

Meeting Summary

National Toxicology Program
Board Of Scientific Counselors'
Ad Hoc Working Group To Review The Criteria
For Listing Substances In The Biennial Report On Carcinogens

Washington Hilton and Towers Hotel, Washington, D.C.
April 24 & 25, 1995,

Background

The Biennial Report on Carcinogens is prepared in response to Section 301 (b) (4) of the Public Health Service Act which stipulates that the Secretary of the Department of Health and Human Services shall publish a report which contains a list of all substances (i) which either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens; and (ii) to which a significant number of persons residing in the United States are exposed. This responsibility has been delegated by the Secretary to the Director, National Toxicology Program (NTP). Dr. Ken Olden, Director of the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program, has initiated a review of the BRC to broaden input to its preparation, broaden the scope of scientific review associated with the Report, and provide review of the criteria used for inclusion of substances in the BRC.

An ad hoc working group of the NTP Board of Scientific Counselors was established to receive public comments on the existing criteria and review and make recommendations on the criteria for listing substances in the BRC. This ad hoc working group had a balance of expertise and views and included representatives from Academia; Industry; Labor; Federal, State and Local Agencies; and Private Organizations. The working group reviewed the criteria in an open, public meeting in Washington, D.C. on April 24 & 25, 1995.

Meeting Summary

The ad hoc working group was chaired by NTP Board of Scientific Counselors member Dr. Arnold Brown of the University of Wisconsin. The meeting agenda and roster of ad hoc Working Group members and the makeup of the three breakout groups is Attachment 3. The working group was divided into three breakout groups to allow for a more in depth discussion of the criteria and the public comments received. Each of the breakout groups were asked to address the following issues in their review of the criteria:

a) The adequacy of existing criteria for listing substances in future Reports; and

b) The incorporation of mechanistic data as part of the criteria for listing substances in future Reports that may include the consideration of sensitive sub-populations as well as procedures to upgrade or downgrade the evaluation of the results of animal bioassay or epidemiology studies.

Plenary Session I was chaired by Dr. George Lucier, Director, Environmental Toxicology Program, NIEHS/NTP and allowed for opening and background presentations by Dr. Kenneth Olden, Director, NIEHS and NTP, Dr. C. W. Jameson, NIEHS/NTP, and Dr. Marilyn Wind, CPSC (NTP Executive Committee BRC Working Group representative). Dr. Lucier then gave the charge to the ad hoc working group to address the two issues outlined above in their review of the criteria and identify areas of consensus, areas of debate, and the knowledge gaps that create the debate. Dr. Lucier then turned the meeting over to Dr. Brown.

Plenary Session II was devoted to the presentation of public comments concerning the BRC criteria. Written comments had been received from the following individuals/organizations and distributed to the ad hoc Working Group prior to the meeting:

North American Insulation Manufacturers Association
Chlorobenzene Producers Association
Dr. Stephen DeVito, US EPA
Dr. E. E. McConnell

Public comments were made during Plenary Session II by the following individuals:

Dr. Charles Axten -	NAIMA
Dr. Nathan Karch -	Karch & Associates
Dr. Matthew Bogdanffy -	Haskell Laboratory
Dr. James Sherman -	Chlorobenzene Producers Association
Dr. Myra Karstadt -	Center for Science in the Public Interest
Dr. Frank Mirer -	United Auto Workers
Dr. E. E. McConnell -	Private Consultant

Comments made during the public comment period ranged from recommending retention of the current criteria with no change, to revising the existing criteria to require the incorporation of available mechanistic data. (A copy of the written public statements provided by the above listed individuals is available upon written request to the NTP Liaison Office, NIEHS, P.O. Box 12233, MD A3-01,

Research triangle Park, NC 27709-2233). Following the public comment session, Dr. Brown directed that each breakout group was to meet individually and, based on the charge given to the ad hoc Working Group by Dr. Lucier, address the BRC criteria.

Upon completion of the discussions of the three breakout groups, the full ad hoc Working Group reconvened in the final Plenary III session. Each breakout group made a report on their deliberations and recommendations. The final report from each breakout group can be found as Attachment 4 of this summary.

