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MAR 26 2003

March 24, 2003

Via E-Mail and Overnight Courier

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
MD EC-14
P.O. Box 12233
Research Triangle Park, NC 27709

Re: National Toxicology Program (NTP), Call for Public Comments on 10 Nominations; Proposed for Listing in the *Report on Carcinogens*, Eleventh Edition; Federal Register, January 22, 2003 (Vol. 68, No. 14)

Dear Dr. Jameson:

The Naphthalene Panel of the American Chemistry Council submits these comments to NTP regarding the nomination of naphthalene for listing in the 11th *Report on Carcinogens* (*RoC*) in response to the January 22, 2003, *Federal Register* notice. In response to previous *Federal Register* notices,[1] the Naphthalene Panel has submitted comments regarding naphthalene on the proposed nomination (comments dated September 24, 2001), the *Draft Background Document* (comments dated October 2, 2002), and the "Working Group for the Report on Carcinogens – RG-2 Naphthalene Review" review (comments dated November 4, 2002). The Naphthalene Panel also made an oral presentation in the brief time period allowed at the Board of Scientific Counselors (BSC) RoC Subcommittee (Subcommittee) meeting on November 19, 2002.

As part of the RoC process, NTP has elicited recommendations on the listing of naphthalene from NTP Staff (the "RG-1" working group), from NTP's Executive Committee (the "RG-2" working group) and from the BSC RoC Subcommittee. Unfortuneately, the RG-1 review occurred before publication of the *Draft Background Document*, the RG-2 review occurred after publication of the background document but before the date for receipt of public comments, and the BSC RoC Subcommittee based its decision apparently in large measure on

[1] 66 Fed. Reg. 38430 (July 24, 2001); 67 Fed. Reg. 14957 (Mar. 28, 2002); 67 Fed. Reg. 36621 (May 24, 2002); 67 Fed. Reg. 59301 (Sep. 20, 2002).

information newly introduced at the Subcommittee meeting and not made available as of this date by NTP either on its website or in a revised background document or even in minutes of the meeting. This simple recitation of the calendar of the nomination, review, and now proposed listing of naphthalene makes evident that there has been no sincere effort to engage public stakeholders in the process, and no effort to ensure that "[NTP's] three scientific review committees are basing their decisions on the same basic material augmented by the additional public comments obtained during the review process."[2] Indeed, members of the public who were not physically present at the Subcommittee meeting are not even aware that a substantial part of the apparent basis for the Subcommittee's recommendation is not part of the public record, was not shared prior to the Subcommittee meeting with either Subcommittee members or the public, and has not been made publicly available to those who may be interested in submitting comments in response to the January 22, 2003 Federal Register notice regarding nomination of naphthalene as *Proposed for Listing in the Report on Carcinogens, Eleventh Edition.*

Despite the Naphthalene Panel's continuing disappointment over past events, *viz* the mischaracterization of the science and the growing list of deficiencies in the process that has been followed to date in the nomination and review of the proposed listing of naphthalene, the Naphthalene Panel remains ever hopeful that, at long last, NTP will adhere to its self-described "transparent" process that is "open and fair, clear to all interested parties"[3] and will consider these comments and attachments as well as those submitted previously. The Naphthalene Panel believes that NTP has no option but to start the review of naphthalene over if the collective record – including the transcript of the Subcommittee meeting - on the proposed listing of naphthalene by NTP is given serious consideration.

SUMMARY

The Naphthalene Panel urges that naphthalene not be listed in the *RoC, Eleventh Edition* for the following reasons:

1. Naphthalene does not meet the criteria to be listed as *Reasonably Anticipated to be a Human Carcinogen*:
    - 1.1. There is no credible evidence from studies in humans that naphthalene is a human carcinogen;
    - 1.2. The animal data are insufficient to conclude that naphthalene is associated with an increased incidence of malignant and/or benign tumors in multiple species or at multiple tissue sites;
    - 1.3. The animal data are insufficient to conclude that naphthalene is associated with an increased incidence of

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2 Letter from Dr. K. Olden, Director of NTP, to Ms. C. Price, Vice-President, CHEMSTAR of the American Chemistry Council dated March 11, 2003.

3 *Ibid.*

malignant and/or benign tumors by multiple routes of exposure;

1.4. The animal data are insufficient to conclude that naphthalene is associated with an increased incidence of malignant and/or benign tumors to an unusual degree with regard to incidence, site or type of tumor, or age at onset;

1.5. Naphthalene does NOT belong to a well defined, structurally-related class of substances whose members are listed in a previous *RoC* as either a known to be human carcinogen or reasonably anticipated to be human carcinogen;

1.6. There is NO convincing relevant information that naphthalene acts through mechanisms indicating it would likely cause cancer in humans; and

1.7. While there is evidence of carcinogenicity in one species of laboratory animals, there are compelling data indicating that napthalene acts through mechanisms which do not operate in humans and therefore, and on those grounds, cannot reasonably be anticipated to cause cancer in humans.

2. Should naphthalene be listed in the RoC, it would be the first substance to be listed based on "clear evidence" in one species of experimental animal, "some evidence" in one sex of a second species, and that is not genotoxic.

3. The process followed by NTP in nominating, reviewing, and potentially listing naphthalene in the *RoC, Eleventh Edition* has not been "open and fair, clear to all interested parties, and maintain[ing] the scientific rigor necessary for decisions regarding the review of agents for inclusion in the *RoC*."[4]

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4 *Ibid.*

1. NAPHTHALENE DOES NOT MEET THE CRITERIA TO BE LISTED AS *REASONABLY ANTICIPATED TO BE A HUMAN CARCINOGEN*

1.1 There is no credible evidence from studies in humans that naphthalene is a human carcinogen

As concluded in the *Draft Background Document*[5] and in the presentation of that document at the RoC Subcommittee meeting,[6] the available human data are insufficient for evaluation of the carcinogenicity of naphthalene to humans. In addition, the review summary reports for both RG-1 and RG-2 each concluded that the very limited human data are insufficient for the evaluation of the carcinogenicity of naphthalene. Further, none of the RoC Subcommittee members appeared to have disagreed with the conclusions in the *Draft Background Document* concerning the insufficiency of the human data and one member, apparently reflecting the consensus view of the Subcommittee stated that the "human evidence isn't helpful, so we are going to be considering the animal evidence predominantly in our discussions."[7]

Nevertheless, the *Draft Background Document* is a document disseminated by NTP that should be accurate and should have provided a detailed explanation of the inadequacies of the two relatively old case studies described -- one an East German study dating from the 1970s and the other African case reports involving the oral intake of naphthalene containing compounds for medicinal purposes. This is particularly the case given that other recent NTP publications about naphthalene (*e.g.*, NTP 1992, 2000) have cited the East German reports of health effects observed in tar distillation workers, and used misleading summaries of these reports as part of the rationale for conducting assays in rodents. For the record the Naphthalene Panel wishes to point out some of the deficiencies of the German study.

NTP has, in its publications about naphthalene, used information contained in the East German reports (Wolf, 1976, 1978) to introduce a calculation that the data indicate a "greater than 4000-fold" increase in the incidence of the laryngeal cancers (NTP, 2000). This "4000-fold" figure appears to result from the ratio of 4/15 (incidence in naphthalene workers) to 6.3/100,000 (incidence in general male population in 1970). The increase in incidence actually presented in Wolf (1978) was a factor of 62. In evaluating the East German reports, the NTP *Draft Background Document* should have expressly stated that, although Wolf (1978) suggested that tar fumes in combination with heat may be causative factors, all four workers who developed laryngeal cancer were smokers, and the 15 workers in the study all were likely to have been exposed to many confounding factors in the workplace described by Wolf. The published statement by NTP (NTP, 2000, page 20) that the Wolf data indicate a "4000-fold" increase in

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5 Draft Background Document at 21.

6 Transcript (11/19/02) at 61.

7 Transcript (11/19/02) at 94.

tumor incidence is an example of an inaccuracy that should be corrected in the *Draft Background Document*.[8]

NTP (2000) also refers to a publication by Kup (1978) as though it contains additional information about workers exposed to naphthalene in East Germany. The Kup publication, however, seems to be a lecture or presentation, apparently before a group of medical scientists or physicians. Kup's report is far from comprehensive and the four cancer cases are not the sole topic of his lecture. They are just mentioned without reference to any cohort, but are clearly the cases discussed in detail by Wolf (1976, 1978). The *Draft Background Document* should include accurate discussions of the Wolf (1976, 1978) and Kup (1978) publications to correct misimpressions resulting from inaccurate discussions in previous NTP publications about naphthalene, such as TR 500 (NTP, 2000) and the suggestion that multiple human evaluations were performed.

The EU Risk Assessment Report concludes the following about the East German studies:

> Two brief reports are available of four cases of laryngeal cancer which occurred in workers engaged in the purification of naphthalene (Wolf, 1976; 1978). It is difficult to define from the reports whether the author identified these four cases independently or whether they were brought to his attention by an external source. However, it is clear from the reports that all the cases were smokers and were exposed to other substances including coal tar volatiles. Overall, no conclusion can be drawn from these reports regarding the role, if any, of naphthalene in the production of these cancers.[9]

The German BAuA (1998) notes the confounding factors in the East German cases and also notes that the cases referred to by Ajao *et al.* (1988) involved oral intake of "a concoction containing naphthalene." As is often the case with case reports, little information is available about the nature of possible confounding influences in the African reports.

EPA's Integrated Risk Information System (IRIS) database for naphthalene, last updated in September 1998, concludes with respect to human carcinogenicity data:

> Available data are inadequate to establish a causal association between exposure to naphthalene and cancer in humans. Adequately scaled epidemiological studies designed to examine a possible association between naphthalene exposure and cancer were not located. Overall, no data are available to evaluate the carcinogenic potential in exposed human populations.

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8 Translations of Wolf's reports were previously submitted to NTP by the Panel in its comments on the Draft Background Document.

9 EU (2002) at Section 4.1.2.8.2

1.2. The animal data are insufficient to conclude that naphthalene is associated with an increased incidence of malignant and/or benign tumors in multiple species or at multiple tissue sites

Mouse Study (NTP, 1992)

The NTP Technical Report for the mouse bioassay on naphthalene (NTP, 1992) found only that there was "some evidence of carcinogenic activity" of naphthalene in female $B6C3F_1$ mice, based on increased incidences of pulmonary alveolar/bronchiolar adenomas in the high dose group.[10] The Technical Report did not make a finding of "clear evidence of carcinogenicity" in the test animals. An NTP study that finds that only "some evidence" of carcinogenicity, as opposed to "clear evidence," should be deemed insufficient in weight to warrant consideration under the NTP "reasonably anticipated to be a human carcinogen" standard.

Further, the statements in the current IRIS database on naphthalene (EPA, 1998) support that the NTP mouse study provides insufficient evidence of the carcinogenicity of naphthalene in mice. Addressing the NTP mouse study, it states: "An inhalation unit risk estimate for naphthalene was not derived because of the weakness of the evidence (observations of predominant benign respiratory tumors in mice at high dose only) that naphthalene may be carcinogenic in humans."[11] Indeed, only a single alveolar/bronchiolar carcinoma appeared among the 135 high dose female mice. No carcinomas were found in male mice. The NTP criteria regarding an increased incidence of malignant and/or combination of malignant and benign tumors clearly are not intended to pertain to an increased incidence of tumors that are so predominantly benign as in the case of the NTP mouse study.

The NTP mouse study (NTP, 1998) should not be considered by NTP for purposes of listing for the additional reason that "the pattern of toxicological evidence indicates that the mouse is more susceptible to the pulmonary toxicity of naphthalene than other species, and therefore the observed pulmonary adenomas seen in mice at [the high dose in the NTP study] are not considered to be of relevance to human health."[12]

Rat Study (NTP, 2000)

The Technical Report on the NTP rat bioassay on naphthalene (NTP, 2000) states that the incidences of neuroblastomas of the olfactory epithelium occurred with positive trends in male and female rats and that the incidence in the high dose females was statistically significant compared to controls. The Technical Report also reports a statistically significant increase in adenomas of the respiratory epithelium. J. Harkema's report, which is appended to the Naphthalene Panel's comments on the *Draft Background Document*, characterizes some of the rat respiratory epithelial tissue neoplasms as carcinomas whereas NTP's report (NTP, 2000) used

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10 NTP (1992) at 36.

11 EPA (1998) at Section II.C.

12 EU (2002) at Section 4.1.2.8.3.

the terminology "adenomas" for all such tumors in the male rats and an increase in that tumor that was not statistically significant in the mid and high dose female rats.[13] While these results indicate an increase in tumors in two different types of nasal tissue, the tumors all occurred in the nasal cavity. Therefore, it is clear that there was not an increase in malignant and/or a combination of malignant and benign tumors in multiple tissue sites because the nasal cavity is a single tissue site.

1.3 The animal data are insufficient to conclude that naphthalene is associated with an increased incidence of malignant and/or benign tumors by multiple routes of exposure

The route of administration in both the NTP rat study (NTP, 2000) and the NTP mouse study (NTP, 1992) was inhalation only and at high exposure concentration as compared to those to which humans would be exposed. Accordingly, by definition there is insufficient evidence from studies on naphthalene to conclude that there is an increased incidence of malignant and/or a combination of malignant and benign tumors by multiple routes of exposure.

1.4 The animal data are insufficient to conclude that naphthalene is associated with an increased incidence of malignant and/or benign tumors to an unusual degree with regard to incidence, site or type of tumor, or age at onset

The only malignant tumor increased in the NTP rat study (NTP, 2000) that possibly could be considered as induced to an unusual degree are the neuroblastomas seen in the nasal olfactory epithelium. The NTP report for that study notes that neuroblastomas of the nasal olfactory epithelium are rare neoplasms in rodents and humans. In addition, the report states that this tumor was not observed in the concurrent controls nor in NTP historical control databases. Even though these are rare tumors, several factors must be considered, before implicating the tumors as unusual under the NTP criteria for *RoC* listing. First, the historical control database for rats fed the NTP-2000 diet used in the NTP naphthalene bioassay is relatively small.[14] Second, the EU Risk Assessment (EU, 2002) stated that the weight-of-the-evidence indicates that naphthalene is non-genotoxic (see discussion below as well as Schreiner, 2003), the tumors develop only at the sites where non-neoplastic inflammatory changes (atrophy, hyperplasia, and metaplasia) occur and thus concluded that the development of the nasal tumors is an apparent consequence of chronic tissue injury, for which an identifiable threshold of effect will exist.[15] Tumors induced by such a common and non-specific mechanism of action should not be considered unusual, particularly when they occur at a site, as in the case of the nasal airway of the rat, where exposure to any irritating agent would be expected to cause inflammatory changes.

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13 NTP (2002) at 36.

14 NTP (2000) at 28-29, 38 (Table 6, note "c").

15 EU (2002) at Section 4.1.2.8.3.

Third, neuroblastomas of the nasal olfactory epithelium have been induced by oral, inhalation, or peritoneal exposure to several structurally unrelated chemicals, and in several of these studies, the induction of the tumors occurred in conjunction with olfactory epithelial non-neoplastic lesions, as in the bioassay on naphthalene.[16]

It also is noted that anatomical, physiological, and metabolic differences between the rat and humans raise substantial questions as to the relevance of the rat nasal tumors to humans. This is discussed in detail in Section 1.7, below, and is another reason that the rat tumors cannot be a basis for listing naphthalene in the *RoC*.

