like the RPF approach and believed that the more scientifically justified approach is a whole mixtures approach, but recognized that the data are not currently available for that type of approach. It was recommended that a reference set of complex mixtures be developed and that this reference set undergo bioassay testing.

The Panel acknowledged that although the RPF approach has its shortcomings and limitations, it is a practical approach that the Agency should continue using, given the current state of the data, but that this should be done in parallel with developing a whole mixtures approach. Some members of the Panel did not think that the assumption of having a common mode of action was necessary for using an RPF approach for PAHs and recommended inclusion of more PAHs if appropriate data for developing a RPF were available.

The Panel generally believed that chapter 3 of the document adequately summarized the previous RPF approaches, but that it could be improved by providing more quantitative information.

Charge Question 4 – Evaluation of the Carcinogenicity of Individual PAHs

Some of the Panel members thought that the list of 74 PAHs were reasonable and that the literature search seemed complete. One additional data source mentioned was the recent IARC monograph on PAHs.

Some Panel members thought that excluding studies where BaP was not tested concurrently was acceptable to reduce data comparability concerns across labs and time. Other members were concerned with the possibility that good data might have been not considered due to this. One suggestion was for EPA to explore the possibility of a daisy-chain approach, where if PAH A were tested concurrently with PAH B, and PAH B were tested concurrently with BaP, then an RPF could be generated for PAH A, even though it was not tested concurrently with BaP.

The Panel had concerns with some of the studies that were included in the approach that only had single dose data. There was also discussion about the Agency's decision to only include studies which had statistical significance. Some members did not agree with excluding studies that did not have statistical significance. There was also a suggestion that quality scores should be assigned to individual studies.

Charge Questions 5 and 9 – Methods for Dose Response Assessment and RPF Calculations and Appendices

There was general agreement among the Panel members that using the benchmark dose (BMD) estimate rather than the lower confidence limit on the benchmark dose (BMDL) was preferred for this RPF approach and that other alternative approaches were not necessary.

The Panel members agreed with the Agency's use of study-specific dose-response data. The Panel believed that this eliminated cross-study effects.

There were concerns about using high response levels to calculate RPFs in single dose studies. There was the suggestion to model single dose data rather than using a point estimate. There was also a concern about combining quantal data and continuous data in RPF calculations.

The Panel members found the Appendices to be generally useful for verifying the RPF calculations, but had several suggestions for improving the organization of the data. They also noted inconsistencies in the BMD software output, which were based on BMDLs rather than on BMDs, which were used in the RPF calculations.

Charge Question 6 – Selection of PAHs for Inclusion in the RPF Approach

There was considerable discussion regarding the need for an assessment of the quality of individual studies in the approach. Some members thought that it would be useful to quantitatively capture study quality, such as through a weighted score. Members did not think

that additional structure-activity relationship information could contribute further to the weight-of-evidence evaluation. The members did not find the discussion of RPF detection limits to be clear and recommended that the document have a better explanation of what the RPF detection limit is and how it is used. It was suggested that the graphical arrays of the calculated RPFs could be better presented as point estimates with confidence limits rather than as bar graphs.

The Panel was a little bit ahead of schedule and decided to proceed to discuss charge question 7.

Charge Question 7 – Derivation of RPFs for Selected PAHs

The Panel members strongly believed that only cancer bioassay data should be used to calculate RPFs and that an RPF should not be calculated for dibenz[a,c]anthracene (which only has cancer-related endpoint data). Some members noted an inconsistent use of cancer-related endpoint data in the document. The Panel did not identify any data that would support the development of route- or target organ-specific RPFs. The Panel generally found it appropriate to assign an RPF of zero, but wanted a description of the study quality supporting that calculation. The Panel had some concerns about the confidence ratings and would prefer statements of confidence of the individual studies as opposed to one for all the studies combined.

The panel recessed for the day at 5:00 pm ET.

Tuesday, June 22, 2010

The Panel was reconvened at 9:00 am ET and the Panel proceeded to discuss their responses to the remaining charge questions.

Charge Question 8 – Uncertainties and Limitations

Several Panel members thought that the biggest uncertainty in the whole approach was the cancer slope factor for BaP. The Panel spent some time reviewing the validation effort contained in the public comments submitted by Dr. Rohr from the Electric Power Research Institute (EPRI)⁸. Several members recommended that EPA should include some sort of validation of the approach in the document.

Charge Question 1 – General Charge Questions

The Panel generally found that the document was well-written, clear, and concise. However, the Panel thought that the document was incomplete. The Panel members thought that EPA generally synthesized the evidence on hand well, but have identified areas where further data are needed. The Panel did not believe that the document did a good job describing how the RPF approach will be used in risk assessments.

