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USWAG

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April 7, 2003

BY FACSIMILE AND ELECTRONIC MAIL

Dr. C.W. Jameson
Department of Health and Human Services
Public Health Service
National Toxicology Program
Report on Carcinogens
MD EC-14
P.O. Box 12233
Research Triangle Park, NC 27709

Re: Comments on the Proposed Listing of Naphthalene in the Eleventh Edition of the National Toxicology Program's Report on Carcinogens

Dear Dr. Jameson:

The Utility Solid Waste Activities Group ("USWAG") provides this response to the National Toxicology Program's ("NTP") request for public comment on the proposed nomination of naphthalene for listing in the *Report of Carcinogens, Eleventh Edition* (the "*ROC*"). *See NTP; Call for Public Comments on the 10 Nominations, Proposed for Listing in the Report on Carcinogens, Eleventh Edition*, 68 Fed. Reg. 3033 (Jan. 22, 2003).[1] USWAG is an informal consortium of the Edison Electric Institute ("EEI"), the American Public Power Association ("APPA"), the National Rural Electric Cooperative Association ("NRECA"), the American Gas Association ("AGA"), and approximately 80 electric utility operating companies located throughout the country. EEI is the principal national association of investor-owned electric power and light companies. APPA is the national association of publicly-owned electric utilities. NRECA is the national association of rural electric cooperatives. AGA is the national association of natural gas utilities. Together, USWAG members represent more than 85 percent of the total

[1] Public comments were due 60 days from this date of this federal register notice. On March 24, 2003, on behalf of NTP, you granted USWAG an extension to file comments by April 7, 2003.

electric generating capacity of the United States and service more than 95 percent of the nation's consumers of electricity and over 93 percent of the nation's consumers of natural gas.

The application of NTP's *ROC* listing criteria demonstrates that there is neither credible nor sufficient evidence to justify a determination that naphthalene is "reasonably anticipated to cause cancer in humans." Accordingly, USWAG strongly believes that naphthalene should not be listed on the *ROC* and urges NTP to withdraw it's *ROC* Draft Background Document for naphthalene and discontinue efforts to list naphthalene on the *ROC*.

NTP's proposed improper listing of naphthalene on the *ROC* will have a substantial and unjustified negative impact on the regulated community. USWAG member companies operate hundreds of facilities around the country, some of which are engaged in site remediation activities which may involve naphthalene compounds. The improper listing of naphthalene on the *ROC* may unnecessarily complicate cleanup activity, extending the time period and costs of remedial activity, while at the same time unnecessarily raising public concerns over unproven cancer risks. NTP's listing of naphthalene may, therefore, directly affect remedial activities by USWAG's members.

In opposing NTP's proposed listing of naphthalene, USWAG joins and incorporates by reference the comments submitted to NTP by the Naphthalene Panel of the American Chemistry Council dated March 26, 2003 (the "Naphthalene Panel's Comments). As outlined in the Naphthalene Panel's Comments and summarized below, USWAG strongly believes that NTP's proposal to list naphthalene on the *ROC* should be dropped because it fails to meet NTP's listing criteria for being "reasonably anticipated to be a human carcinogen."

I. The NTP Has Failed To Demonstrate The Naphthalene Meets The Criteria For Listing As A Reasonably Anticipated Human Carcinogen.

A. The NTP Listing Criteria.

Section 301(b)(4)(A) of the Public Health Services Act directs the Secretary of Health and Human Services to publish a report which contains "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 people residing in the United States are exposed . . ." 42 U.S.C. § 241(b)(4)(A). The biennial *ROC* prepared by the NTP is intended to meet this statutory requirement.

In 1996, the NTP revised its criteria for listing substances in the *ROC*. *See The NTP Revised Criteria for Listing Substances in the Biennial Report on Carcinogens*,

61 Fed. Reg. 50,499 (Sept. 26, 1996). Under these revised criteria, a substance can only be listed on the *ROC* as being "reasonably anticipated to be a human carcinogen" (the basis for the proposed listing of naphthalene) if:

> (1) 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, could not adequately be excluded, or
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> (2) There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates that there is an increased incidence of malignant and/or combined benign and malignant tumors: (a) in multiple species or at multiple tissue sites, or (b) by multiple routes of exposure, or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or
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> (3) 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 Annual or Biennial Report on Carcinogens as either a known to be human carcinogen, or reasonably anticipated to be human carcinogen or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Id. at 50,499-50,500 (collectively referred to herein as the "NTP Criteria").

B. The NTP Has Failed To Demonstrate That Naphthalene Meets The NTP Criteria For Listing On The *ROC*.

Naphthalene should not be listed on the *ROC* because the substance does not meet the NTP Criteria for listing. *See* Naphthalene Panel's Comments at pp. 2-16. In particular, naphthalene should not be listed in the *ROC* because (1) there is no credible evidence from studies in humans that naphthalene is a human carcinogen; (2) data from animal studies provides insufficient evidence of carcinogenicity under the NTP Criteria; and (3) naphthalene does not belong to any well defined, structurally-related class of substances known or reasonably anticipated to be human carcinogens.

(1) There Is No Credible Evidence From Studies in Humans That Naphthalene Is A Human Carcinogen.

