U.S. House of Representatives

Committee on Science, Space, and Technology
Subcommittee on Investigations & Oversight

and

Committee on Small Business
Subcommittee on Healthcare and Technology

HEARING CHARTER

"How the Report on Carcinogens Uses Science to Meet its Statutory Obligations, and its Impact on Small Business Jobs"

Wednesday, April 25, 2012
10:00 a.m. – 12:00 p.m.
2318 Rayburn House Office Building

PURPOSE

On April 25, the Committee on Science, Space, and Technology Subcommittee on Investigations & Oversight, and the Committee on Small Business Subcommittee on Healthcare and Technology, will hold a hearing to examine the Report on Carcinogens (RoC). This joint hearing will provide Members an opportunity to understand how the U.S. Department of Health and Human Services' (HHS) National Toxicology Program (NTP), an interagency program administered by the National Institute of Environmental Health Sciences (NIEHS), produces the RoC. Given the interest generated by the 12th RoC last year, and particularly as NTP embarks on preparations for the 13th RoC, the committees are interested in understanding the history of the RoC, how NTP uses science to meet its statutory obligations, and the RoC's impact on stakeholders, particularly small businesses.

BACKGROUND

The RoC's Legislative History

The RoC is a biennial report mandated by Congress to identify substances[1] that may pose a hazard to human health by virtue of their carcinogenicity. Although the law[2] originally called for annual reports, the reporting was made biennial in 1993.[3]

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[1] NTP Website, *Since You Asked – 12th Report on Carcinogens*, available at: http://www.niehs.nih.gov/news/sya/sya-roc/index.cfm; (hereinafter NTP Website – Since You Asked); NTP defines substances as "agents, substances, mixtures, or exposures (collectively called substances) that may potentially put people in the United States at an increased risk for cancer. Listed in the RoC are a wide range of substances, including metals, pesticides, drugs, and natural and synthetic chemicals."

[2] P.L. 95-622, (Community Mental Health Centers Act, Amendments), available at: http://history.nih.gov/research/downloads/PL95-622.pdf.

Congress passed the law establishing an annual RoC in 1978 as a consequence of oversight hearings on the National Cancer Institute (NCI). The concept of an annual report was raised by witnesses who testified that no agency maintained a comprehensive list of carcinogenic chemicals at the time. Congressman Andrew Maguire of New Jersey introduced legislation that initially required NCI to publish a report with a list of all known or suspected carcinogens.[4] The report was to include three elements:

- *a list of all known or suspected carcinogens;*
- *information concerning the nature of exposure and number of individuals exposed; and*
- *an evaluation of the efficacy of existing regulatory standards designed to control suspected carcinogens.*[5]

He hoped the report would "educate the public, serve as a point of reference for scientists and regulators, and evaluate the activities of the regulatory agencies, who are not immune to pressure from the outside."[6]

Congressman Maguire's bill was folded into a different bill[7] sponsored by Florida Congressman Paul Rogers, Chairman of the Committee on Interstate and Foreign Commerce Subcommittee on Health and the Environment. Chairman Rogers' bill expanded on Congressman Maguire's bill and transferred the responsibility to produce the report to the then-Department of Health, Education, and Welfare, now the Department of Health and Human Services. Ultimately, Congress passed the Senate version of these proposals,[8] which made some changes to the House language, including a critical edit to **better reflect the intent of the legislators in what they expected of the annual report**. Specifically, the Senate bill change included:

> *"a replacement of the phrase 'suspected carcinogens' with 'substances…reasonably anticipated to be carcinogens,' in order to make it absolutely clear in the statute that there must be reasonable ground for designating a substance as a putative carcinogen."*[9]

Chairman Rogers further clarified the "regulatory importance of the Annual Report"[10] by stating that the:

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[3] P.L. 103-43, (National Institutes of Health Revitalization Act of 1993), available at: http://history.nih.gov/research/downloads/PL103-43.pdf.

[4] H.R. 10190, the Cancer Prevention Act, introduced by Rep. Andrew Maguire (D-NJ), December 1, 1977, available at: http://www.congress.gov/cgi-lis/bdquery/D?d095:1:./temp/~bdMhBZ:@@@L&summ2=m&:dbs=n:|/billsumm/billsumm.php?id=2|.

[5] U.S. Congress, Office of Technology Assessment, "Identifying and Regulating Carcinogens," OTA-BP-F1-42, Washington, DC: U.S. Government Printing Office, November 1987 (hereinafter OTA Report).

[6] Ibid.

[7] H.R. 12347, the Biomedical Research and Research Training Amendments, introduced by Rep. Paul Rogers (D-FL), April 25, 1978, available at: http://www.congress.gov/cgi-lis/bdquery/D?d095:1:./temp/~bdJjb7:@@@L&summ2=m&:dbs=n:|/billsumm/billsumm.php?id=2|.

[8] S. 2450, the Biomedical Research Extension Act, introduced by Sen. Edward Kennedy (D-MA), January 27, 1978, available at: http://www.congress.gov/cgi-lis/bdquery/D?d095:1:./temp/~bdjAJk:@@@L&summ2=m&:dbs=n:|/billsumm/billsumm.php?id=2|.

[9] Congressional Record, Volume 124 – Part 28, October 14, 1978.

[10] OTA Report, *supra*, note 5.

> *"intention of the legislation was that listing in the annual report would be a first step in regulation, one triggering a review by the agencies responsible for enforcing various laws regulating carcinogens."*[11]

These changes, including the 1993 update to a biennial reporting schedule, form the background of the current law. *(Appendix 1).*

The RoC is a cumulative document of substances listed in one of two categories, as either "known" to be a human carcinogen, or "reasonably anticipated" to be a human carcinogen. (Appendix 2). Each edition of the report includes substances listed in past reports, in addition to the new substances in the most recent version, along with any changes to the status of previously listed substances. Since the law's inception in 1978, only twelve reports have been published in the 31 years between the first RoC in 1980, and the 12th in 2011. The 12th RoC lists 240 substance profiles – 54 listed as "known" carcinogens and 186 as "reasonably anticipated" to be carcinogens.[12] Over the course of the 12 reports, only nine substances have been delisted from the report (*see Appendix 3*) and a similar number have moved from the "reasonably anticipated" to be a carcinogen list to the "known" to be a carcinogen list.

Federal Chemical Assessment Programs

There are multiple federal agencies that produce a variety of chemical assessment reports with which the House Science, Space, and Technology Committee is familiar. For example, the Agency for Toxic Substances & Disease Registry (ATSDR), another HHS agency, performs certain functions that are congressionally-mandated. ATSDR conducts:

> *"public health assessments of waste sites, health consultations concerning specific hazardous substances, health surveillance and registries, response to emergency releases of hazardous substances, applied research in support of public health assessments, information development and dissemination, and education and training concerning hazardous substances."*[13]

Notably, this Committee has held several hearings on the U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) program, which maintains a database of chemicals that provide a hazard identification and dose-response analysis. This information, when combined with estimates of exposure, allow regulatory agencies to produce a risk assessment.

