October 22, 2004

Dr. Barbara Shane
NTP Executive Secretary,
National Institute of Environmental Health Sciences
PO Box 12233, MD A3-01
Research Triangle Park, NC 27709-2233

Re: National Toxicology Program's Board Of Scientific Counselors Meeting October 26, 2004: Comments on CERHR Small Dataset Process and the Concept Review Paper for Application of Automated Techniques to Toxicity Testing

Dear Dr. Shane:

The American Chemistry Council (ACC) is pleased to offer these comments on two matters slated for discussion by the National Toxicology Program's (NTP's) Board Of Scientific Counselors (BSC) at its upcoming October 26, 2004 meeting. ACC requests that NTP consider the perspective we provide in these comments on 1) the proposed Center for the Evaluation of Risks to Human Reproduction (CERHR) Small Dataset Process, and 2) the Concept Review paper on Application of Automated Techniques to Toxicity Testing as these programs move forward.

For over three decades the American Chemistry Council[1] and its member companies have played an active role in screening and testing chemical substances, developing

[1] The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through health and environmental research and product testing, Responsible Care®, and common sense advocacy designed to address major public policy issues. The business of chemistry is a $460 billion enterprise and a key element of the nation's economy. It is the nation's largest exporter, accounting for ten cents out of every dollar in U.S. exports. Chemistry companies invest more in research and development than any other business sector. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, working closely with government agencies to improve security and to defend against any threat to the nation's critical infrastructure. As a science-driven industry, the business of chemistry – through the Council's Long Range Research Initiative and thorough research, screening and testing of specific chemicals by individual member companies – provides significant support for scientific research to better understand and characterize the potential risks from chemical exposures.

risk assessments and implementing science-based risk management policies. ACC supports NTP's research and testing efforts, and in particular encourages the use of more mechanistic data in hazard and risk assessments.

The Council believes that the proposed CERHR Small Dataset Process, in an apparent desire to 'streamline' CERHR efforts, would result in a significant step backwards. It is unclear how the proposed changes would lead to improvements, and in fact, ACC is concerned that the proposed changes would weaken both the scientific quality and the public participation processes of CERHR.

With respect to NTP's proposed approach to move forward with Application of Automated Techniques to Toxicity, NTP's Concept Review Paper has a number of critical gaps that should be addressed before NTP proceeds with implementation. Application of mechanistic data by NTP requires both understanding of the mechanistic endpoint in terms of the assay and scientific consensus on the relevance of the endpoint to the disease process in humans, both of which must be considered in the context of dose. Development of a database, as NTP appears to be proposing, of results from un-validated assays is contraindicated, not only on general scientific grounds, but also by the ICCVAM Authorization Act of 2000 (42 U.S.C. 2851). ACC believes NTP is obliged to provide and/or develop the critical scientific information regarding the relevance, reliability, and appropriate use of the assays before they are employed. Unless such assays are validated first, NTP (and others) will lack the requisite information needed for interpreting the results with sufficient scientific confidence.

1. Proposed CERHR Small Dataset Process

The CERHR process that has been developed by NTP involves the comprehensive and thorough review and interpretation of the best available science, conducted in a manner that fosters scientific dialogue, transparent decision-making, open meetings and stakeholder involvement. The interactive scientific model put into practice in the current CERHR process is to be commended. ACC is concerned that the NTP's proposed CERHR Small Dataset Process could significantly degrade the integrity of the CERHR process and result in substandard and scientifically weaker work products and final reports.

The information provided on NTP's proposed changes to the established CERHR process lack details needed to evaluate the merits of the proposal. For example, it is unclear how NTP proposes to determine which materials will go through the small dataset evaluation and which through the regular CERHR process. Will there be a distinction in the statements of conclusions that will be reached? Will a small dataset evaluation include some indication of data needs, and if so, is NTP planning to develop guidance on levels of evidence needed to reach such conclusions to ensure uniformity of application?

The current CERHR process fosters opportunities for substantive scientific dialogue among the most qualified chemical-specific and subject matter specific experts during the most critical stages of the process, including the comprehensive literature evaluation and writing/review of the draft report. However, the proposed Small Dataset process appears to remove several important components of this process. Specifically, the proposed Small Dataset Process 1) eliminates outside expert involvement in developing/writing the first public review draft of the Report; 2) eliminates open public discussions of the initial draft report; 3) eliminates expert panelists as authors (and substitutes NTP authorship); and 4) eliminates expert panelists as authors of the 'Conclusions' and 'Recommendations' sections.