1.5 Naphthalene does NOT belong to a well defined, structurally-related class of substances whose members are listed in a previous *RoC* as either a known to be human carcinogen or reasonably anticipated to be human carcinogen.

No scientifically sound inferences about the carcinogenicity or gentoxicity of naphthalene can be made by an overly broad comparison of naphthalene's structure to polyaromatics hydrocarbons (PAHs). Biologically active PAHs share a common mechanism for genotoxicity and carcinogenicity based on their structure, which allows for metabolic conversion via the CYP1A1 enzyme to an active dihydrodiol-epoxide. Unlike the PAHs, the metabolism of naphthalene is under the control of the CYP2F enzyme family, not the CYP1A family, and does not lead to the formation of a dihydrodiolepoxide but instead form naphthalene-1,2-oxide.

While some chemists would agree that naphthalene can be technically classified as a PAH for purposes of definitional nomenclature, the importance of PAHs as a group is associated with their biological activity. Naphthalene is both biologically and structurally distinct from biologically active genotoxic and carcinogenic PAHs. Biologically active PAH's share a common mechanism for genotoxicity and carcinogenicity based on their structure. Although planar fused ring compounds (PAHs) vary considerably in their biological activity, genotoxic PAHs are indirect-acting or promutagens, meaning that genotoxicity is expressed following metabolic conversion of the PAH to an active species. The mechanism by which PAHs are thought to induce tumor formation is via interaction with genetic material within target cells, either frank mutagenicity or interference with normal genetic biology as a result of PAH-adduct formation with nuclear material. Accordingly, it is generally observed that the genotoxic potency of PAHs closely parallels the carcinogenic potency. However, this relationship is based on experience with PAHs having greater than two fused rings. Naphthalene does not have greater than two fused rings and results of numerous studies suggests that it is not mutagenic (see Section 1.6), *i.e.*, naphthalene does not appear to interact with DNA. Moreover, photomutagenicity, or the property of enhancing the mutagenicity of non-ionizing radiation, has been reported for carcinogenic PAHs (with greater than two fused rings) and can account for the observation of a lack of mutagenicity in highly carcinogenic neutral PAH mixtures (Selby,

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16 NTP (2000) at 42.

1986). There are no reports of the photomutagenicity of naphthalene. The presence of antimutagens in carcinogenic PAH mixtures has also been suggested to account for the difference in activity observed between isolated components of a mixture and the intact mixture (Slaga, 1979). There is no information suggesting that naphthalene can exhibit activity of the type associated with PAHs having greater than two fused rings.

There is information to suggest that the active structure of some PAHs is a reactive arene oxide, in older literature termed the bay region diol-epoxide. A bay region diol-epoxide is formed in a PAH when three rings are fused in a way to create a pocket, the "bay". Bay region diol epoxides are formed enzymatically in humans by a P450 enzyme, CYP1A1. The ability and ease of a PAH to form a bay region diol epoxide can be calculated. This has lead to a great deal of work in structure-activity-relationship (SAR) assessment of the potential for carcinogenicity of PAH compounds - but only PAH compounds with three or more fused rings.

In addition to the recognition of the importance of the bay region to genotoxicity and carcinogenicity of PAHs, it has been observed that the addition of a substituent group, almost always a methyl group, in or opposite to the bay region containing the epoxide impacts on PAH biologic activity. There are numerous examples of the alkylation of the PAH (with a methyl group) both enhancing and eliminating PAH tumorigenicity and mutagenicity (Saas, 1996; Slaga, 1979, Thakker, 1979).

The large and long-standing body of information relating to carcinogenic characteristics of PAHs, whether it be induction or suppression of genotoxic/carcinogenic activity, has not been associated with naphthalene. To date, a unified SAR theory does not exist to account for the observations of PAH carcinogenicity, particularly for PAHs that are substituted beyond the methyl state (nitroaromatics and branched chain alkylated PAHs, for instance). Various illuminating bodies of work have evaluated the carcinogenic effect of methyl-, ethyl-, and propyl-substitutions on fused-ring PAHs such as chrysene. Methylation has been shown to transform inactive PAHs to active and to deactive carcinogenic PAHs. For example, methylchrysene is a more potent lung carcinogen than chrysene, but ethyl- and propyl-chrysene are less potent. Similarly, bay region methylation of dimethylbenzanthracene, a potent mutagen and carcinogen, completely blocks mutagenic and carcinogenic activity. However, none of these observations characteristic of PAH carcinogenicity have been found applicable to "PAHs" with less than three fused rings. In fact, no approach to PAH carcinogenic SAR, whether involving electron cloud density theories or methods of analysis involving statistics and artificial intelligence, includes naphthalene in the paradigm.

Accordingly, the statement by a member of the RoC Subcommittee that, because of napththalene's structure, "naphthalene belongs to an agent, substance, or mixture which belongs to a well-defined structurally-related class of substances...I would suggest that naphthalene is a two-ringed PAH, and as everybody in this room knows, PAHs have relatively strong evidence as to their carcinogenicity"[17] does not comport with the body of toxicology knowledge assembled on the carcinogenic characteristics of PAH compounds.

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[17] Transcript (11/19/02) at 99-100.

1.6 There is NO convincing relevant information that naphthalene acts through mechanisms indicating it would likely cause cancer in humans

Presentations made by representatives of NTP and of the Naphthalene Panel at the RoC Subcommittee meeting on November 19, 2002 both included summaries of the well studied metabolism of naphthalene. A key point made by both presenters was the relationship of naphthalene metabolism to species-specific organ toxicity. The species- and tissue-specific toxicity has been attributed to difference in metabolism (Sweeney *et al.*, 1996; O'Brien *et al.*, 1985).

As shown in Figure 1, naphthalene is metabolized by cytochrome P450 isoenzymes to naphthalene-1,2-oxide (also referred to as naphthalene epoxide) and subsequently to 1,4,-naphthalediol and 1,2-naphthalenediol. The diols are oxidized, either enzymatically or non-enzymatically to 1,4-naphthoquinone and 1,2-naphthoquinone, respectively. In the mouse lung naphthalene metabolism favors the formation of the 1R2S-oxide while in the rat and hamster lung, metabolism predominantly goes through the 1S2R-oxide. The differences in tissue responses between rats and mice have been ascribed to stereoisomeric differences (Buckpitt *et al.*, 2002). The relationship of this differential metabolism and its potential relationship to the formation of lung tumors in mice and nasal olfactory tumors in rats have been described in previous documents submitted by the Naphthalene Panel`.

During the Subcommittee deliberations, a Subcommittee member opined that the metabolism of naphthalene should be looked at in a complex fashion rather than focusing on the stereochemistry of the epoxides and that only mechanistic pathways that are entirely believable and reasonable and should be considered seriously when the Subcommittee makes its final decision[18]. The alternative metabolism proposed by the Subcommittee member was that of the three ring (and greater) PAHs. Section 1.5 of these comments contains discussion of the differences between PAHs with three or more rings and naphthalene. The Naphthalene Panel takes issue with the characterization that the role of epoxides in tissue injury is not believable and reasonable. The literature over the past 20 years supports the role of naphthalene epoxide in tissue-specific toxicity (see recent review by Buckpitt *et al.*, 2002). An alternative pathway suggested by this Subcommittee member posits that the naphthoquinones and the reactive oxygen species that follow are an important mechanistic pathway that could, in part, explain the carcinogenicity of naphthalene. Extensive research on naphthalene metabolism does not support this.

The Naphthalene Panel agrees that it is important to evaluate appropriate mechanistic pathways in assessing risks associated with xenobiotics. Further, the Panel does agree that the literature demonstrates that low levels of naphthoquinones may be formed via metabolism of naphthalene. In its discussions, however, the RoC Subcommittee failed to give sufficient consideration to well established metabolic pathways and potential mechanisms of

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[18] Transcript (11/19/02) at 111.

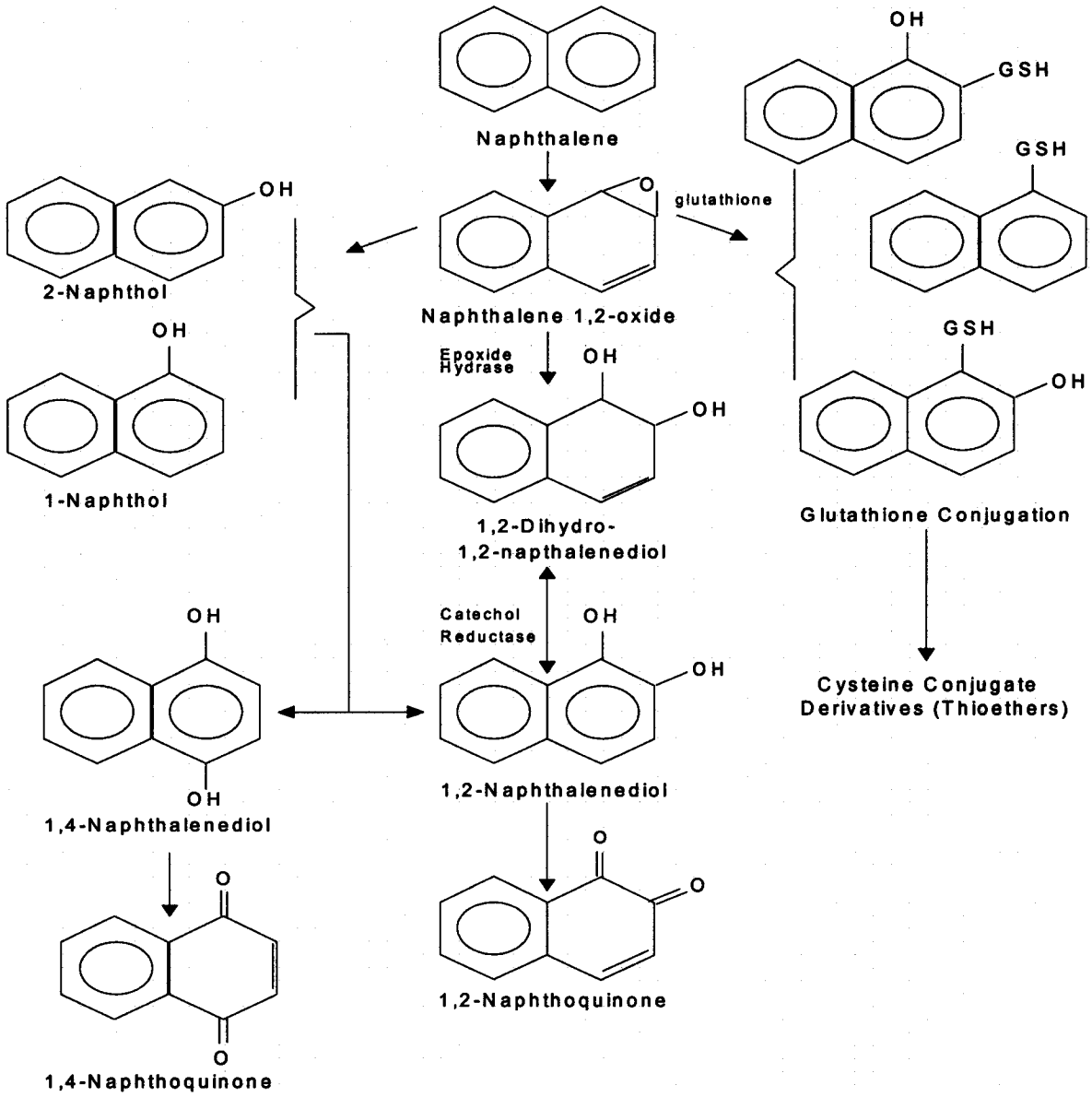
tumorigenicity but rather focused solely on speculations that a minor metabolite should be considered relevant in contradiction to all published research on naphthalene metabolism.

Recently published studies evaluated the formation of hemoglobin and albumin adducts by naphthalene-1,2-oxide, 1,2-naphthoquinone and 1,4 naphthoquinone after naphthalene administration to F344 rats (Waidyantha *et al.*, 2002; Troester *et al.*, 2002). Results show that the levels of hemoglobin adducts formed with the epoxide greatly exceeds the levels of adducts from either of the quinones. In contrast, the amounts of naphthoquinone bound to albumin are very similar to the amounts of epoxide bound to albumin. In light of discussions by the RoC Subcommittee focused on the importance of naphthoquinone, the question is whether the levels of naphthoquinone produced during metabolism of naphthalene rise to levels of toxicological concern.

To support the relevance of naphthoquinones in the tumorigenic process data, a document was presented to the Subcommittee that apparently included published data from the literature thought to be germane to the naphthalene review. This document was prepared outside of the public comment period and not shared with the public before, at or after the meeting. Nonetheless, this document became the main focus of the Subcommittee's deliberations regarding naphthalene.

Following the meeting, the Naphthalene Panel was supplied four citations from the literature that apparently were included in the new document presented to the Subcommittee (Flowers-Geary *et al.*, 1996; McCoull *et al.*, 1999; Penning *et al.*, 1999; Yu *et al.*, 2002). None of these publications involves evaluation of naphthalene. Rather each addresses the synthesis, reactivity, binding, and mutagenicity of PAH o-quinones. These papers support a conclusion the PAH o-quinones and reactive oxygen species generated by o-quinone are mutagenic. The papers are silent about naphthalene.

Figure 1. Proposed pathways for Naphthalene metabolism (from ATSDR report, update 1995)



When evaluating naphthalene, it is important to consider results from studies with naphthalene *per se* in relationship to similar studies with metabolites. A RoC Subcommittee member stated that "the argument that naphthalene is not genotoxic is simply not true unless one decides to eliminate or not take into consideration the products of metabolism."[19] The Naphthalene Panel does not concur with this statement for the following reasons:

A. Testing of metabolites at high concentrations is not relevant to low levels of metabolites generated *in vivo*.

B. The genotoxic potential of naphthalene *per se* has been extensively evaluated. Review of the published literature shows that there are 33 non-mammalian and mammalian cell *in vitro* assays giving negative results. Additionally, there are four *in vivo* assays that were negative. A number of the *in vitro* studies were conducted under conditions of metabolic activation and, of course, naphthalene would be metabolized in the *in vivo* studies. If naphthoquinone formation were significant, positive responses would have been expected. Clearly, this is not the case. For example, a RoC Subcommittee member cited positive findings for four Ames strains tested with naphthoquinone as providing strong evidence of potential mutagenicity for naphthalene.

   The conditions (*i.e.*, metabolic activation or non-activation) were not stated. The literature contains ten Ames studies with naphthalene, covering 33 evaluations covering five tester strains (six assays with TA1535; eight assays with TA1537; eight assays with TA100; nine assays with TA98; and two assays with TA1538) under conditions of both metabolic activation and non-activation (Schreiner, 2003). These studies were negative and support a conclusion that the level metabolically produced naphthoquinone do not rise to the level of inducing genotoxicity.

   It was also stated by the *RoC* Subcommittee member that positive results from a "modern" mutational frequency study with p53 needs to be taken with some seriousness as opposed to more traditional mutagenicity assays. It should be noted that these "modern" results were derived from an *in vitro* study with PAH o-quinones (Yu *et al.*, 2002) and the study authors concluded that no mutants were observed with PAH o-quinone alone. This study, although presented as supporting the genotoxicity of naphthoquinone, does not.