Each breakout group had addressed the two issues outlined in the charge given by Dr. Lucier. Breakout group 1 stated in their report that the existing criteria were found not to be adequate and suggested revision of the criteria to include use of available mechanistic data that is relevant for improving hazard identification. The report from breakout group 2 stated there was unanimity from their members that the criteria should be updated and that mechanistic data should be utilized in the listing process. Group 2 recommended significant revisions to the existing criteria including the incorporation of additional listing categories. Breakout group 3 report stated that their members were of the general consensus that the current criteria are adequate for the stated purpose of the BRC, however minor revisions and clarifications to the existing criteria were considered to be appropriate. In summary, it was the recommendation of breakout groups 1 & 3 that the existing two categories of the current criteria for listing substances in the BRC should remain with revisions to category 2 to allow for all scientific evidence to be considered. This will allow for the best scientific judgment to be used in consideration of substances for listing in the BRC. Breakout group 2 recommended a more significant expansion of the current criteria which included the incorporation of additional listing categories of "presumptive evidence of carcinogenic activity" and "laboratory animal carcinogen presumed not to be a human carcinogen".

Based on the reports from the three breakout groups and the ensuing discussions during the final plenary session of the entire ad hoc Working Group, the NIEHS/NTP determined that, while there was not complete agreement concerning the adequacy of the current criteria for listing substances in the BRC, it was the general consensus of the entire ad hoc Working Group that the existing criteria should be revised and clarified. The recommended revisions are to permit consideration of more mechanistic information in listing substances in the BRC. As indicated in the three breakout group reports, the area of debate was how extensive the modifications should be. The discussions during Plenary Session III indicated that the majority of the ad hoc Working Group members felt the revised criteria should maintain the current 2 categories with revisions to assure that all scientific evidence is considered to allow for the best scientific judgment. It was also apparent from these discussions that there was consensus that the BRC is a hazard identification document and not to be used as a quantitative risk

assessment for the listed substances. It is based on these considerations and recommendations that the NIEHS/NTP has proposed revised criteria for listing substances in the BRC. The proposed revised criteria are attached to this summary report as Attachment 2. These proposed revisions are consistent with the discussion and recommendations of the majority of the ad hoc Working Group and the current legislation regarding the Biennial Report on Carcinogens. These proposed revised criteria will be available to the public for review and comment and presented to the NTP Board of Scientific Counselors at their June 29, 1995, meeting. The Board will review the report and recommendations; receive public comment on the report; and develop Board recommendations concerning the selection criteria. Further review will include the PHS Environmental Health Policy Committee and the NTP Executive Committee.

The ad hoc Working Group made several additional general recommendations concerning the Biennial Report on Carcinogens. These included recommending that a formal mechanism be established for the re-evaluation of substances previously listed in the BRC to determine if listing is still warranted. As a result of this recommendation, the NTP will evaluate the current procedures for de-listing a substance and, if necessary, revise it. It was also recommended by the Working Group that the NTP should stimulate discussion (e.g., workshops, discussion papers) on the use of mechanistic data in hazard identification. The recent NTP workshop on "Mechanism-Based Toxicology in Cancer Risk Assessment: Implications for Research, Regulation and Legislation" held January 11-13, 1995, and the upcoming Workshop on Validation and Regulatory Acceptance of Alternative Test Methods" planned for October 30-November 1, 1995 are examples of how this recommendation will be acted upon. The NTP plans to continue these types of activities in the future.

ATTACHMENT 1

CURRENT BRC CRITERIA

For the purpose of the BRC, the degrees of evidence are as follows:

1. Known To Be Carcinogens:

There is sufficient evidence of carcinogenicity from studies in humans that indicates a causal relationship between the agent and human cancer.

2. Reasonably Anticipated To Be Carcinogens:

a. There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded, or

b. There is sufficient evidence of carcinogenicity from studies in experimental animals that indicates that there is an increased incidence of malignant tumors: (a) in multiple species or strains, or (b) in multiple experiments (preferably with different routes of administration or using different dose levels), or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset. Additional evidence may be provided by data concerning dose-response effects, as well as information on mutagenicity or chemical structure.