While the Report on Carcinogens is also a source for decision-making by regulatory agencies at the federal and state levels, the NTP states that the RoC is a:

> *"hazard identification document and does not present quantitative assessments of the risks of cancer associated with exposure to these substances. Thus a listing in the RoC*

[11] Ibid.
[12] U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, *Report on Carcinogens*, Twelfth Edition, 2011, available at: http://ntp.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf (hereinafter 12th RoC).
[13] ATSDR Website, *About ATSDR*, available at: http://www.atsdr.cdc.gov/about/index.html.

> *only indicates a potential hazard and does not estimate cancer risks to individuals associated with exposures in their daily lives."*[14]

Notwithstanding NTP's disclaimer, the RoC does not operate in a vacuum. Last year's release of the 12th edition of the RoC demonstrated this fact with the coverage it received, particularly in reference to its upgrade of formaldehyde from a "reasonably anticipated" carcinogen to a "known" carcinogen, and a first-time listing of styrene as a substance "reasonably anticipated" to cause cancer. The styrene listing even resulted in a lawsuit against HHS,[15] and caused concerns for businesses that use the substance who questioned the scientific rationale behind the listing.

Concerns about the RoC, identified in public comments and during listening sessions last year as NTP commenced preparations for the 13th RoC, include among others: a policy of soliciting, but not responding to public comments; lack of independence in its peer review process; lack of clarity in its definitions as to what constitutes a substance to be listed as either "reasonably anticipated" or "known" to cause cancer; cherry picking studies to support its listings; ignoring certain statutory requirements; and a failure to keep up with advances in modern methods of evaluating carcinogenicity. [16]

Beyond these science and process concerns about NTP, for stakeholders such as the small businesses testifying today, the consequences of a listing in the RoC are severe, as effects include: increased compliance costs to meet additional regulations; a freeze on new hires or new investments in the business because of uncertainties associated with a RoC listing; confusion to consumers and employees about the true health risks of a substance listed in the RoC; and insurance concerns relative to workers' compensation policy coverage being raised or dropped.

It is particularly noteworthy that the release of the 12th RoC last year was delayed in part due to a National Academy of Sciences' review of EPA's IRIS assessment of formaldehyde. The Academies:

> *"strongly questioned EPA claims that exposure to formaldehyde can result in increased risk of a leukemia and other cancers that had not previously been associated with formaldehyde, asthma, and reproductive toxicity."*[17]

NTP disagreed with the Academies' assessment, and attached an addendum to the 12th RoC claiming that:

> *"[b]ecause the NAS document is not an independent hazard assessment, it has limited applicability to the NTP's RoC evaluation of formaldehyde. The RoC evaluation involved a multistep comprehensive assessment of the literature, and resulted in a narrative justification for the NTP's conclusions that was developed independently from*

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[14] NTP Website: Since You Asked, *supra*, note 1.
[15] *SIRC v. Sebelius*, June 14, 2011, available at: http://www.styrene.org/news/pdfs/06-16-11-SnyderDeclaration.pdf.
[16] NTP Website, *Background Information on Development of the Process for Preparation of RoC*, available at: http://ntp.niehs.nih.gov/?objectid=13BBADB8-AFDA-7523-3C14A341F04C9BBC (hereinafter NTP Website – Background Information).
[17] Maria Hegstad, "NAS Sets Back EPA Proposal For Strict Formaldehyde Risk Assessment," *Environmental NewsStand*, April 8, 2011, available at: http://insideepa.com/201104082360407/EPA-Daily-News/Daily-News/nas-sets-back-epa-proposal-for-strict-formaldehyde-risk-assessment/menu-id-95.html.

> *the EPA IRIS assessment. Neither the NTP listing process nor the justification for the listing of formaldehyde in the RoC was reviewed by the NAS."*[18]

This disagreement ultimately led Congress to direct the National Academy of Sciences to review the 12th RoC's classification of formaldehyde and styrene.

ISSUES

Definitions of "Known" and "Reasonably Anticipated" *(Appendix 2)*

There is a great deal of uncertainty in NTP's listing criteria for deciding how substances should be categorized. To be a "known" carcinogen, NTP requires there be an **undefined** "sufficient evidence of carcinogenicity from studies in humans."[19] To be a "reasonably anticipated" carcinogen requires "limited evidence of carcinogenicity from studies in humans."[20] It is unclear what constitutes "limited evidence."

Such ambiguity causes enormous confusion, as critics have argued that NTP:

> *"reserve[s] to itself the discretion to consider whatever information it wants, to exclude whatever information it wants, and to evaluate that information in accordance with whatever ad hoc criteria it wants to apply."*[21]

Moreover, without any data identifying levels of exposure or the circumstances under which a RoC substance is cancerous, any listing in the document appears hazardous to the average person. Further confusing the issue is NTP's disclaimer that a:

> *"listing in the Report on Carcinogens does not by itself mean that a substance will cause cancer. Many factors, including the amount and duration of exposure, and an individual's susceptibility to a substance, affect whether a person will develop cancer."*[22]

NTP Response to Public Comments

While NTP solicits public comments during the preparation of the RoC, it does not, practically speaking, respond to them. As part of the 12th RoC, NTP did respond to select comments, but only after the 12th RoC was published.

Soliciting public comments is merely half the process – the more critical half requires replying to them. Such an action could be of great value not only to those who submit comments, but also to NTP as it would provide a level of transparency to the RoC by demonstrating to commenters and

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[18] Addendum to the 12th Report on Carcinogens, available at: http://ntp.niehs.nih.gov/ntp/roc/twelfth/addendum.pdf (hereinafter RoC Addendum).
[19] NTP Website, *Listing Criteria*, available at: http://ntp.niehs.nih.gov/?objectid=03C9CE38-E5CD-EE56-D21B94351DBC8FC3 (hereinafter NTP Website – Listing Criteria).
[20] Ibid.
[21] Dr. Richard Belzer, "The Report on Carcinogens – What Went Wrong and What Can be Done to Fix It," January 2012, available at: http://cei.org/sites/default/files/Richard%20B%20Belzer%20-%20The%20Report%20on%20Carcinogens.pdf (hereinafter Belzer Paper).
[22] NTP Website - Since You Asked, *supra*, note 1.

review panel members exactly how NTP has considered the comments. As it stands now, one will have to take NTP's word that it considers comments because the 13th RoC makes no accommodation for responding to comments – that step has been removed since the last RoC. *(Appendix 4 and 5).*

It bears highlighting that in a November 16, 2004 'prompt' letter from the Office of Management and Budget (OMB) to the National Institutes of Health (NIH), the Administrator of the Office of Information and Regulatory Affairs (OIRA) echoed similar concerns after noting the "six distinct information quality correction requests [under the Information Quality Act] related to either the NTP Report on Carcinogens or to the NTP review process for individual substances."[23]

Under the federal Information Quality Act (IQA)[24] and the implementing guidelines,[25] federal agencies are required to maximize the quality, integrity, utility and objectivity of the information they disseminate.[26] Scientific information must be reproducible and transparent, and sound statistical and research methods must be used to develop analytical results.[27]

