NATIONAL TOXICOLOGY PROGRAM'S RESPONSE TO PUBLIC COMMENTS AND DISCUSSION ON THE PREPARATION AND REVIEW OF THE REPORT ON CARCINOGENS RECEIVED AT THE JANUARY 27, 2004 PUBLIC MEETING

BACKGROUND

In response to concerns from people within the United States regarding the relationship between their environment and cancer, the U.S. Congress mandated, as part of the Public Health Service Act (Section 301(b)(4), as amended), that the Secretary, Department of Health and Human Services (DHHS), publish a report which contains a list of all substances (1) which either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens, and (2) to which a significant number of persons residing in the United States (US) are exposed. The Secretary delegated responsibility for preparing these reports to the National Toxicology Program (NTP). The NTP is an interagency program within DHHS headquartered at the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health.

The Report on Carcinogens (RoC) is an informational scientific and public health document that identifies and discusses agents, substances, mixtures, or exposure circumstances that may pose a hazard to human health by virtue of their carcinogenicity. It serves as a meaningful and useful compilation of data on (1) the carcinogenicity (ability to cause cancer), genotoxicity (ability to damage genes), and biologic mechanisms (modes of action in the body) of the listed substances in humans and/or in animals, (2) the potential for human exposure to these substances, and (3) Federal regulations to limit exposures. The RoC does not present quantitative assessments of the risks of cancer associated with these substances. Thus listing of substances in the RoC only indicates a potential hazard and does not establish the exposure conditions that would pose cancer risks to individuals in their daily lives. Such formal risk assessments are the responsibility of the appropriate federal, state, and local health regulatory and research agencies.

In 1994, the NTP Director initiated a review of the RoC to 1) broaden input for the preparation of the report, 2) broaden the scope of scientific review associated with the RoC, and 3) provide review of the criteria used for listing substances in the RoC. This review of the criteria was open to the public and included participation by, and input from, many interested parties, including academia, industry, labor, private organizations, and federal, state, and local agencies. In 1996, the Secretary approved the revised criteria, which allow for consideration of all relevant information, including mechanism of action, when making decisions about listing nominations in the RoC, and the NTP Director announced revisions to the process for reviewing nominations for listing in or removal from the RoC. The revised process included: 1) addition of an external peer review that would be conducted by members of the NTP Board of Scientific Counselors in a public forum with opportunity for public comment, 2) opportunities for additional public input throughout the review process, and 3) establishment of a formal review

mechanism for the consideration of removing (delisting) substances from the RoC. The NTP began using the revised process and revised criteria with the 8th Edition of the RoC, which was published in 1998.

During preparation of the 8th and 9th RoCs, the NTP received comments from interested stakeholders on the proposed listings, the listing criteria and the procedures used in review of nominations to the RoC. In response to this input, the NTP held a public meeting in October 1999 to revisit the review process and the listing criteria. The NTP appreciated the input received at this meeting and moved forward with implementing some changes in the review process for preparing future RoCs. The NTP felt that changes in the listing criteria were not needed at that time. The NTP's response to the comments made and the discussions held at that meeting are available on the NTP RoC web site (http://ntp-server.niehs.nih.gov/NewHomeRoc/ResponsePub.html).

NTP PUBLIC MEETING ON THE ROC HELD JANUARY 27, 2004

The NTP has continued to consider public comments received on the review process and listing criteria and has conducted its own internal evaluation of the process used for the review of nominations to the 10th and 11th RoCs. Based upon this input, the NTP has made some revisions to the procedures for preparing background documents and reviewing nominations for future RoCs. The NTP held a public meeting on January 27, 2004, at the Lister Hill Center Auditorium, National Library of Medicine, National Institutes of Health in Bethesda, Maryland, to receive public comment on the current review process and on the current listing criteria used for evaluating those nominations. Dr. Lynn Goldman from the Johns Hopkins Bloomburg School of Public Health in Baltimore, Maryland, chaired the meeting. Assisting Dr. Goldman was a panel whose membership included:

- Two members of the NTP Board of Scientific Counselors who serve on the RoC Subcommittee: Dr. Hillary Carpenter, Minnesota Department of Health, and Dr. Elizabeth Delzell, School of Public Health at the University of Alabama in Birmingham.
- A former member of the NTP Board of Scientific Counselors who served on the RoC Subcommittee: Dr. Rafael Moure-Eraso, University of Massachusetts in Lowell.
- A member of the NTP Executive Committee Review Group for the RoC (RG2): Dr. Mark Toraason, National Institute of Occupational Safety and Health of the Centers for Disease Control and Prevention, Cincinnati, Ohio.