The Council believes that the proposed Small Dataset Process, in an apparent desire to 'streamline' CERHR efforts, would result in a significant step backwards by NTP, and would weaken both the scientific quality and the public participation processes. The current CERHR process fosters opportunities for substantive scientific dialogue among the most qualified chemical-specific and subject matter specific experts during the most critical stages of the process. The proposed changes would eliminate this.

While the current open and transparent CERHR process may take more time than the proposed Small Dataset approach, this allows for enhancing scientific quality and dialogue, and should be viewed as time well spent. Clearly, the initial work product of the current CERHR is greatly strengthened in terms of scientific rigor by a process that includes recognized subject matter experts from a diverse array of applicable fields and affiliations working in a collaborative manner to develop the initial public review draft report. As proposed, the Small Dataset process, particularly at the crucial report drafting stages, is very likely to miss expertise relevant to understanding significant issues for a particular chemical.

NTP is to be commended for seeking input on ways to improve hazard and risk characterizations. However, ACC believes NTP <u>should not</u> consider implementing changes to the CERHR processes which would degrade the existing open and transparent process and reduce opportunities for independent experts to meaningfully participate in critical phases of data review and evaluation and drafting of conclusions. In fact, ACC previously suggested that NTP could improve the Report on Carcinogen process by modeling it along the lines of the interactive scientific model put into practice in the current CERHR process (see attachment1). Now, it appears NTP is moving towards degrading the CERHR process, at least for Small Dataset substances, to model it along the lines of the far-from-perfect existing RoC process.

2. Concept Review Paper: Application of Automated Techniques to Toxicity Testing

In its Concept Review Paper, NTP is proposing to develop and implement automated technologies to evaluate and perhaps predict the toxicological impacts of environmental agents, even in the absence of classical toxicity test evaluations. The proposal suggests a primary objective of automated techniques is to provide "…more rapid screening systems…if only for ranking agents for more extensive testing." However, the Concept Review Paper does not describe a research strategy indicating how screening information gleaned from automated testing can or will be translated into meaningful predictions of actual adverse responses in whole animal test systems (e.g., cancer, reproductive, neurotoxicity, etc.), specific target organs, and whole animal dose-response. Knowledge of potential mechanism(s) alone is not sufficient to make such judgments, which represent the core data elements of the risk assessment paradigm. For example, *in vitro* information that a chemical has an oxidant mode of action is not sufficient to predict what type of toxicity may be observed (e.g., cancer, red blood cell hemolysis, cataracts, etc), what are potential target organs (e.g., lung, pancreatic beta cells, etc.), or what are the precise impacts of pharmacokinetic influences on potential dose response (e.g., first-pass metabolism, detoxification pathways, differential clearance mechanisms, etc.). ACC believes the primary objective and value of mechanism-based automated techniques ultimately will be to provide information that critically improves the interpretive value of whole animal toxicity tests for estimation of adverse human health effects.

ACC is certainly supportive of use of mechanistic data in risk assessments. However, as formulated, NTP's Concept Review Paper has a number of critical gaps that should be addressed before NTP proceeds in implementing this approach. There are several critical gaps:

1. Insufficient detail to understand the specific mechanisms or models that are proposed for evaluation

2. No description of the process that NTP will follow to ensure methods are validated before they are routinely applied and used for decision-making

3. No description of the systematic and orderly process that is needed to apply data from individual automated methods or batteries of assays for extrapolation and decision making regarding the relevance to humans (and likelihood of occurrence) of adverse effects at environmentally germane exposure conditions.

4. As described, the approach NTP appears to be proposing places method validation too late in the process.

Incorporating better mechanism-based approaches into toxicology, hazard assessment and risk characterization is a goal shared by academia, government agencies and industry. While classical whole animal toxicology studies may have limitations, such as concerns regarding interspecies and high-to-low dose extrapolations, these observational studies have been, and will remain, necessary for sound regulatory and risk decisions. Nevertheless, mechanism-based based approaches can in part compensate for deficiencies in classical toxicity studies by providing critical ancillary data that improves confidence in interpretation and extrapolation of study results to potential human risks.