To "instill public confidence in the NTP process and Report on Carcinogens,"[28] the OIRA Administrator suggested:

> *"[W]hen NTP receives comments from the public on substances being reviewed for listing or delisting in the Report on Carcinogens, NTP should prepare a response-to-comments document and make this document available to the public in a timely manner. The Report on Carcinogens already acknowledges that 'opportunities for public comment and participation are an integral part of the review process.' To fully realize the value of the comment process, NTP should prepare and disseminate a response-to-comments document before completion of a substance's review. This document would improve the transparency of the process and assure the public that their perspectives have not only been sought but also considered. Moreover, the discipline of preparing this document will ensure that the scientists responsible for the Report on Carcinogens have systematically considered and addressed all the significant scientific comments that NTP has received. It would also be desirable for this document to be made available before an NTP review committee evaluates a particular substance. With this structure, the members of these important committees will also have the benefit of both the insights of the public and the NTP's responses to these comments."*[29]

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[23] Letter from OIRA Administrator Dr. John D. Graham to NIH Director Dr. Elias A. Zerhouni, November 16, 2004, available at http://www.reginfo.gov/public/prompt/nih_ntp111604.pdf (hereinafter OIRA Letter to NIH); "'Prompt' letters are a mechanism created in 2001 that OIRA uses to pro-actively suggest issues that agencies might address." OIRA Q&A's, available at http://www.whitehouse.gov/omb/OIRA_QsandAs.

[24] Treasury and General Government Appropriations Act for Fiscal Year 2001, Pub. L. No. 106-554, § 515, 114 Stat. 2763A-153 to 2763A-154, 44 U.S.C. § 3516 note (2000).

[25] Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies, 67 Fed. Reg. 8452 (Feb. 22, 2002) (hereinafter OMB IQA Guidelines); HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public, available at http://aspe.hhs.gov/infoquality/Guidelines/index.shtml; NIH Guidelines for Ensuring the Quality of Information Disseminated to the Public, available at http://www.aspe.hhs.gov/infoquality/Guidelines/NIHinfo2.shtml.

[26] OMB IQA Guidelines, 67 Fed. Reg. at 8452.

[27] Ibid.

[28] OIRA Letter to NIH, *supra*, note 23.

[29] Ibid.

Peer Review Transparency

Part of the process for the 13th RoC includes peer review of the draft RoC Monograph by an NTP Peer Review Panel. Although the schematic (*Appendix 4*) identifies these peer review panels as federally chartered advisory groups, several concerns have been raised about them, including the charge questions - what they will be and where they will come from - and the extent of public input into their formulation.[30] It is also unclear whether these advisory groups fit Federal Advisory Committee Act (FACA) criteria such as membership balance, objectivity, and accessibility to the public.[31]

Concerns also exist over the NTP's Board of Scientific Counselors (BSC), which are involved twice during the 13th RoC process - once to review the "draft concepts for substances proposed for evaluation," (*Appendix 4*) and then again when it is "present[ed] information regarding the peer review and revised draft RoC Monograph." (*Appendix 4*). The use of the word 'present' is unclear, as it suggests the BSC may not be given the option to review, comment, and provide feedback on the revised draft RoC Monograph.

Administration Guidance on Regulatory Process

On January 20, 2009, President Obama's then-Chief of Staff Rahm Emanuel issued a memo to the heads of executive departments and agencies on regulatory review. The following language in the memo is of interest to this hearing:

> *"As used in this memorandum, 'regulation' has the meaning set forth in section 3(e) of Executive Order 12866 of September 30, 1993, as amended; this memorandum covers 'any substantive action by an agency (normally published in the Federal Register) that promulgates or is* ***expected to lead to the promulgation of*** *a final rule or regulation, including notices of inquiry, advance notices of proposed rulemaking, and notices of proposed rulemaking.'"*[32] *(emphasis added).*

NTP's position is that the RoC is a "science-based, authoritative public health communicated tool, not a regulatory document."[33] But the Emanuel memo specifically covers actions by agencies that 'promulgate or is **expected to lead to the promulgation of** a final rule or regulation.' Arguably, the RoC is covered in this definition because NTP acknowledges that

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[30] NTP Website – Background Information, *supra*, note 16.

[31] Wendy R. Ginsberg, "Federal Advisory Committees: An Overview," *Congressional Research Service*, (R40520), January 24, 2011, available at: http://www.crs.gov/Products/R/PDF/R40520.pdf; "FACA defines an 'advisory committee' as 'any committee, board, commission, council, conference, panel, task force, or other similar group, or any subcommittee or other subgroup thereof' that is 'established by statute or reorganization plan,' 'established or utilized by the President,' or 'established or utilized by one or more agencies.' All advisory bodies that fit this definition, however, are not necessarily entities that must adhere to FACA."

[32] Memo from Rahm Emanuel, Assistant to the President and Chief of Staff, to Heads of Executive Departments and Agencies, January 20, 2009 (effective after 12:00pm), available at: http://www.whitehouse.gov/sites/default/files/omb/assets/information_and_regulatory_affairs/regulatory_review_012009.pdf.

[33] Memo from NIEHS and NTP Director Linda Birnbaum, to HHS Secretary Kathleen Sebelius, "Follow-up Information on the Report on Carcinogens, Twelfth Edition," December 2, 2010.

"[c]ertain regulatory agencies have chosen to base certain of their regulatory actions on a listing of a substance in the *Report on Carcinogens*."[34]

Moreover, applying the principles of the Emanuel memo to the RoC would also appear to honor the legislative intent of the law creating the RoC, when then-Chairman Rogers explained that the:

> *"intention of the legislation was that listing in the annual report would be a first step in regulation, one triggering a review by the agencies responsible for enforcing various laws regulating carcinogens."*[35]

Interagency Review and Decision-Making

Typically, substances listed in the RoC are selected after an interagency committee reviews the nominations.[36] This rather informal - and closed - process involves a scientist-representative from each of nine designated agencies, yet, once a substance goes through an interagency review early in the RoC process, it is almost certain to be listed in the final report. It is very rare for a substance to be reviewed and not recommended for a listing. The 12th RoC identifies three substances - over the course of twelve reports in 31 years - that were "formally considered for listing by the NTP and, after evaluation by the Report on Carcinogens review groups, were recommended not to be listed in the Report on Carcinogens."[37] When one considers that the 12th RoC contains 240 substance profiles, it raises questions about the role of public comments and review groups in the RoC.