ATTACHMENT 2

Proposed Revised BRC Criteria

For the purpose of the BRC, the degrees of evidence are as follows:

1. **Known to be Human Carcinogens:**
There is sufficient evidence of carcinogenicity from studies in humans that indicates a causal relationship between the substance and human cancer.

2. **Reasonably Anticipated to be Human Carcinogens:**
 - a. There is limited evidence of carcinogenicity from studies in humans which indicate that causal interpretation is credible but that alternative explanations such as chance, bias or confounding could not adequately be excluded, or

 - b. There is sufficient evidence of carcinogenicity from studies in experimental animals that indicates there is an increased incidence of malignant and/or combined benign and malignant tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor or age at onset.

Conclusions regarding carcinogenicity in humans or experimental animals should be based on scientific judgment. Consideration may be given to relevant information on dose response, route of exposure, chemical structure, sensitive sub populations, genetic effects or other data relating to mechanism of action, and/or factors that may be unique to a given substance. There may be substances for which there is less than sufficient evidence of carcinogenicity in humans or laboratory animals but for which there are compelling data indicating that the substance could reasonably be anticipated to cause cancer in humans. Conversely, there may be substances for which there is sufficient evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore reasonably be anticipated not to cause cancer in humans.

5/24/95

ATTACHMENT 3

Meeting Agenda
ad hoc Working Group Roster
Breakout Group Member List

MEETING AGENDA

**National Toxicology Program
Board Of Scientific Counselors'
Ad Hoc Working Group for the
Review of the Criteria for Listing Substances in
The Biennial Report On Carcinogens**

**Washington Hilton and Towers Hotel
1919 Connecticut Avenue N.W.
Washington, D.C.**

April 24 & 25, 1995

Sunday, April 23, 1995

- 6:00 - 8:00 PM **Registration**
Terrace Level Lobby
- 8:00 - 9:00 PM **Meeting of ad hoc Working Group Chair, Breakout
Chairs, Rapporteurs, and Facilitators with NTP Staff**
Kalorama Room, Terrace Level

Monday, April 24, 1995

- 8:00 - 9:00 AM **Public Registration for ad hoc Working Group Meeting**
Jefferson Room, Concourse Corridor
- 8:00 - 9:00 AM **Registration of ad hoc Working Group Members**
Concourse Level Lobby
- Plenary Session I:** Jefferson Room, Concourse Level
Dr. George Lucier; Director, Environmental Toxicology Program,
NIEHS/NTP
Chair of Session I
- 9:00 - 9:10 **Opening Remarks:**
Dr. Kenneth Olden; Director, NIEHS/NTP
- 9:10 - 9:40 **Background of the Biennial Report on Carcinogens:**
Dr. C. W. Jameson, Environmental Toxicology Program, NIEHS/NTP
- 9:40 - 10:00 **NTP Executive Committee's BRC Working Group Perspective:**
Dr. Marilyn Wind, Director, Division of Poison Prevention & Scientific
Coordination, CPSC
- 10:00 - 10:15 **Charge to the Working Group**
Dr. Lucier
- 10:15 - 10:45 **Break**

Monday, April 24, 1995 (Continued)

Plenary Session II: Jefferson Room, Concourse Level
Dr. Arnold Brown; University of Wisconsin
Chairman, ad hoc Working Group

10:45 - 12:30 Public Comment

Dr. Charles W. Axten -	NAIMA
Dr. Nathan J. Karch -	Karch & Associates
Dr. Matthew S. Bogdanffy -	Haskell Laboratory
Dr. James Sherman -	Chlorobenzene Producers Association
Dr. Myra Karstadt -	Center for Science in the Public Interest
Dr. Frank Mirer -	United Auto Workers
Dr. E. E. McConnell -	Private Consultant

12:30 - 1:30 Lunch

Breakout Session I

1:30 - 5:30 Breakout Groups Convene

Dr. Arnold Brown; University of Wisconsin
Chairman, ad hoc Working Group

Breakout Group 1: State Room, Terrace Level

Chair:	Dr. Harry Vainio, Institute of Occupational Health, Finland
Rapporteur:	Dr. Thomas Goldsworthy, CIIT
Facilitator:	Dr. Bryan Hardin, NIOSH