C. A *RoC* Subcommittee member stated "...you really can't apply weight of evidence across genotoxicity studies."[20] This statement was made to override the weight of evidence from naphthalene genotoxicity studies that

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19 Transcript (11/19/02) at 108-109.

20 Transcript (11/19/02) at 126.

> is overwhelmingly negative. It may be that this Subcommittee member is unaware of the mutagenicity risk assessment procedures published by EPA that are used in evaluating the carcinogenic potential of pesticides and industrial chemicals (Russell *et al.*, 1984; EPA, 1986). These procedures are a weight of evidence analysis of all genetic toxicity data and affirm the conclusion reached by various regulatory bodies, including IARC and NTP, that the weight of evidence from naphthalene genotoxicity studies is overwhelmingly negative (Schreiner, 2003).

It seems that the underlying mechanistic information presented by NTP in its *Draft Background Document* (NTP, 2002) and its oral presentation, and by the Naphthalene Panel in its comments and oral presentation at the RoC Subcommittee meeting was lost in the Subcommittee's debate over metabolism of (three ring) PAHs.

The Naphthalene Panel agrees that mechanistic pathways should have been considered seriously when the committee made its final determination.[21] Inexplicably, as the transcript of the meeting shows, the RoC Subcommittee's evaluation of mechanistic considerations focused little attention on the nasal olfactory tumors, especially given that naphthalene is not genotoxic. Considerations such as mechanisms of tumor formation are well recognized components of the risk characterization process (Williams and Paustenbach, 2002) and are one of the factors to be considered under NTP's listing criteria.

1.7 While there is evidence of carcinogenicity in rats, there are are compelling data indicating that napthalene acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans

NTP's listing criteria state that even where there is evidence of carcinogenicity in laboratory animals for a particular agent, where there are compelling data indicating that the agent acts through mechanisms which do not operate in humans, the agent would not reasonably be anticipated to cause cancer in humans and therefore would not be listed in the *RoC*.

There are compelling data indicating that naphthalene causes nasal tumors in rats by mechanisms that do not operate in humans. Anatomical, physiological, and metabolic differences between the rat and humans raise substantial questions as to the relevance of the rat nasal tumors to humans. Human nasal physiology is significantly different from that of rodents. A primary site of action for toxic effects in rats is the olfactory epithelium, which comprises a significant portion of the total nasal cavity. The rat is an obligatory nose breather and must rely on olfaction for survival. The olfactory mucosa in rats is a highly developed system of cellular structures that performs complicated integration of olfaction and air humidification. Approximately 50% of the total surface area of the posterior region of the rat nasal cavity is comprised of the olfactory epithelium (Gross *et al.*, 1982; Uriah and Maronpot, 1990). Inhaled

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[21] Transcript (11/19/02) at 111.

vapors need traverse only a few millimeters past the resistant respiratory epithelium to reach the sensitive olfactory tissue in rats.

By comparison, the total surface area for chemical exposure is much less in humans (by a factor of five) since human nasal turbinates are much less convoluted than in the rodent. The olfactory epithelium comprises only about 10% of the human nasal cavity and is confined to the posterior dorsal region of the nasal cavity (Frederick *et al.*, 1994). The ciliated respiratory epithelium is the major lining of the human nasal cavity. In humans, inhaled vapors must traverse several centimeters through the ciliated respiratory epithelium before reaching the olfactory epithelium. Through mucociliary actions, the respiratory epithelium provides a protective system for the olfactory epithelium and other respiratory tissues. As a result of these differences, the efficiency of extracting chemicals from air inhaled through the nose is much less in humans than in rodents, which rely heavily on their sense of smell to locate food. The resulting dose deposited to the human olfactory epithelium, in particular, from inspired air is far less than for rodents for any given naphthalene concentration in air.

As noted above, irritation occurred in the nasal olfactory and respiratory epithelium in the NTP rat study (as well as in the NTP mouse study). Also as explained, it is likely that irritation plays a central role in the induction of nasal tumors seen in the rat. This conclusion is supported by the fact that naphthalene is largely negative in genotoxicity studies. Moreover, both the Draft EU Risk Assessment,[22] as well as the EU Scientific Committee on Occupational Exposure Limits,[23] concur that chronic cytotoxicity is the likely mechanism for the tumorigenic effects of naphthalene in the rat nasal cavity. Given the factors discussed above, it appears unlikely that such chronic cytotoxicity in olfactory epithelium would occur in humans under conditions of naphthalene use.

Differences in the rate of metabolism and the character of the metabolites of naphthalene in rats and humans also support the hypothesis that the NTP rat bioassay results are not relevant to humans. Of all mammalian species, the human has the greatest capacity for the detoxification of naphthalene epoxide, the initial metabolite of naphthalene. This epoxide is a reactive and short-lived intermediary metabolite, which is thought to be the proximate carcinogen in the rat causing the neuroblastoma. Humans metabolize naphthalene epoxide at a rate 6-fold greater than rats, providing a protective mechanism from naphthalene effects. As explained by Kitteringham, *et al.* (1996), " . . both rodent species [(rat and mouse)] showed consistently low (epoxide hydrolase) activity which, coupled with the possibility of differences in substrate specificity, cautions against the choice of rodent species for toxicity testing of compounds for which epoxide intermediates are suspected metabolites" (Kitteringham et al., 1996).

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22 Draft EU Risk Assessment, at Section 4.1.2.8.3.

23 SCOEL (Scientific Committee on Occupational Exposure Limits) (2001). "Recommendation from Scientific Committee on Occupational Exposure Limits for Naphthalene." SCOEL/SUM/90 final, June, 2001.

In light of the foregoing anatomical, physiological, and metabolic considerations, there are substantial questions about the relevance of the rat nasal tumors to humans. These questions are of sufficient degree to preclude a finding that naphthalene is "reasonably anticipated to be a human carcinogen," under conditions of use. This conclusion is corroborated by the mechanistic information discussed in Section 1.6 above.

2. SHOULD NAPHTHALENE BE LISTED IN THE ROC, IT WOULD BE THE FIRST SUBSTANCE TO BE LISTED BASED ON "CLEAR EVIDENCE" IN ONE SPECIES OF EXPERIMENTAL ANIMAL, "SOME EVIDENCE" IN ONE SEX OF A SECOND SPECIES, AND THAT IS NOT GENOTOXIC[24].

The scientific findings summarized above do not suggest that naphthalene should be listed as "reasonably anticipated" to be a human carcinogen. As noted in Section 1.2 above, the basis for "some evidence" of carcinogenicity in female mice is one carcinoma in one of 135 female mice. This evidence is weak at best. Importantly, NTP should not use naphthalene or any other individual substance to affect a "change by precedent" in RoC listing evidence requirements. Any change to NTP's listing criteria should be submitted for review to RG-1 and RG-2 followed by a notice in the Federal Register that would allow all affected parties, including other agencies, the opportunity for review and comment.

3. THE PROCESS FOLLOWED BY NTP IN NOMINATING, REVIEWING AND POTENTIALLY LISTING NAPHTHALENE IN THE *ROC, ELEVENTH EDITION* FALLS FAR SHORT OF NTP'S COMMITMENT TO BEING "OPEN AND FAIR, CLEAR TO ALL INTERESTED PARTIES, AND MAINTAIN[ING] THE SCIENTIFIC RIGOR NECESSARY FOR DECISIONS REGARDING THE REVIEW OF AGENTS FOR INCLUSION IN THE *ROC*."

The Naphthalene Panel believes strongly that the events that transpired at the November 19, 2002, RoC Subcommittee meeting with respect to naphthalene were serious transgressions of scientific rigor and due process. These are described in detail in the Naphthalene Panel's letters of March 3, 2003 and November 27, 2002 to Dr. Kenneth Olden, Director NTP. Those letters and Dr. Olden's responses dated January 27, 2003 and March 11, 2003 are attached and should be considered part of the Naphthalene Panel's submitted comments.

In summary, the transgressions included an unexpected technical presentation focussed on information of no apparent utility to understanding naphthalene carcinogenicity delivered to the Subcommittee by the Chairman of the Subcommittee who subsequently voted on the disposition of naphthalene. The presentation allegedly included new information purporting to relate naphthalene to the carcinogenicity of PAHs that had neither been shared prior to the meeting with the Subcommittee, nor since made a part of the public record. At least some of the

[24] Transcript (11/19/02) at 98.

information provided (the four citations discussed in Section 1.6, above) concerned major metabolites of PAHs with three or more rings and did not address naphthalene. Moreover, this objectionable and inappropriate approach has continued to this day, with the apparent approval of NTP, as none of the materials presented are yet part of the public record. Indeed, none of this information was available for public comment before the Subcommittee meeting, after it, or at present. The information is only available through a request for the meeting transcript, included as an attachment to these comments.

A possibly even more glaring process error is the fact that the *Draft Background Document* on naphthalene remains in its orignal form, with its contents unchanged from its August 26, 2002, cover date. Neither the RG-1 findings nor the RG-2 findings are reflected in the *Draft Background Document* despite the requirements of NTP's own procedures that the *Draft Background Document* be so revised. Both on its web site and in correspondence from Dr. Olden, the *Draft Background Document* is described as the "document of record" for RoC decisions. Further, in Dr. Olden's letter of March 11, 2003, it is stated that NTP does "not alter the background document throughout the review period unless serious errors are detected in it. This assures that our *three scientific review committees are basing their decisions on the same basic material augmented by additional public comment obtained during the review process*" [italics added for emphasis]. The problem with this is it assumes the *Draft Background Document* is fundamentally correct when issued. Where, as here, the *Draft Backround Document* is fundamentally flawed and despite repeated requests to remedy these flaws, the document remains unchanged, presumably only because of the process reasons given in Dr. Olden's letters. This contributes to the appearance and perceptions that NTP's solicition for public comment is little more than a meaningless exercise in the form of transparency rather than the function; in going through the motions of stakeholder involvement rather than the actions.

More to the point, in this instance, NTP's actions betray a double standard. On the one hand, the naphthalene *Draft Background Document* remains unchanged despite voluminous evidence offered by the Naphthalene Panel that it is materially incorrect. On the other hand, when the Chairman of the RoC Subcommittee spoke at the November meeting, presented for the first time new data and his interpretation of this data to his colleagues on the Subcommittee, the public was expressly denied an opportunity to comment on these data. This denial continues to this day as none of the presentation, remarks, or other "new" information relating to PAHs with three or more rings presented at the RoC Subcommittee meeting are available for comment. The Chairman's exercise of executive perogitive was inappropriate last November, continues to be inappropriate, and is in sharp contrast with NTP's stated ideal that the three scientific review committees (two of which met before the end of the comment period on the *Draft Background Document*) based their decisions on the "*same basic material augmented by additional public comment obtained during the review process.*" Clearly, this is not the case as the PAH information is unrelated to the "same basic material" embodied by the *Draft Background Document*.

Rather than repeat here in detail all the many procedural errors and due process transgressions the Naphthalene Panel already has brought to NTP's attention, the November 27,

2002 and March 3, 2003 letters are attached and incorporated by reference here. Additionally, and for purposes of clarity and to ensure the record is complete, Dr. Olden's January, 27, 2003 and March 11, 2003 responses to the Naphthalene Panel's letters also are attached, as is a copy of the transcript of the November 19, 2002 Subcommittee meeting.

Based on the objectivity, utility and integrity of the data used to to date by NTP throughout the review of naphthalene, if NTP does not withdraw the *Draft Background Document* and consider naphthalene anew, the Naphthalene Panel will be forced to consider an Information Quality Act Petition requesting a "Predissemination Review" of the proposed listing of naphthalene in the Eleventh RoC.

CONCLUSION

The Naphthalene Panel renews its request that NTP immediately withdraw the *RoC Draft Background Document* for naphthalene, for all the reasons noted above and in the Panel's prior submissions. Further, the Panel requests that NTP suspend all further action on napthalene until the *Draft Background Document* has been revised to reflect fully and accurately all available information and comments submitted on the recommendation to list napthalene. The Panel also renews its request that NTP nullify the vote on napthalene by the RoC Subcommittee and schedule napthalene for review at the next RoC Subcommittee meeting. Acceding to these minimal requests and giving the review of naphthalene a fresh start will go a long way towards correcting the procedural and due process infractions that have characterized the listing process thus far. If NTP declines to provide this reasonable relief, the Naphthalene Panel asks that NTP advise the Naphthalene Panel of its decision before forwarding a recommendation to list naphthalene to the Secretary, Department of Health and Human Services and allow the Naphthalene Panel to meet with NTP.

If you seek additional information, please call or e-mail Dr. Anne P. LeHuray at (703) 741-5630 or ***anne_lehuray@americanchemistry.com***.

Sincerely yours,

Signature

Courtney M. Price
Vice President, CHEMSTAR

Attachments

cc: Mr. Tommy Thompson, Department of Health and Human Services (HHS)
Dr. K. Olden, NTP
Dr. Christopher Portier, NTP
Dr. Dr Elias A. Zerhouni, Director, National Institutes of Health (NIH)

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Attachment A

Condensed Transcript
National Institute of Environmental Health Sciences
National Toxicology Program (NTP)
Board of Scientific Counselors

Report on Carcinogens (ROC) Subcommittee Meeting

November 19, 2002

CONDENSED TRANSCRIPT

NATIONAL INSTITUTE OF

ENVIRONMENTAL HEALTH SCIENCES

NATIONAL TOXICOLOGY PROGRAM (NTP)

Board of Scientific Counselors

Report On Carcinogens (ROC) Subcommittee

Meeting

November 19, 2002

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Page 55

DR. JAMESON: Thank you, Dr. Froines. I would like to present you with some background information on the nomination of naphthalene for listing in the Report on Carcinogens. The background document was prepared for the National Toxicology Program by Technology Planning and Management Corporation, TPMC. They are the support contractor for the Report on Carcinogens. Helping us with the background document on naphthalene was Dr. Rick Hailey who is a veterinary pathologist on...

DR. FROINES: Excuse me, Dr. Jameson. I need to interrupt here. For this compound, I am stepping down as the chair so I can be an active participant in the discussion, and Dr. Allan Smith will chair the committee for the purposes of naphthalene.

DR. SMITH: Thank you, Dr. Jameson.

DR. JAMESON: Thank you.

Page 54

Okay, the second compound is naphthalene, and the first...we just decided to go ahead with naphthalene and not take a break. Does anyone strongly disagree with that?

(No response.)

DR. FROINES: Okay, let's go ahead. Dr. Jameson?

Page 56

I had indicated that the background document was prepared for the NTP our support contractor, TPMC, and to help us with this background document, Dr. Rick Hailey, a veterinary pathologist on staff at the NIEHS reviewed the document for us. Dr. Hailey is the head of the bioassay technical support group in the pathology laboratory at NIEHS.

Naphthalene is a polycyclic aromatic hydrocarbon, if you will. It was nominated for listing, possible listing, in the Report on Carcinogens by NIEHS based on an NTP bioassay showing clear evidence of carcinogenicity in rats and some evidence of carcinogenicity in female mice.

As far as human exposure to naphthalene is concerned, the principal use of naphthalene is use as a chemical intermediate for the production of chemicals such as phthalic anhydride, insecticides. It

Page 57

is used to prepare chemicals and also used to make sulfonate surfactants. Other uses reported for naphthalene include use as a moth repellant in mothballs, and it has been used in the past as a deodorant, although our current information indicates it may not be used for that presently.