Materials Cited

The following meeting materials are available on the SAB website: <http://www.epa.gov/sab>, at the [June 21-23, 2010 PAH Mixtures Review Panel Meeting page](#):

¹ Federal Register Notice Announcing the Meeting

² Agenda for June 21-23, 2010 Public Meeting

³ Oral Statement by Dr. Annette Rohr, Electric Power Research Institute (EPRI)

⁴ Oral Statement by Dr. Anne LeHuray, Pavement Coatings Technology Council (PCTC)

⁵ Oral Statement by Dr. Kimberly Wise, American Petroleum Institute (API)

⁶ Oral Statement by Mr. Matthew Forister, Association of American Railroads (AAR)

⁷ Charge to the Polycyclic Aromatic Hydrocarbon (PAH) Mixtures Review Panel

⁸ Public Comments Submitted by Dr. Annette Rohr, Electric Power Research Institute (EPRI)

ATTACHMENT A - ROSTER

U.S. Environmental Protection Agency Science Advisory Board Polycyclic Aromatic Hydrocarbon (PAH) Mixtures Review Panel

CHAIR

Dr. Nancy K. Kim, Senior Executive, New York State Department of Health, Troy, NY

MEMBERS

Dr. Shantu Amin, Professor, Department of Pharmacology, Penn State Hershey Cancer Institute, Penn State College of Medicine, Hershey, PA

Dr. Frederick Beland, Director, Division of Biochemical Toxicology, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, AR

Dr. James Chen, Senior Biomedical Research Service/Senior Mathematical Statistician, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, AR

Dr. John DiGiovanni, Professor and Coulter R. Sublett Chair in Pharmacy, Division of Pharmacology and Toxicology and Department of Nutritional Sciences, Dell Pediatric Research Institute, The University of Texas at Austin, Austin, TX

Dr. Marilie Gammon, Professor, Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC

Dr. David Gaylor, President, Gaylor and Associates, LLC, Eureka Springs, AR

Dr. Nicholas Geacintov, Professor, Chemistry, New York University, New York, NY

Dr. Chris Gennings, Professor, Department of Biostatistics, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA

Dr. Joshua Hamilton, Chief Academic and Scientific Officer; Senior Scientist, Bay Paul Center for Comparative Molecular Biology and Evolution, Marine Biological Laboratory (MBL), Woods Hole, MA

Dr. Edmond LaVoie, Professor and Chair, Department of Pharmaceutical Chemistry, College of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ

Dr. Aramandla Ramesh, Assistant Professor, Biochemistry and Cancer Biology, School of Medicine, Meharry Medical College, Nashville, TN

Dr. Benjamin Rybicki, Senior Scientist, Department of Research
Epidemiology and Biostatistics, Henry Ford Hospital, Detroit, MI

Dr. Paul Strickland, Professor, Environmental Health Sciences, Bloomberg School of Public
Health, Johns Hopkins University, Baltimore, MD

Dr. Emanuela Taioli, Professor, Department of Epidemiology and Biostatistics, School of
Public Health, State University of New York (SUNY) Downstate Medical Center, Brooklyn, NY

SCIENCE ADVISORY BOARD STAFF

Mr. Aaron Yeow, Designated Federal Officer, U.S. Environmental Protection Agency,
Washington, DC

ATTACHMENT B – Other Attendees
SAB PAH Mixtures Review Panel Public Meeting

June 21, 2010

Name	Affiliation
Beck, Nancy	OMB
Birchfield, Norman	EPA
Carlson-Lynch, Heather	Syracuse Research Corporation (SRC)
DiCosmo, Bridget	Inside EPA
Forister, Matthew	Association of American Railroads (AAR)
Goyak, Katy	Exxon Mobile
Gelhaus, Martin	EPA
Kadry, Abdel	EPA
Keshava, Channa	EPA
Kurtz, Katherine*	Navy
Lehuray, Anne	Pavement Coatings Technology Council
Newhouse, Kathleen	EPA
Rhazi, Nadia	GAO
Rice, Glenn	EPA
Rohr, Annette*	Electric Power Research Institute (EPRI)
Stickney, Julie	Syracuse Research Corporation (SRC)
Strong, Jamie	EPA
Teuschler, Linda	EPA
Walker, Tereille	EPA
Wise, Kimberly	American Petroleum Institute (API)

June 22, 2010

Name	Affiliation
Birchfield, Norman	EPA
Carlson-Lynch, Heather	Syracuse Research Corporation (SRC)
Dannan, Ghazi	EPA
DiCosmo, Bridget	Inside EPA
Gelhaus, Martin	EPA
Kurtz, Katherine*	Navy
Lehuray, Anne	Pavement Coatings Technology Council
Rice, Glenn	EPA
Rohr, Annette*	Electric Power Research Institute (EPRI)
Teuschler, Linda	EPA

*Participated via teleconference

June 23, 2010

Name

Carlson-Lynch, Heather
DiCosmo, Bridget
Gelhaus, Martin
Kurtz, Katherine*
Lehuray, Anne
Rhazi, Nadia
Rice, Glenn
Rohr, Annette*
Teuschler, Linda

Affiliation

Syracuse Research Corporation (SRC)
Inside EPA
EPA
Navy
Pavement Coatings Technology Council
GAO
EPA
Electric Power Research Institute (EPRI)
EPA

*Participated via teleconference