Tentative Agenda
NTP Public Meeting
Report on Carcinogens (RoC) Review Process
Lister Hill Center Auditorium
National Library of Medicine, National Institutes of Health
Bethesda, Maryland

January 27-28, 2004

January 27th

8:30 – 9:00 AM	Registration
9:00 – 9:10 AM	Welcome and Opening Remarks Dr. Christopher Portier, Director Environmental Toxicology Program, NIEHS/NTP
9:10 – 9:20 AM	Chairman Remarks Dr. Lynn Goldman, Johns Hopkins University
9:20 – 9:35 AM	Discussion of October 1999 RoC Public Meeting Dr. Bernard Goldstein Rutgers University
9:35 – 10:00 AM	Overview of RoC History and Review Process Dr. C W Jameson, Head Report on Carcinogens, NIEHS/NTP
10:00 – 10:45 AM	Presentation 1 – 3
10:45 – 11:00 AM	Break (*15 minutes*)
11:00 – 11:20 AM	Discussion
11:20 – 12:05 PM	Presentation 4 – 6
12:05 – 12:30 PM	Discussion
12:30 – 1:30 PM	Lunch
1:30 – 2:15 PM	Presentation 7 – 9
2:15 – 2:35 PM	Discussion
2:35 – 3:00 PM	Continuation of comments/discussion (if necessary)
3:00 – 3:15 PM	Break (15 minutes)
3:15 – 4:30 PM	Continuation of comments/discussion (if necessary)
4:30 – 5:00 PM	Recap of First Day's Discussions

January 28th (if necessary)

9:00 – 9:10 AM	Chairman Remarks
9:10 – 10:30 AM	Continuation of comments/discussion
10:30 – 10:45 AM	Break (*15 minutes*)
10:45 – 11:30 PM	Continuation of comments/discussion
11:30 – 12:00 PM	Recap/Close of Meeting

Report on Carcinogens, Proposed Listing/Delisting Procedures

Nominations for listing or delisting (removing) an agent, substance, mixture, or exposure circumstance in the RoC should be submitted to the NTP[1] (footnotes are defined). Nominations must contain a rationale for listing or delisting as either a "known human carcinogen" or a "reasonably anticipated human carcinogen." Appropriate background information and relevant data (*e.g.*, journal articles, NTP Technical Reports, IARC listings, exposure surveys, release inventories, etc.) that support the nomination should be provided or referenced when possible.

A nomination for listing or delisting in the RoC is evaluated initially by the NIEHS/NTP RoC nomination review committee, composed of scientists from the NIEHS/NTP staff, to determine if the information available for a nomination indicates the criteria for listing can be applied and warrants formal consideration by the NTP. This committee is provided with the information submitted with each nomination and any relevant supplemental materials identified by RoC staff. The committee reviews the information provided for each nomination and makes a recommendation for either continuing with the formal review for listing or delisting or not pursuing the nomination at this time. The rationale for dropping a nomination would be the lack of sufficient information for applying the listing criteria or, in the case of nominations for delisting, the absence of significant new information published since the original listing. The recommendations of this committee are submitted to the Director, NTP for approval. Those nominations not accepted for review will be returned to the original nominator who is invited to resubmit the nomination with additional justification, which may include new data, exposure information, etc. The NTP Executive Committee[2] and the NTP Board of Scientific Counselors are informed of all nominations not accepted for review for listing or delisting in the RoC.