Strength-of-Evidence vs. Weight-of-Evidence

Two common approaches in how scientific studies are assessed and evaluated include a strength-of-evidence (SOE) approach and a weight-of-evidence (WOE) approach. One of our witnesses, in recent public comments before the Board of Scientific Counselors regarding NTP's proposed revisions to the process for preparation of the RoC explained the issue thus:

> *"Although the draft [of the 13th RoC] speaks of addressing 'all information that may bear on a listing decision' and 'integrat[ing] the overall body of evidence,' it lacks a defined commitment to employing a weight-of-evidence approach to data evaluation. Such evaluations provide a systematic approach to describing how varied data contribute to the questions at hand, which for the RoC, means the considerations leading to potential human carcinogenicity classification. Thus, it is not sufficient to simply 'integrate' all data that argue for a listing, as is represented by the strength-of-evidence approach used*

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[34] Ibid.
[35] OTA Report, *supra*, note 5.
[36] Process for Preparation of the Report on Carcinogens, NTP, available at: http://ntp.niehs.nih.gov/NTP/RoC/Thirteenth/Process/FinalRoCProcesswithFig.pdf; (hereinafter NTP's RoC Preparation Process); "Interagency review is invited from agencies represented on the NTP Executive Committee, including the Consumer Product Safety Commission, Department of Defense, Environmental Protection Agency, Food and Drug Administration, National Cancer Institute, National Center for Environmental Health/Agency for Toxic Substances and Disease Registry, National Institute of Environmental Health Sciences, National Institute for Occupational Safety and Health, and Occupational Safety and Health Administration."
[37] 12th RoC, *supra*, note 12.

> *in past Report on Carcinogen reviews and which remains implied in the proposed revisions. Rather, a weight-of-evidence review demands a visible commitment to, and articulation of, standardized data presentation and analysis of all countervailing evidence, and weighs the associated strengths and weaknesses of those data in supporting listing classifications."*[38]

Moreover, the National Research Council of the National Academies had the following to say about a WOE approach in its review of EPA's formaldehyde assessment last year (*Appendix 6*):

> *"A weight-of-evidence approach such as that provided in EPA's RfC [Reference Concentration] Methodology (U.S. EPA, 1994) or in EPA's proposed guidelines for carcinogen risk assessment (U.S. EPA, 1999a) should be used in assessing the database for an agent. This approach requires a critical evaluation of the entire body of available data for consistency and biological plausibility. Potentially relevant studies should be judged for quality and studies of high quality given much more weight than those of lower quality. When both epidemiological and experimental data are available, similarity of effects between humans and animals is given more weight. If the mechanism or mode of action is well characterized, this information is used in the interpretation of observed effects in either human or animal studies. Weight of evidence is not to be interpreted as simply tallying the number of positive and negative studies, nor does it imply an averaging of the doses or exposures identified in individual studies that may be suitable as points of departure (PODs) for risk assessment. The study or studies used for the POD are identified by an informed and expert evaluation of all the available evidence (EPA 2002b, Pp 4-11 to 4-12)."*[39]

Studies considered for a RoC listing do not follow a WOE system as NTP does not identify a WOE framework to characterize the value, or 'weight,' of studies considered in determining a substance's carcinogenicity.

<u>The RoC's Statutory Obligations</u>

RoC Schedule

NTP has had a difficult time meeting its publication schedule. The 1st RoC was published in 1980, two years after the law's enactment, which initially called for an annual report. Although the 2nd RoC came out in 1981, the 3rd RoC was published in 1983 and the 4th was largely unavailable until 1986.[40] The 1993 change in the law allowing for biennial publications has not led to a more timely schedule considering the six years that lapsed between the publication of the 11th RoC in 2005 and the 12th last year.

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[38] James S. Bus, Ph.D., DABT, ATS, The Dow Chemical Company, Public Comment to the Board of Scientific Counselors re: National Toxicology Program Proposed Revisions to the Process for Preparation of the Report on Carcinogens, December 15, 2011, available at: http://ntp.niehs.nih.gov/NTP/About_NTP/BSC/2011/December/PublicComm/Bus20111215.pdf.

[39] "Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde," National Research Council of the National Academies, April 8, 2011 (hereinafter NAS Formaldehyde Report).

[40] OTA Report, *supra*, note 5.

Significant Number of Persons Exposed

The RoC is required to list substances *"to which a significant number of persons residing in the United States are exposed." (Appendix 1).* While the 12th RoC acknowledges the statutory requirement, it goes on to say:

> *"Some substances that have been banned or restricted in use (e.g., safrole, arsenical pesticides, and mirex) are listed either because people who were previously exposed remain potentially at risk or because these substances still are present in the environment."*[41]

No indication is given as to what constitutes a significant number of persons, nor how the substances listed in the 12th RoC impact such an undefined significant number of persons residing in the U.S.

Nature of Exposure and Number of Persons Exposed

The RoC is required to provide *"information concerning the nature of such exposure and the estimated number of persons exposed to such substances." (Appendix 1).* NTP falls short of meeting these statutory requirements, claiming:

> *(a) that four of its participating agencies "are responsible for regulating hazardous substances and limiting the exposure to and use of such substances,"*[42] *and*
> *(b) "[b]ecause little information typically is available, estimating the number of people who could be exposed and the route, intensity, and duration of exposure for each substance is a difficult task."*[43]

In ignoring these requirements, NTP explains that the RoC is a hazard identification document only because:

> *"the 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."*[44]

NTP further offers in the 12th RoC that:

> *"other types of information, such as data on use, production, and occupational or environmental exposure, can be used to determine whether there is (or was) exposure in the United States, and this information is included in each substance profile."*[45]

But, as critics have pointed out, this may not be sufficient:

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[41] 12th RoC, *supra*, note 12.
[42] Ibid.
[43] Ibid.
[44] Ibid.
[45] Ibid.

> *"The requirement to quantify the number of persons exposed serves a critical purpose, which is to ensure that the NTP focuses on high-priority substances and is not distracted by minutiae. As for the nature of exposure, it is reasonable to infer that Congress intended the NTP to focus on environmental and occupational cancer risks because it was these circumstances on which Congress was focused at the time it enacted the law. The NTP does not estimate the actual number of persons exposed…it relies on mass and volume indicators in lieu of exposure indices."*[46]

How a Federal Standard for a Substance Decreases the Public Health Risk

The RoC is required to provide *"a statement identifying for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in the list under subparagraph (A), the extent to which, on the basis of available medical, scientific, or other data, such standard, and the implementation of such standard by the agency, decreases the risk to public health from exposure to the substance." (Appendix 1).*

The RoC addresses this requirement by:

> *"providing in each profile a summary of the regulations and guidelines, if any, that are likely to decrease human exposure to that substance. Some of these regulations and guidelines have been enacted for reasons other than the substance's carcinogenicity (e.g., to prevent adverse health effects other than cancer or to prevent accidental poisoning of children). These regulations are included in the profiles because reduction of exposure to a suspected or known carcinogen is likely to reduce the risk for cancer."*[47]

While the above might be helpful information, it lacks the analysis the law requires of the RoC, which would be to connect the *"effluent, ambient, or exposure standard established by a Federal agency"* and the *"extent to which, on the basis of available medical, scientific, or other data, such standard, and the implementation of such standard by the agency, decreases the risk to public health from exposure to the substance." (Appendix 1).*

NTP's explanation for not meeting this requirement is that it is "beyond the scope of this report to provide detailed information or interpretation concerning the implementation of each regulatory act, and no attempt is made to do so."[48]

<u>Route of Exposure/Mechanism of Action/Mode of Action</u>

According to NTP's listing criteria:

> *"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*

[46] Belzer Paper, *supra*, note 21.
[47] 12th RoC, *supra*, note 12.
[48] Ibid.