In the Concept Review Paper, the authors seem to request blanket authorization to pursue any and all 'automated techniques' under the rubric that automation and further acceleration of in vitro or mechanistic assays will without doubt provide critical data needs that will improve health risk decision making. Such a simplistic approach belies the fact that application of mechanistic data by NTP requires both understanding of the mechanistic endpoint in terms of the assay and scientific consensus on the relevance of the endpoint to the disease process in humans, both of which must be considered in the context of dose.

While there is certainly value to seeking mechanism-based refinements to classical toxicology studies, the concept of transitioning current bioassays to mechanism-based alternatives, although desirable, must be done cautiously and with focused attention on appropriate "validation" of assay endpoints (or battery results) to well characterized and accepted understandings of disease processes. All laboratory toxicity tests must be standardized and validated in advance of their use in regulatory decision-making. Use of standardized and validated toxicity methods facilitates scientific interpretation of study results, promotes clear and consistent risk assessment analyses and enhances public confidence in the use of test results for protection of public health. This becomes a very important issue when new assays or screening batteries are developed. Validation, however it is defined, is not a simple process and will require significant time and resources before alternative assays/batteries can be used with confidence for hazard characterization.

Most, if not all, mechanistic assays will <u>not</u> measure an effect that is translatable to an adverse human health effect per se. Such mechanistic or screening assays are designed to detect substances that have the potential to interact with one or more components of a biological system. They do not detect adverse effects, and thus are not sufficient for either a screening or a complete hazard characterization or risk assessment, because such assays do not represent the biological complexity of the intact organism. Therefore, as part of its efforts to develop more mechanistic information, NTP must articulate how the test method's results will be used as information to make decisions. This is sometimes referred to as a testable prediction model. A clear synthesis of this prediction model is necessary in order for

the validation study to perform an adequate and sufficient evaluation of the test method. Thus, an agreed prediction model will be central to the evaluation of validation study results, i.e., whether the method has been successfully validated.

NTP's capacity to perform classical bioassays (modified by mechanism-based refinements as appropriate) is an important and unique resource that must not be set aside without careful and rigorous scientific examination and public dialog. Significant opportunity remains to refine conventional toxicology studies to make them more informative for providing data leading to improved understanding of risk and emerging human health questions. Mechanisms for defining more scientifically defensible selections of both the low and high dose ranges in classical toxicology studies are essential to improving the applicability of these studies to estimating potential human health risks resulting from low-level environmental exposures. Creative incorporation of mechanism-based approaches into classical bioassays will improve interpretational confidence of the relevance of both LOAEL and NOAEL responses to potential human risk (i.e., improved understanding of the shape of the dose-response curve, particularly at low exposure levels).

To facilitate more and better use of mechanistic data and information into NTP's programs requires much, much more than simply additional contracts for more data collection via automated technologies. NTP must first formulate the goals of its effort, to include description and justification of the mechanisms/endpoints targeted, then develop a strategy to achieve the goals, and have these reviewed & discussed in scientific and stakeholder communities prior to initiating the efforts.

In the absence of clear definition of goals, large scale in vitro screening using automated or mechanistic assays will likely lead to misinterpretation and misapplication of results because, unless such assays are validated first, NTP (and others) will lack the requisite information that is needed for interpretation of the results with suitable scientific confidence. Understanding of the relevance and reliability of an assay or battery (automated or manual) is a requisite first step, not the last step. If, as stated by NTP, their goal is to use such automated assays/batteries to predict the toxicological impacts of environmental agents in the absence of classical toxicity test evaluations, validation is needed because it is the step whereby the reliability of the prediction model is evaluated. Understanding an assay's performance against the prediction model is necessary to interpreting and applying the results.

Development of a database, as NTP appears to be proposing, of results based on un-validated assays is contraindicated, not only on general scientific grounds, but also by the ICCVAM Authorization Act of 2000. The ICCVAM Authorization Act of 2000 (42 U.S.C. 2851) dictates that any new or revised acute or chronic toxicity test method, including animal test methods and alternatives, must be determined to be valid for proposed use "prior to an Agency requiring, recommending, or encouraging the application of such test method."