Environmental exposure to naphthalene can come from a number of sources, putritive emissions during the distillation of naphthalene or the handling of naphthalene in the preparation of other compounds. Also, the evaporation of naphthalene from mothballs is another major source of exposure to naphthalene in the environment.

It is estimated, based on urban areas, inhalation exposure to naphthalene, based on an average of about 1 g/m3, in urban areas, individuals could be exposed to up to 19 g/m3 per day. There is also a potential for environmental exposure

Page 58

dermally to people handling or wearing clothes that have been stored with mothballs.

Occupational exposure is also in the area of...also done by inhalation or dermal exposure. There is information that would indicate that in the industrial setting, naphthalene is present as both a vapor and a particulate, because naphthalene very readily, and in industry, it has been found that usually, if a vapor and a particulate are present, then the concentration of naphthalene as a particulate is higher than it is in the vapor state.

The National Occupational Exposure Survey, the latest information we have which I will give you the data on, estimates that greater than 100,000 workers are potentially exposed to naphthalene.

This gives you an idea of the consumption of naphthalene in the United States. The information

Page 59

background documents indicates that U.S. production of naphthalene peaked around 1968 with the production at that time of about 900 million pounds. Production decreased, then, into the '80s, and by 1982, the production was down to about 354 million pounds, and in 2000, the production level was reported at 235 million pounds.

This particular graph here is showing the consumption of naphthalene for what we use naphthalene in the United States. The vast majority is used in the preparation of phthalic anhydride, and the figure here for 2000 is 146 million pounds. Naphthalene sulfonates appear to be increasing in importance for consumption of naphthalene, and you can see, over this time period, you can see it seems to be increasing. The use of naphthalene in pesticides appears to be decreasing in this time period with the use of naphthalene in other applications remaining fairly

Page 60

constant.

As far as human cancer studies with naphthalene, there are two case series studies reported in the literature. One is laryngeal and other cancer reported in a group of dermally exposed workers. This is a report where there are 4 laryngeal cancers plus 1 case each of gastric and colon cancer, and these are a cancer cluster that were reported in a group of 6 of 15 distillation plant workers in Germany.

The other study is of colorectal carcinoma, and this is reported for a group of men who used Perferal, and this is a medical medicinal used by certain products. Some detail of this particular study, of the 23 cases diagnosed between 1982 and 1984, there were 11 cases of...11 of the 23 cases reported were in men who were under 30 years of age. Half the patients with early onset reported the use of Preferal which is a

Page 61

naphthalene medicinal and was used to treat anal-rectal problems in these cases. The other half of the people where the tumor was observed could not remember if they had used the Preferal or not.

The overall evaluation is that there is insufficient evidence for the evaluation of carcinogenicity in humans based on the human studies.

What we have now is the experimental studies in animals. This is the NTP two-year inhalation study. Groups of male and female V63 Equa mice and Fisher rats were exposed to naphthalene vapor 5 hours...I am sorry...6 hours a day for 5 days a week. The mice were exposed for 104 weeks, and rats were exposed for 105 weeks. The exposure concentration in mice was 0, 10, and 30 ppm, and in rats, the exposure levels were 0, 10, 30, and 60 ppm.

In both the rat and the mouse studies, there was no significant

Page 62

effect on body weights of the exposed animals, and survival of the exposed animals was comparable to control animals.

A graph of the lung tumors that were observed in the V63 Equa mice, lung tumors were observed in both males and females, and adenomas...I'm sorry. These were alveolar bronchiolar adenomas, carcinomas, and adenomas and carcinomas combined. There was a significant increase in adenomas and adenomas or carcinomas combined in the female rats at the high dose levels. There was also a significant positive trend for these particular compounds, both for the adenoma and the adenoma and carcinoma combined.

In the males, we saw the same tumors that we saw in the females. However, the incidence of the tumors in the males were within historical control values.

So, the NTP concluded that

Page 63

there was no evidence of carcinogenicity for naphthalene in the male mice and some evidence of carcinogenicity in the female mice based on the increased incidence of the adenoma and the adenoma/carcinoma combined in the high dose group.

For the rat study, there was statistically significant increase in adenomas of the respiratory epithelium, showed a dose related trend, and there were significant increases at all three dose levels. This is a very rare tumor seen in the Fisher rat. It was reported at the time that none of these tumors had been seen in any of the historical controls. The pathology description of this tumor was that it was very large...some of the tumors were very large and invasive and even went into the olfactory lobe of the brain, and I believe it was in one animal in the high dose and one animal in the low dose that had metastasis to the lung

Page 64

from these particular tumors.

These adenomas were also observed in the female mice, again pointing out that these are very rare tumors, but they were not seen at a significant level.

There were also neuroblastomas observed in both the male and female rats. The neuroblastoma also is a very rare tumor in the Fisher rat. It was seen at a dose related trend in the males and a dose related trend in the females and also at a significant level in the high dose female rats.

So, based on this evaluation, the NTP concluded that there was clear evidence of carcinogenicity in male Fisher rats and also clear evidence of carcinogenicity in the female Fisher rats.

Looking at some of the selected non-neoplastic lesions that were observed, there were chronic...in the mice, there was observed chronic

Page 65

inflammation of the nose and lung, hyperplasia of the respiratory epithelium in the nose, and metaplasia of the olfactory epithelium, and all of these non-neoplastic lesions are attributed to naphthalene exposure and the naphthalene.

In rats, there was seen atypical basal cell hyperplasia of the olfactory epithelium. This is also a rare observation not reported in other NTP bioassay reports, and this basal cell hyperplasia was observed in anywhere to 88 to 98 percent of the animals that were exposed to naphthalene. In addition, they observed chronic inflammation of the lungs in the males of the Fisher rat, and there was alveolar epithelial hyperplasia in the lungs of the female rats.

So, all these non-neoplastic lesions support the neoplastic lesions that were observed in the studies.

There are some additional

Page 66

experimental studies of naphthalene reported in the literature. Some mice were treated. A group of 30 females were exposed to 0, 10, 30 ppm of naphthalene for 6 months. Survival in the study was by exposure. The authors reported no significant increase in lung adenomas in this study. There was significant increase in the number of tumors per tumor-bearing lung reported in this study, but it was also reported by the authors that the number of tumors per tumor-bearing lung in the controls was significantly lower than in the controls.

Other studies on naphthalene that have been reported in the literature, IP or subcutaneous studies. There was a study of CD1 mice that were treated intraperitoneal. In this particular study, mice were treated to 0.05 molar naphthalene in DMSO in day 1, 8, and 5 of life. So, the total dose to these animals was 1.75 M per

Page 67

mouse, and then the animals were held. At weaning, they were separated into groups of 31 male and a group of 16 females, and they were held for a total of 52 weeks. At 52 weeks, the animals were sacrificed, and no tumors were observed in this study.

There is another study reported where BDI1 or BDIII3 rats were treated by both intraperitoneal and subcutaneous injections, and animals were treated either intraperitoneal, and another group was treated subcutaneously with 20 mg of naphthalene in oil, and the animals were treated for 40 weeks and then held until they died.

For the group of animals that were treated intraperitoneal, they survived for 900 days. With subcutaneous injection, those animals survived 700 days. The author reported no tumors in this particular study, but the study is considered inadequate, basically, because of the

Page 68

small number of animals used, and no information was given on the control animals other than the fact that the treated animals survived as long as controls.

There was also another study reported in the literature where BDI1 and BDIII3 rats again were used. They were treated...I'm sorry. A group of 21 animals were treated naphthalene in the feed at 10 to 20 mg/day for 6 days/week and treated for 100 weeks. After 100 weeks, they were held until they died, and the average...I'm sorry...they survived up to 800 days which is comparable to the...the authors report it is comparable to the controls. Again, no tumors were observed. This study, again, is considered inadequate for the low number of animals used in the dosing group and the fact that not enough information on the controls was cited.

As far as genotoxicity, there is little evidence of mutagenic

Page 69

activity for naphthalene. Positive results have been obtained in assays for micronucleus formation, chromosomal aberrations, and chromosomal recombinations in vitro. There is also an in vivo assay reported where oral administration of naphthalene to Sprague-Dawley rats caused oxidative stress and DNA breakage in the liver and brain. In these studies, they were both a single dose experiment where the animals were treated with, I believe it was, 1100 mg/kg as a single dose, and the other was a multiple dose study where the animals were treated with 120 mg/kg/day for 120 days, and in both of those studies, the naphthalene caused oxidative stress and DNA breakage.

Other relevant data, as far as absorption and distribution studies of naphthalene, metabolites were found in the urine of workers with a good correlation found between naphthalene exposure and the 1-naphthol exposure

Page 70

in their urine. So, it is obviously being absorbed in the workplace.

It is also determined to be absorbed through the skin in humans and has been detected in human adipose and breast milk samples. There are a number of animal studies that indicate absorption following...absorption of naphthalene...excuse me...following oral, dermal, and inhalation exposure.

I apologize for the quality of this slide. This is a slide of the metabolism of naphthalene. Naphthalene is metabolized by the p450 enzyme. I put this up here to show that it forms two stereoisomers of the 1,2 epoxide, the 1R2S oxide and 1S2R oxide, and these oxides are further metabolized with glutathione. This appears to be the major metabolic pathway for this material.

In this slide, I explain it a little more clearly. The naphthalene is bioactivated by the p450 into stereoisomers of the naphthalene 1,2-

Page 71

oxide that I showed previously. It is the 1R2S epoxide or the 1S2R epoxide. There appears to be information in the literature that shows a correlation between the rates of the formation of the 1R2S epoxide and selective toxicity. There is also data reported that the Mouse1 microsome metabolism favors the formation of what I will refer to as the more toxic R-S epoxide, whereas rat and human lung data would indicate that they favor the, quote, what I would call the less toxic S-R epoxide.

It has also been shown that the rate of metabolism of naphthalene in the mouse lung is about 10 times greater than in the rat and about 100 greater than in humans.

Other studies have shown that the rat and mouse olfactory epithelium favors metabolism to the 1R2S or what I refer to as the more toxic epoxide with the rate in rats being approximately half that of the mouse

Page 72

for this particular study in the olfactory epithelium.

The recommendations that we got for naphthalene, the R21 which is the NIEHS recommendation for our Report on Carcinogens recommended that it be listed in the report as reasonably anticipated to be a human carcinogen. The vote on this recommendation was six yes to one no. The one no vote was cast, because that particular member felt that the data in the mouse was limited and questioned the relevancy of the nasal tumors in rats to humans.

The RD2 or the NTP Interagency Working Group, the other interagency governmental committee that reviews our nominations, really did not make a recommendation for naphthalene. We had a very intensive discussion. There was a motion to list naphthalene as being reasonably anticipated to be a human carcinogen, and there were four yes votes to that motion and four

Page 73

no votes, the no vote being for the same reason that the RD1. These members felt that the data were limited in mice and the relevancy of the tumors in rats to humans.

Another motion was made not to list naphthalene in the Report on Carcinogens, and that also resulted in a 4:4 tie. So, the RD2 felt that they should go forward with no recommendation or could not make a recommendation for this particular combination.

I would also mention...I don't have this on the slide, but I would also mention that the IARC has recently reviewed naphthalene. The monograph on naphthalene should be published very early in 2003, but they have indicated on their website a summary of the review, and I believe that summary indicates that the IARC found that there was sufficient evidence of carcinogenicity in laboratory animals and that they

Page 74

propose to list it as a Group 2B possible human carcinogen. I believe that information is available on their web site.

Public comments, we received a number of public comments. The American Chemistry Council submitted an extensive comments on the nomination and also the background document, and these comments were supported by the American Coke and Coal Chemical Institute, Honeywell Commercial Systems, Industries, and Riley Industry Reports.

DR. SMITH: Thank you, Dr. Jameson. Questions from the subcommittee?

(No response.)

DR. SMITH: There being none...

DR. FROINES: Just one comment. I am going to be discussing a document that I wrote on naphthalene later, but I have the IR review abstract, and I would appreciate it if

Page 75

we could pass it around to members of the committee...subcommittee.

DR. SMITH: It has been suggested that we take a little break now to go traveling through that way and also to get copies of the...distributed so that we can have a quick look at that. So, can we take a little...

DR. FROINES: My comments also were given this morning so that I will be going through them, so, during the break, you should read them.

DR. SMITH: Let's take a 10-minute break.

(WHEREUPON, a brief recess was taken.)

DR. SMITH: Ready to start again? I have had distributed the summary of the IR document, and it is available on the table over there if you want to see it. With that, the written comments as the naphthalene panel of the American Chemistry Council, and they have been

Page 76

distributed to all subcommittee members. In addition, there is a request to make an oral presentation by Dr. Vincent Piccarillo on behalf of the ACC naphthalene panel. Is Dr. Piccarillo here?

SPEAKER: Yes.

DR. SMITH: Thank you.

DR. CARPENTER: Let me ask a question before he starts regarding the presentation before the break.

DR. SMITH: One moment. We...maybe I didn't allow time for people to ask questions about the...

DR. CARPENTER: The previous presentation.

DR. SMITH: Yes, presentation by Dr. Jameson. Yes, Dr. Carpenter?

DR. CARPENTER: I am curious...when I read the document, I noticed the presence of carcinomas in males versus females, and there is what appeared to me, at least, to be

Page 77

a fairly high number of carcinomas in the male. I see no statistical analysis other than the fact that there is no trend, and the results appear to be disregarded in the writeup based on the fact that it fell within historical controls, carcinomas that are typically seen. Could I have maybe a little clarification about the thought that goes into...the thought process that is involved in that?

It seems like, to me, when I see a zero in a control group and then 3 and 7 carcinomas in the treated groups, that looks like that might be at least a finding which should be considered.

DR. SMITH: Dr. Jameson?

DR. JAMESON: Dr. Carpenter, I think that will prove to be a very critical aspect of the board's, that they might suggest that we defer that question a little bit until after we finish all the presentations.

Page 78

DR. CARPENTER: As long as we get an answer, okay.

DR. SMITH: Okay, let's do that. Dr. Piccarillo? Thank you.

DR. PICCARILLO: Good morning. On behalf of the naphthalene panel of the American Chemistry Council, we appreciate the opportunity to speak to you this morning about naphthalene. The assessment of the carcinogenic potential and the classification for naphthalene clearly requires an understanding of both the genotoxicity of the molecule as well as its inter-species metabolism. Both genotoxicity and metabolism have been extensively published in the literature, and this work continues today.

Dr. Jameson covered, really, a lot of the points I had planned to discuss today, so I will briefly go over the points that I think are very important.

In your discussions regarding

Page 79

naphthalene, there are four major issues that need to be considered. The first, of course, is that naphthalene is not likely to be a genotoxic carcinogen. There is no evidence of mutagenicity in short-term tests, and naphthalene does bind proteins; however, it does not appear to be DNA active.

Secondly, species and site selectivity in rodents correlates with the susceptibility to cytotoxicity, and the cytotoxicity, in turn, appears to be related to the risk of naphthalene metabolism to the epoxide.

The third item is the kinetics of metabolism in rats and mice really don't differ. However, when we take a look at the human example, the activity in the rodent species is more than 100-fold rate of that seen in human cells.