Breakout Group 2: Caucus Room, Terrace Level

Chair:	Dr. Thomas Slaga, M.D. Anderson Cancer Center
Rapporteur:	Dr. Lauren Zeise, State of California EPA
Facilitator:	Dr. William Allaben, NCTR

Breakout Group 3: Conservatory Room, Terrace Level

Chair:	Dr. Norman Drinkwater, McArdle Laboratory
Rapporteur:	Dr. John Dement, Duke University
Facilitator:	Dr. Jean Parker, EPA

5:30 Adjourn for the Day

5:30 - 6:30 Meeting of ad hoc Working Group Chair, Breakout Chairs,
Rapporteurs, and Facilitators with NTP Staff
Conservatory Room, Terrace Level

Tuesday, April 25, 1995

Breakout Session II

9:00 - 12:00 Breakout Groups Reconvene

Breakout Group 1: State Room, Terrace Level

Chair: Dr. Harry Vainio,
Institute of Occupational Health, Finland

Rapporteur: Dr. Thomas Goldsworthy, CIIT

Facilitator: Dr. Bryan Hardin, NIOSH

Breakout Group 2: Caucus Room, Terrace Level

Chair: Dr. Thomas Slaga,
M.D. Anderson Cancer Center

Rapporteur: Dr. Lauren Zeise, State of California EPA

Facilitator: Dr. William Allaben, NCTR

Breakout Group 3: Conservatory Room, Terrace Level

Chair: Dr. Norman Drinkwater, McArdle Laboratory

Rapporteur: Dr. John Dement, Duke University

Facilitator: Dr. Jean Parker, EPA

12:00 PM Breakout Groups Adjourn

12:00 - 1:00 Lunch

Plenary Session III: Jefferson Room, Concourse Level
Dr. Arnold Brown; University of Wisconsin
Chairman, ad hoc Working Group

1:00 - 1:30 Report from Breakout Group 1
Dr. Dr. Harry Vainio, Institute of Occupational Health, Finland

1:30 - 2:00 Report from Breakout Group 2
Dr. Thomas Slaga, M.D. Anderson Cancer Center

2:00 - 2:30 Report from Breakout Group 3
Dr. Norman Drinkwater, McArdle Laboratory

2:30 - 3:00 Break

3:00 - 4:20 Final Discussions and Recommendations

4:20 - 4:30 Closing Remarks
Dr. Kenneth Olden; Director, NIEHS/NTP

4:30 PM ad hoc Working Group Adjourns

**National Toxicology Program
Board Of Scientific Counselors'
Ad Hoc Working Group for the
Review of the Criteria for Listing Substances in
The Biennial Report On Carcinogens**

LIST OF AD HOC WORKING GROUP MEMBERS

NTP Board Members

Dr. Arnold Brown	University of Wisconsin Medical School
Dr. Thomas Goldsworthy	Chemical Industry Institute of Toxicology
Dr. Franklin Mirer	International Union, UAW
Dr. Jerry Ward	National Cancer Institute
Dr. Hiroshi Yamasaki	IARC

Academia

Dr. Eula Bingham (absent)	Univ. of Cincinnati
Dr. John Dement	Duke University Medical Center
Dr. Norman Drinkwater	McArdle Laboratory , Univ. of Wisconsin
Dr. Kathleen Dixon	Univ. of Cincinnati, Dept. of Environ. Health
Dr. Karen Medville	Cornell University
Dr. Gunter Oberdorster	Univ. of Rochester, Dept. Env. Medicine
Dr. Regina Santella	Columbia University, Dept. Environ. Sciences
Dr. Thomas Slaga	Univ. of Texas, M.D. Anderson Cancer Center
Dr. Rafael Moure	University of Massachusetts / Lowell
Dr. Bailus Walker	Howard University
Dr. Cheryl Walker	Univ. of Texas, M.D. Anderson Cancer Center

Industry

Dr. Gerard Egan	Exxon Biomedical Sciences Inc.
Dr. Clay Frederick	Rohm & Haas
Dr. Judith MacGregor	Toxicology Consulting Services
Dr. Roger McClellan	Chemical Industry Institute of Toxicology
Dr. Larry Roslinski	Ford Motor Company
Dr. Donald Stevenson	Former Director of Toxicology, Shell Oil Co.