Seven persons registered to speak at the public meeting (Appendix 1) and included representatives from industry, academia, and non-profit organizations.

MODIFICATIONS TO THE ROC NOMINATION REVIEW PROCESS DISCUSSED AT THE PUBLIC MEETING

The NTP outlined the following modifications in the development of background documents beginning with the 12th Edition of the RoC:

- Establishment of the NIEHS/NTP Nomination Committee for the RoC in order to make the initial identification/selection of nominations for review independent of the review process for listing. This committee is comprised of senior NIEHS/NTP staff who review the information provided for each nomination and make a recommendation for either continuing with the preparation of a background document for a formal review or not pursuing the nomination at this time. Previously, the NIEHS/NTP Review Group for the RoC (RG1) evaluated the preliminary information for nominations to the RoC and recommended which nominations should go forward for formal review and have a background document prepared.
- The NTP's increased use of substance-specific experts to write and/or review the background documents on nominations to continue to improve their quality.
- In response to requests for earlier public accessibility of the background documents, the NTP also indicated it would place background documents accepted as the "documents of record" for nominations to the RoC on the NTP web site at least 30 days prior to initiation of the scientific review process for possible listing in or removal from the RoC.

NTP RESPONSE TO PUBLIC COMMENTS

The majority of the comments focused on a more transparent review process and more opportunity for involvement by the public in that process as early and as often as possible. Some comments identified specific suggestions regarding changes, ranging from modifying or adding additional steps to the existing RoC review process to completely revising it. Other comments focused on the role of the NTP Executive Committee in the RoC review process, the revision of background documents, the publication of the RoC, and the listing criteria.

The NTP is committed to maintaining an open and transparent process for preparation of the RoC that is unencumbered by special interest, that is a high-quality, open scientific review of the nominations, that allows stakeholder input at multiple levels, and that uses the best, publicly available, peer-reviewed science. The NTP believes that the process and criteria used for review of nominations to the RoC are basically sound; however, public input did identify some areas where procedural modifications, as noted below, would strengthen the review process, enhance stakeholder involvement, and improve communication. The NTP greatly appreciates the input received from all parties regarding issues of concern and will move forward with making some changes immediately and will continue to consider other recommendations for future implementation.

COMMENTS RELATED TO EARLIER INPUT, GREATER INTERACTION WITH STAKEHOLDERS AND GREATER TRANSPARENCY DURING THE SCIENTIFIC REVIEW PROCESS

COMMENT

There should be a complete revision of the RoC nomination review process to one using the NTP's Center for the Evaluation of Risks to Human Reproduction (CERHR) process as a model (*see* about CERHR, http://cerhr.niehs.nih.gov). The commenter felt that the CERHR process is more open and allows greater input from the public or stakeholders.

(NTP Note: The CERHR process has a single scientific review step that includes preparing a background document on the chemical being reviewed and convening an expert panel that meets in a public forum to assess the scientific evidence on the chemical and reach conclusions regarding its potential as a reproductive and/or developmental hazard for humans. These conclusions are submitted for public comment and used by the NTP in formulating its opinion regarding any potential hazard to humans.)

RESPONSE

The NTP believes that it can achieve the goals of greater transparency, early input by the public, increased interaction with stakeholders, and the greater use of substance-specific experts by making the modifications identified at the meeting (noted above) rather than completely revising the review process. The review process includes an initial Federal Register notice announcing new RoC nominations before the scientific reviews begin. This notice solicits and encourages the public to submit detailed information on the candidate nominations such production, current uses, exposure, and identification of any issues related to the potential carcinogenicity of a substance that should be considered during their review. The NTP requests this information before the formal review process begins, so that the substance-specific expert panel convened for each nomination can consider the comments when drafting or reviewing the nomination's background document.

