DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Toxicology Program
P.O. Box 12233
Research Triangle Park, NC 27709

January 18, 2005

Courtney M. Price
Vice President, CHEMSTAR
American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22209

Dear Ms. Price:

I am responding to your Request for Correction of Information ("the Request") dated April 1, 2004 and submitted on behalf of the American Chemistry Council's Naphthalene Panel (the Panel) pursuant to Section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001[1] (the Information Quality Act or IQA) and the guidelines issues by the Office of Management and Budget (OMB Guidelines),[2] the National Institutes of Health (NIH) of the U.S. Department of Health and Human Services (HHS) (NIH Guidelines)[3] and the HHS (HHS Guidelines)[4]. The Request concerns the background document on naphthalene and the scientific review of naphthalene for possible listing in the 11th Report on Carcinogens (RoC).[5]

---

[1] 44 U.S.C. 3516 note.

[2] *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility and Integrity of Information by Federal Agencies,* 67 Fed. Reg. 8452 (February 22, 2002), available at http://www.whitehouse.gov/omb/fedreg/reproducible2.pdf.

[3] *Guidelines for Ensuring the Quality of Information Dissemination to the Public*, available at http://www.hhs.gov/infoquality.

[4] *Guidelines for Ensuring the Quality of Information Dissemination to the Public*, available at http://www.hhs.gov/infoquality/part1.html.

[5] We note that the Panel submitted written comments on the nomination and/or review of naphthalene on September 24, 2001, October 2, 2002, November 4, 2002, and March 24, 2003. As is our process, the NTP posted the Panel's comments along with those of other persons/groups who commented on naphthalene on the RoC web site (http://ntp.niehs.nih.gov/index.cfm?objectid=ADAEC564-F1F6-975E-76C24D4639BD3613) and provided them, as submitted, to the applicable review groups for their consideration. Specifically, the RG1, which met June 10, 2002, and the RG2, which met on October 2, 2004, received and was tasked with reviewing your comments dated September 24, 2001. The RoC Subcommittee met November 19, 2002 and received and was tasked with reviewing the comments you submitted September 24, 2001, October 2, 2002, and November 4, 2002. Finally, the NTP Executive Committee met August 21, 2003 and received and was tasked with reviewing all four sets of your comments. As to the concerns raised now about the process for the November 19th RoC Subcommittee meeting, the Panel previously raised them in separate letters dated November 27, 2002 and March 3, 2003, from Ms. Courtney M. Price, to Dr. Kenneth Olden. The NTP has responded to these points, in separate letters dated January 27, 2003 and March 11, 2003, respectively, to Ms. Price from Dr. Olden.

Specifically, the Panel requests that the agency correct three documents: the Background Document for Naphthalene and the Summaries of the NIEHS/NTP RoC Review Group (RG1) and NTP Executive Committee Interagency Working Group for the RoC (RG2) meetings. Additionally, based generally on your contention that the Background Document for Naphthalene is flawed, and thus all activity involving it represents "fruit of the poisonous tree," you have asked that the agency "rescind" the RG2 meeting with regard to naphthalene (and hold a new RG2 meeting) and the vote of the November 19, 2002 NTP Board of Scientific Counselors RoC Subcommittee (RoC Subcommittee) meeting and re-convene a new RoC Subcommittee to reconsider naphthalene at a future meeting.

In the alternative, you have asked that the NTP staff, NIH's Office of Communications and Public Liaison (OCPL), and the NTP Executive Committee "undertake a comprehensive pre-dissemination review of the entire record of the listing proceeding as it relates to naphthalene before any recommendation is made concerning listing naphthalene in the Eleventh RoC by the NTP Director."[6]

Before I respond to your concerns, I would like to briefly summarize the process used for the review of nominations to the 11th RoC.

Process for Reviewing Nominations to the 11th RoC

The review of all nominations to the 11th RoC, including naphthalene, followed a formal, multi-step process that solicited and incorporated public comment. Initially, the NTP published a notice in the Federal Register (July 24, 2001) and in the NTP newsletter that announced the nominations to the 11th RoC selected for review and solicited public comments on them. In addition, the NTP invited the public to submit relevant information on their carcinogenicity, production, use, and human exposure and also asked for the identification of any scientific issues related to the listing that should be addressed during the reviews. The NTP next initiated preparation of the background document on each nomination, which summarized the relevant scientific information relating to its human exposure and carcinogenic potential. The background document is intended to provide concise, comprehensive, and unbiased summaries of all relevant information found in the peer-reviewed scientific literature. The information contained within the background document is factual and includes no opinion or views from the NTP regarding what the data mean. The background document for naphthalene was made available to the public on the NTP website on August 26, 2002.

