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Regulatory and Trade
Counsellors

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BY FAX Feb 12, 1999: (919)541-2242

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
79 Alexander Driver, Rm 3217
P.O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Jameson:

We are writing on behalf of Anheuser-Busch to provide supplemental comments on the proposed RoC listing of alcoholic beverages pursuant to the December 14, 1998 *Federal Register* notice. A copy of our previous submission on behalf of Anheuser-Busch is attached.

Anheuser-Busch, Inc. is the world's largest brewer. As a company and industry leader, Anheuser-Busch is committed to promoting responsible use of its products. Every year, Anheuser-Busch sponsors a number of programs designed to remind its customers that responsible drinking by adults is the only acceptable drinking practice. For example, Anheuser-Busch sponsors "Family Talk About Drinking," a program consisting of a guidebook and video developed by authorities in the areas of education, alcohol treatment, and family counseling; "Caring Connections," a step-by-step guide to help concerned adults, lay people, educators and others make a positive difference in the lives of at-risk children; and "Training for Intervention Process," a program that trains bartenders, waiters, waitresses, and convenience store clerks in responsible serving techniques in an effort to help prevent alcohol abuse, drunk driving and underage drinking. Any information regarding the safety of its product is always a concern to Anheuser-Busch.

We recognize that it is the official position of NTP that listing a substance in the Report does not establish that the substance presents a risk to persons in their daily lives. As NTP stated in the Preamble to the *8th Report on Carcinogens*: "Risk assessments are not conducted by the National Toxicology Program for substances in the Report. The listing of a substance in the Report, therefore, does not establish that any such substance presents a risk to persons in their daily lives."

It is, however, widely acknowledged that the public may rely on the NTP Report on Carcinogens ("RoC") as "one of the few major sources of objective, peer-reviewed information on carcinogenic substances."[1] As such, the RoC might be relied upon by the public as standing for the proposition that a substance presents a risk to them when used in their daily lives even though this is not the message NTP intends to convey. This public reliance makes it likely that a determination of carcinogenicity by NTP will have an impact on Anheuser-Busch and could have an overall net negative impact on public health, contrary to the fundamental purpose of the Report.

We reiterate our request that NTP make determinations for listing in a manner consistent with its statutory mandate by performing a thorough review and independent analysis of the relevant literature. We would especially like to encourage the Executive Committee to consider the problems and issues expressed by the members of the RoC Subcommittee during their meeting in December 1998. The events of that meeting both emphasize the procedural deficiencies in the NTP listing process and demonstrate that a listing for "alcoholic beverage consumption" at this time would not and could not be based on scientific judgment supported by thorough consideration of all relevant information.[2]

Lack of Expertise on Alcohol and Dietary Issues

A thorough review of all relevant literature is particularly important given the lack of expertise in alcohol and dietary issues as well as epidemiology among the members of the Subcommittee. This lack of expertise was evident from the confusion reflected in the transcript. Alcohol beverages are not like other substances that have been examined by NTP in the past. The nature of a food product and of the NTP review process dictate a review by scientists with expertise in these areas.

Panel Requests Decision-making Criteria

As discussed in our previous submission, the NTP has not set forth its criteria for making a determination as to the sufficiency of the human evidence for making a determination of carcinogenicity. During the December public review meeting, a member of the RoC Subcommittee requested that the NTP provide the Subcommittee with decision criteria to assist in analyzing and

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[1] Synthetic Organic Chemical Manufacturers Ass'n v. Secretary, Dep't of Health and Human Services, 720 F.Supp. 1244, 1248 (W.D. La. 1989). *See also*, *8th Report on Carcinogens*, Introduction at 1 ("The People of the United States of America, concerned with the relationships between their environment and cancer have asked, through the U.S. Congress, for information about substances that cause cancer or might cause cancer.").

[2] *See* Preamble to the *8th Report on Carcinogens*: "Considerations regarding carcinogenicity in humans or experimental animals are based on scientific judgment with consideration given to all relevant information."

classifying the epidemiologic studies.[3] Another member also made a reference to the lack of consistent decision rules during the review of diesel exhaust emissions.[4] These comments reflect the concern of Subcommittee members about the complete lack of decision-making criteria and the inconsistent results that can result from that lack of criteria. The lack of consistent criteria is also apparent from the conflicting opinions expressed by the members of the Subcommittee during the decision-making process.