The NTP announces its intent to review and solicits public comments on all nominations accepted for review through announcements in the Federal Register and NTP publications. The NTP will initiate an independent search and review of the literature and prepare a background document for each nomination under consideration. The comments received in response to the public announcement are used to help identify issues that should be addressed in the background documents. The background documents are prepared with the assistance of an expert consultant(s) who have expertise and/or knowledge for the specific nomination. Background documents are prepared according to the following general format:

1 Introduction

Information contained in this section includes chemical identification such as synonyms, trade names, CAS Registry numbers, molecular formula, molecular

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[1] National Toxicology Program, Report on Carcinogens, P.O. Box 12233, 79 T.W. Alexander Drive, Bldg. 4401, Room 3118, MD EC-14, Research Triangle Park, NC 27709; contact information: Dr. C. W. Jameson, phone (919) 541-4096, fax: (919) 541-0144, email: jameson@niehs.nih.gov

[2] Agencies represented on the NTP Executive Committee include: Agency for Toxic Substances and Disease Registry (ATSDR), Consumer Product Safety Commission (CPSC), Environmental Protection Agency (EPA), Food and Drug Administration (FDA), National Center for Environmental Health of the Centers for Disease Control and Prevention (NCEH/CDC), National Institute for Occupational Safety and Health/CDC (NIOSH/CDC), Occupational Safety and Health Administration (OSHA), National Cancer Institute of the National Institutes of Health (NCI/NIH), and National Institute of Environmental Health Sciences/NIH(NIEHS/NIH)

structure, etc. Also included are physical-chemical properties and identification of structural analogs or metabolites.

2 Human Exposure

Information contained in this section can include use; production; analysis; environmental occurrence including environmental release, drinking water and food content and occurrence in consumer products; environmental fate in air, water, and soil; environmental and occupational exposures; biological indices of exposure; and regulations including occupational exposure limits and "other" standards and criteria.

3 Human Studies

Information contained in this section can include traditional cancer epidemiology investigations including case control and cohort studies as well as data from clinical studies.

4 Experimental Carcinogenesis

Information in this section can include experimental animal investigations of potential carcinogenesis including long term bioassays, experiments where the substance is administered in conjugation with known carcinogens or factors that modify carcinogenic effects, studies to investigate a defined precancerous lesion and experiments on the carcinogenicity of known metabolites and derivatives.

5 Genotoxicity

Information in this section can include investigations of genetic and related effects including gene mutation and chromosomal damage.

6 Other Data Relevant to Evaluation of Carcinogenicity and its Mechanisms

Information contained in this section can include metabolism, absorption, distribution and excretion of the substance, other toxic effects, and data derived from the study of tissues or cells from humans and/or experimental animals exposed to the substance in question, which can be useful for evaluating whether a relevant cancer mechanism is operating in people.

Data used in the preparation of Sections 3 through 6 of the background document must come from publicly available, peer-reviewed sources.

The final draft of the background document for each nomination will be reviewed by the NIEHS/NTP RoC Review Committee (RG1) that is composed of senior scientists from the NIEHS/NTP staff. The RG1 is asked to review the background document for content and determine if it is adequate for use in reviewing the nomination and applying the criteria for listing in the RoC. Upon determination of adequacy, the background document is considered the final document of record and is placed on the NTP RoC web site. A notice is then published on the NTP list-server and the NTP web site announcing the availability of the background document for a nomination. Notification of the availability of background documents by mail can also be requested by contacting the NTP[3]. The formal review of a nomination will not begin

[3] Contact information provided in footnote 1.

for at least 45 day after the announcement of the availability of the background document for that nomination. All comments received within this time period will be distributed to the RoC review committees and also become part of the public record.

FORMAL REVIEW STEPS

Nominations under consideration by the NTP for listing in or delisting from the RoC undergo a multi-step, scientific review process that includes several opportunities for public comment. The following text briefly describes that process.

NIEHS/NTP RoC Review Committee (RG1)

The RG1 conducts a formal review of nominations for listing in or delisting from the RoC. The RG1 reviews the background document for each nomination and all public comments received in response to the Federal Register announcement of the intent to review a nomination and any comments received on the background document. The RG1 conducts a scientific review of the nomination applying the criteria and provides comments and makes its recommendations to the Director, NTP for listing or delisting it in the RoC.