The formal review of nominations to the 11th RoC also included evaluation by two federal scientific review groups (RG1 and RG2) and a standing subcommittee of the NTP Board of Scientific Counselors (RoC Subcommittee)-a federally chartered advisory group. Prior to

[6] We note some confusion about the meaning of this alternative request as we are uncertain about what is meant by the phrase "pre-dissemination review of the entire record of the listing proceeding." However, please be advised that all applicable pre-dissemination review standards will be met for dissemination of the 11th RoC.

initiation of scientific review of the nominations, the RG1 reviewed the background document on each nomination to determine if it was adequate for use in reviewing the nomination and applying the criteria for listing in the RoC. After RG1's acceptance of the background document, it was considered the document of record for the nomination and made available on the NTP RoC web site. As the document of record, the background document did not change during the review process; however, any comments received on it were added upon receipt to the record for that nomination, which was and remains publicly available, and became part of the review package provided to the review committees.

After acceptance of the background document, the scientific review of the nomination by the three groups began. Each review group met independently and reviewed the relevant data on the carcinogenicity and the exposure of U.S. residents to the nominated substances. An integral part of the review process was the solicitation and consideration of public comments during this review process. Public comments were solicited three times. Comments received during the course of a review became part of the public record, were provided to the scientific review committees as part of the review package for consideration in evaluating each nomination, and, upon receipt, were posted on the NTP RoC web site. Note that the sequential nature of this process resulted in comments accumulating throughout the reviews. Each scientific review committee assessed whether the information was sufficient to apply the criteria for listing and made a formal recommendation to the NTP regarding whether to list or not list the nomination in the 11th RoC. The NTP published the RoC Subcommittee's recommendation on naphthalene in the Federal Register (68FR3033) and invited public comments at that time on it as well as the recommendations of RG1 and RG2.

Following completion of the scientific review, the NTP provided the review packages and the recommendations of the three scientific review committees to the NTP Executive Committee for evaluation and recommendations regarding listing the nominations in the 11th RoC. The NTP Director then received the recommendations of the three review groups and the Executive Committee along with the review packages for each nomination. The NTP Director, in turn, evaluated this information, formulated a recommendation regarding listing of each nomination, and submitted these recommendations in the form of a draft 11th RoC to the Secretary, HHS, for review and approval. The Secretary will issue the 11th RoC after reviewing and approving these recommendations.

Request for Correction of the Background Document

In the Request, you assert that the NTP's policy of relying on a finalized background document as the "document of record" for review purpose does not meet the information quality guidelines. You also claim, based on comments that you previously submitted during the nomination review process (i.e., on September 24, 2001, October 2, 2002 and March 24, 2003), that the text of the Background Document fails to satisfy the applicable information quality guidelines.

The Background Document is a reference document that compiles and summarizes publicly available, relevant information from both positive and negative studies on a nomination. It serves as a resource that the review groups can use in applying the RoC criteria for review of the nomination and in formulating their opinion on whether to recommend listing the nomination in the RoC. As described in the Introduction of the 10th RoC, "[t]he BD [Background Document] emphasizes information concerning the carcinogenicity and related toxicological evidence for the substance nominated. The document may also include information on exposure provided by study reports and monographs."[7]

First, with regard to your concern about the NTP's policy decision not to revise the Background Document of record on a nomination after it is finalized, please be aware that NTP follows this policy to ensure that all review groups are provided the same background document for their review of a nomination. This policy ensures that the review groups receive the same baseline toxicology and carcinogenicity information on the nominations in order to (1) prevent confusion among the groups and the public regarding what background information is being considered in the reviews, (2) reduce the potential for error in the dissemination of information on the nominations to the review groups, (3) ensure the adequacy of the scientific literature considered by the three scientific review groups in their evaluation of the nominations, and (4) help maintain the integrity of the review process. But, additionally, to address any concerns about the document and to ensure that all comments and expressed concerns are also available, the NTP provides the review groups with submitted public comments. In this way, NTP aims to ensure that reviewers can evaluate the scientific information and reach their own conclusions regarding the comments' validity and the adequacy of information to support a nomination. In the case of the Background Document for Naphthalene, we do not believe that this policy choice compromised the quality of the information it contained.[8]

As you are aware, the NTP has held public meetings (most recently October 1999 and January 2004) to consider public comments received on the RoC review process and listing criteria and has conducted its own internal evaluation of the process used for the review of nominations to the 10th and 11th RoCs. Based upon this input, the NTP has made some revisions to the procedures for preparing background documents and reviewing nominations for future RoCs.[9] For example, in response to requests for earlier public accessibility of the

---

[7] 10th RoC, Introduction available at http://ehp.niehs.nih.gov/roc/toc10.html.

