NTP Report on Carcinogens Review Process

The Report on Carcinogens (RoC) is a Congressionally mandated document that identifies and discusses agents, substances, mixtures, or exposure circumstances (collectively referred to as "substances") that may pose a hazard to human health by virtue of their carcinogenicity. Substances are listed in the report as either *known* or *reasonably anticipated to be human carcinogens*. The National Toxicology Program (NTP) prepares the RoC on behalf of the Secretary of Health and Human Services (HHS). The RoC review process is described below and consists of four major parts: (1) nominations and selection of candidate substances, (2) scientific review of candidate substances, (3) peer review of draft substance profiles, and (4) preparation of the RoC and transmittal to Congress and the public. A schematic of the RoC review process is provided at the end of this section.

Nominations and Selection of Candidate Substances

The NTP invites nominations for consideration for listing in the RoC from anyone in the public and private sectors. Nominations may seek to list a new substance in the RoC, reclassify the listing status for a substance already listed, or remove a substance already listed. Nominations should be submitted to the NTP[1] at http://ntp.niehs.nih.gov select "Provide Input to NTP." Nominations must contain a rationale or reason for the review and, if possible, appropriate background information and relevant data (e.g., journal articles, NTP Technical Reports, International Agency for Research on Cancer Monographs, exposure surveys, and release inventories) to support the rationale.

The NTP initially evaluates each nomination to determine whether the scientific information available for a nomination justifies its formal review and consideration. Those nominations proposed for review proceed as discussed below. The reason for not going forward with review of a new nomination would be the lack of sufficient information[2] for applying the listing criteria[3] (see Introduction). The reason for not proceeding with a nomination to reclassify or remove a current listing would be the absence of significant new scientific information published since the original listing. Those nominations not selected for review are returned to the original nominator who is invited to resubmit the nomination with additional information such as new data, exposure information, etc. that justifies a formal review. The NTP may defer or terminate the review of a proposed nomination at any time if relevant information becomes available that warrants the NTP's reconsideration of the substance's review. In such cases, the nominator, the NTP Board of Scientific Counselors (BSC),[4] the NTP Executive Committee,[5] and the public would be notified of this action.

The NTP announces nominations proposed for review and solicits public comments through announcements in the *Federal Register* and NTP publications. These announcements ask for relevant information concerning carcinogenicity of the substance as well as data on current production and information on exposure and patterns of use. Comments received in response to the public announcements are used to (1) refine the list of nominated substances to identify the candidate substances that will proceed through the full review process and (2) identify scientific issues that should be addressed in the preparation and/or review of the draft background document for an individual candidate substance. In addition, the NTP invites the public to nominate scientists to serve on an expert panel[6] for each specific candidate substance. An expert panel will be convened to provide peer review of the draft background document, make a recommendation for the candidate substance's listing status in the RoC, and provide the scientific justification for that recommendation.

Scientific Review of Candidate Substances

The scientific review of a candidate substance consists of three major steps: (1) preparation of the draft background document, (2) review by an expert panel at a public meeting, and (3) internal review by two independent federal committees.

Draft Background Documents

The NTP prepares a draft background document for each candidate substance under consideration. The background documents may be prepared with the assistance of a consultant(s) with expertise and/or knowledge relevant to the specific candidate substance. Background documents are prepared following the general format presented below. Background documents do not contain any opinion regarding the listing status for the candidate substance. Data used to prepare Sections 3 through 5 must come from publicly available, peer-reviewed sources.

1. Introduction

This section describes the properties (e.g., chemical, physical or biological) of the candidate substance and states the scientific rationale for review. For chemicals, it contains the following sections (1) chemical identification, including synonyms, trade names, CAS Registry numbers, molecular formula, and molecular structure, (2) physical-chemical properties, and (3) identification of structural analogues or metabolites. For other types of agents (e.g., biological, exposure circumstances, or physical), it provides appropriate information to define the candidate substance.