> *other data relating to* ***mechanism of action or factors that may be unique to a given substance****."*[49] *(emphasis added).*

Yet, in the Addendum to the 12th RoC, NTP says:

> *"****Appreciation of 'mode of action,'*** *or an understanding of how exposure to a given substance might lead to cancer, is an important piece of supporting evidence, but* ***is not a requirement for listing in the RoC.****"*[50] *(emphasis added).*

Analyzing these two comments side-by-side, it appears as though NTP can pick and choose parts of its listing criteria to apply to the studies that exist on any given substance. It is worth referencing EPA's "*Guidelines for Carcinogen Risk Assessment*" to understand the significance of mode of action. EPA emphasizes that:

> *"In evaluating an agent's mode of action, it is usually not sufficient to determine that some event commences upon dosing. It is important to understand whether it is a necessary event that plays a key role in the process that leads to tumor development versus an effect of the cancer process itself or simply an associated event."*[51]

A recent article on NTP's decision to list styrene in the 12th RoC has this to say about mode of action:

> *"risk assessors need to understand as best they can the 'mode of action' (MOA) by which a substance acts biologically within and upon an organism. In many cases, this understanding will help confirm that humans are likely to react the same way as the test animal. But in some cases, this will show that what happened in the test animal is unlikely to happen in humans because of the differences between the species."*[52]

The article further explains that such is the case with styrene, because:

> *"Tumors in laboratory animals have been observed in only one species - mice - and the known plausible biological mechanism by which styrene could cause cancer is specific to the mouse lung and is not relevant to humans."*[53]

<u>Delisting a Substance</u>

There are no guidelines on the process for delisting a substance beyond a mention that one can nominate a substance for delisting in the same way that one nominates a substance for listing in a RoC. However, it is not easy to delist a substance once it is on the RoC, as it takes years, if not decades, to accomplish, and even then, it may not really be delisted. For example, saccharin,

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[49] NTP Website – Listing Criteria, *supra*, note 19.
[50] RoC Addendum, *supra*, note 18.
[51] EPA, "Guidelines for Carcinogen Risk Assessment," March 2005, available at: http://www.epa.gov/osa/mmoaframework/pdfs/CANCER-GUIDELINES-FINAL-3-25-05[1].pdf
[52] Julie E. Goodman, Lorenz R. Rhomberg and Robyn L. Prueitt, "Why Styrene Should Not be Classified as a Human Carcinogen And Does Not Belong in the NTP's 12th Report on Carcinogens," *Bloomberg BNA Daily Environment Report*, March 12, 2012, available at: http://www.gradientcorp.com/alerts/pdf/Styrene.pdf.
[53] Ibid.

which was last listed in 1998 in the 8th RoC, was first listed in the 2nd RoC in 1981 as 'reasonably anticipated' to be a human carcinogen.[54] More interesting is the attempt to delist glass wool, which was first listed in 1994 in the 7th RoC. As described in a December 14, 2011 letter from SBA's Office of Advocacy to the Director of the Office of the Report on Carcinogens:

> *"After more than ten years of research, glass wool was nominated for delisting in 2004. However, instead of delisting the substance the NTP modified the substance profile which excluded certain varieties of glass wool that are 'not biopersistent' in the lung.*
>
> *In the 12th RoC glass wool does not appear either as a delisted substance or as a listed substance, causing additional confusion. The listing to 'delisting' process for glass wool took more than 20 years."*[55]

RoC and IARC

The International Agency for Research on Cancer (IARC) is part of the World Health Organization (WHO). IARC's mission is to "coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer prevention and control."[56] Through international Working Groups, IARC prepares and publishes:

> *"critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The[se] Monographs represent the first step in carcinogen risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans."*[57]

It is easy to make comparisons between the RoC and IARC's cancer Monographs, given that they're both hazard identification documents, and in the case of the RoC, is largely considered to be influenced by IARC's work. Unlike the RoC however, IARC maintains five categories for classifying its substances:

- *Group 1: Carcinogenic to humans – 107 agents;*
- *Group 2A: Probably carcinogenic to humans – 63 agents;*
- *Group 2B: Possibly carcinogenic to humans – 271 agents;*
- *Group 3: Unclassifiable as to carcinogenicity in humans – 509 agents; and*
- *Group 4: Probably not carcinogenic to humans – 1.*[58]

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[54] 12th RoC, *supra*, note 12.
[55] Letter from Winslow Sargeant, Chief Counsel for Advocacy, to Ruth Lunn, Director, Office of the Report on Carcinogens, December 14, 2011, available at: http://ntp.niehs.nih.gov/NTP/RoC/Thirteenth/Process/PublicComm/SBA20111214.pdf.
[56] International Agency for Research on Cancer website, available at: http://www.iarc.fr/ (hereinafter IARC Website).
[57] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Preamble, 2006, available at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf.
[58] IARC Website, *supra*, note 56.

The RoC has the two categories – "known" to be carcinogenic and "reasonably anticipated" to be carcinogenic. *(Appendix 2).*

While the IARC's five cancer classification categories appear to provide more flexibility and clarity than the RoC, the IARC process also has its own limitations, as, like the RoC, it too is a hazard identification document.

Impact on Small Business

The listing or upgrade of a substance in the RoC has both immediate and long-term impacts on small businesses and creates an atmosphere of uncertainty.[59] While NTP claims the RoC is not a regulatory document, federal and state agencies and state legislators use the RoC as a basis for regulatory and legislative actions without conducting or requiring more comprehensive risk assessments. Small businesses concerned about increased compliance costs due to regulations triggered by the recent listing of styrene are delaying making investments and holding off on hiring additional employees.[60] Some small business owners are also concerned that the increased operating costs may force them to move their facilities outside of the United States.[61]

Federal agencies rely on the information provided in the RoC[62] and use it as a substantive source of information to make regulatory decisions. Under the Occupational Safety and Health Administration's (OSHA) existing Hazardous Communication Standard (HCS), safety data sheets (SDSs) and labeling requirements are triggered by a RoC listing.[63] OSHA recently revised the HCS but retained the requirement that RoC listings be included on SDSs.[64] Small businesses that have hazardous chemicals in their workplace are required to use the SDSs to inform and train employees.[65] In addition, OSHA-regulated laboratories must adopt special procedures for a substance that is listed in the RoC.[66] EPA's reliance on the 11th RoC led it to add 16 chemicals listed in the RoC to its list of toxic chemicals subject to reporting under section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 and section 6607 of the Pollution Prevention Act of 1990.[67]

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[59] Mike Verespej, "Congressmen ask for review of styrene safety," *Plastics News*, November 9, 2011, http://plasticsnews.com/headlines2.html?id=23645 (hereinafter Verespej Article).

[60] Ibid.

[61] Ibid.