[8] We note, however, that policy choices are not subject to challenge under the information quality guidelines. In this case, you have asserted, without reference, that this policy choice, in and of itself, represents a failing. We disagree because the agency concurrently makes all comments available and it clearly explains that once the RG1 determines that the background document is adequate for reviewing the nomination, it is considered the document of record. Nomination and Review Process – 11th RoC available at http://ntp-server.niehs.nih.gov/ntpweb/index.cfm?objectid=B2580696-F1F6-975E-726E312CCF078AAE or from Dr. C.W. Jameson, Report on Carcinogens, NIEHS/NIH, PO Box 12233, MD EC-17, Research Triangle Park, NC 27709.

[9] The NTP response to comments received at those meetings are posted on the NTP RoC web site at http://ntp-server.niehs.nih.gov/ntpweb/index.cfm?objectid=720162CF-BDB7-CEBA-FC560DF109D40A44.

background documents, the NTP now places background documents accepted as the "documents of record" for nominations to the RoC on the NTP web site at least 30 days prior to initiation of the scientific review process for their possible listing in or removal from the RoC. Any comment received on a background document becomes part of the public record and, upon receipt, is added to the review package that is distributed to the formal review committees. So, as indicated above, the NTP makes every effort to ensure that reviewers can evaluate the scientific information and reach their own conclusions regarding the validity of any comments received and the adequacy of the information in their evaluations.

Second, with respect to the specific text of the Background Document for Naphthalene, we believe that it satisfies the applicable information quality guidelines.[10] Regarding the "objectivity" criterion, the Background Document for Naphthalene is an unbiased presentation of information on peer-reviewed studies with both positive and negative findings. According to the OMB Guidelines, "[i]f the data and analytic results have been subjected to formal, independent, external peer review, the information may generally be presumed to be of acceptable objectivity."[11] The Background Document only discusses carcinogenicity and toxicology information from publicly available, peer-reviewed sources. On pages 11-15 of the Request you raise specific issues with regard to study findings presented in the Background Document to Naphthalene. I will point out that the NTP will only respond to issues you raise that question the accuracy of factual information. I will not respond to other issues where you ask the NTP to formulate and assert its opinion regarding the interpretation of study findings presented in the Background Document for Naphthalene, because it would be inappropriate to do so. In background documents, the NTP declines to draw conclusions about the data described or include interpretative information and evaluation like you have requested, because, in the NTP's view, to do so could introduce bias. Instead the NTP rests such judgment with the scientists reviewing these documents and the attendant comments submitted on them by the public.

- On page 11 of your Request you state: "[p]age 21:...the Background Document should explain in detail why the three-decades old East German reports of the health effects observed in tar distillation workers, Wolf (1976, 1978) as cited in NTP (1992) and (2000), can fairly be construed as evidence of carcinogenicity in humans...The discussion of these reports should also incorporate additional comments and correct misleading and incorrect description of the Wolf studies made by NTP in its reports on naphthalene..." The NTP believes that the descriptions of the Wolf studies (1976, 1978) in the Background Document are correct. Furthermore, the Background Document clearly states on page 21, "[t]he available evidence are insufficient for evaluation of naphthalene in humans." The NTP does not believe that the Wolf (1976, 1978) studies provide clear evidence of carcinogenicity in humans and would refer you to the final

[10] According to the OMB Guidelines, 67 Fed. Reg. at 8459, Section V., "'[u]tility' refers to the usefulness of the information to the intended users." "Objectivity" focuses on "whether disseminated information is being presented in an accurate, clear, complete, and unbiased manner" and whether it is "accurate, reliable, and unbiased."

[11] OMB Guidelines, 67 Fed. Reg. at 8459, Section V.3.b.i.

sentence of Section 3 Human Cancer Studies contained on page 21 of the Background Document that states "[t]he available data are insufficient for evaluation of the carcinogenicity of naphthalene in humans." The other issues you raise request the NTP to draw conclusions or include interpretative information and evaluation in the Background Document on Naphthalene and it is the NTP's policy not to do so.