2. Human Exposure

This section provides a summary of relevant data documenting both present and past exposures. It typically provides information on use, production, environmental occurrence, and exposure (including release and fate in air, water, soil, and food), exposure to the general population (e.g., occurrence in consumer products or medical devices), occupational exposure, biological indices of exposure, and regulations and guidelines to limit exposure.

3. Human Cancer Studies

This section summarizes traditional cancer epidemiology studies (mainly case-control and cohort studies, but may also include descriptive studies and case reports). Data from clinical studies may also be included.

[1]National Toxicology Program, Report on Carcinogens Center, P.O. Box 12233, MD K2-14, Research Triangle Park, NC 27709.

[2]Lack of sufficient information means that adequate studies (such as animal, human, or mechanistic), which are critical for evaluation of the carcinogenicity of the nomination, are not currently available in the peer-reviewed literature.

[3]The criteria for listing a substance in the RoC are available at http://ntp.niehs.nih.gov see "Report on Carcinogens."

[4]The BSC is a federally chartered advisory committee whose members are appointed by the Secretary, HHS. The BSC provides advice to the NTP Director on matters relating to scientific program content and evaluates the scientific merit of the NTP's intramural and collaborative programs.

[5]The NTP Executive Committee is composed of the heads (or their designees) of federal research and regulatory agencies and provides advice to the NTP on policy issues.

[6]An expert panel is an *ad hoc* group of scientists with relevant expertise and knowledge selected by the NTP from the public and private sectors. Nominations to serve on specific expert panels are solicited from federal and nonfederal sources. The final selections for membership are based upon providing a balanced and unbiased group of highly qualified individuals and are made in accordance with the Federal Advisory Committee Act and HHS implementing regulations.

4. Studies in Experimental Animals

This section summarizes experimental animal studies of potential carcinogenesis including long term bioassays, subchronic studies, initiation and promotion studies, and studies of known metabolites.

5. Other Relevant Data

This section discusses the available, relevant mechanistic and other scientific information that would be needed to understand the toxicity and potential carcinogenicity of the candidate substance and that would be useful for evaluating the carcinogenic potential of the substance in people. For a specific substance, it may include information on (1) absorption, distribution, excretion and metabolism, (2) genetic damage and related effects, (3) mechanistic studies and considerations, (4) toxicity, and (5) the carcinogenicity and mutagenicity of structural analogues.

When the initial draft is completed, the NTP posts the draft background document on the RoC Web site. Availability of the draft background document is announced on the NTP listserv and in other NTP publications. Draft background documents are also available on compact disks or in hardcopy upon request (see Contact Information, below).

Expert Panel Meeting

The NTP convenes an expert panel for each candidate substance. The NTP publishes a *Federal Register* notice at least 60 days prior to the expert panel meeting announcing the meeting and availability of the draft background document. The public is invited to attend this meeting and provide oral and/or written comments on the draft background document. The public may also provide opinion on the listing status for the candidate substance. All comments received within this time period become part of the public record that will be reviewed by the expert panel and are posted on the RoC Web site. The expert panel is first charged to peer review the background document. Once the peer review is complete, the NTP asks the expert panel (1) to apply the RoC listing criteria to the relevant scientific evidence and make a recommendation regarding the listing status for the candidate substance and (2) to provide the scientific justification for that recommendation. The expert panel will also submit a report that contains (1) its peer review comments on the draft background document and (2) its recommendation for listing in the RoC and the scientific justification for that recommendation. The NTP will post the expert panel's report on the RoC Web site and publish a *Federal Register* notice inviting comment on the expert panel's recommendation for listing status and the scientific justification for that recommendation. The NTP will also prepare a response to the expert panel's peer review comments on the draft background document that will be made available to the public on the RoC Web site upon release of the RoC.

Following the expert panel meeting, NTP staff reviews and considers the expert panel's peer review comments and any public comments as it finalizes the background document on the candidate substance. The final version of the background document is then posted on the RoC Web site. Availability of the final background document and the expert panel report is announced through the NTP listserv.