Therefore, NTP is obliged to provide and or develop the critical scientific information regarding the relevance, reliability, and appropriate use of the assays before they are employed to develop data for an NTP database such as that proposed. Clearly, in accordance with ICCVAM, "the scientific and regulatory rationale for the test method, including a clear statement of its proposed use" must be available. To simply gather data from yet to be validated assays, and assemble it in a database, without first addressing how data from individual assays/batteries should be interpreted (information which is developed as part of the method validation) is not only a breach of sound scientific practice, it appears to be contrary to the spirit and/or the letter of the law (ICCVAM authorization Act of 2000).

As proposed, NTP appears to be suggesting that validation be postponed until after a considerable degree of test substances have already been assayed. This should be discouraged. What is needed first is for NTP to develop a conceptual model that includes, for each mechanism, a postulated mode of action framework that describes what the assay will measure along the pathway of toxicity, and how the information will be used within an overall assessment framework (how it will be interpreted and how it will be integrated with other relevant data to address an overall evaluation of potential impacts to health). Then, before launching wide scale evaluations of a large number of test articles, NTP needs to be certain that the assay proposed is valid for the intended purpose. If not, then NTP should not proceed with wide scale evaluations, but instead should undertake validation of the assay.

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ACC appreciates the opportunity to offer these recommendations for enhancing the scientific quality and credibility of the NTP's program efforts. ACC requests that NTP fully consider these comments and recommendations and appropriately respond before initiating NTP's proposals related to 1) modifying the existing CERHR process; and 2) launching an unclear plan centered on data gathering using Automated Techniques. Please address any questions on these comments or related matters to Dr. Richard Becker by phone at 703/741-5210 or by e-mail at Rick_Becker@AmericanChemistry.com.

Sincerely,

Richard A. Becker, Ph.D., DABT
Senior Toxicologist and Senior Director

Attachment 1(Comments from ACC to NTP dated 30 January 2004 regarding Report on Carcinogens)

January 30, 2004

Dr. Christopher Portier
Associate Director, National Toxicology Program
National Institute of Environmental Health Sciences
PO Box 12233, MD A3-02
Research Triangle Park, NC 27709-2233

Re: National Toxicology Program's Public Meeting to Discuss the Review Process And the Listing/Delisting Criteria Used for the Report on Carcinogens

Dear Dr. Portier:

The American Chemistry Council is pleased to respond to the National Toxicology Program's (NTP's) request for comments on the Review Process and the Listing/Delisting Criteria Used for the Report on Carcinogens (68 FR 67692, Dec. 3, 2003). For over three decades the American Chemistry Council[1] (ACC) and its member companies have played an active role in screening and testing chemical substances, developing risk assessments and implementing science-based risk management policies. ACC supports NTP's research and testing efforts, and in particular encourages the use of more mechanistic data in hazard and risk assessments. The NTP's Reports on Carcinogens (RoCs) are both nationally and globally significant documents in the area of chemical assessment, and ACC thus welcomes – and commends NTP for initiating – this effort to ensure that progress is

[1] The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through health and environmental research and product testing, Responsible Care®, and common sense advocacy designed to address major public policy issues. The business of chemistry is a $460 billion enterprise and a key element of the nation's economy. It is the nation's largest exporter, accounting for ten cents out of every dollar in U.S. exports. Chemistry companies invest more in research and development than any other business sector. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, working closely with government agencies to improve security and to defend against any threat to the nation's critical infrastructure. As a science-driven industry, the business of chemistry – through the Council's Long Range Research Initiative and thorough research, screening and testing of specific chemicals by individual member companies – provides significant support for scientific research to better understand and characterize the potential risks from chemical exposures.

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made to improve the RoC process. To that end, ACC offers the following comments and recommendations to improve the scientific accuracy and the transparency of the process. Specifically, ACC recommends that NTP:

- consider strengthening the scientific quality and public participation processes in the development of RoC actions by adapting and building on the process currently used by its own Center for the Evaluation of Risks to Human Reproduction (CERHR); and

- clarify the listing/delisting criteria it uses for the RoC to ensure that "a known to be a human carcinogen" determination is made only when there is sufficient epidemiological evidence of carcinogenicity from epidemiological or clinical studies that indicate a causal relationship, based on the weight of the scientific evidence, between exposure to the agent, substance or mixture and development of cancer in humans.

