

Report on Carcinogens

Year 2003

The Report on Carcinogens (RoC), previously called the Annual Report on Carcinogens, is prepared in response to section 301 of the Public Health Service Act, as amended. The law mandates that the Secretary, Department of Health and Human Services (DHHS) 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 person residing in the United States are exposed. The Secretary has delegated responsibility for preparation of the RoC to the National Toxicology Program (NTP). The NTP relies on assistance from other Federal health research and regulatory agencies and non-governmental institutions for preparation of the RoC.

The RoC is an informational scientific and public health document that identifies and discusses agents, substances, mixtures, or exposure circumstances that may pose a carcinogenic hazard to human health. It serves as a meaningful and useful compilation of data on the (1) carcinogenicity, genotoxicity, and biologic mechanisms of the listed substances in humans and/or animals, (2) the potential for exposure to these substances, and (3) the regulations promulgated by Federal agencies to limit exposures. The report does not present quantitative assessments of carcinogenic risk. Listing of substances in the RoC, therefore, does not establish that such substances present carcinogenic risks to individuals in their daily lives. Such formal risk assessments are the purview of the appropriate Federal, State, and local health regulatory and research agencies.

The NTP solicits and encourages broad participation from individuals or parties interested in nominating agents, substances, mixtures or exposure circumstances for listing in or delisting (removing) from the RoC. Anyone may submit a nomination for consideration by the NTP. Nominations must include a rationale for listing or delisting and can be submitted to Dr. C.W. Jameson, Head of the Report on Carcinogens Group, at the address provided below. Appropriate background information and relevant data (e.g., journal articles, NTP Technical Reports, International Agency for Research on Cancer listings, exposure surveys, release inventories, etc.) that support the nomination should be provided or referenced when possible. The NTP follows a formal process for evaluation of nominations accepted for review that includes scientific review and public comment.

The most recent RoC, the 10th Edition, was released publicly on December 11, 2002. Hard copies and CDs of the 10th RoC are available from the Environmental Health Information Service (see below). A list of the nominations under consideration for the 11th Edition is available on the NTP web site or by contacting Dr. Jameson. The NTP anticipates completing the scientific review of nominations under consideration for the 11th RoC by the end of 2003. The 11th RoC is scheduled for release in 2004. Nominations received in 2003 will be considered for possible listing in or delisting from the 12th Edition of the RoC, which is scheduled for release in 2006.

Nominations for listing or delisting may be submitted by any interested party by contacting:
Dr. C. W. Jameson, NTP, Report on Carcinogens, 79 Alexander Drive, Building 4401, MD EC-14, P.O.
Box 12233, Research Triangle Park, NC 27709; Phone: 919/541-4096;
E-mail: jameson@niehs.nih.gov

To obtain the Report on Carcinogens, 10th Edition, contact:
NIEHS Environmental Health Perspective ATTN: Order Processing, 1001 Winstead Drive Suite 355, Cary,
NC 27513; Telephone: 866-541-3841; Fax (919) 678-8696; email: ehponline@niehs.nih.gov; Web Site:
<http://www.ehponline.org>

Report on Carcinogens Listing Criteria

The criteria for listing an agent, substance, mixture, or exposure circumstance in the Report on Carcinogens (RoC) are as follows:

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.

It should be emphasized that the category "known to be human carcinogen" requires evidence from human studies. This evidence 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. The listing criteria presented here were adopted and applied since the Eighth Edition of the RoC, which was published in 1997. Listing criteria for substances listed in earlier editions of the report are outlined in the introductions to those editions.

Report on Carcinogens, Eleventh Edition Listing/Delisting Procedures

Nominations for listing or delisting (removing) an agent, substance, mixture, or exposure circumstance in the Report on Carcinogens (RoC) should be submitted to the National Toxicology Program (NTP)¹. 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 Review Group (RG1), composed of senior scientists from the NIEHS/NTP staff, to determine if the information provided indicates that the nomination warrants further consideration by the NTP. If it is determined that the submitted nomination does not contain sufficient information to warrant consideration, it is 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 Committee² 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 solicits public comments on all nominations accepted for review through announcement in the Federal Register and NTP publications. The NTP initiates an independent search and review of the literature and prepares a background document for each nomination under consideration. The background documents are prepared with the assistance of a consultant or a panel of consultants who have expertise and/or knowledge for the specific nomination that is relevant to its evaluation of carcinogenicity. 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 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

¹ National Toxicology Program, Report on Carcinogens

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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)

substance is administered in conjunction 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. In special cases, the review groups listed below may be asked to provide formal peer-review for a document the NTP deems to be important to the review but has otherwise not received peer-review; such a document would need to be publicly available.

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, composed of senior scientists from the NIEHS/NTP staff, conducts the initial review of a nomination for listing in or delisting from the RoC and in that review, considers all public comments received in response to the announcement of the nomination. The RG1 first reviews the background document prepared for the nomination and determines if it is adequate for use in reviewing the nomination and for applying the criteria for listing in the RoC. Upon acceptance of the background document, it is then considered the final document of record. The RG1 then proceeds with scientific review of the nomination and makes a recommendation for listing or delisting in the RoC. After the background document becomes the final document of record, it is placed on the NTP RoC web site with a notice published on the NTP list-server and the NTP web site announcing its availability.

It is possible that the RG1 review of the background document for a nomination may determine that there is insufficient relevant information to apply the criteria for listing in or delisting from the RoC. In this situation, the review of the nomination stops and the NTP will inform subsequent RoC review groups and the NTP Executive Committee of this action and why further review is not warranted. The original nominator is notified of the RG1 action and is invited to resubmit the nomination with additional relevant information and justification. All nominations not reviewed beyond RG1, because of the lack of sufficient relevant information, are included in the subsequent edition of the RoC with the reason(s) why they were not considered further.

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

The RG2, a governmental interagency scientific review group, conducts the second 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 announcements of nominations accepted for review. Upon completion of its review, the RG2 provides comments and makes its recommendations 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 meeting and 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. 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 the nominations and the review groups’ recommendations for each (to list, to delist, or not to list in the RoC), and solicits the third and 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 to date are presented to the NTP Executive Committee for review and comment. The NTP Executive Committee reviews the information on the nominations and provides its opinion 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 opinion 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.