Internal Reviews by the Government

Following the expert panel meeting, the NTP goes through a number of reviews that are internal to the government to develop an initial listing status for each candidate substance to the RoC. The internal review process is closed to the public and consists of separate meetings of two groups: (1) an interagency scientific review group (ISRG) and (2) the NIEHS/NTP scientific review group (NSRG). Both groups are provided with all relevant information (including the background document, the expert panel report, and any public comments received to date) on the candidate substances and asked to apply the listing criteria to this information and make a recommendation on the listing status of the candidate substance.

Peer Review of Draft Substance Profiles

Taking into consideration the listing recommendations of the expert panel, the NSRG, and the ISRG, and the public comments, the NTP prepares a draft substance profile[7] with a listing recommendation for each candidate substance. Once the draft substance profile is developed, the NTP convenes a meeting of the BSC to peer review the draft substance profiles for candidate substances to the RoC. The NTP publishes a *Federal Register* notice at least 60 days prior to the BSC meeting announcing the meeting and the availability of the draft substance profiles. The public is invited to attend this meeting and provide oral and/or written comments on the draft substance profiles. All comments received within this time period become part of the public record for review by the BSC and posted on the RoC Web site. The NTP makes available to the BSC all relevant information. The BSC is charged to determine whether the scientific information cited in the draft substance profile for a candidate substance is technically correct, clearly stated and supports the NTP's policy decision regarding its listing in the RoC. The BSC is not asked to review the NTP's decision regarding listing status. The BSC prepares and submits a peer review report to the NTP that describes the nature and scope of its findings and conclusions concerning the NTP's draft substance profiles.

Preparation of Draft RoC and Transmittal

The NTP responds to the peer review report and drafts the next edition of the RoC. The draft RoC is submitted to the NTP Director for review. The Director distributes the draft RoC to the NTP Executive Committee for consultation, review, and comment. Following approval of the draft RoC by the Director, a final draft of the RoC is prepared and submitted to the Secretary, HHS for review and approval. Upon approval of the RoC, the Secretary transmits it to the U.S. Congress, and the report is published and disseminated to the public. The NTP publishes a notice in the *Federal Register* and NTP publications that announces availability of the report and identifies the listing outcome for each candidate substance that underwent formal review for the RoC. At this time, the NTP posts the BSC's peer review report, the NTP's response to that report, and the NTP's response to the expert panel peer review comments on the draft background documents on the RoC Web site. In addition, for the *Twelfth Report on Carcinogens,* the NTP will prepare a response to public comments received on candidate substances since issuance of the expert panel report[8] and will post the response on the RoC Web site.

The NTP makes the latest edition of the RoC available electronically on the NTP RoC Web site (http://ntp.niehs.nih.gov and select "Report on Carcinogens"), on compact disk, and in printed form. For information on how to request a printed or electronic copy, contact Dr. Ruth M. Lunn.

[7]The RoC contains substance profiles for each candidate substance. Full substance profiles are developed for substances *known* or *reasonably anticipated to be human carcinogens* and contain the listing status, summarize the scientific information that supports the recommendation, and provide information on use, exposure and production. Limited substance profiles are developed for candidate substances not listed in or delisted from the RoC, which vary in content on a case-by-case basis.

[8]The NTP's preparation of a response to public comments will be done on a trial basis for the *Twelfth Report on Carcinogens.* The NTP will assess the merit of responding to public comments following completion of the *Twelfth Report on Carcinogens* and determine whether any change is needed in the review process with regard to this practice.