The basis for and the details of these recommendations are explained below.

1. Strengthening the Scientific Process: **the Case for Qualitative Change**

ACC and others have criticized the process and procedures followed by NTP to develop recommendations for listing chemicals in the RoC for many years[2]. Some of the major shortcomings of the RoC which have been previously communicated to NTP include:

- Failure to Prepare Up-to-Date, High-Quality Background Documents for Substances Recommended for Listing
- Too Little Time for the Preparation and Consideration of Scientific Comments on Listing Recommendations
- Insufficient Opportunity for Scientific Interchange with the Peer Review Body
- Failure to Involve Knowledgeable Outside Experts in Chemical-Specific Reviews
- NTP classifications that Differ From Those of Other Expert Scientific Bodies Without Clear Rationale or Justification
- Lack of Clear Guidance on the Standards That Need to Be Met for Listing Classifications and Use of the Term "Known Human Carcinogen" In The Absence Of Adequate Human Epidemiological Data

[2] Such criticisms are not repeated in detail in these comments -- the intent here is provide thoughtful commentary on a path forward for NTP to consider undertaking to improve the RoC. Should NTP have need of copies of past ACC communications critiquing the RoC, NTP may contact ACC and these will be supplied.

- Absence of Documented Rationales for Decisions of the Interagency Review Group (RG-2), and the Board of Scientific Counselors (BSC) Subcommittee or the NTP Executive Committee

ACC believes that the process and procedures currently employed by NTP for the RoC do not compare favorably with the processes that other agencies and scientific review bodies follow in hazard evaluations of potential carcinogenic agents. The current RoC process still does not foster opportunities for substantive scientific dialogue among the most qualified chemical-specific and subject matter specific experts during the most critical stages of the process, including the comprehensive literature evaluation/writing and review of the Draft Background Review Document. There continue to be instances where the RoC work products could have benefited from the participation of well-recognized experts. Further, the RoC procedures for public/stakeholder participation fall well short of what is needed to demonstrate a commitment to truly meaningful participation. Even though extensive comments are often submitted highlighting new data or important mechanistic or interpretative information relevant to critical studies, the Background Review Document is typically not revised and there is no indication whether such comments are actually considered or addressed.

ACC acknowledges that NTP's efforts over the years to make incremental changes in the RoC process have led to incremental enhancements, but there are many areas that remain problematic, and both the scientific processes and the public/stakeholder procedures used by NTP -- even as proposed in the current FR notice -- are still in need of substantial improvement. To upgrade the NTP RoC process, the ACC suggests NTP consider implementing specific improvements, which are detailed below, to restore confidence in, and improve the scientific integrity of, the RoC process.

2. Strengthening the Scientific Process: **Fundamental Principles**

The foundation of RoC listings and delistings should be a comprehensive and thorough review and interpretation of the best available science, conducted in a manner that fosters scientific dialogue, transparent decision making, open meetings and stakeholder involvement. These are fundamental principles, widely supported by the NTP, other Federal agencies and departments, academia, industry and other stakeholders. In its review of the RoC process, NTP should be focused on ensuring that these fundamental principles are enhanced. Such a focus would also ensure that the RoC process comports with the Information Quality Act (IQA), including the peer review provisions that the Office of Management and Budget (OMB) has proposed to add to its IQA Guidelines. As the RoC process stands now, there is no doubt that it does not satisfy the OMB's peer review requirements for "especially significant regulatory information" like the RoCs. (For example, the peer reviewers do not prepare any sort of report of their deliberations.) Moreover, at least one substantial IQA challenge has been filed against the 10th RoC. Improvements to the RoC process would substantially reduce the likelihood of such challenges in the

future. Now is the time for NTP to consider more sweeping alternatives to the existing process.

Fortunately, with the CERHR, NTP itself has implemented a hazard characterization process that goes a long way to overcoming many of the scientific and process shortcomings of the current RoC process. ACC suggests that, as NTP considers potential reforms to the RoC process, it consider whether there are lessons to be learned from the process developed by its own CERHR. Figure 1 illustrates the current CERHR process, as described on the Center's website[3]. The CERHR process involves numerous opportunities for substantive public/stakeholder involvement, including the opportunitunities to:

- nominate substances,
- comment on nominated substances,
- comment on substances recommended for review,
- submit nominations of scientists to serve on the Expert Panels,
- comment on the Draft Expert Panel Report for each substance,
- participate in open and collegial, in-depth Expert Panel meetings, and
- comment on the final Expert Panel Report.