- On pages 12 - 14 of your Request you state: "[p]ages vi, 27, 31, 53:...the Background Document should clarify the meaning of the terminology in referring to the "carcinogenicity of naphthalene in rats and mice in several places...The Background Document should also discuss that there is no convincing relevant evidence that naphthalene acts through mechanisms indicating it would likely cause cancer in humans...." The issues you raise request the NTP to draw conclusions or include interpretative information and evaluation in the Background Document on Naphthalene and it is the NTP's policy not to do so.
- On page 14 of your Request you state: "[p]ages 27-30 (Section 4.2.1):...this section should not only include the discussion from the September 24, 2001, comments referenced above with regard to rat nasal tumors, but should explain in greater detail..." The issues you raise request the NTP to draw conclusions or include interpretative information and evaluation in the Background Document on Naphthalene and it is the NTP's policy not to do so.
- On page 14, you state: "[p]ages 33-38, (Section 5): the section on genotoxicity should discuss the additional genotoxicity studies identified in the October 2, 2002, Comments at pages 10-11 and in a recent publication by Schreiner (2003), including in particular the standard *in vivo* studies that are described...Further,...naphthalene is not genotoxic." In the Background Document on Naphthalene, the NTP describes the data that indicates, in general, naphthalene is not mutagenic in bacteria or mammalian cell systems, but was genotoxic in some, but not all, test systems and then goes on to describe the positive and negative genotoxicity data. After the Background Document is finalized and becomes the document of record, it remains unchanged throughout the review process. As explained above, the reason for this policy decision is to ensure that all reviewers and the public receive the same information without interjection of bias or opinion by NTP. However, the comments you submitted were posted on the NTP RoC web site and provided to all review groups so that they were aware of the studies you referenced.

The Background Document for Naphthalene received a full and complete review by RG1 prior to its posting on the NTP RoC web site and the NTP accepted public comments on it thereafter.

Additionally, the NTP believes that the "utility" criterion is satisfied. The Background Document for Naphthalene is useful for the reader. It is a public resource document that provides information from published, publicly available studies on naphthalene including its use, production, exposure, toxicology, and carcinogenicity, and it is available in both electronic and printed formats.

The NIH Guidelines require the use of "[t]he best available science and supporting studies, particularly peer-reviewed studies, conducted in accordance with sound and objective scientific practices" in the Background Document.[12] As noted above, publicly available, peer-reviewed technical reports and scientific articles are the primary sources of data used to prepare a background document.

With regard to your suggestion that more current information might be available on the production, exposure, use, and environmental fate of naphthalene, my staff checked the references you provided and consulted with our federal agency partners to be sure that the information on naphthalene is up-to-date in its profile in the 11th RoC, should the Secretary approve its listing. In response to your request that the Background Document "correct any factual errors or omissions that were noted by RG1 and then subsequently by RG2," I am not aware that any were identified; however, I am confident that if any errors or omissions had been identified by either group, they would have been addressed and corrections of any factual errors made in the background document.

Request for Correction of The RG1 and RG2 Review Summaries

Regarding the review summary reports from RG1 and RG2, you argue that they "fail to meet the requirements for objectivity." We believe that the information provided in both review summaries is objective and has utility. It is accurate, clear, complete, and unbiased and should be useful to the reader. Members of the respective review groups, not NTP staff, prepare the review summaries that are approved by the respective review group prior to their dissemination. They provide a summary of each review group's discussion and conclusions regarding the human and animal data for carcinogenicity, exposure, and other factors. They also include any recommended action and information regarding any dissenting votes. Contrary to what you state, the RG1 review summary provides details on the key issues that led RG1 to its recommendation on naphthalene. As stated in the RG1 review summary, "[t]he committee felt that the NTP two-year inhalation study in F344 rats provided strong evidence for the carcinogenicity of naphthalene in that species...The majority of the committee felt that naphthalene should be listed as *reasonably anticipated to be a human carcinogen*, based on the rare nasal tumors in rats, but supported by an increased incidence of lung adenoma in female mice."[13] Moreover, contrary to your suggestion that "[t]he RG2 summary review similarly fails to explain how each of the two groups in the split vote reached their respective recommendations," the review summary for RG2 highlights the issues raised during the discussion and explains the rationale for each motion and the reason for dissenting votes. Therefore, we believe that the RG1 and RG2 review summaries meet the Guideline's requirements for objectivity.