Potential Consumer Confusion

Several members of the RoC Subcommittee expressed concern that a NTP listing for "alcoholic beverage consumption" could create confusion among the consuming public.[5] The potential for consumer confusion is considerable in the context of alcohol beverages. Alcohol beverages have been consumed for centuries and are part of a healthy diet for many adult consumers, the vast majority of whom consume responsibly. A stark pronouncement by NTP that alcohol beverages are carcinogenic could confuse consumers who are unaware that NTP's determination is merely a hazard identification and does not establish that alcohol beverages present a risk to persons in their daily lives. In addition, the information provided by the NTP listing could conflict with the information published in the joint HHS/USDA *Dietary Guidelines for Americans*.

Confusion Over Authority to Modify Listing

The RoC Subcommittee acknowledged the evidence for the health benefits of moderate alcohol consumption.[6] Some members of the Subcommittee expressed discomfort with the implications of listing "alcoholic beverage consumption" as a carcinogen, and suggested modifying the wording of the listing to reflect a listing for "alcoholic lifestyle."[7] However, the Subcommittee members were instructed that their charge only allowed them to vote either yes or no on proposed listing language and that they could not qualify the listing to indicate that cancer hazard was only "known" to exist at higher levels of consumption or was associated with an alcoholic lifestyle.[8]

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[3] Transcript of the RoC Subcommittee Meeting, December 3, 1998, at 558.

[4] Transcript of the RoC Subcommittee Meeting, December 3, 1998, at 418.

[5] Transcript of the RoC Subcommittee Meeting, December 2, 1998, at 166-167.

[6] *Id.* at 165-167 ("[T]here have been a number of studies that suggest for low to moderate consumption there are some beneficial effects.").

[7] *Id.* at 124, 143.

[8] The Subcommittee did, however, recommend modifying the narrative discussion in the Report, which is separate from the listings and is more technical and far less likely to be consulted by the public, to indicate that risk is more pronounced at higher levels of consumption. But the fact that this information would be "buried" in the body of the report and would not be made a part of the listing clearly bothered

(continued...)

It is clear that the NTP staff administering the RoC Program and the RoC review committees are operating under the assumption that their authority is restricted to answering simply yes or no as to whether a substance is either "known" or "reasonably anticipated" to cause cancer, and that they do not have authority to recommend that any proposed listing go beyond this. We believe that a review of the NTP authorizing statute and its legislative history materials will show clearly that Congress did not intend to create such a restricted authority and intended listings to be considerably more informative.[9]

Although the RoC states that it is a hazard identification document, it is clear from the legislative history of the Congressional directives establishing the Program that Congress intended that the agency should provide some indication of the relative potency and risk of an agent under review where possible.[10] As stated in the Draft Background Document, "[p]otential health benefits of low alcohol beverage consumption should be recognized as well as the detrimental effects of heavy consumption."[11] Although the NTP recognizes the validity and importance of the information on the health benefits of alcohol, the proposed listing fails to recognize this information.

The Subcommittee's discussion about listing an "alcoholic lifestyle" rather than "alcoholic beverage consumption" in the RoC further emphasizes the uniqueness of this proposed listing. Because of concerns related to this unique situation, three members of the Subcommittee voted against listing alcoholic beverage consumption as a carcinogen, and one member abstained from voting.

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[8](...continued)
some Subcommittee members. *See* Transcript of the RoC Subcommittee Meeting at 164. It was also mentioned during the discussion that this issue had been raised during the first nonpublic internal review of the listing proposals.

[9] The legislative history materials indicate that the RoC should provide "where possible, estimates of the magnitude of the risk each [substance] poses", "the relative risk posed by each substance", "the relative toxicity" of an agent, and information on "subpopulations expected to be at higher than average risk". Neither the legislation nor its legislative history indicate an intent to restrict the pertinent information that can be provided in a listing.