ACC urges NTP to consider adding the comparable opportunities for public/stakeholder interaction in a similar RoC listing and delisting process, as discussed below.

3. Strengthening the Scientific Process: NTP Should Consider Adapting the CERHR Process for the RoC

ACC believes that NTP's RoC process could be greatly improved by adapting and building on the interactive scientific model put into practice in the CERHR process. ACC suggests the following adaptation of the CERHR process for consideration by NTP as a possible revision to the RoC process (the proposed process is also illustrated in Figure 2):

- Listing & Delisting Nominations
    - Maintain an open nomination process which includes interested individuals, federal and state agencies, NTP staff, labor unions, and industry. Listing and delisting nominations may be accompanied by a dossier explaining the rationale and supporting data for the nomination.

- Nomination Review Committee
    - RoC staff prepares dossiers on candidate chemicals and supplies the dossiers to the Nomination Review Committee annually.

[3] http://cerhr.niehs.nih.gov/aboutCERHR/index.html#Chemical%20Review%20Process

  - Nomination Review Committee reviews dossiers and recommends proposed candidate chemicals giving highest priority to chemicals nominated based on scientific evidence regarding the potential carcinogenicity of the nominated substance (taking into account potential for human exposure).
  - Proposed candidate chemicals (for either listing or delisting) transmitted to Associate Director, NTP who finalizes the list of proposed candidate chemicals for public comment.
- Solicitation of Public Comment on Agents Selected by the Associate Director of NTP
  - Federal Register notice announces selected chemical(s) and solicits public comment, new data and planned studies, information on exposure and use patterns, and nominations of individuals qualified to serve on the Expert Panel
- RoC Nomination Review Committee Review
  - Reviews expert panel member recommendations
  - Recommends Expert Panel members to Associate Director, NTP, for final approval
- Request for Scientific & Public Review/Comments and Development of Review Draft of Expert Panel Report
  - Federal Register notice announces the Expert Panel meeting and requests public comments to be submitted in writing and/or made at this meeting
  - Expert Panel Meeting to discuss dossier, receive scientific input from non-panelists, and public comments
  - Expert Panel participants review available scientific studies (dossier, other scientific data/studies/information and public comments) and prepare the Review Draft Expert Panel Report
- Expert Panel Meeting – Release of the Review Draft Expert Panel Report for comment
  - The Panel meets in public session to discuss its draft report (which would provide a comprehensive review of the literature) and to prepare the final Panel report
  - Meeting includes adequate time for presentation of public comments and for substantive interaction between commentators and panelists
- Request for Scientific & Public Review/Comments on Final Expert Panel Report
  - Federal Register notice announces availability of Expert Panel report and requests public comment. This report is a product of the Expert Panel and is available on the NTP website or from NTP
  - NTP RoC Peer Review Committee conducts peer review and provides written report on their deliberations (including a response to comments)
- NTP Draft Monograph
  - RoC staff prepares a Draft Monograph on the chemical(s) evaluated based on the Final Expert Panel Report

- Final Solicitation of Public Comments
    - Federal Register notice announces availability of Draft Monograph and requests public comments
- NTP Interagency Executive Committee Approval
    - The Draft Monograph is transmitted to the Interagency Executive Committee along with the final public comments for review and approval (to include a report on response to comments)
- Final Monograph Submitted to Director NTP and Secretary DHHS for Approval and Publication
    - RoC staff revises the Monograph as directed by the Interagency Executive Committee
    - Monograph (with chapter on response to comments) is transmitted to Director NTP for approval
    - Director NTP recommends approval to Secretary DHHS
    - The Monograph is made publicly available and is distributed to federal and state agencies and interested stakeholders

Clearly, such changes to the RoC as proposed for consideration would present new challenges to the NTP. While implementing a more open and transparent process that allows for enhancing scientific quality and dialogue may take more time than the current approach, this should be viewed as time well spent. Clearly, the initial work product of the Expert Panel would be greatly strengthened in terms of scientific rigor by implementing a process that includes recognized subject matter experts from a diverse array of applicable fields and affiliations working in a collaborative manner to develop the Background Review Document. As currently structured, the RoC process, particularly at the crucial report drafting stages, is very likely to miss expertise relevant to understanding significant issues for a particular chemical. One method that may warrant consideration is the model used by other scientific bodies (e.g., EPA's Science Advisory Board): to have a core group of standing expert scientists who serve as members of the Expert Panel, and to augment the Expert Panel, as needed, with additional experts who have either knowledge of the science for that chemical, or expertise in a germane discipline needed for the review of a specific chemical.