---

[12] NIH Guidelines at Section V.2.d. and Section VII.

[13] *RG1 Review Summary Document for Naphthalene,* available at http://ntp-server.niehs.nih.gov/index.cfm?objectid=03CA0BBE-9561-1E86-6438319191108C7E.

Request for Correction of the RG2 Proceedings and the NTP Board of Scientific Counselors RoC Subcommittee Proceedings

As a preliminary matter, please note that the OMB, HHS, and NIH Guidelines provide for *correction* of disseminated *information.* Thus, NTP does not agree that your request under the information quality guidelines for new processes, in the form of new meetings and new votes, is appropriate. For example, as we will explain below, your suggestion that the "proceedings" of the RoC Subcommittee, a standing subcommittee of a duly formed federal advisory committee, are wholly subject to the IQA guidelines is inappropriate. Neither the OMB Guidelines, nor the HHS and NIH Guidelines, specify that the guidelines' administrative complaint processes provide a mechanism to request rescission or re-formation of duly constituted meetings of agency committees like the RG2 or RoC Subcommittee. Accordingly, in our view, the OMB, NIH, and HHS Guidelines do not warrant that the agency "rescind" the meetings and votes of, or re-convene, the RG2 and RoC Subcommittee.

While the IQA does not address proceedings or procedures of meetings and is not a mechanism to rescind a meeting or vote, I would like to clarify the procedures applicable to the RoC Subcommittee meeting, as the RoC Subcommittee is comprised of both federal and non-federal employees. The Federal Advisory Committee Act (FACA, PL 92-463), which sets forth procedures for federally chartered advisory committees, governs the RoC Subcommittee proceedings. The RoC Subcommittee is a standing subcommittee of the NTP Board of Scientific Counselors and follows the rules of FACA in its conduct. The RoC Subcommittee provides advice, its proceedings are held in public forums so that the deliberations are open, and there is opportunity for all interested parties to hear the discussions and provide comment if desired. The RoC Subcommittee members act as independent scientists and, as such, are free to raise scientific issues for consideration and discussion at their meetings. The meeting minutes provide a summary of the proceedings and actions, and they are publicly available on the NTP web site or from the executive secretary. However, these minutes are not subject to the IQA because they do not represent agency views.

Additionally, as you know from the letters sent to Ms. Price from Dr. Kenneth Olden on January 27, 2003 and March 11, 2003, the NTP has previously responded to the Panel's concerns about the proceedings of the Subcommittee meeting. The NTP again reviewed the transcript of the November 2002 meeting and concluded that it was conducted properly. The meeting complied with FACA, and conflict of interest issues for members were reviewed prior to the meeting. In addition, it is the NTP's practice for the chair to step down in situations where he/she wishes to participate in the evaluation of a nomination. As a member of the Subcommittee, Dr. Froines was permitted to provide comments; however, he stepped down as chair during the deliberations on naphthalene in order to prevent any prejudicial influence. As noted in the transcript, please be assured there was considerable discussion among the Subcommittee members regarding the scientific evidence on the metabolism of

naphthalene and its carcinogenicity and regarding application of the RoC criteria. At that time, they had before them the comments that the Panel had previously submitted on September 24, 2001, October 2, 2002, and November 4, 2002.

Conclusion

In conclusion, we believe that the Background Document on naphthalene, the RG1 summary report, and the RG2 summary report satisfy the HHS and NIH Guidelines issued pursuant to the IQA. Furthermore, while the IQA is not a proper mechanism to request that the agency rescind the RG2 and RoC Subcommittee meetings, we reviewed the conduct of those meetings and found that they comply with all applicable requirements.

I would like to let you know that you may appeal our agency's decision either in writing or electronically within 30 days of receiving this response. Your request should state the reasons for your appeal. It does not need to reference a tracking numbers. The request may be sent electronically to InfoQuality@od.nih.gov or in hard copy to the Associate Director for Communications, Office of the Director, National Institutes of Health, Building 1, Room 344, 9000 Rockville Pike, Bethesda, Maryland 20892. If the appeal is sent in hard copy, please clearly mark the appeal and outside envelop with the phrase "Information Quality Appeal."

Sincerely,

/s/

Christopher J. Portier, Ph.D.
Associate Director