Greater public participation is also achieved by making the background documents available on the NTP web site at least 30 days before any of the review committees meet to make a listing recommendation, thus allowing the public an opportunity to comment on the background document prior to the beginning of the formal nomination review. All public comments received for a nomination become part of the public record and, when received, are included in its review package. The review package is assembled as a nomination moves through the formal review process and includes all public comments received to date, the background document, and the recommendation for listing/removal from the individual review committees once their review is completed. The NTP instructs the review committee members to consider all components of the review package in their deliberations and recommendations. In addition, the NTP believes that the NTP Board of Scientific Counselors RoC Subcommittee meeting is an important step in making the review process transparent,

because this is a public meeting with opportunity for stakeholders to present their comments openly to the external peer review committee, NTP staff, and other meeting attendees.

COMMENT

NTP should formally announce nominations being considered by the NIEHS/NTP Nominating Committee, solicit public comments on them, and consult with experts before the committee reviews the potential nominations.

RESPONSE

The NIEHS/NTP Nominating Committee's role is to examine the information submitted with a nomination that justifies the request for its review and determine if the information is sufficient for the NTP to proceed with a formal review of that nomination. The NIEHS/NTP Nomination Committee provides its recommendations for the list of candidate nominations to the NTP who, after approval by the Director, publishes a Federal Register notice that invites public comment on the candidate nominations and solicits information about their carcinogenicity, use, exposure, and production and identification of any issues that should be considered during their review. The NIEHS/NTP Nomination Committee makes no recommendation regarding whether a nomination should be listed in or removed from the RoC and therefore the NTP feels that public comment is not warranted at this point in the process.

COMMENT

The process should allow for sufficient time for the public to review the background document and submit public comments, and time for the review committees to review the public comments.

RESPONSE

The NTP plans to place the background document for a nomination on the NTP web site at least 30 days before any of the scientific review committees meet to evaluate a nomination and make a listing recommendation. The NTP believes that this will provide the public an opportunity to review the background documents and, if desired, to provide comment or other information prior to initiation of the formal review of the nominations. As is the NTP's practice, any comments or other information received on a nomination will become part of its public record and be included in the materials provided to the review groups. The NTP believes that the earlier availability of the background documents should improve public accessibility and enhance communication and transparency.

COMMENT

Public comments should have a written response

RESPONSE

The NTP does not believe that a written response to public comments is necessary or appropriate. All comments received on a nomination are part of its public record and are provided without NTP commentary to the scientific review groups for their independent consideration. The NTP instructs all substance-specific experts involved in writing or reviewing a background document to consider available public comments before submitting a final document and also instructs the three scientific review groups to consider all public comments in their evaluation. The NTP serves as the facilitator of the preparation and review of the background documents and of the evaluation of the nominations by the three scientific review groups. The NTP feels it would be inappropriate to provide its opinion regarding the interpretation of any comments, because it could impose potential bias, affect the quality of the review, and prevent the NTP Director from receiving independent recommendations from the review groups.

COMMENT

The process should be more transparent by making minutes, comments, and reviews from all three scientific review committees available to the public

RESPONSE

The NTP believes that the current process of providing a review summary document for each nomination prepared by both RG1 and RG2 is appropriate and provides adequate documentation of these reviews. The summary includes a discussion of the major issues discussed, the scientific justification for listing or delisting, and the vote for their final recommendation for the nomination. The NTP Board of Scientific Counselors RoC Subcommittee meets in a public forum, the deliberations are open to all interested parties, the transcript is available upon request, and the minutes for these meetings are posted on the NTP web site. The recommendations and votes of all three scientific review groups are also made available to the public in a <u>Federal Register</u> notice that solicits final comments on the nomination prior to the NTP Executive Committee meeting.

COMMENTS RELATING TO THE REVIEW OF BACKGROUND DOCUMENTS

COMMENT

The panel of substance-specific experts should review public comments submitted on the background document and the NTP should revise the background document based on the panel's comments. The background documents should be revised as they move through the review process.