NTP Executive Committee's Interagency Working Group for the RoC (RG2)

The RG2, a federal government interagency scientific review group, also conducts a scientific review of nominations to the RoC. The RG2 assesses whether relevant information for a nomination is available and sufficient for listing in or delisting from the RoC. The RG2 reviews the original nomination and all public comments received in response to the Federal Register announcement of the intent to review a nomination and any comments received on the background document. Upon completion of its review, the RG2 provides comments and makes its recommendations to the Director, NTP for listing or delisting the nominations in the RoC.

Board of Scientific Counselors RoC Subcommittee (External Peer Review)

The third step in the review process is external scientific peer review of the nominations by a standing subcommittee of the NTP Board of Scientific Counselors ("the RoC Subcommittee"). The RoC Subcommittee serves as an independent peer review group that assesses whether the relevant information available for a nomination is sufficient for listing or delisting it in the RoC. The RoC Subcommittee reviews nominations in an open public meeting. Prior to this public review, a notice is published in the Federal Register and NTP publications announcing the public meeting, a reminder of the availability of the background documents and soliciting public comment on the nominations. The notice invites interested groups or individuals to submit written comments and/or address the RoC Subcommittee during the public review meeting. The RoC Subcommittee reviews the original nomination and all public comments received in response to the Federal Register notices including the announcement of the intent to review a nomination and the announcement of the public meeting, any comments received on the background documents, and comments received at the public meeting. Upon completion of its review, the RoC Subcommittee provides comments and makes its recommendations for listing or delisting the nominations in the RoC.

Final Public Comment

Upon completion of the reviews by RG1, RG2 and the RoC Subcommittee, the NTP publishes in the Federal Register and NTP publications the nominations and the review groups' recommendations for each (to list, to delist, or not to list in the RoC), and solicits final public comment and input on the nominations.

NTP Executive Committee
The recommendations of RG1, RG2 and the RoC Subcommittee and all public comments received in response to all Federal Register announcements and the background documents are presented to the NTP Executive Committee for review and comment. The NTP Executive Committee reviews the information on the nominations and provides the Director, NTP its recommendations for listing or delisting them in the RoC.

NTP Director
The NTP Director receives the independent recommendations for the nominations from RG1, RG2 and the NTP Board RoC Subcommittee, the recommendation of the NTP Executive Committee and all public comments received concerning the nominations. The NTP Director evaluates this input and any other relevant information on the nominations and develops recommendations to the Secretary, Department of Health and Human Services (DHHS) regarding whether to list, delist, or not list the nominations in the RoC.

Secretary, Department of Health and Human Services
The NTP prepares a final draft of the RoC based on the NTP Director's recommendations and submits it to the Secretary, DHHS for review and approval. Upon approval of the RoC, the Secretary submits it to the U. S. Congress as a final document. The submission of the RoC to Congress constitutes publication of the report and it becomes available to the public at that time. The NTP publishes a notice of the publication and availability of the latest edition of the RoC, indicating all newly listed or delisted agents, substances, mixtures or exposure circumstances in the Federal Register and NTP publications.

Report on Carcinogens
Criteria for Listing
Agents, Substances, Mixtures or Exposure Circumstances

Known To Be Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Reasonably Anticipated To Be Human Carcinogen:

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 factors, could not adequately be excluded,

or

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign 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,

or

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

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. For example, there may be substances for which there is 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 not reasonably be anticipated to cause cancer in humans.

Clarification of Criteria

Some questions have arisen regarding information from studies involving humans and how this is applied to the listing of a substance determined to be a "known human carcinogen". The "known human carcinogen" category requires evidence from studies of humans. This can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues from humans exposed to the substance in question and useful for evaluating whether a relevant cancer mechanism is operating in people.

There have also been some misunderstandings regarding the application of the final paragraph of the criteria which begins, "Conclusions regarding carcinogenicity in humans or experimental animals..." Since these criteria were first published on September 26, 1996 (61 FR 50499-50500), the paragraph has applied to both the "known to be human carcinogen" and the "reasonably anticipated to be human carcinogen" categories and will continue to apply (64 FR 19188, April 19, 1999).