The NTP has recognized that there is "insufficient evidence for the evaluation of carcinogenicity [of naphthalene] in humans based on human studies." Transcript of NTP Board of Scientific Counselors *ROC* Subcommittee Meeting, dated November 19, 2002 at 61, *see also* Naphthalene Panel's Comments at p. 4. This conclusion -- that

available data are inadequate to establish a causal connection between exposure to naphthalene and cancer in humans -- is consistent with findings in EPA's Integrated Risk Information System ("IRIS") database for naphthalene, which concludes that "[a]vailable data [from human studies] are inadequate to establish a causal association between naphthalene and cancer in humans." EPA IRIS Summary of Naphthalene at Section II.A.2, *see also* Naphthalene Panel's Comments at p. 5.

(2) Data From Animal Studies Provides Insufficient Evidence Of Carcinogenicity Under The NTP Criteria.

There is insufficient evidence of carcinogenicity in animal studies to demonstrate an increased incidence of malignant or a combination of malignant and benign tumors (a) in multiple species or at multiple tissue sites, or (b) by multiple routes of exposure, or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset. *See* Naphthalene Panel's Comments at pp. 6-8.

As detailed in the Naphthalene Panel's Comments, the 1992 NTP Mouse Study relied on by NTP in its proposed listing decision found tumors that were overwhelmingly benign (a single carcinoma in 135 mice). Furthermore, NTP itself recognized that mice are more sensitive to pulmonary toxicity of naphthalene than other species. *See* Naphthalene Panel's Comments at p. 6, citing 1992 NTP Mouse Study. These and other weaknesses in the 1992 NTP Mouse Study are insufficient evidence to demonstrate carcinogenicity in "multiple species" necessary to list naphthalene on the *ROC*. *Id.* Moreover, the 2002 NTP Rat Study relied on by NTP in its listing decision fails to meet the criterion for "multiple tissue sites" since both tumor types identified in the rat study where in found the nasal cavity. *Id.* at 6-7.

There is also insufficient evidence of carcinogenicity in animal studies to demonstrate an increased incidence of tumors by multiple routes of exposure. *See* Naphthalene Panel's Comments at p. 7. There was just a *single* route of exposure in both the 1992 NTP Mouse Study and the 2000 NTP Rat Study relied on by NTP in its decision to list naphthalene, namely inhalation at high exposure concentrations. *Id.* This single route of exposure is insufficient to establish the requisite multiple exposure routes to demonstrate the carcinogenic potential of naphthalene with animal studies under NTP's Criteria.

Finally, the data from animal studies are also insufficient for NTP to conclude that naphthalene is associated with increased incidence of tumors to an unusual degree with regard to incidence, site or type of tumor, or age at onset. *See* Naphthalene Panel's Comments at p. 7-8. The rare neuroblastomas seen in the 2000 NTP Rat Study should not be considered induced to "an unusual degree" because the historical data base for the NTP-2000 diet used in this study is small, the weight of evidence

indicates that naphthalene is non-genotoxic, and because the tumors induced in this study developed only at sites where non-neoplastic inflammatory changes occurred. *Id.* These factors, along with the anatomical, physiological, and metabolic differences between the rats and humans (e.g., nasal surface area, efficiency in extracting substances from air inhaled through the nose, and the rate of metabolism of the reactive expoxide metabolite) together demonstrate that the rat nasal tumors identified in the 2000 NTP Rat Study are not an appropriate basis for NTP to make a conclusion regarding the potential human carcinogenicity of naphthalene.

(3) Naphthalene Does Not Belong To Any Well Defined, Structurally-Related Class Of Substances Known Or Reasonably Anticipated To Be Human Carcinogens.

The Naphthalene Panel's Comments demonstrate that the NTP cannot make sound inferences regarding the carcinogenicity of naphthalene by comparison to the substance's structural relationship with polyaromatic hydrocarbons ("PAHs"). *See* Naphthalene Panel's Comments at p. 8. While naphthalene has been identified as a two-ring PAH, it is biologically and structurally distinct from those PAHs considered potentially genotoxic and carcinogenic. *Id.* Naphthalene does not have greater than two fused rings, suggesting that it does not appear to interact with DNA (*i.e.*, it is not mutagenic) and cannot form the reactive bay region diol-epoxide, which is associated with the carcinogenicity of other PAH compounds. *Id.* at 8-9. Furthermore, unlike PAHs that are suspected to be genotoxic and carcinogenic, naphthalene is metabolized via the CYP2F enzyme family and not the CYP1A family. *Id.*

Conclusion

For these reasons, and for all the reasons set forth in the detailed Naphthalene Panel's Comments, USWAG strongly urges NTP to withdraw it's *ROC* Draft Background Document for naphthalene and discontinue efforts to list naphthalene on the *ROC*. In particular, USWAG requests that the NTP suspend all further action on naphthalene until the Background Document has been revised to reflect fully and accurately all available information and comments submitted on the recommendation to list naphthalene.

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If USWAG can be of further assistance to EPA in this effort or can respond to

any questions, please contact the USWAG Executive Director, James Roewer (202-508-5645) (jim.roewer@uswag.org).

Very truly yours,

Steve Pattison

Stephen L. Pattison
Chairman, Utility Solid Waste Activities Group