RESPONSE

The NTP believes that making continual changes in a background document would create confusion in the review process. The NTP also believes that greater transparency can be achieved by having the same background document for a nomination available to all review groups and the public. All public comments received on a nomination are added to its public record, posted on the NTP web site, and added to the review package provided to the three scientific review committees. The review committees are instructed to consider the public comments in their review of a nomination.

COMMENTS ON THE ROLE OF THE NTP EXECUTIVE COMMITTEE

COMMENT

The NTP Executive Committee should not review individual nominations because they do not have the time needed to review the background document and other materials. Instead, the role of the NTP Executive Committee should be to evaluate the review process.

RESPONSE

The NTP disagrees. The NTP Executive Committee provides advice to the NTP on policy and technical issues. This committee serves an important role in reviewing nominations to the RoC prior to the NTP Director making recommendations to the Secretary regarding whether to list/delist the nominations.

COMMENTS RELATED TO PUBLICATION OF THE ROC

COMMENT

The listing profile should be subjected to public comments before the RoC is published.

RESPONSE

The NTP does not believe that this is operationally feasible or needed. The NTP Director makes a recommendation on each nomination to the Secretary, DHHS who makes the final decision regarding its listing in the RoC. Releasing the profile for new listings before the Secretary has approved the RoC would result in premature and possibly misleading information to the public. The information within a listing profile is not new, but is based upon the discussions and recommendations of the scientific reviews groups, public comments, and information within the background document. Each profile is intended to serve as a meaningful and useful compilation of data on the carcinogenicity, genotoxicity, and biologic mechanisms of the listed substances in humans and/or in animals; the potential for human exposure to these substances; and Federal regulations to limit exposures to the substances. Appropriate Federal regulatory agencies review the profiles to ensure that the

information on regulations is accurate and complete. The NTP periodically revises a profile for a listing if new, relevant information becomes available.

COMMENT

The listing profile should give specifics about the scientific findings, *for example,* laboratory strain, type of tumor, route of exposure, and exposures identified in epidemiological studies that cause cancer, and should also discuss benefits of the substance.

RESPONSE

The NTP would note that the listing profiles are not meant to be inclusive of all available scientific information, but summaries of information supporting the listing. The RoC is a public health hazard identification document; therefore, the NTP strives to achieve a balance between discussing the details relevant to the listing and writing the profiles in a manner that can be understood by the scientific community as well as the general public.

COMMENT

A suggestion was made that regulatory agencies issue a Preliminary Notice of Intent for new listings within their jurisdiction when the RoC is released. This notice would provide information concerning what actions the agency would take as a result of the listing or delisting decision.

RESPONSE

The NTP does not have the legal authority to require that the regulatory agencies issue such notices. However, the NTP will convey this sentiment to the NTP Executive Committee.

COMMENTS RELATED TO THE LISTING CRITERIA

COMMENT

The criteria state that decisions on carcinogenicity should take into consideration all relevant data, including mechanistic data, and provide an example on how mechanistic data may be used to remove a listing from the RoC. Some commentators felt that the criteria should also provide a description of how mechanistic data can be used to support a listing.

RESPONSE

The NTP believes that the criteria provide adequate guidelines for evaluating carcinogenicity for listing in the RoC. The criteria state that all relevant information, including mechanistic data, be considered for listing a substance. Although the example provided in the criteria describes the use of mechanistic data for not listing a substance, the NTP feels that the criteria are clear regarding the role mechanistic data can play in reviewing a substance and believes that it is not necessary to give examples of all possible situations.

COMMENT

One comment suggested that the evidence for listing a substance as a known human carcinogen should be restricted only to human epidemiological studies.

RESPONSE

The NTP would note that since 1996 the criteria have stated that to be listed as a known human carcinogen there must be "sufficient evidence from studies in humans." They also state: "Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance." The NTP has published a clarification of the criteria (Federal Register: April 2, 1999 (Volume 64, Number 63) Pages 15983-15984) that states that studies in humans "can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people." Therefore, in applying the criteria for listing a substance as a known human carcinogen, consideration of all relevant information from studies in humans is not restricted only to human epidemiological studies.

Speakers' List
National Toxicology Program
Report on Carcinogens Public Meeting
January 27, 2004

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