Next, please. The last item is that metabolism of naphthalene in 1 microsomes from primates is at least

Page 80

an order of mag...in primates and monkeys is at least an order of magnitude lower than any rodent species tested and 100-fold lower than that in mice.

Next, please. As I mentioned, the first issue is the genotoxicity of naphthalene. The weight of the evidence clearly shows that naphthalene is not genotoxic.

In Dr. Jameson's presentation, he did discuss a few positive findings that were seen in literature studies. However, an overall review of the published literature shows that there are nearly 40 mutagenicity studies that have been conducted with naphthalene.

When you take a look at that number, there are 33 non-mammalian and mammalian in vitro assays that gave negative results, there are 4 in vivo assays which also were negative, and when you take a look at that weight of evidence versus the few positive

Page 81

studies, clearly, the weight of evidence shows that we are not dealing with a genotoxic carcinogen here, that there must be an epigenetic mechanism at play in the induction of tumors. Hopefully, some of the data I will show you today will demonstrate that that mechanism relates to the differential metabolism between species.

Species and site selectivity and cytotoxicity is very important. Next, please. This table summarizes the results on various tissues upon oral administration of naphthalene at doses approaching the LD50 for both the mouse and the rat. The cytotoxicity was measured by histological evaluation of specific tissues.

As you can see in the mouse, the majority of findings were in the bronchioles with other findings being located in the trachea. In the rat, however, cytoxicity was not observed

Page 82

in the lung tissues per se, and the majority of the findings, pathological findings, were limited to the olfactory epithelium. In the mouse, olfactory changes were noted only at the highest dose.

This clearly shows that there is some species sensitivity for specific tissue.

Next. Dr. Jameson covered the metabolism of naphthalene to some extent, but this elaborates the metabolism a bit more. Of course, we are starting with the parent molecule, naphthalene, and as he noted, the mouse lung favors the formation of the 1R2S oxide and moves to what, for the particular purposes that you are going to see in the following slide, the formation of conjugate 2. In the rat, hamster, and monkey lung, however, the predominant metabolism goes through the 1S2R oxide with the formation, subsequently, of conjugate 1 and conjugate 3.

Page 83

Another point that is very important is that in the mouse, there is a great deal of specificity for cytotoxicity in the Clara cell in the lungs, and it appears that the mechanism involves the formation of the 1R2S oxide with an interaction with proteins by some mechanism which is yet undefined to induce Clara cell toxicity.

Next, please. In the olfactory tissues, however, in the nasal epithelium, we do see a difference in the metabolism from that of the lung. In the olfactory epithelium for both the mouse and the rat, the predominant metabolism follows the pathway of the 1R2S that it follows in the predominant pathway in the lung of the mouse.

So, across these species, it appears that we have the same pattern of metabolism occurring in the nasal epithelium which, as I said, is different from that of the lung, but

Page 84

the point that you need to note is that even though the patterns are similar, the amount of metabolism, the rate of metabolism in the mouse is double that of the rat.

But a key issue that has to be looked at, too, is the fact that, as we have said, the metabolism in the rat nasal epithelium is clearly different from that seen in the lung, and when we take...do a comparison of the conjugate 2...or, excuse me, conjugate 3 from the 1R2S metabolism compared to the amount of metabolism that is conjugates 1 and 3 from the 1S2R metabolism, the rate of metabolism through the alternate pathway is about 36 fold greater than that through the normal metabolism pattern seen in the lung of the rat.

The kinetics of metabolism of naphthalene by recombinant SIP2F from the rat and the mouse do not differ. However, when you take a look at human tissues...and Dr. Buckett's laboratory

Page 85

at UC-Davis has done a lot of work with human lung tissue...discovered that the activities in the human lung for 2F1 are more than 1000-fold lower than that seen in the rodent species. Again, if you are looking at a mechanism related to the metabolism, clearly, the human is substantially different from that of the rodent species, at least for the lung.

Next, please. The SIP2R forms among species appear to have quite a few similarities in regards to the amino acid sequence, and this slide just shows the numbers of amino acid sequences that are comparable among the species.

Next, please. This table summarizes the activity of the recombinant proteins from the mouse, the rat, and the human. Again, in looking at the V maxis here, you can see there is a substantial difference in the enzyme activities when you compare the human to the two rodent

Page 86

species.

Next, please. The metabolism of naphthalene through primates, including both the monkey and the human, is an order of magnitude slower than any rodent species tested and 100 times slower than that in the mouse.

Current research is ongoing at this point in looking at the rate of naphthalene metabolism using primate olfactory epithelium tissue. We anticipate that because of the fact that we do see such large differences in the metabolism which appears to relate to the cytotoxicity of the lung that similar findings in the olfactory epithelium would be very germane to the evaluation of the potential for cancer risk in humans. That is, if we see the same lower potential for metabolism of naphthalene to whatever cytotoxic chemical there is being formed that this may, indeed, show that the type of olfactory tumors that we see in the rat may be, again, a

Page 87

specific type of tumor for that particular species, and, as has been mentioned earlier, these nasal tumors may not be relevant to man anyway.

The work that we talked about in the monkey is currently being conducted at UC-Davis, and we expect that the results of these studies will be available in approximately one year. I have seen some of the unpublished data from the literature, but I feel it is inappropriate to discuss those unpublished results today, but I would hope that, at least, this group would take that into consideration that there are significant data still being generated on the metabolism of naphthalene in the primate species.

Next. To conclude, as we have discussed, it appears that the tumors in the mouse appear to be species-specific and related somehow to the metabolic pathway which ultimately may lead to cytotoxicity as demonstrated

Page 88

by the destruction of the Clara cell in the mouse lung. The nasal tumors in rats, we feel, are also likely a result of cytotoxic injury, and that cytotoxic injury is a result of the metabolism that is occurring in the olfactory epithelium. We have shown some of the data here, and as I have said, we are also looking at the human...excuse me...primate, and, hopefully, we will get to the human tissue to demonstrate that these differences may be a species-related effect.

All of the previous study and all of the studies that we have seen in the literature strongly support a conclusion that there is a correlation between the rate of metabolism and the cytotoxicity seen in the animal species and that there are substantial differences in the rates of metabolism in the rodent and the primate models. Again, these are major considerations that you need to consider in your

Page 89

deliberations.
It was mentioned that naphthalene went before an IARC panel back in February, and I have not seen the summary that has come out of that, although I was in Leon at the time of the meeting and knew much of what happened in those deliberations, and the panel there had many of the same problems that the RG1 and the RG2 had in Canada, and that is looking at the metabolism and looking at the relevance of the lung tumors and the nasal tumors to human carcinogenesis.
And I know that it is going to be quite a bit of deliberation for this group to bring these issues to closure, and I feel that if you should need any further information, the naphthalene panel will be more than happy to provide it to you.
Thank you.
DR. SMITH: Thank you, Dr. Piccarillo.
Any questions from the

Page 90

subcommittee for Dr. Piccarillo?
(No response.)
DR. SMITH: Well, thank you very much for your presentation.
Any other comments from those present, public comments?
(No response.)
DR. SMITH: Well, let's proceed now to the formal reviews. I think the first reviewer for this is Dr. Carpenter.
DR. CARPENTER: Again, everybody has copies of my comments that are in front of you. It looks like some of my symbols didn't transpose entirely accurately, but what I will do is summarize what I thought when I finished the review.
I think that there is more than sufficient information to determine if exposure is really an issue with naphthalene. Its industrial uses with their occupational exposures or the chance for occupational exposures are high...

Page 91

DR. SMITH: Excuse me. Can you sit closer to the mic or...
DR. CARPENTER: I have too much junk in front of me.
There is the potential for environmental exposure. Naphthalene is an environmental contaminant. I note here that APSBR has reported naphthalene as present in over a third of the Superfund sites that have been reported in the United States, so there is both occupational and environmental exposures.
Relative to carcinogenicity, I feel it is clear that naphthalene is carcinogenic in rats, and although the evidence is equivocal, naphthalene is also carcinogenic in mice, and I am sure there will be a lot more discussion about that, so I will just let it go at that.
I agree with the fact that the hetero for a given toxicity is fairly limited, but there is good evidence that naphthalene does cause oxidative

Page 92

stress and DNA damage, resulting in the potential for toxic mechanism.
I think that...well, I have a statement here that the well-documented differences in response to naphthalene are likely due to species differences in anatomy and physiology that were just presented to us, but the importance of these factors in the carcinogenic response is not to this knowledge. It seems clear to me that naphthalene is a threshold carcinogen, and I think it is likely that we don't see more tumors, because we just are not reaching the levels that are carcinogenic in humans.
Epidemiological evidence linking naphthalene to cancer in humans is poor, but there doesn't appear to be any mechanistic reason why naphthalene wouldn't be carcinogenic in humans, provided the exposures were sufficient. And I think that is a real key here that we are dealing with in the exposure-related issue.

Page 93

I think that some of the comments that were made in the material that was presented to us make that same argument. The EUSCOEL proceedings speculate that if you avoid exposure and avoid cytotoxicity that you avoid carcinogenicity. I think that is a good argument for a dose-response relationship, biomechanistic relationship.

I think what we are dealing with here with this review is we are talking about hazard ID. The fact is that I have seen nothing in this review that indicates that humans don't have the same mechanisms that the rodents do. So, I think that this document, the strength of the information, is for hazard ID and that the real problem that we are faced with is strength of exposures, and that will be a real problem for people who have to do risk assessment analysis for this material based on the carcinogenicity of it.

Page 94

I voted to list as reasonably anticipated to be a human carcinogen.

DR. SMITH: Thank you, Dr. Carpenter. Next is Dr. Frumpkin.

DR. FRUMPKIN: Thanks. I'll echo a lot of what Dr. Carpenter said, so I'll be very brief.

We do have exposure. I think the human evidence that is available isn't helpful, so we are going to be considering the animal evidence predominantly in our discussions.

I saw the same results that you all saw and thought hard about the comments in terms of different preferences for metabolic pathways in the different species that have been observed, about the changes in nasal anatomy between rodents and humans, about the role of prior tissue inflammation before the development of tumors, and I didn't see anything that gave me reassurance that they should not...that there would not be a carcinogenic effect in humans, although

Page 95

I think that, as Dr. Carpenter said, that the question of dose is extremely important here.

So, for those reasons, I, too, voted to list as reasonably anticipated to be a human carcinogen.

DR. SMITH: Thank you. Dr. Roberts?

DR. ROBERTS: Thank you. I concur with the previous comments about exposure. There were some comments from that naphthalene panel that perhaps in the background document overestimated the number of workers that are currently exposed, but that may well be the case. I suppose they are probably in as good a position as anyone to know how many workers are exposed. I think perhaps that should be corrected in the background document, but it would be very useful for that purpose if there were some kind of formal documentation that the NTP could use or cite in terms of the number of workers that

Page 96

are currently exposed.

But there doesn't seem to be any disagreement that there is about...a sufficient number of individuals exposed. So, I think in terms of listing criteria, this is not an important issue. Clearly, we have sufficient exposure.

This, for me, was a tough call in terms of recommending listing or not listing, and as I looked at the issue of whether or not there is a response in multiple species, it seems to me that we have clear evidence in both genders in rats, evidence in male mice, some evidence in female mice, and I agree, I think, with those descriptors again being placed on those studies.

In trying to sort out whether or not that was enough, in other words, some evidence in mice was enough to qualify for multiple species, I looked for some precedent. It would be very helpful to me if

Page 97

people could even say oh, this is just like such and such a compound where we had the same kind of level of evidence and there was a vote to list or a vote not to list, so I looked for some guidance or precedent but, unfortunately, couldn't find any.

I then went about sort of looking through the 9th Report on Carcinogens and what is available on the 10th and tried to look at the evidence for those as well as looking about for other chemicals that have roughly the same kind of evidence for carcinogenicity as exists now for naphthalene. By that, I don't mean that exactly, but, I mean, for clear evidence for both genders in one, some evidence in the other species, little or no evidence for genotoxicity, and insufficient evidence for human carcinogenicity, and there is a handful of chemicals that fit into those criteria. None of them is listed.

Page 98

Now, I realize that is not a perfect argument for what is automatically nominated for listing, but as I step back and look at it, I see that, you know, there are chemicals with essentially the same kind of weight of evidence that aren't in the list; chemicals that are on the list have stronger weights of evidence. So, that really significantly diminished my enthusiasm for listing this chemical based on multiple species, and, in fact, my preliminary recommendation was not to list.

The piece that I am not about and I would like to hear from other members of the panel is whether or not the rat nasal tumor response is sufficient unusual to qualify on that basis. Is the nasal tumor sufficiently unusual that that then becomes essentially the pivotal observation that drives listing for this? And I would like to hear from

Page 99

pathologists on the panel and other folks that have...

DR. SMITH: Those are the three primary reviewers. Also, Dr. Froines has prepared a brief document which is distributed and on which I would invite him to speak to you now.

DR. FROINES: You may have made one mistake; it may not be entirely brief, but...

I'll start out with the conclusion that, basically, I think that naphthalene meets the criteria under number 3 to an unusual degree with regard to incident site or tumor or age of onset with respect to the animal...to the rat studies. I think that the mouse work is extremely interesting. It is not fully sufficient, I think, but it is certainly supportive. So I would argue that it is supportive.

I would also argue that naphthalene belongs to an agent,

Page 100

substance, or mixture which belongs to a well-defined structurally-related class of substances, and in that regard, I would suggest that naphthalene is a two-ringed polycyclic aromatic hydrocarbon, and as everybody in this room knows, PAHs have relatively strong evidence as to their carcinogenicity.

In addition to that...and this is what I will come to in my more prepared comments...the naphthoquinones, I think, also fall into a class of compounds with documented toxicity.

Now, I wanted to make some comments at the outset. One, I think this...the reason I wanted to step down as chair and make these comments was because I considered naphthalene to be a particularly important compound. I direct an air pollution research center in southern California, and you will notice that the ATSBR suggested that the urban airborne

Page 101

concentrations are about 0.95 g/m3. In Los Angeles, we have the best of everything, of course, and we get up to about 6 g/m3, but even at 0.95 g/m3 for which most of you probably don't have a reference point, I just wanted to tell you that if you compare that concentration of naphthalene with the concentration, for example, of benzoyl pyrene, the differences are a factor of 10,000. In other words, the concentration of naphthalene in Los Angeles air is 104 times as great as the concentration of the other...of larger-ring PAHs.

So, what we have in urban areas is an issue of public health significance precisely because the concentrations of the vapor phase and partial-bound naphthalene is extremely high. So, it certainly meets the exposure criteria and puts a burden on us to take this one very, very seriously.

The second comment I wanted to

Page 102

make is on both the presentations this morning...and Dr. Carpenter alluded to this...I found them, at some level, speculative, and I found them speculative insofar as they argue about the metabolic differences, and I know Allan Buckett very, very well, and I have interacted with him over the years on a number of occasions and respect his work, and I think the work is important.

However, in the context of this discussion, we are attempting to identify the compound; we are not conducting a risk assessment. So, we need to be very careful to differentiate risk assessment data from more qualitative information.

And I will read you one thing from one of the submitted comments. It says, Results of extensive studies of genotoxicity by standard methods demonstrate that naphthalene and naphthoquinone do not induce point mutations in vitro in bacterial cells

Page 103

with or without exogenous metabolic activation or in human cell lines with inherent metabolic capabilities, suggesting that a single hit linear model of carcinogenesis is unlikely.

