DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Toxicology Program (NTP) Proposed Revised Criteria for Listing Substances in the Biennial Report on Carcinogens (BRC) and Notice of Meeting of the NTP Board of Scientific Counselors

Background

A public meeting of the NTP Board of Scientific Counselors' ad hoc Working Group to Review the Criteria for Listing Substances in the Biennial Report on Carcinogens (BRC) was held on April 24 and 25, 1995, at the Washington Hilton and Towers Hotel, 1919 Connecticut Avenue NW., Washington DC. The purpose of the meeting was to receive public comments on the current criteria for listing substances in the BRC, and to review and make recommendations on these criteria. The issues addressed by this ad hoc group were: (1) The adequacy of existing criteria for listing substances in future Reports; and (2) the incorporation of mechanistic data as part of the criteria for listing substances in future Reports which 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. A background and discussion document prepared by the NTP for use by the ad hoc working group and also for review and comment by the public, is available upon request. Copies of this document can be obtained by contacting the NTP Liaison Office at NIEHS, P.O. Box 12233, Research Triangle Park, NC 27709, or by FAX to (919) 541–0295.

This meeting was the first step in the review of the criteria and was open to the public. The meeting began with a plenary session which provided background on the BRC and a public comment session. The working group then broke into three breakout groups, with each breakout group addressing the same above listed issues. The final session of the meeting was a plenary session at which time each breakout group reported on their deliberations. The chairperson, rapporteur, and facilitator of the three breakout groups completed draft reports of their group's discussions and recommendations and submitted it to the Chairperson of the ad hoc working group. The Chairperson, working with NIEHS/NTP staff, completed a draft summary report of the criteria review meeting which subsequently was sent to all ad hoc working group members for editing and corrections. A copy of the revised summary report is printed below. Also printed below are the current and proposed revised criteria developed by the NIEHS/NTP based on the input of the NTP Board of Scientific Counselors' ad hoc working group.

Action-Request for Public Input on the Proposed Revised Criteria

The NTP seeks comments and views on the proposed revised criteria which follows. Public input concerning the proposed revised criteria for listing a substance in the BRC is important to the review process and is encouraged. A further opportunity for comment will be provided during a meeting of the NTP Board of Scientific Counselors in the NIEHS Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, 111 Alexander Drive, Research Triangle Park, North Carolina, on June 29 , 1995. The primary agenda topic for this meeting concerns the summary report and recommendations of the ad hoc working group of the NTP Board from their review of the criteria for listing substances in the BRC on April 24 and 25, 1995. This meeting is open to the public, and public input concerning the criteria for listing a substance in the Biennial Report on Carcinogens is encouraged. Formal oral comments during the NTP Board meeting will be limited to five minutes to permit maximum participation. Written comments accompanying oral statements are encouraged. To assure consideration by the Board at this meeting, written comments must be submitted to Dr. Larry G. Hart, Executive Secretary for the NTP Board of Scientific Counselors and received by June 23, 1995. Registration to attend is not required; however, to ensure adequate seating, we ask that those planning to attend let us know. To register, submit written comments or announce intention to make oral comments on the criteria review report, receive information on the agenda, or be put on the mailing list for summary minutes subsequent to the meeting, please contact: Dr. L. G. Hart, P.O. Box 12233, Research Triangle Park, NC 27709; telephone: (919) 541–3971; FAX: (919) 541–0719.

Dated: May 30, 1995.

Kenneth Olden,

Director, National Toxicology Program.

Attachments

Summary Report of the Meeting of the National Toxicology Program's 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 and 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 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.

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 clairifications 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. 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.

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.

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.

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

Dr. Arnold Brown(Chairman)—University of Wisconsin Medical School
Dr. Bill Allaben—FDA/NCTR
Dr. Carl Barrett—NIEHS
Dr. Eula Bingham—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. Gerard Egan—Exxon Biomedical Sciences Inc.
Dr. Clay Frederick—Rohm & Haas
Dr. Thomas Goldsworthy—Chemical Industry Institute of Toxicology
Dr. Bryan Hardin—NIOSH
Dr. David Longfellow—NCI
Dr. Judith MacGregor—Toxicology Consulting Services
Dr. Roger McClellan—Chemical Industry Institute of Toxicology
Dr. Karen Medville—Cornell University
Dr. James Melius—Center to Protect Workers' Rights
Dr. Beth Mileson—NC State Department of Health
Dr. Franklin Mirer—International Union, UAW
Dr. Rafael Moure—University of Massachusetts / Lowell
Dr. Gunter Oberdorster—Univ. of Rochester, Dept. Env. Medicine
Dr. Jean Parker—EPA/ORD
Dr. Janet Phoenix—Environmental Health Center, Washington, DC
Dr. Resha Putzrath—Georgetown Risk Group, Washington, DC
Dr. David Rall—Asst. Surgeon General, USPHS (Ret.)
Dr. Larry Roslinski—Ford Motor Company
Mr. Sheldon Samuels—Workplace Health Fund
Dr. Regina Santella—Columbia University, Dept. Environ. Sciences
Dr. Loretta Schuman—OSHA
Dr. Ellen Silbergeld—Environmental Defense Fund and the U of MD
Dr. Thomas Sinks—Nat'l Center for Env. Health, CDC
Dr. Thomas Slaga—Univ. of Texas, M.D. Anderson Cancer Center
Ms. Yee Wan—Stevens ATSDR
Dr. Donald Stevenson—Former Director of Toxicology, Shell Oil Co.
Dr. Lorenzo Tomatis—Former Director, IARC
Dr. Harri Vainio—Institute of Occupational Health, Finland
Dr. Vanessa Vu—EPA/OPPTS
Dr. Bailus Walker—Howard University
Dr. Cheryl Walker—Univ. of Texas, M.D. Anderson Cancer Center
Dr. Jerry Ward—National Cancer Institute
Dr. Marilyn Wind—CPSC
Dr. Sidney Wolfe—Public Citizens Group, Washington, DC
Dr. Hiroshi Yamasaki—IARC
Dr. Lauren Zeise—State of California EPA

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