[62] Addition of National Toxicology Program Carcinogens; Community Right-to-Know Toxic Chemical Release Reporting, 75 Fed. Reg. 72,727, 72,729, November 26, 2010 (hereinafter Community Right-to-Know); The EPA has stated that the "RoC is an excellent and reliable source of information on the potential for chemicals covered therein to cause cancer in humans." Ibid.

[63] 29 C.F.R. § 1910.1200 (2011).

[64] U.S. Department of Labor, Occupational Safety & Health Administration, Modification of the Hazard Communication Standard (HCS) to conform with the United Nations' (UN) Globally Harmonized System of Classification and Labeling of Chemicals (GHS), available at: http://www.osha.gov/dsg/hazcom/hazcom-faq.html. OSHA modified and published the revised Hazardous Communication Standard on March 26, 2012. Hazardous Communication,77 Fed. Reg. 17,574 (March 26, 2012) (to be codified at 29 C.F.R. pts. 1910, 1915, and 1926). The new regulatory requirements will be phased in between December 1, 2013 and June 1, 2016. Ibid. at 17,582. Employers must be in compliance with the existing or revised HCS, or both, during the phase-in period.

[65] Hazardous Communication, 77 Fed. Reg. 17,574, 17,577 (March 26, 2012) (to be codified at 29 C.F.R. pts. 1910, 1915, and 1926).

[66] 29 C.F.R. § 1910.1450(e)(viii) (2011).

[67] Community Right-to-Know, *supra*, note 62.

On the state-level, a number of worker and community right-to-know and regulatory requirements in other states are also automatically triggered.[68] The listing of a substance in the RoC triggers California Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986.[69] States may also propose new standards as a result of a substance listing. Citing the recommendation of an NTP expert panel in the 12th RoC, California's Office of Environmental Health Hazard Assessment (OEHHA) recently published its Draft Public Health Goal for Styrene in Drinking Water.[70]

In addition to the regulatory burdens, a listing may also cause confusion as to the true public health risk posed by a substance, which can have an economic impact on small business. As previously mentioned, the NTP states that "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."[71] However, this disclaimer may not allay the concerns that any exposure to the substance has the potential to cause cancer and lead to legislative action to protect the public's health.

In 2010, Colorado state legislators, concerned about chemicals that cause cancer or reproductive toxicity in personal care products, introduced a bill that in part defined "chemical identified as causing cancer or reproductive toxicity" as a substance listed in the RoC.[72] The legislation would have banned all sales and distribution of personal care products that contain a substance listed in the RoC as "known" or "reasonably anticipated" to be a carcinogen.[73] Among those substances is methyleugenol, a naturally occurring substance present in a number of essential oils including rose, hyacinth, anise, basil, and citronella, which was originally listed in the 10th RoC as reasonably anticipated to be a human carcinogen.[74] The ban would have been enforced through a private right of action that would have allowed citizens to bring an action against a manufacturer.[75] Small businesses found in violation of the law would have been subject to civil penalties of $5,000 for a first offense and $10,000 for subsequent offenses.[76]

The listing of Styrene in the 12th RoC has the potential to impact a substantial number of small businesses as thousands of companies across the country use the substance.[77] For example, over 3,000 small and medium-sized companies represented by the American Composites Manufacturers Association use styrene-polyester resin and glass fiber to manufacture a variety of

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[68] *See* 010-00 ARK. CODE. R. 012 (2012); 105 MASS. CODE REGS. 670.010 (2011); MINN. R. 5206.0100 (2011); N.J. ADMIN. CODE § 12:100-7.7 (2012); 34 PA. CODE § 323.5 (2012).
[69] CAL. HEALTH & SAFETY CODE § 25249.5-25249.13 (2012).
[70] OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT, CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY, PUBLIC HEALTH GOALS FOR CHEMICALS IN DRINKING WATER, STYRENE 2 (2010). OEHHA recommended a Public Health Goal of 0.5 parts per billion (ppb) (0.5 micrograms/liter) for styrene in drinking water (a much lower level than the federal EPA maximum contaminant level goal of 100 ppb (0.1 milligrams/liter).
[71] 12th RoC, *supra*, note 12.
[72] H.B. 10-1248, 67th Gen. Assem., 2d Sess. (Colo. 2010) (hereinafter CO Bill).
[73] Ibid.
[74] 12th RoC, *supra*, note 12.
[75] CO Bill, *supra*, note 72.
[76] Ibid.
[77] American Composites Manufacturers Association Questions and Answers about Styrene, January 21, 2010, available at http://www.acmanet.org/ga/advocacy/Questions&Answers-about-Styrene.pdf.

products including: major components for wind and solar energy; ballistic panels that protect our troops; residential bathtubs, showers, and countertops; recreational boats; and light-weight components that improve the fuel economy of cars, trucks, and mass transit vehicles.[78] The industry estimates that manufacturing plants that use styrene or styrene-derived products employ 500,000 people.[79]

An Oregon composites manufacturer that uses styrene believes that the RoC listing of styrene affected its insurance coverage. Miles Fiberglass and Composites' workers' compensation insurance policy, which was up for renewal in 2011, was dropped, and the small business is now paying $144,000 annually, as compared to its previous rate of $73,000.[80]

Companies are also concerned about potential litigation which may drive up insurance costs. A recent article noted that "[a]ttorneys are primed for a wave of toxic torts over exposure to formaldehyde, which U.S. regulators identified as a 'known carcinogen' last summer."[81]

Legal Challenges, and Agency Comments

Various RoC listings have also been subject to challenges by affected businesses and trade associations in the courts.[82] Before the 12th RoC was finalized, the Chief Counsel for Advocacy of the U.S. Small Business Administration sent a letter to the Secretary of the Department of Health and Human Services citing small business concerns about the NTP process.[83] In 2011, after the 12th RoC was finalized, the Chief Counsel for Advocacy again wrote to the Secretary of Health and Human Services and outlined the potential economic impact on small businesses of a RoC listing, concerns with the 12th RoC review process, and concerns about the proposed changes for the 13th RoC.[84] The Chief Counsel for Advocacy:

> *"urge[d] the HHS to review and evaluate the RoC's purpose and objectives and to consider whether, if substantial changes cannot be made, the RoC should continue to play a role in the federal government's chemical risk assessment program."*[85]

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[78] Ibid.
[79] Ibid.
[80] Verespej Article, *supra*, note 59.
[81] Erin Fuchs, "Formaldehyde Cancer Link Could Spur Modest Tort Wave," *Law 360*, April 17, 2012.
[82] *See Tozzi v. U.S. Dep't of Health & Human Servs*., 271 F.3d 301 (D.C. Cir. 2001); *The Fertilizer Inst. v. U.S. Dep't of Health & Human Servs*., 355 F. Supp. 2d 123 (D.D.C. 2004); *Synthetic Organic Chem. Mfrs. Ass'n v. U.S. Dep't of Health & Human Servs*., 720 F. Supp. 1244 (W.D. La. 1989).
[83] Letter from Winslow Sargeant, Chief Counsel for Advocacy to Kathleen Sebelius, Sec'y of Health & Human Servs, December 1, 2010, available at http://www.sba.gov/sites/default/files/hhs10_1201.pdf.
[84] Letter from Winslow Sargeant, Chief Counsel for Advocacy to Kathleen Sebelius, Sec'y of Health & Human Servs, November 22, 2011, available at http://www.sba.gov/sites/default/files/Advocacy_Comment_Letter-Report_On_Carcinogens.pdf. Advocacy resent this letter to Ruth Lunn, Director, Office of the Report on Carcinogens, on December 14, 2011.
[85] Ibid.