That is not our role. It is not our role to decide whether or not a single hit linear model of carcinogenesis is the issue before us. So, I think that we need...and I should say, parenthetically, that that sentence is incorrect, and I'll come to that.

I think Ron Melnick from NISH wrote a very nice paper recently on the role of epoxides, and I won't belabor you with his comments. I quoted them in my document, but, clearly, A-ring oxide formation, epoxide formation, there is significant evidence for carcinogenicity associated with that, those intermediates, as a result of K-RAS and p53 mutations, and I think people in this room are aware of that, and I don't need to emphasize

Page 104

that.

What I wanted to do was to spend some time talking about metabolic pathways, because I don't think it has been adequately dealt with. One of the things I think is clear is that in humans, in the urine of humans, 1-naphthol, 2-naphthol, 1,2-naphthoquinone, and 1,4-naphthoquinone have been reported in the urine of humans. In addition to the naphthols, 1,2-dihydronaphthalene diol was a stable intermediate produced from human microsomal lung tissue. All these derive from the initial metabolism of naphthalene into A-ring oxide.

Now, I wanted...I want you, if you would, to look at the document that I prepared, to look at the figures on the last page, and you will see something that wasn't emphasized in the other presentations about the metabolism of naphthalene. From the most recent speaker, you will notice the dihydro diols here going to

Page 105

quinone, but he didn't emphasize that very much.

DR. PORTIER: Dr. Froines, could we have a copy...you have an overhead for that, do you not?

DR. FROINES: I think so. To find it would be a major...it's probably down there by my...I wanted to emphasize here a pathway that I consider to be extremely important with respect to the carcinogenicity of naphthalene, namely, that the dihydro diol that is formed...and there is no argument about that. It is a major metabolite. It is found in microsomes; it is found in humans...that a principal pathway is through the catalytic activity of dihydro diol, the hydrogenase, which takes you to a catechol, and the catechol is subsequently formed the PAH quinone.

Not only that, but it has been mentioned by others that this semi-quinone, quinone redox cycling process

Page 106

results in oxidative stress with the reduction of molecular oxygen to superoxide anion radical with subsequent Benton type chemistry going to hydrogen peroxide and a hydroxyl radical, so that this pathway with naphthalene is extremely important.

In our laboratories, we have been studying the quantitative formation of reactive oxygen from the naphthoquinones, and you find one molecule of a 1,2- or 1,4-naphthoquinone will produce tens of thousands to hundreds of thousands of molecules of reactive oxygen, because the naphthoquinones act catalytically. They don't act stoichiometrically.

They also undergo 1,4-microedition reactions in which they act as electrophiles and will bind with DNA as electrophiles. So, you have two pathways that are possible, the catalytic activity through the formation of reactive oxygen species on the one hand and the electrophillic

Page 107

activity on the other.

I won't take time, because, presumably, most of you are aware of that, but in this case, this is an example of the reaction of the ortho-quinone, 1,2- compound, with DNA, and you can see 1:56:05 formation, and then there is the modifications that occur from reactive oxygen species.

So that this pathway is extremely important when we consider naphthalene, and all the emphasis up to the present has been on the formation of the oxides when, in fact, it seems to me that a primary mechanism for carcinogenicity of naphthalene is by the quinone. Within that context, let me just discuss briefly some of the other factors.

1,2- and 1,4-naphthoquinone are mutagenic in the Ames test. They are mutagenic in four test restraints, TA97a, TA100, TA1041 and TA98. The 2-methyl derivative which most people know as meta-dione has also been shown

Page 108

to be mutagenic.

We have quantitatively documented the generation of reactive oxygen species from both the 1,2- and 1,4-naphthoquinone.

And let me read to you from a paper from Penning from 2002. Penning has argued that one of the most commonly mutated genes in lung cancer is a p53 tumor suppressor gene with a preponderance of T to t transversions which he argues is a signature mutation. In a yeast reporter system, Penning demonstrates greater than 46 percent mutations in p53 where GC-TA transversions from the naphthalene metabolite 1,2-naphthoquinone. Their conclusion is PAH ortho-quinones act as endogenous mutagens leading to p53 mutations.

So, the argument that naphthalene is not genotoxic is simply not true unless one decides to eliminate or not take into consideration the products of

Page 109

metabolism. And as I mentioned here, the formation of n7 guanine adducts has been demonstrated from naphthoquinone metabolism.

Now, let me make a few comments about the bioassays. The first point, I think, needs to be emphasized and reemphasized, and that is that the neuroblastomas are rare tumors which satisfies the definition to an unusual degree in a single experiment, et cetera. These are rare tumors, and if you look at the data, the NTP 2000 historical controls found zero cancers out of 299 males, zero cancers out of 299 females, and this is not a particularly small number of controls by any stretch of the imagination.

And, of course, there is no evidence that the feed was linked to the tumor. The NIH07, as you note in my document, the NIH07 feed has not seen these cancers in other species.

I think one has to be very careful...and we do this all the time

Page 110

these days...to suggest that cytotoxicity and carcinogenicity follow a common mechanism. It seems to me that the evidence in these studies does not necessarily support those findings.

I read with some interest Jack Harkema's report to the panel, comments. Jack Harkema is a member of our air pollution research center. I work with him very closely, I respect him a great deal, and if you read his report very closely, he does document the differences in species between the rat and human in terms of nasal passages, and at the end, he suggests that more research is necessary in a classic academic context. That is what we all do, of course.

But there is no evidentiary basis, based on Harkema's document, that would argue persuasively for a species-specific mechanism of action. Quite the opposite. I think that what Jack's work demonstrates is that there

Page 111

are differences, we need to think about those differences, but they don't deny the basic facts of the carcinogenicity bioassays. And I think that that kind of speculation makes it more difficult but doesn't necessarily illuminate the final answers.

So, I would argue that when we look at the metabolism in a complex fashion rather than simply focusing on the stereochemistry of the epoxide formation, what we find are mechanistic pathways that are entirely believable and reasonable and that we should consider them quite seriously when we think about making our final determination. Obviously, we have a very well-defined structural class of substances in this case, and as I already said, the mouse is obviously not sufficient, but it certainly provides importance evidence.

Finally, in conclusion, I think that one needs to look at the

Page 112

metabolic information from a hazard identification standpoint, and in that regard, the metabolites, that is, the naphthoquinones certainly...and the reactive oxygen species that follow certainly are an important mechanistic pathway that could, in part, explain the carcinogenicity of these compounds.

Dr. Portier?

DR. PORTIER: Yes, Dr. Froines, just for the record, your figure 2 and figure 3, are those from a published document?

DR. FROINES: Those are from a published document by Trevor Penning at the University of Pennsylvania, and I will give you the reference, if you would like.

DR. PORTIER: That would be great, if you could just give us the reference afterwards. Thank you.

DR. FROINES: Afterwards. Okay.

DR. SMITH: Other comments, questions from the

Page 113

subcommittee?
DR. FROINES: Oh, I should say one other thing. I'm sorry. I've mentioned the catalytic behavior, but I did want to mention that lots of times, one doesn't see reports of these quinones as much as one might expect, and what we have found in our laboratory is that they are very difficult to analyze in terms of the GC/MS, and we've had to develop new methods of analysis using acetic anhydride derivatization in order to adequately quantify the 1,2- and 1,4-naphthoquinones. So, I think some of the fact that you haven't seen them as much as one might hope is based on the fact that you simply can't analyze for them using traditional methods.
DR. SMITH: Yes.
DR. POPP: Yes. I think there is a lot of data on the table with this particular compound and a lot of it very interesting and data that leads to the need for additional

Page 114

data, again, addressed in Jack Harkema's document. I think that where this really comes down to for our purposes today is the question that Dr. Roberts raised and, I think, Dr. Froines really answered, and that is, what criteria should we be looking at to make the decision today?
And I believe that the issue comes to whether we have a tumor that is to an unusual degree in regards to incident site or type of tumor or age at onset, as read straight out of the criteria, and I think it comes down to even a subset of that, and that is an unusual degree in terms of tumor type.
There is no doubt that the neuroblastoma is a very, very unusual tumor type for the rodent. It is documented in the material we have. The table shows us 299 male, 299 female rats, all of which are negative with the current NIH 2000 diet. The previous diet, we have background of over 1000 females, over 1000 males,

Page 115

and, again, the incidence is zero, and that is consistent with pathologist, if you go talk around, who read carcinogenicity studies. That is consistent with, I am sure, everyone's experience with this strain of rat and any other strain of rat, as far as I know. In other words, it is a very rare tumor.
So, I think when you look at the numbers here where, in one set, we have an incidence of over 25 percent of this particular tumor.
The next point is that this is very, very clearly a malignant tumor, too. I think, for the non-pathologists, the term neuroblastoma may leave one wondering, but just read the description in the original NTP report, and the local invasion, in several cases, through the cribriform plate into the brain, there is no doubt that this is a malignant tumor.
The diagnosis of malignancy, of course, is supported by Jack Harkema's

Page 116

reading. He used a slightly different terminology. I believe he called it neuroepithelioma olfactory...neuroepithelioma carcinoma olfactory, clearing indicating that a number of these are malignant tumors.
So, again, I personally think that it comes down to the issue of do we have a malignant tumor to an unusual incidence, and I think the data clearly says we do.
DR. SMITH: A quick question of clarification. The table in the document refers to metastases and invasion. Which is it?
DR. FROINES: Where are you looking in the document?
DR. SMITH: At page .29. I was quite intrigued that the metastases listed 4 out of the 12 tumors at the high dose in females, but it is just a minor point of clarification.
DR. FROINES: I'm sorry.
SPEAKER: In the

Page 117

description.
DR. FROINES: Oh, oh, I'm sorry. Yeah, in essence, it's a matter of terminology. I don't think there is any difference here. I was looking back in the original document, and I believe it stated that there was invasion through the cribriform plate. One could use view that as metastasis. I would personally view it as local invasion, but it makes no difference. Metastasis or invasion is malignancy.
DR. SMITH: Thank you. Other comments, questions? Yes?
DR. CARPENTER: Could we get back to mine?
DR. SMITH: Oh, sure.
DR. CARPENTER: One of the real questions that I saw raised in the comments was the fact that the mouse data were, by and large, not significant, because they didn't show both sexes, and when I look at that closer, you know, I understand the idea of historical controls, but,

Page 118

clearly, you have got an increase in adenomas compared to the experimental controls, and there would appear to be an increase in carcinomas compared to the experimental controls, but I don't remember anything in the document...maybe a faulty memory...but I don't remember anything in the document where that was discussed other than to say that it was not considered to be significant based on historical controls, and I kind of wonder about that. Can we get an explanation?
DR. PORTIER: Perhaps it would help to know a little bit about how a pathologist, if I could just tell you a little bit about how these tumors were diagnosed. These are generally...the difference between an adenoma and a carcinoma is generally one of size. It is not one of fundamental character.
So, the typical background rates in males for the BCC mouse for

Page 119

adenomas, at least now, run about 15 percent for adenomas and 15 percent for carcinomas. We saw zero carcinomas in this particular study.
The naphthalene study was done some time ago, and the mouse study was done before the rat study. So, I can't tell you about whether the diagnostic criteria were the same at that time as they are now or the adenoma and carcinoma, but I think it is unusual to see zero carcinomas in a control group in mice. So...
DR. CARPENTER: But you saw both male and female?
DR. PORTIER: Well, the female generally runs less. They run about half the combined lung tumors than the males. So, they generally run about 15 percent total combined tumors for the females. So, to see no carcinomas in females is less than usual, but to see no carcinomas in males, just based on the numbers...
I'm sorry. I'm speaking solely

Page 120

of the control groups. Did that help?
DR. CARPENTER: I guess it goes back to lack of understand of this local control and the importance compared to the experimental controls, and you gave me a little bit more information, but the techniques may be different now in terms of interpretation of the pathology which would make the use of historical controls less appropriate in my mind.
And my real question is why didn't somebody in this report make a bigger deal out of the fact that you do see what appears to be, although it is listed as a non-significant trend, an increase in adenomas and carcinomas compared to control is the bottom line. It seems to me that that would be an important point of discussion at the very least.
DR. POPP: Let me ask a question about the use of controls. My understanding of how the NTP has always used control data is the

Page 121

immediate historical control data. In other words, you would have been using historical control data from the time at which the study was done. So, I don't think whether there has been any drifting criteria or not is really relevant, I don't believe.

DR. PORTIER: The studies are generally...obviously, concurrent control is the first line of comparison.

DR. POPP: Right.

DR. PORTIER: And statistics here are not significant. So, one would then rely on historical control information which, in any case, would argue that there were more carcinomas in historical control animals than appeared here. So, it would argue that it is even less of a concern.

DR. SMITH: Can I ask a question on...

DR. PORTIER: I just want to answer Dr. Carpenter's

Page 122

question sort of directly, hopefully. Now, looking through the naphthalene study in the mouse, that was done in 1992. The primary tests that were used at that time, they used three primary statistical tests for evaluating, the trend test, the Peters life table analysis, and the logistic regression prevalence test.

And if you look at p values across those three tests and see that the trend test has a margin of 0.05 statistical significance; the logistic regression is not at all significant, 0.5; and the lethality...lethal tumor analysis is negative, the interpretation of the entity at that time in looking at that type of evaluation for something that had such changes in survival early on, as this particular study did, was a difficult decision by the panel in terms of making a final review of this, and I think that is probably what happened here, is in looking at these, because

Page 123

there was a survival difference, in looking at these p values, they really didn't know what to call it in terms of their overall evaluation.

John, did you...

DR. SMITH: I was actually going to ask for the p values. What was the first one you mentioned, the first test of actual p values?

DR. PORTIER: The line table test...this is on page A86 in your background document looking at mice, alveolar-bronchial adenomas and carcinomas, the logistic...the line table test gives p value of 0.363 with a negative trend; the logistic regression test gave a p value of 0.68[illegible] and the trend test gives a p value of [illegible]054. All of those are trend tests, and the difference between the logistic regression test and the life table test has to do with the assumption of whether the tumors you are looking at are lethal

Page 124

or not lethal, and in the case where you have big survival differences, you get big switches, big switches in the statistical significance, anything in the direction of the finding for statistical significance.

This would not happen with current methods used by the NTP, but we don't have those numbers in front of us to be able to tell you what the answer would be based on current statistical methods.

DR. SMITH: Of those tests, the ones that are based on incidence, as I understand it, is the Armitage trend and...was that a one-tailed test, p value?

DR. PORTIER: In this case, no, that would be a two-tailed test p value. It is a squared two-tailed evaluation.

DR. SMITH: Thank you.

DR. JAMESON: One point that I neglected to bring out in my presentation...I meant to and I

Page 125

apologize...is there was a significant decrease in survival of the control animals in the male mice in this study. It was attributed to fighting. So, that may also contribute to why you see a zero in the carcinomas in the control in this particular group study, because there was a significant decrease in the survival of the control animals.

DR. CARPENTER: I actually make a comment in my document here about that, too, and I wonder about using a control group that apparently underwent such stress that most of it was eliminated by the end of the study.

DR. SMITH: Test data exposed.

DR. CARPENTER: In this case, yes.

DR. SMITH: Any other comments? Dr. Phillips?