4. Clarifying the Listing/Delisting Criteria

Adopting the variant of the CERHR process discussed above would go a very long way to assuring the scientific quality of the RoCs. NTP should address one other substantive matter, however: clarifying its listing/delisting criteria for the RoC. Among the most important judgments to be made in issuing the RoC is whether the weight of the scientific evidence is sufficient to conclude that a substance is "known to be a human carcinogen." Such a classification will greatly intensify the level of regulatory and public concern surrounding exposure to the substance, and therefore the determination should be based on careful and thorough analysis. Yet, in contrast to other agencies and scientific bodies, NTP has to date not fully described or elaborated on the standards it will apply in judging whether the weight of the

available scientific data are sufficient to demonstrate a causal relationship between exposure to the substance and human carcinogenicity.

ACC urges NTP to clarify its listing/delisting criteria used for the RoC. Specifically, a "known to be a human carcinogen" determination should only be made if there is sufficient evidence of carcinogenicity from epidemiological studies that indicates a causal relationship between exposure to the agent, substance or mixture and human cancer. Mechanistic or other scientific information should not be used to bolster insufficient epidemiological evidence in an effort to satisfy the "known to be a human carcinogen" criteria.

For many years, NTP relied exclusively on epidemiological studies to satisfy its "known to be a human carcinogen" criteria. Regrettably, NTP modified its criteria in 1996 to allow mechanistic information to be used to shore up insufficient epidemiological studies. By expanding its criteria in this manner, NTP rendered effectively meaningless the distinction between "known to be a human carcinogen" and "reasonably anticipated to be a human carcinogen," thus frustrating the legislatively mandated distinction between the two. For example, currently, a substance for which NTP has limited human epidemiology data and relevant mechanistic data could be classified as either "known" or "reasonably anticipated." A substance for which there is limited epidemiological data and relevant mechanistic data should, at most, only be classified as "reasonably anticipated to be" and not "known to be a human carcinogen." Otherwise, this NTP policy results in the same regulatory priority being given to substances with vastly different weights of evidence. There should be clear policy distinction between determinations based on strong human epidemiological evidence and determinations that are based primarily on mechanistic data and inference. Maintaining a clear distinction between the two listing determinations is sound public policy. Such a distinction allows the scientific and public health communities, as well as regulators, to prioritize limited resources for the purposes of conducting research and protecting public health.

In addition, NTP should consider whether another classification is warranted in addition to "known" and "reasonably anticipated". There may be instances where the overall weight of the scientific evidence falls short of both criteria. As it now stands, there may be a tendency to "force" a classification into "reasonably anticipated" when the available scientific evidence may actually be much less. In this respect, a multiple level classification system, with appropriately worded text descriptions, would seem to offer a much better opportunity to fully and accurately communicate to the public the scientific evidence for such a substance with limited data -- in a manner that transparently reflects the true degree of confidence in the scientific data and evaluations. Clearly, a weight of the evidence approach is needed, particularly when there are multiple studies of varying quality that are not consistent. The criteria NTP develops and applies need to be explicit, transparent to stakeholders/public, and applied uniformly across substances and across time.

5. Conclusions

NTP is to be commended for seeking input on ways to improve the RoC listing and delisting process. ACC believes NTP should consider implementing changes which enhance the scientific quality of the review documents; to foster scientific dialog among subject matter experts; and to increase opportunities for meaningful stakeholder/public input. ACC has suggested that NTP consider adapting the CERHR process for the RoC. Implementing a more open and transparent process, such as that recommended, should result in higher quality scientific documents, greater opportunities for independent experts to meaningfully participate and therefore improved decision-making.