WITNESSES

Panel I:

- **Dr. Linda S. Birnbaum**, Director, National Institute of Environmental Health Sciences & National Toxicology Program, U.S. Department of Health and Human Services
- **Mr. Charles A. Maresca,** Director of Interagency Affairs, Office of Advocacy, U.S. Small Business Administration

Panel II:

- **Dr. James S. Bus**, Director of External Technology, Toxicology and Environmental Research and Consulting, The Dow Chemical Company
- **Dr. L. Faye Grimsley,** Associate Professor, Tulane School of Public Health and Tropical Medicine, Department of Global Environmental Health Sciences
- **Ms. Bonnie Webster**, Vice President, Monroe Industries, Inc.
- **Ms. Ally LaTourelle**, Esq., V.P. Government Affairs, Bioamber, Inc
- **Mr. John E. Barker**, Corporate Manager, Environmental Affairs, Safety and Loss Prevention, Strongwell Corporation
- **Dr. Richard B. Belzer**, President, Regulatory Checkbook

APPENDIX 1[86]

History of the RoC - Congressional Mandate (1978)

In response to concerns from people within the United States regarding the relationship between their environment and cancer, in 1978 the U.S. Congress mandated, as part of the Public Health Service Act, (see Section 301(b)(4), as amended)[1], that the Secretary, Health and Human Services (HHS), publish a biennial report which contains:

A. a list of all substances
    i. which either are known to be carcinogens or may reasonably be anticipated to be carcinogens and
    ii. to which a significant number of persons residing in the United States are exposed;
B. information concerning the nature of such exposure and the estimated number of persons exposed to such substances;
C. a statement identifying
    i. each substance contained in the list under subparagraph (A) for which no effluent, ambient, or exposure standard has been established by a Federal agency, and
    ii. for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in the list under subparagraph (A), the extent to which, on the basis of available medical, scientific, or other data, such standard, and the implementation of such standard by the agency, decreases the risk to public health from exposure to the substance; and
D. a description of
    i. each request received during the year involved
        I. from a Federal agency outside the Department of Health, Education, and Welfare for the Secretary, or
        II. from an entity within the Department of Health, Education, and Welfare to any other entity within the Department, to conduct research into, or testing for, the carcinogenicity of substances or to provide information described in clause (ii) of subparagraph (C), and
    ii. how the Secretary and each such other entity, respectively, have responded to each such request.

[86] NTP Website, *History of the RoC*, available at: http://ntp.niehs.nih.gov/?objectid=03CA7EEA-CBAA-EB17-20B4B2C329C5DDCF.

APPENDIX 2[87]

NTP Listing Criteria for the RoC

The criteria for listing an agent, substance, mixture, or exposure circumstance in the 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.

**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.*

[87] NTP Website – Listing Criteria, *supra*, note 19.

APPENDIX 3[88]

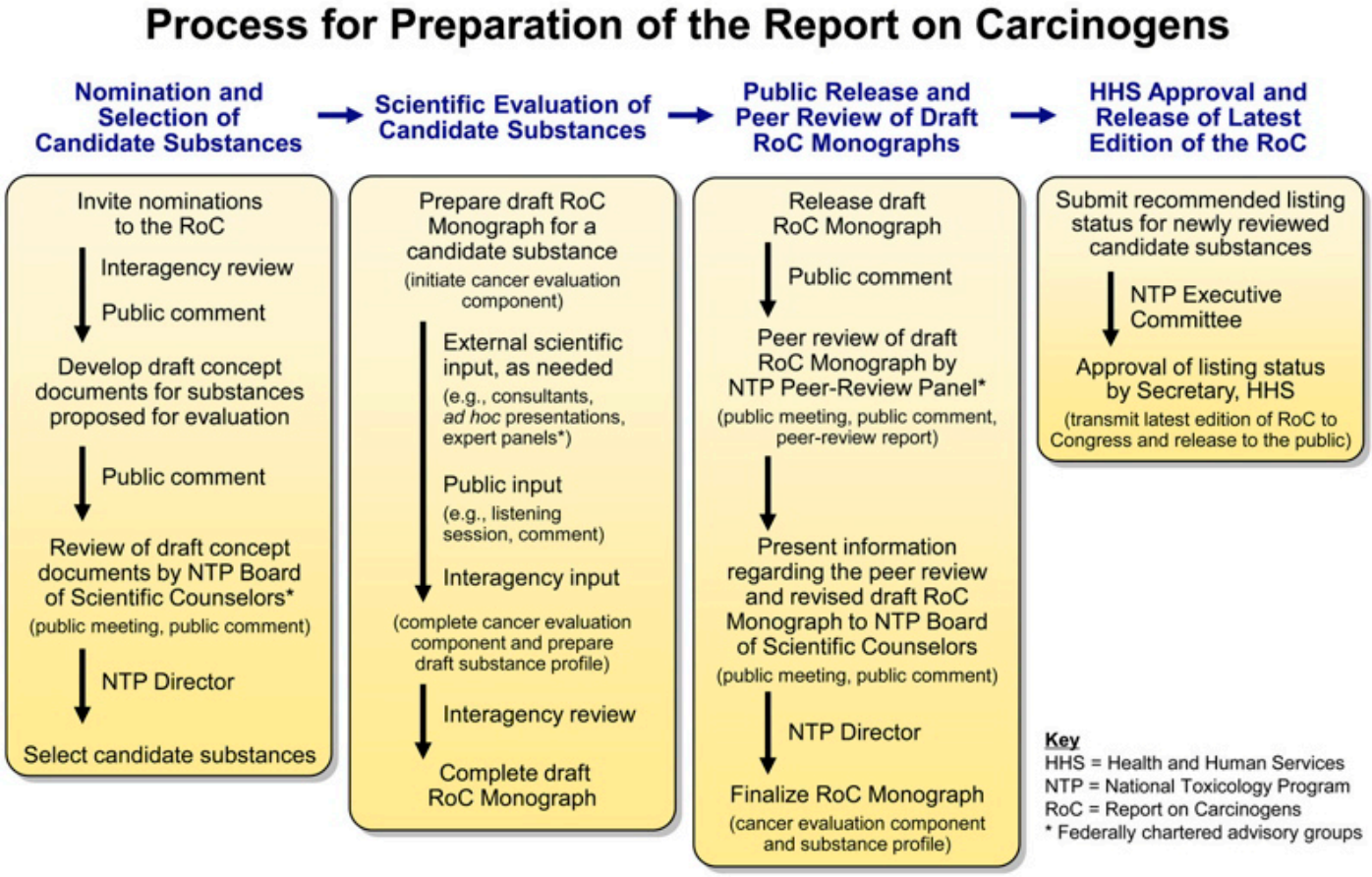
Substances Delisted from the Report on Carcinogens