Labor

Dr. James Melius
Mr. Sheldon Samuels

Center to Protect Workers' Rights
Workplace Health Fund

Public/Environmental Groups and Environmental Justice Organizations

Dr. Sidney Wolfe
Dr. Ellen Silbergeld
Dr. Janet Phoenix

Public Citizens Group, Washington, DC
Environmental Defense Fund and the U of MD
Environmental Health Center, Washington, DC

State and Local Health Departments

Dr. Beth Mileson
Dr. Lauren Zeise

NC State Department of Health
State of California EPA

Carcinogenesis Experts

Dr. Resha Putzrath
Dr. Thomas Sinks
Dr. David Rall
Dr. Lorenzo Tomatis(absent)
Dr. Harri Vainio

Georgetown Risk Group, Washington, DC
Nat'l Center for Env. Health, CDC
Asst. Surgeon General, USPHS (Ret.)
Former Director, IARC
Institute of Occupational Health, Finland

NTP Executive Committee Representatives

ATSDR	-	Ms. Yee Wan Stevens
CPSC	-	Dr. Marilyn Wind
EPA/ORD	-	Dr. Jean Parker
EPA/OPPTS	-	Dr. Vanessa Vu
FDA/NCTR	-	Dr. Bill Allaben
NCI	-	Dr. David Longfellow
NIEHS	-	Dr. Carl Barrett
NIOSH	-	Dr. Bryan Hardin
OSHA	-	Dr. Loretta Schuman

NIEHS / NTP Staff

Dr. Kenneth Olden,	Director, NIEHS and NTP
Dr. George Lucier,	Director, Environmental Toxicology Program,
Dr. Bill Jameson,	Executive Secretary for the ad hoc Working Group
Dr. John Bucher,	Chief Toxicology Branch, ETP,
Ms. Sandy Lange,	Director, NTP Liaison Office
Mr. Dan VanderMeer,	Director, Office of Program Planning and Evaluation

**Breakout Groups of
National Toxicology Program (NTP)
Board Of Scientific Counselors'
Ad Hoc Working Group for the
Review of the Criteria for Listing Substances in
The Biennial Report On Carcinogens (BRC)**

Overall ad hoc Working Group Chair: Dr. Arnold Brown

	<u>Breakout 1</u>	<u>Breakout 2</u>	<u>Breakout 3</u>
Chair:	Dr. Eula Bingham (absent) Dr. Harry Vainio (acting)	Dr. Thomas Slaga	Dr. Norman Drinkwater
Rapporteur:	Dr. Thomas Goldsworthy	Dr. Lauren Zeise	Dr. John Dement
Facilitator:	Dr. Bryan Hardin	Dr. Bill Allaben	Dr. Jean Parker
	Dr. James Melius	Dr. Kathleen Dixon	Dr. Carl Barrett
	Dr. Rafael Moure	Dr. David Longfellow	Dr. Gerard Egan
	Dr. Resha Putzrath	Dr. Judith MacGregor	Dr. Clay Frederick
	Dr. Ellen Silbergeld	Dr. Roger McClellan	Dr. Karen Medville
	Dr. Donald Stevenson	Dr. Gunter Oberdorster	Dr. Beth Mileson
	Dr. Vanessa Vu	Dr. David Rall	Dr. Franklin Mirer
	Dr. Cheryl Walker	Dr. Larry Roslinski	Dr. Janet Phoenix
	Dr. Jerry Ward	Mr. Sheldon Samuels	Dr. Regina Santella
	Dr. Marilyn Wind	Ms. Yee Wan Stevens	Dr. Loretta Schuman
	Dr. Sidney Wolfe	Dr. Bailus Walker	Dr. Thomas Sinks
		Dr. Hiroshi Yamasaki	Dr. Lorenzo Tomatis(absent)

ATTACHMENT 4

Final Reports from the Three Breakout Groups