ACC appreciates the opportunity to offer both substantive and procedural recommendations for enhancing the scientific quality and credibility of the RoC. ACC appreciates your consideration of these comments and recommendations. If you or NTP staff have any questions on these comments or related matters, please contact Dr. Richard Becker by phone at 703/741-5210 or by e-mail at Rick_Becker@AmericanChemistry.com.

Sincerely,

Original Signed by	*Original Signed by*	*Original Signed by*
Sarah H. Brozena	Courtney Price	C.T. “Kip” Howlett, Jr.
Acting Staff Leader	Vice President	Vice President, CCC
Public Health Team	CHEMSTAR	Executive Director

cc: Ms. Anna Lee Sabella
Report on Carcinogens Group
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Figure 1. The CERHR Process

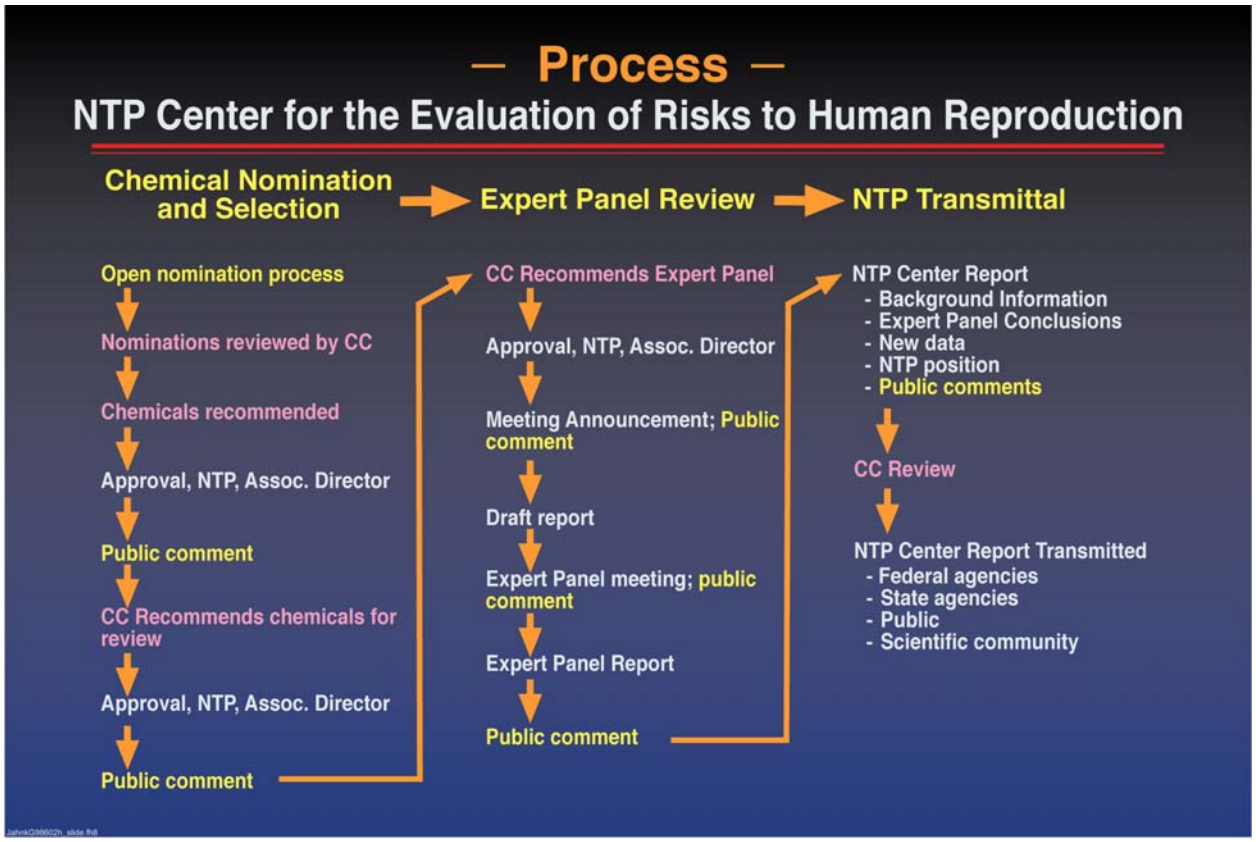

Figure 2
Recommended Process for Strengthening the RoC