Substance Name	CAS Number	Last Listing	Reason for Delisting
Chloramphenicol	56-75-7	*known*	Human data considered inadequate
Aramite	140-57-8	First RoC (1980) *reasonably anticipated* Fourth RoC (1985)	No U.S. residents exposed
N,*N*-Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine)	494-03-1	*known* Fourth RoC (1985)	No U.S. residents exposed
Cycasin	14901-08-7	*reasonably anticipated* Fourth RoC (1985)	No U.S. residents exposed
Methyl iodide	78-88-4	*reasonably anticipated* Fourth RoC (1985)	Reevaluated by IARC; evidence now considered equivocal
5-Nitro-*o*-anisidine	99-59-2	*reasonably anticipated* Fifth RoC (1989)	Insufficient evidence of carcinogenicity
p-Nitrosodiphenylamine	156-10-5	*reasonably anticipated* Fifth RoC (1989)	Insufficient evidence of carcinogenicity
Ethyl acrylate	140-88-5	*reasonably anticipated* Eighth RoC (1998)	See following profile
Saccharin	81-07-2	*reasonably anticipated* Eighth RoC (1998)	See following profile

[88] 12th RoC, *supra*, note 12.

APPENDIX 4[89]

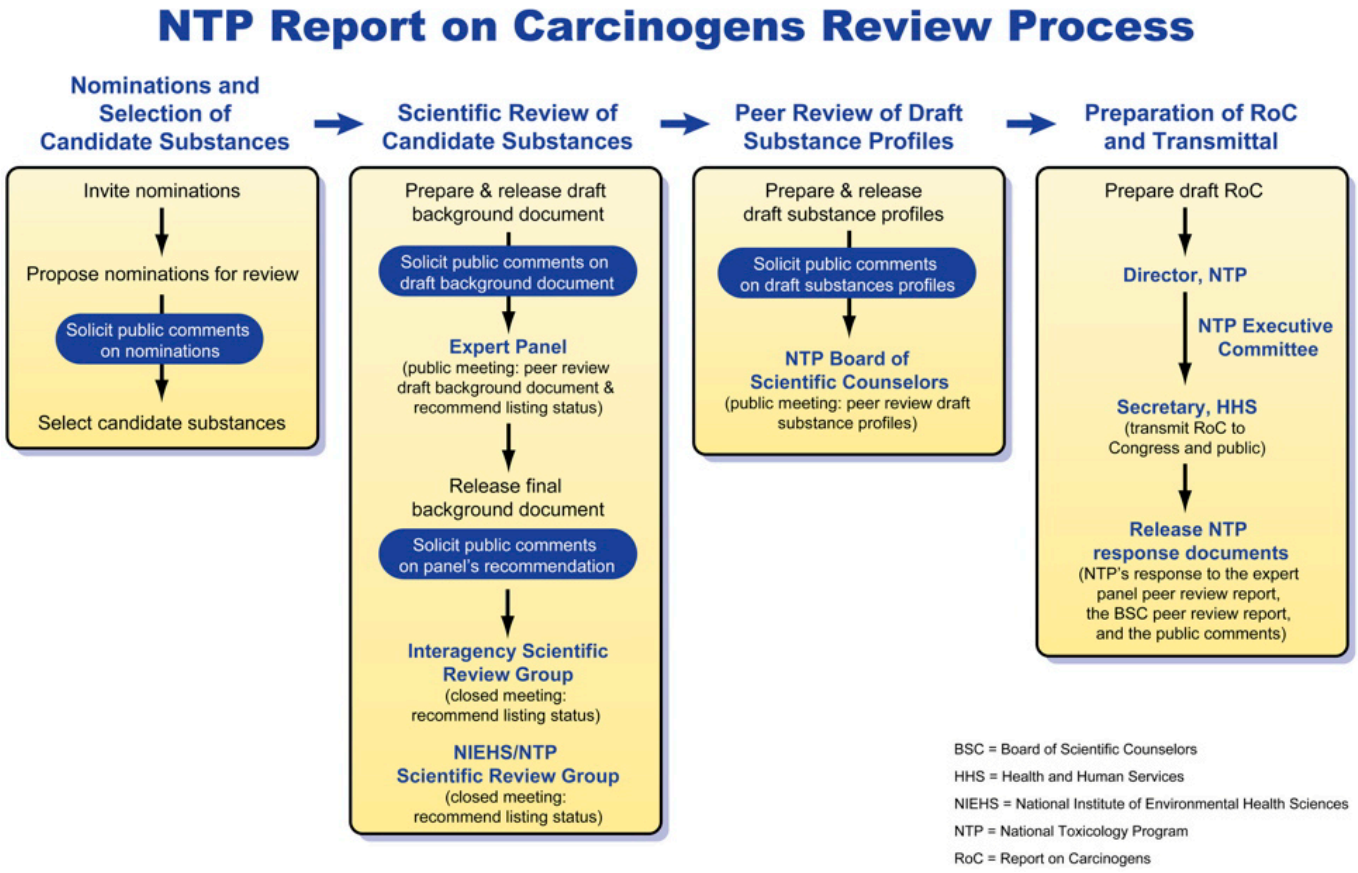
Schematic of the Process for the 13th Report on Carcinogens



[89] NTP Website, *Process for the Preparation of the Report on Carcinogens*, (13th RoC), available at: http://ntp.niehs.nih.gov/?objectid=3756DE0C-FA7A-404B-3F72194C30ABD961.

APPENDIX 5[90]

Schematic of the Process for the 12th Report on Carcinogens



[90] NTP Website, *Review Process for the 12th Report on Carcinogens*, available at: http://ntp.niehs.nih.gov/?objectid=03C9C7CF-CF9E-913D-882FBAB402BADA19.

APPENDIX 6[91]

FIGURE 4-5 Conceptual view of a weight of evidence (WOE) assessment. This figure illustrates the critical considerations within a WOE assessment of toxicity data.

- **Rigor** is the degree of proper conduct and analysis of a study; greater weight is generally given to more rigorous studies.
- **Statistical Power** is the ability of a study to detect effects of a given magnitude.
- **Corroboration** means that specific effects are replicated in similar studies, similar effects are observed under varied conditions and /or similar effects are observed in multiple laboratories.
- **Reproducibility** means that an effect is observed in multiple species by various routes of exposure.
- **Relevance to Humans** means that similar effects are observed in humans or in a species taxonomically related to humans or at doses similar to those expected in humans.
- **Plausibility to Humans** is the determination of whether a similar metabolism, mechanisms of damage and repair, and molecular target of response could be expected to occur in humans, based on an evaluation of the biologic mechanism of a toxic response in animals.
- **Database Consistency** is the extent to which all of the data are similar in outcome and dose (exposure-response) and are operating under a single biologically plausible assumption (mode of action).

Source: Adapted from Gray et al. 2001, EPA 2006, Pp 29-30.

[91] NAS Formaldehyde Report, *supra*, note 39.