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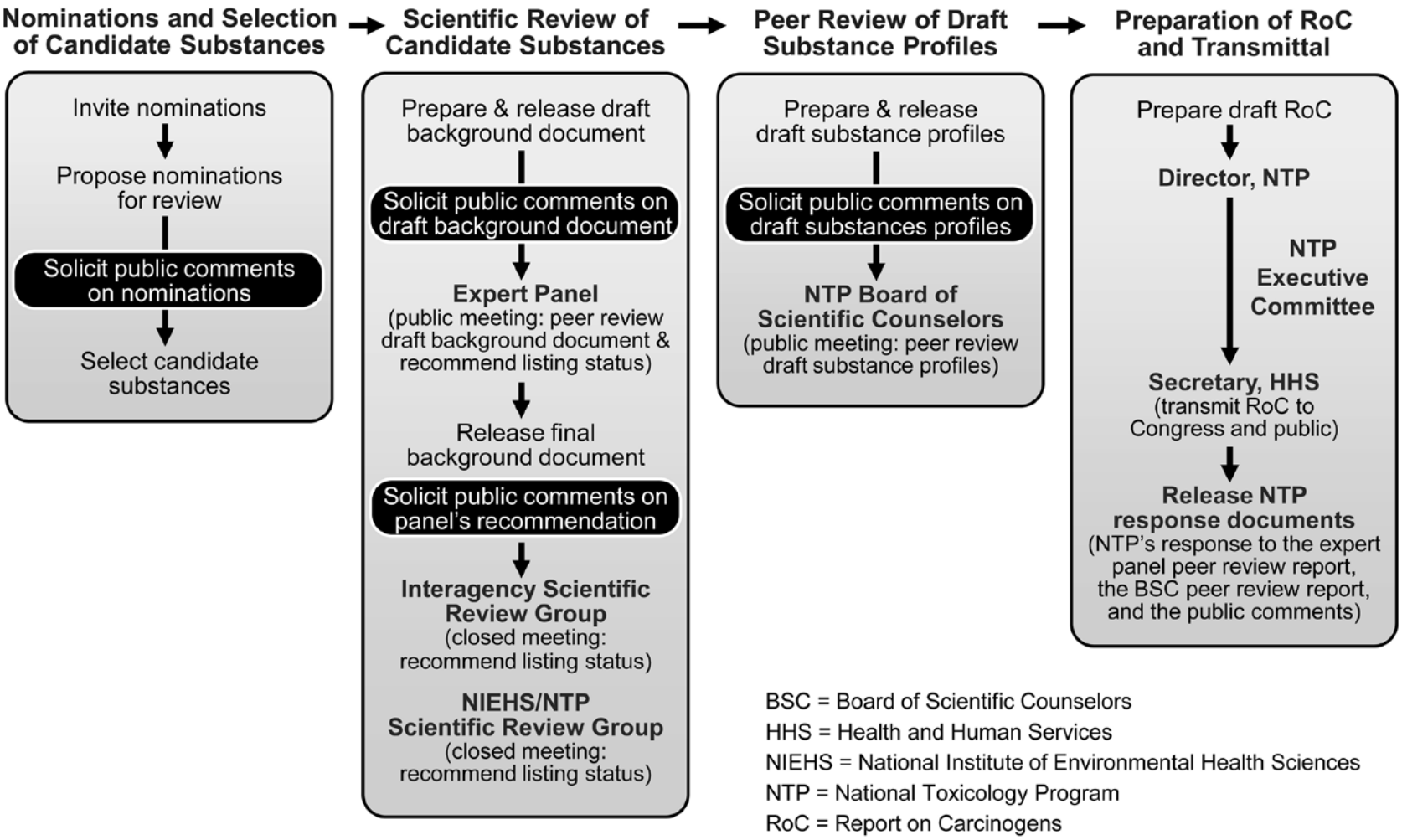

BSC = Board of Scientific Counselors
HHS = Health and Human Services
NIEHS = National Institute of Environmental Health Sciences
NTP = National Toxicology Program
RoC = Report on Carcinogens

Contact Information

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NTP Listserv

The NTP listserv is an e-mail distribution list used to disseminate information on NTP activities. To subscribe, visit http://ntp.niehs.nih.gov and select "Contact Us."