[10] "The committee intends that this should be a comprehensive document containing an updated list of all known or suspected carcinogenic agents, the nature of exposure and the approximate number of persons exposed to such agents. The relative toxicity of such agents should be described, to the extent such information is known, whether or not any of these act synergistically, the levels of exposure to be expected from certain occupations, geographic areas, food or consumer goods, and the identification of subpopulations expected to be at higher than average risk." H.R. Rep. No. 1192, 95th Cong. 2d Sess. at 28(1978). "It is the committee's intent that any such list include not only the name of the substance, but the data which supports the inclusion of each compound on the list, any uncertainties on the data yet to be resolved, and where, possible, estimates of the magnitude of the risk each poses." Cong. Rec. Oct. 10, 1978, p. 34938.

[11] Draft RoC Background Document for Alcohol Beverage Consumption, pp. 3-4.

In fact, Dr. Michele Medinsky, one of the two assigned reviewers, voted against the listing. She stated during the meeting that: "The confounders are common in a lifestyle typically associated with excessive alcohol consumption, including smoking, inadequate nutrient intake, and viral infection. Because of the prevalence of these other risk factors in the alcoholic lifestyle, for me it was impossible to separate high alcohol consumption from these other confounders."[12] Dr. Medinsky also stated in her written reviewer's comments to the Subcommittee that: "Most studies show that moderate alcohol consumption has little or no effect on cancer at any site . . . . The confounders in the epidemiology studies preclude an attribution of any risk to any particular factor, including alcohol."

Other Unresolved Issues

The meeting also left unanswered many questions with regard to whether consumption of alcohol beverages alone is a carcinogen. Dr. Eula Bingham abstained from voting and stated in explanation: "I just don't think we have dealt with [the synergism issue] in a way that satisfies me."[13] In addition, Dr. Steven Belinsky stated: "I think this may be a unique scenario for us where we are having [sic], yes, alcohol and tobacco definitely increases your risk for cancer, but the question is is alcohol alone a human carcinogen."[14] In fact, during the meeting one member of the Subcommittee, Dr. Mirer, expressed interest in reviewing data to address committee concerns about the synergism issue. Dr. Longnecker replied to this concern by referring to one of his papers which was not available to the members of the Subcommittee in their materials, and was therefore not reviewed by them before their vote. The foregoing demonstrates the prematurity of the proposed listing and underscores the need for additional scientific review and deliberation.

Concern About Objective Scientific Review

The following excerpt from the RoC Subcommittee meeting is taken from the introduction given by Dr. Hooper during his review of dioxin (review of which took place prior to the review of alcohol beverage consumption):

> [T]hese guys are not people you want to invite to your lawn party, these candidates. Don't invite them home to babysit your daughter. These are not great actors. And we didn't cause them to be this way They had a previous history when they came here. They had quite a long track record. And I mean, basically they are a bunch of killers, rapists, multiple murderers, et cetera, and we have to decide whether they are going to be in for life or are you going to go 2 to 20 or whatever. And that is the negotiation that is going on. [Emphasis added]

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[12] *See* Transcript of the RoC Subcommittee meeting at 121-122.

[13] *Id.* at 167.

[14] *Id.* at 137.

During the review of alcoholic beverages consumption the criminal analogy resurfaced as Dr. Medinsky stated: "I think we could charge alcohol with a number of violations, but I wouldn't be willing at this point to go to cancer in and of itself."[15] This assumption that all of the substances that are proposed for listing are "guilty" of crimes undermines the objectivity of the "scientific" review that is undertaken by the Subcommittee.

Lack of Meaningful Opportunity for Public Comment During Hearing

Another problem with the NTP process is the rigidity of the schedule followed by the Subcommittee during its public meeting. We believe that the five minute limit for each public commentator is insufficient, especially since the issues addressed by the presentations involve complex scientific information. The Subcommittee reviewed ten other substances during their two day meeting, and was not given sufficient time for a thorough review of each substance and certainly not sufficient time to properly debate and analyze the issue in a careful, thoughtful way essential for reaching a decision for alcohol beverage consumption.