DR. PHILLIPS: I could just make a brief comment on the

Page 126

genotoxicity data. The comment was made that on the weight of evidence, it was overwhelmingly negative. I think you really can't apply weight of evidence across genotoxicity studies.

What a genotoxicity study tells you is...they are all inherently flawed in how they do it. That's why any compound has to be considered by a large battery of tests, and there are regulatory tests, and then there are non-regulatory tests, and sometimes compounds are negative on the regulatory tests, but the come up on a non-regulatory one.

So, I think, when looking at naphthalene, there obviously are a large number of tests which are negative. Mostly, bacterial tests, in vitro are negative, and what that probably is telling us is that we don't have the right system there for metabolically activating naphthalene at all.

There are some positives, and

Page 127

there are some also some tests missing here that haven't been done, as far as I can see, such as a bone marrow micronucleus assay. So, we don't have the complete set of even the regulatory ones, but there are some positive ones.

I think what you have to do with this data...and I'll have to confess I haven't done it...is to look at each study on its merits rather than trying to apply a sort of score card as to how many tests are positive and how many negative. So, there are some positives here, and I think that has to be taken into consideration.

DR. SMITH: Dr. Froines?

DR. FROINES: I just wanted to reemphasize that with the quinone data that there are four Ames tests...Ames strains that are positive. So, it is rather, at least by the sort of traditional...I agree with everything Dan said. I think that even in an attritional context, there

Page 128

are positive results, especially in the p53 which is a modern mutational frequency study that needs to be taken with some seriousness as opposed to the more traditional mutagenicity assays that we tend to list.

DR. SMITH: I take it the strain work, it has appeared in publication?

DR. FROINES: Yes, it's...I think it represents a very important finding, in fact.

DR. SMITH: Now, on the table, at least, there is some difference of opinion as to how this chemical should be classified, and I think in the final discussion, we ought to try to discover or bring out if there have been any other changes in viewpoints or any points of clarification or questions that might alter the way some of us vote...or I won't be voting...some of us will be voting.

DR. ROBERTS: Yes, and

Page 129

as I mentioned in my comments, the issue that was sort of outstanding for me was the...and I thought was a pivotal issue on this one was the issue of the criteria with regard to the unusualness of the tumor response in the male rats, and I thought Dr. Popp gave me a very good response that I found convincing. So, I would think that that...agree with him that that's, in my mind, the most compelling basis to list this compound.

DR. SMITH: Any other points? Discussions?

(No response.)

DR. SMITH: Can somebody move...make a motion to...

DR. CARPENTER: I move that naphthalene be...that we vote to consider naphthalene or list naphthalene as reasonably anticipated to be carcinogenic in humans.

DR. FRUMPKIN: Second.

DR. SMITH: Seconded by...

Page 130

Frumpkin. Ready to vote? I am a novice. It's my one chemical discussion. You will be replaced.

DR. FROINES: Absolutely.

DR. SMITH: Any discussion?

(No response.)

DR. SMITH: Calling the vote. Those in favor?

(Show of hands.)

DR. SMITH: It's a unanimous vote. Thank you.

I suggest that we stop for lunch. What time do we meet back?

DR. WOLFF: 1:15.

DR. SMITH: It is 12:15, so, 1:15.

SPEAKER: Is lunch served, or are we on our own?

DR. WOLFF: You are on your own. Actually, the hotel has a restaurant, and if you just walk out the front door, you'll see a number of eateries on the street and adjacent to

Attachment B

Correspondence

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

American Chemistry Council *Good Chemistry Makes It Possible*

November 27, 2002

Via FedEx and E-Mail

Kenneth Olden, Ph.D.
Director,
National Toxicology Program
MD B2-01
P.O. Box 12233
Research Triangle Park, NC 27709-2233

Re: National Toxicology Program (NTP) Board of Scientific Counselors (BSC) Report on Carcinogen (RoC) Subcommittee Review of Proposed Naphthalene Listing at the November 19, 2002 Meeting

Dear Dr. Olden:

I write on behalf of the Naphthalene Panel (Panel) of the American Chemistry Council to protest the grave procedural improprieties that occurred during the BSC RoC Subcommittee's November 19, 2002, meeting to review naphthalene's listing as a carcinogen. To rectify these serious breaches of due process – which are detailed below – we request that you nullify the Subcommittee's vote on naphthalene and take other corrective measures. The nomination to list naphthalene should be returned to the Subcommittee to allow panel members and other interested parties to review and comment on new information – disclosed for the first time at the November 19 meeting – and the naphthalene listing should be taken up again at the next BSC RoC Subcommittee meeting. If, after reading why we propose these steps, you decline to provide our requested relief, we would ask for an immediate meeting with you to discuss this matter before you make a final decision to recommend listing naphthalene to the Secretary of the Department of Health and Human Services.

The Panel worked diligently and in good faith to supply pertinent information in a timely fashion to the NTP to prepare for the November 2002 Subcommittee meeting. These efforts were made in the spirit of transparency, consistent with the NTP's commitment to conduct NTP proceedings with openness and due process. We were surprised when the Subcommittee Chairman, Dr. John R. Froines removed himself from the role of Chairman during consideration of naphthalene so that he could express his views on the naphthalene nomination and then vote on its proposed listing. We do not dispute that it was appropriate for Professor Froines temporarily to cede the role of Chairman to permit participation in scientific

deliberations. Nor do we object to a knowledgeable scientist offering a dispassionate, unbiased opinion, based on scientific knowledge, on the proposed listing of naphthalene. The views expressed, however, were neither dispassionate nor unbiased, but constituted new information offered in a context devoid of due process and transparency. Indeed, the timing of Dr. Froines' presentation precluded any opportunity for others interested in and at least equally knowledgeable about these matters to address his statements on their merits. Dr. Froines' actions were plainly not those of a member of an "independent peer review group" consistent with the charge given to Subcommittee reviewers, and strongly suggest egregious bias.

Rather than working as an active participant of the Subcommittee and contributing to its discussions, Professor Froines pursued his own agenda and caught meeting participants completely unprepared by presenting new information that had not previously been shared with the Subcommittee, nor made a part of the public record. After NTP staff made their oral presentation of the basis of the nomination of naphthalene, and after presentation of interested stakeholder comments, the Subcommittee recessed briefly during which time Dr. Froines distributed written materials to Subcommittee members. Copies of these materials were not made available to the public before, during or, to our knowledge, after the meeting. During his presentation, Dr. Froines referenced a metabolic pathways diagram and was asked by a Subcommittee member to show the diagram to the Subcommittee. He was unable to do so. Dr. Froines discussed research results and was asked by NTP staff if the research had been published. He reported that it had, but was unable to provide any references to the published work.

During his remarks, Dr. Froines argued that naphthalene should be listed for at least three reasons. Scientific documentation of none of these points was part of the record before the Subcommittee.

First, Dr. Froines argued that naphthalene belongs to the class of chemicals known as polycyclic aromatic hydrocarbons (PAHs) which, he stated, are "known carcinogens." It is well known that the scientific community lacks consensus on the categorization of naphthalene as a PAH, and that it is inaccurate and scientifically indefensible to state categorically that all PAHs are "known carcinogens." The International Agency for Research on Cancer (IARC) has expressly addressed this issue. Volume 32 of the *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* discusses the carcinogenicity data on 42 PAH compounds. Following the Preamble, IARC scientists state that "only condensed aromatic hydrocarbons and aza arenes with three or more rings are considered" in their review of PAHs and heterocyclics that have been tested for carcinogenicity[1] and that occur in the environment. More importantly, it is well known that the classification of PAHs is disputed. Although it is true that 15 or so PAHs are considered as known experimental or animal carcinogens, and several are considered to be human carcinogens, many others are not

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[1] Although the NTP bioassays on naphthalene were not completed until after publication of IARC volume 32 in 1983, at least three independent cancer bioassays and one cell transformation assay on naphthalene were published at the time of the IARC review. Included in that Monograph are reviews on a number of PAH compounds with less experimental data available than that for naphthalene in 1983.

considered carcinogenic at all. Anthracene, fluoranthene, 1-methylchrysene, and pyrene are examples of PAHs that have been evaluated for carcinogenicity and are considered not carcinogenic by IARC, by NTP, and by the U.S. Environmental Protection Agency (EPA).[2] There is no information, however, regarding categorization of naphthalene as a PAH in any of the nomination or background materials presented by NTP in support of the nomination of naphthalene to the RoC.

A second reason given by Dr. Froines for listing naphthalene is that it is a component of "urban air pollution." While undoubtedly the case, as naphthalene is a component of gasoline as well as other incompletely combusted organic sources such as cigarette smoke and burning wood, occurrence in "smog" alone is not a reason for listing naphthalene as a carcinogen. The Subcommittee was not provided nor given the opportunity to consider any data regarding evidence of carcinogenicity related to exposure to naphthalene in urban air pollution as it may relate to human cancer incidences.

A third reason offered by Dr. Froines to list naphthalene, and equally of concern, was his summary dismissal of published research on the metabolism of naphthalene and certain of its primary metabolites, calling this research "speculative." This "speculative" metabolism data are those presented by NTP in its assessment of naphthalene as well as by other governmental science agencies such as IARC, the U.S. Agency for Toxic Substances and Disease Registry (ATSDR), and the United Kingdom's Health and Safety Executive. Promoted in its place was research conducted in Dr. Froines' laboratory and said to have been published. The alternative metabolic pathway presented contains mutagenic metabolites, and is itself considered speculative, at best, by other academic researchers in the field. Although Dr. Froines admitted that standard genotoxicity assays for naphthalene were negative, he stated that certain specialized genetic toxicology studies (for which no data were presented) would demonstrate positive responses when metabolism is considered.

Metabolism is considered in the standard genetic toxicology assay. Metabolic activation is included in most *in vitro* assays with both bacterial and mammalian cells. Further, *in vivo* studies are considered more predictive than *in vitro* studies because direct metabolism occurs in the animal model. As presented in comments submitted to NTP by the American Chemistry Council Naphthalene Panel[3], nearly 40 genotoxicity studies have been published on naphthalene. The weight-of-evidence plainly demonstrates that naphthalene is not genotoxic. This has been recognized by NTP and other United States and international scientific agencies. Considering the role of metabolism in this large volume of genetic toxicology studies, it would be expected that a metabolite as significant as that described by Dr. Froines, in combination with the high test concentrations or doses used, would have led to significant positive results in a large number of the genetic toxicology assays of naphthalene. Such is not the case, however.

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2 *See* EPA's Integrated Risk Information System (IRIS) documents for these chemicals, available online at http://www.epa.gov/iris/.

3 Public comments submitted to NTP regarding the proposed naphthalene listing are posted on NTP's web site at http://ntp-server.niehs.nih.gov/newhomeroc/roc11naphthalene.html.

We are deeply concerned that the new information presented to the Subcommittee during its deliberations, including categorically incorrect statements regarding PAHs and naphthalene, unsubstantiated assertions regarding naphthalene's genotoxicity, and remarks concerning naphthalene's alleged role in urban air pollution inappropriately influenced the Subcommittee's decision to vote to list naphthalene. We are especially troubled that none of the information on which Dr. Froines relied was the subject of prior notice, public comment, or deliberation by the RG1 and RG2 Committees. None of the new information is included in the naphthalene background document. Most importantly, none of the new information was externally peer reviewed, which is precisely what the Subcommittee is charged with doing, because one of the Subcommittee members served the dual role of "independent peer reviewer" and sole source of the information. Subcommittee members cannot have it both ways and we request that you, as Director of the NTP, not countenance these improprieties.

The Panel respectfully submits that, if the new data and interpretations of these data introduced at the Subcommittee meeting are of integral relevance to the evaluation of naphthalene's carcinogenicity, there is every reason to have made the data and the arguments available to Subcommittee members and to the public in a timely fashion, and to have allowed appropriate consideration of these data before decisions were made. NTP has gone to great lengths to make the RoC listing process more transparent, and has succeeded, for example, in making relevant documents highly accessible through effective use of the NTP website. Dr. Froines did not make these materials available beforehand. A recommendation to list naphthalene based on information not in the public record has compromised the listing process and the transparency of that process with respect to naphthalene.

In light of the foregoing, we request that you nullify the Subcommittee's vote on naphthalene, refer the naphthalene nomination back to the Subcommittee, request that Dr. Froines submit to the record all pertinent information that he wishes to be considered for listing purposes, allow interested parties an opportunity to review and comment upon the new information, and re-consider naphthalene's nomination at the next RoC Subcommittee meeting. This relief must be provided to fulfill the letter and spirit of NTP's RoC listing procedures. If you decline to provide this relief, we ask that you advise us of your decision before you forward a recommendation to list naphthalene to the Secretary to enable us to meet with you to discuss this matter.

The Panel believes strongly that NTP's scientific credibility has been compromised by the events of the November 19, 2002, RoC Subcommittee meeting and that it is essential you provide the relief requested to restore the credibility that has been lost as a consequence of these events. The message that NTP would communicate in failing to provide the relief requested is a chilling one, and could significantly harm the distinguished reputation you and others have worked hard to promote. We are confident that you will work quickly to renew NTP's commitment to scientific rigor, due process, and openness, and look forward to your response.

If you require additional information, please contact Dr. Anne P. LeHuray at (703) 741-5630 or *anne_lehuray@americanchemistry.com*.

Sincerely,

Courtney M. Price,
Vice President, CHEMSTAR

cc: Dr. Christopher Portier, NTP
Dr. C.W. Jameson, NTP
Dr. Henry Falk, Agency for Toxic Substances & Disease Registry (ATSDR)
Mr. Thomas Moore, Acting, U.S. Consumer Product Safety Commission (CPSC)
Ms. Christine Whitman, U.S. Environmental Protection Agency (USEPA)
Dr. Mark McClellan, Commissioner, Food & Drug Administration (FDA)
Dr. Richard Jackson, National Center for Environmental Health (NCEH)
Dr. Andrew von Eschenbach, National Cancer Institute (NCI)
Dr. Ruth Kirschstein, Acting, National Institutes of Health (NIH)
Dr. Kathleen Rest, Acting, National Institute for Occupational Safety & Health (NIOSH)
Dr. John L. Henshaw, Occupational Safety & Health Administration (OSHA)

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January 27, 2003

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

Dear Ms. Price:

Thank you for your letter dated November 27, 2002, on behalf of the Naphthalene Panel of the American Chemistry Council (ACC) concerning the National Toxicology Program's (NTP) review of naphthalene for possible listing in the Report on Carcinogens (RoC). Your letter raises issues regarding the naphthalene nomination review at the November 19-20, 2002, meeting of the NTP Board of Scientific Counselors RoC Subcommittee. Rather than addressing each point you raise, I offer the following comments. First, I would point out that members of this NTP advisory group are encouraged to bring any published information beyond that provided in the background documents before the Subcommittee for consideration if the member feels it is relevant to the discussion of a nomination. I would also note that public and subcommittee member comments, both written and oral, sometimes raise new issues or provide the Subcommittee new details about a nomination. If new published data are discussed in written or oral comments, we make every effort to provide the references to the Subcommittee and the public before the end of the meeting if a copy of the article is available to us. This was the case for the naphthalene review. A list of the articles provided is enclosed for your information.

I believe that the procedures currently in place provide a full and fair consideration of the nominations for the RoC, and allow one to determine if sufficient information is available to base judgments of whether or not a nomination should be included in the RoC as a *known* or *reasonably anticipated* human cancer hazard. I am sorry that I cannot meet with you concerning the naphthalene nomination, as it is my practice not to meet with individual stakeholders concerning a nomination to the RoC. Let me assure you that any recommendation we will be making to the Secretary for listing substances in the Eleventh Edition of the RoC will be based on sound scientific judgments which were reached following a detailed and complete review of all available information and comments.

I appreciate your input and will see to it that your comments are included on the NTP RoC website with the other public comments received for naphthalene. For your information, the NTP is in the process of preparing a Federal Register notice containing the recommendations from all three scientific reviews and soliciting final public comment for the 11th RoC nominations that completed review in 2002. We encourage you to submit comments in response to that notice.

Thank you for your interest in the NTP's Report on Carcinogens.

Sincerely yours,

Signature

Kenneth Olden, Ph.D.
Director

Enclosure

Publications Provided by Dr. John Froines

1. Flowers-Geary L, Bleczinski W, Harvey RG, Penning TM. Cytotoxicity and mutagenicity of polycyclic aromatic hydrocarbon *o*-quinones produced by dihydrodiol dehydrogenase. *Chemico-Biological Interactions* 99:55-72 (1996).
2. McCoull KD, rindgen D, Blair IA, Penning TM. Synthesis and characterization of polycyclic aromatic hydrocarbon *o*-quinone depurinating N7-guanine adducts. *Chemical Research in Toxicology* 12:237-246 (1999).
3. Penning TM, Burczynski ME, H C-F, McCoull KD, Palackal NP, Tsuruda LS. Dihydrodiol dehydrogenases and polycyclic aromatic hydrocarbon activation: generation of reactive and redox active *o*-quinones. *Chemical Research in Toxicology* 12(1):1-15 (1999). [This articles contains the 2 figures: Scheme 2 and Figure 3]
4. Yu D, Berlin JA, Penning TM, Field J. Reactive oxygen species generated by PAH *o*-quinones cause change-in-function mutations in *p53*. *Chemical Research in Toxicology* 15:832-842 (2002).

COURTNEY M. PRICE
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March 3, 2003

Via FedEx and E-Mail

Kenneth Olden, Ph.D.
Director
National Institute of Environmental Health Sciences
National Toxicology Program
P.O. Box 12233
Research Triangle Park, NC 27709-2233

Re: National Toxicology Program (NTP) Board of Scientific Counselors (BSC) *Report on Carcinogens (RoC)* Pertinent to Naphthalene

Dear Dr. Olden:

Thank you for your letter dated January 27, 2003, sent in response to the Naphthalene Panel (the Panel) of the American Chemistry Council's November 27, 2002, letter. We appreciate your reaffirmation of the NTP's commitment to base *RoC* listing recommendations on "sound scientific judgments" that are the product of "a detailed and complete review of all available information and comments." It is precisely because at this point the naphthalene listing process cannot yield sound scientific judgments consistent with NTP's own procedural requirements or applicable legal mandates that we write. The Panel wishes to ensure that you are fully aware of the significant breaches in this process that have occurred with respect to consideration of naphthalene during the listing process. Because of these improprieties, discussed in detail below, we request that NTP immediately withdraw the *RoC* Background Document for Naphthalene and suspend the comment period on the NTP's Call for Public Comment published on January 22, 2003,[1] as it relates to naphthalene until the Background Document has been revised to reflect fully and accurately "all available information and comments." Acceding to this request is the only course available to NTP that does not compromise its commitment to transparency and due process.

The Panel believes strongly, for all the reasons carefully set forth in our November letter, that the events that transpired on November 19, 2002, at the *RoC* Subcommittee meeting with respect to naphthalene were serious transgressions of due process.[2] An unexpected technical presentation on naphthalene was delivered to the Subcommittee that

1 68 Fed. Reg. 3033 (Jan. 22, 2003).

2 For your convenience, we append a copy of our letter and your response to it.

included new information that had neither been shared prior to the meeting with the Subcommittee, nor made a part of the public record. This objectionable and inappropriate approach has continued to this day, with the apparent approval of NTP, as *none* of the materials presented -- not the document prepared and distributed to Subcommittee members, not the four technical references provided to NTP after the meeting, not a single word of that presenter's extensive oral remarks -- are yet part of the public record. None of this information was available for public comment before the Subcommittee meeting, after it, or as we write. Indeed, members of the public who were not physically present at the Subcommittee meeting are not even aware that a substantial part of the basis for the Subcommittee's decision is not part of the public record.

This transgression alone is sufficiently egregious to warrant the relief the Panel seeks. In addition, however, the inappropriate behavior that occurred at the Subcommittee meeting is entirely consistent with a course of conduct that is outcome determinative and gives the appearance of bias. More glaring than this transgression is the fact that the Background Document on Naphthalene remains in its original form, its contents unchanged from its August 26, 2002, cover date. The RG1 findings are not reflected in the Background Document, despite the passage of eight months since the RG1's review on June 10, 2002. Similarly, the RG2 findings are not reflected in the Background Document, despite the passage of over four months since the RG2's review date of October 2, 2002. Finally, public comments on the Background Document, such as those submitted by the Panel on October 2, 2002, apparently have not been considered.

None of the newly introduced materials presented and discussed by Subcommittee members at the RoC Subcommittee meeting are reflected in the Background Document. This particular omission is made all the more conspicuous given that the vote on naphthalene's listing was twice split down the middle after two motions at the close of the RG2 Committee review. Indeed, RG2 Committee members were so divided, the Chairman took the unusual step of abstaining from casting a tie-breaking vote and no recommendation was forwarded by the Committee to you for your consideration. The oral representations about the relevance of unreviewed materials made at the RoC Subcommittee meeting were apparently very persuasive as the motion to list naphthalene was "passed by unanimous vote (9/0)."[3] Unless the Background Document is withdrawn and rewritten, however, only those who actually attended the Subcommittee meeting will ever know what the Subcommittee found so persuasive. This eclipsing of transparency falls far short of the standard you describe in your letter as one requiring the "detailed and complete review of all available information and comments." Given the Naphthalene Background Document's state of arrested development, and the absence anywhere, including the recent *Federal Register* notice and the NTP website, of a clear statement of the Subcommittee's deliberative process for voting as it did, NTP's solicitation of "final" public comments on the naphthalene listing is, at a minimum, a meaningless exercise as there is no new information on which to comment. In fact, without granting the relief we seek, NTP's continued solicitation of "final" public comments will only serve to mislead further the public as

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[3] 68 Fed. Reg. at 3035.

well as the agencies that participate in and rely upon NTP, contributing to a situation much worse than meaningless.

These serious lapses cannot be harmonized with NTP's often stated and very public commitment to transparency, openness, and due process. NTP stated, for example, at the end of the preparation of the 9th *RoC*:

> The NTP is committed to maintaining an open and transparent process for preparation of the *RoC* that is unencumbered by special interests; includes high quality and open scientific review of substances nominated for listing/delisting; uses the best, publicly available, peer reviewed science; and allows for stakeholder input at multiple levels.... The NTP greatly appreciates the input from all parties and will move forward in implementing some changes immediately while considering other recommendations for possible implementation in the future. In making these changes to the *RoC*'s preparation and review, the NTP is committed to providing the resources needed to ensure their successful implementation.[4]

Similarly, in NTP's responses to previous comments on deficiences in the listing process, NTP wrote:

> In reply to the suggestion that the NTP respond to individual comments, the NTP will continue to revise the background documents during the deliberations by Review Groups 1 and 2 (RG1 and RG2, respectively). *Following completion of RG2's review, the background documents are considered the document of record and will not be changed in response to any subsequent stakeholder input except to correct errors* [italics added for emphasis]. The NTP will make public comments received on all nominations available on its world-wide-website. All comments received by published deadlines will continue to be made available to the BSC *RoC* Subcommittee for its use in the review of nominations. All comments received will also be provided to the NTP Executive Committee and the NTP Director. A summary of stakeholder opinion for each nomination will also continue to be provided to the Secretary.
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> In response to the concerns expressed about unevenness in the quality of the background documents, the NTP will expand the use

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[4] NTP, "Response to Public Comments and Discussion on the Preparation and Review of the *Report on Carcinogens*" (last revised Oct. 30, 2001), available at http://ntp-server.niehs.nih.gov/NewHomeRoC/ResponsePub.html.

> of external, compound-specific experts in their preparation. In addition, these experts will now be invited, as needed, to participate in the BSC *RoC* Subcommittee's meetings and discussions as well. Such situations would include instances where the experts contribute significantly to preparation of the background document or where the scientific issues for the nomination are unusually complex and/or controversial. The NTP believes that this addition of compound-specific expertise will strengthen the BSC *RoC* Subcommittee's review of the nominations.[5]

These safeguards are fair and appropriate, and reflect the high standards NTP has set for itself. They do not, however, reflect the process that has been used for naphthalene's nomination. The Background Document for Naphthalene is in no sense the "document of record," as it documents nothing of the record since last August. Nonetheless, this is the document on which NTP is seeking "final" public comment. The *RoC* Listing Subcommittee meeting last November similarly was characterized by highly unusal, and in our view, impermissible departures from past practices, including the Chairman's self-removal from his role during the consideration of naphthlene so that he could express unsupported, unreviewed comments on naphthalene's nomination and then vote on its proposed listing. In essence, he was acting as a stakeholder. None of this presentation is part of the record, despite the availability of the transcript of the Subcommittee meeting and, presumably, the document distributed to Subcommittee members, but not to the public at the time of the meeting or since.

Other anomolies have occurred in the listing process. For example, the time between the RG2 deliberations (October 2, 2002), the due date for comments (November 4, 2002), and the scheduling of the Subcommittee meeting (November 19-20, 2002) was unually compressed. Typically, more time is allowed to prepare and submit comments. This compressed timeframe is certainly not reflective of the "early input from stakeholders" anticipated in NTP's earlier commitment to ensure "issues critical to evaluating the listing/delisting are addressed during development of the background documents and are considered throughout the review process." In short, the entire listing process for naphthalene has been compromised. As Director of the NTP, and guardian and champion of its commitment to transparency, we urge that you ensure due process is observed. These breaches must be remedied if NTP is to make good on its commitment to transparency and sound science.

To remedy these breaches, the Panel requests that NTP immediately announce in the *Federal Register* its decision to withdraw and rewrite the *RoC* Listing Background Document for Naphthalene and to suspend the public comment period seeking "final" comments on the naphthalene listing. Once the Background Document has been rewritten, and all available and relevant materials essential to naphthalene's listing have been made available to the public, NTP should restart the comment period and seek public comment for an additional 60-day period.

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5 *Id.*

The Panel continues to believe that the vote taken with regard to naphthalene at the November, 2002 Subcommittee meeting should be nullified and, after all relevant information has been submitted for review, naphthalene should be reconsidered at the next Subcommittee meeting. Failure to do as requested would violate NTP's own operating requirements and expose NTP to allegations of non-compliance with the principles of due process and Office of Management and Budget, Department of Health and Human Services, and National Institutes of Health guidelines for ensuring data quality.[6]

The Panel strongly urges you to remedy these breaches to avert the need for the Panel to pursue other avenues of recourse. As comments on the January 22, 2003 *Federal* Register Notice are due by March 24, we request that you respond by March 14. If the relief requested is not granted, and as you are unable to meet with us, we plan to seek a meeting with Secretary Thompson to discuss this matter.

The Panel looks forward to hearing from your office promptly. If you require additional information, please call or e-mail Dr. Anne P. LeHuray at (703) 741-5630 or anne_lehuray@americanchemistry.com.

Sincerely yours,

<Signed>

Courtney M. Price
Vice President, CHEMSTAR

Attachments

cc: Dr. Christopher Portier, NTP
Dr. C.W. Jameson, NTP
Mr. Tommy Thompson, Department of Health and Human Services (HHS)
Dr. Dr Elias A. Zerhouni, Director, National Institutes of Health (NIH)

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6 The HHS Information Quality Guidelines are available at http://www.hhs.gov/infoquality/.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

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

March 11, 2003

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

Dear Ms. Price:

Thank you for your letter dated March 3, 2003, regarding your concerns about naphthalene. In your letter, you request that the NTP withdraw and rewrite the Report on Carcinogens (RoC) Listing Background Document for Naphthalene ("the Naphthalene Document"), extend the public comment period, nullify the vote on naphthalene by the NTP Board of Scientific Counselors RoC Subcommittee ("the RoC Subcommitee") at its review on November 19, 2002, and bring naphthalene back to the RoC Subcommittee at its next meeting. I cannot agree to any of these requests. The first two requests are discussed below and the remaining requests have been dealt with in my previous response dated January 27, 2003, and will not be addressed again in this correspondence.

The Naphthalene Document is the document of record for all three scientific reviews and will remain the document of record. According to our process, we include all available public comments with the background document and do not alter the background document throughout the review period unless serious errors are detected in it. This assures that our three scientific review committees are basing their decisions on the same basic material augmented by the additional public comments obtained during the review process. I believe that this process is both open and fair, clear to all interested parties, and maintains the scientific rigor necessary for decisions regarding the review of agents for inclusion in the RoC.

My staff informs me that none of the initial two scientific review committees found serious flaws in the Naphthalene Document that would require it being rewritten. Also, I understand that the Naphthalene Document, the recommendations from Review Group 1 (RG1) and Review Group 2 (RG2), and all public comments received to date are posted on the NTP web site. In addition, I am told that the RoC Subcommittee publicly noted your written concerns regarding the exposure information for naphthalene and concluded that there was sufficient exposure to warrant review of this agent for inclusion in the RoC. I also understand that you refer to other sources of exposure information on naphthalene in your comments and we would be happy to receive that information from you.

I do not agree with your assessment that a written copy of the verbal presentations from the RoC Subcommittee's review must be available to the record prior to the onset of a final comment period. Historically, the NTP has never published the meeting transcript, but it is available upon request. The minutes from the RoC Subcommittee meeting on November 19, 2002, are not yet available on our web site, but these minutes serve more to guide the reader on the progress of the meeting than on the detailed substantive arguments of the presenters and the RoC Subcommittee. The NTP does recognize the importance of informing the public about differences in opinions within each RoC scientific review group with regard to recommended actions for individual nominations; therefore, we publish the reason(s) for any negative votes or abstentions in the Federal Register. The Federal Register notice published January 22, 2003, (Vol. 68, No. 14, Pages 3033 - 3036) containing the recommendations and votes from the three scientific review groups for the set of nominations that includes naphthalene, also contains this explanatory information for any dissenting votes or abstentions. Hence, I see no reason to extend the public comment period due to a lack of a summary from this public meeting.

As you are aware, public comments received in response to this notice will be posted on the RoC web site along with the other comments received to date. I would encourage you to submit comments in response to the January 22nd Federal Register notice. For your information, in the past my staff has included comments received after published deadlines in their briefing to me prior to my developing a recommendation on RoC nominations for the Secretary.

I am sorry that I cannot meet with you concerning this matter, as it is my policy not to meet with individual stakeholders concerning a nomination to the RoC. Please be assured that I have not yet made a decision on the NTP recommendation for any of the nominations being considered for listing in the 11th RoC; and before doing so, I will carefully review the minutes from the review groups' meetings, their recommendations, and all public comments.

I appreciate your providing me input about your concerns.

Sincerely yours,

Signature

Kenneth Olden, Ph.D.
Director