In addition, it seems that a commentator whose presentation is criticized by a member of the NTP staff should be given an opportunity to rebut the criticisms advanced. This opportunity was clearly not afforded the presenters at the Subcommittee meeting. For example, in the context of the alcohol beverages discussion, Dr. Longnecker, a member of the NTP staff and the individual whose paper provided the primary support for many of the conclusions in the RoC Draft Document, criticized the information presented by Dr. Waddell in his presentation.[16] Dr. Longnecker was not present at the entire meeting, but was brought in to answer questions that some members of the Subcommittee had about his paper -- the same paper that was heavily relied upon by the RoC Draft document. Apparently because Dr. Longnecker is an employee of NIEHS he is able to participate in the meeting even though he is not a member of the Subcommittee. In contrast, Dr. Waddell was not even given an opportunity to refute Dr. Longnecker's criticisms, and was certainly not allowed to contribute any further to the discussion than he was able to do in his five minute presentation.

A further consideration to be given to the NTP process is the short period of time between receipt of public comments by the members of the Subcommittee and the date of the meeting. Given the complexity of the available scientific information, and the wealth of information available, it is clear that the Subcommittee does not have time to review all of the available information referred to by the public comments before its meeting.

NTP Reliance on Longnecker and Tseng Review

Another problem that is raised by the relationship between Dr. Longnecker and the NTP is the heavy reliance placed on the draft, "in press" book chapter by Longnecker and Tseng. The Longnecker-Tseng review was relied on by Dr. Jameson for a summary of the human evidence in

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[15] *Id.* at 124.

[16] *See* Transcript of the RoC Subcommittee meeting at 139-141.

his lead presentation to the Subcommittee.[17] It was also relied on in the Draft Background Document.[18] Furthermore, during the Subcommittee discussions, Dr. Longnecker presented what he called "my interpretation of the data", which undoubtedly included this most recent prominently displayed work.[19] The Longnecker-Tseng study is not an appropriate source for the NTP review because it was neither published nor subjected to peer review. The NTP's RoC listing procedures allow only consideration of literature that has been published and peer-reviewed.[20] The Longnecker study is intended for publication in a book, and there is no indication that it has been or will be peer-reviewed at any time. Because Longnecker's study uses an unorthodox method to select, aggregate and interpret the data, it is particularly important that it be carefully peer-reviewed.

In conclusion, the reliance of the public and other agencies on the RoC emphasizes the importance of the NTP process and makes it even more clear that any NTP determination to list a substance as a carcinogen must be made after a thorough peer review. It is clear from many of the issues raised by the members of the Subcommittee that there are many unanswered questions and concerns with regard to the proposed listing of alcoholic beverage consumption in the 9th Report on Carcinogens. We urge the Committee to consider these comments and our earlier submission in making its decision about the proposed listing, and to not reach any decision until it has completed a thorough and independent review of the available literature, and addressed the concerns raised by the Subcommittee.

Sincerely,

Bruce Scott Levinson

Attachment

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[17] Transcript at 104-06, explaining slide entitled "Human Studies" with column headings "CANCER SITE", "Number of Studies Showing Association", "Estimated RR (95% CI) for 3 Drinks/Day", and "Comments". The aggregated relative risks ("Estimated RR" in column 3) from the studies shown in column 2, are specifically noted as "Taken from Longnecker and Tseng . . . (in press, 1998)." The "Comments" column in the slide focused on dose response, and the "Dose Response Relationships" section of the Draft Background Document, at page 3-3, relies on the Longnecker and Tseng analysis (again, cited as "in press").

[18] Draft Background Document at 3-3, in section on "Dose-Response Relationships", a subject, which, as noted above, was the focus of the "Comments" portion of Dr. Jameson's slide on human studies. Additionally, the entire Longnecker and Tseng review is printed as Appendix III of the Draft Background Document, where it is cited both as "in press" and "Draft 1.2 (11-28-97)".

[19] Transcript at 139-41.

[20] *8th Report on Carcinogens* at 3 (2d col.) and 231 (1st col.); transcript of RoC Subcommittee discussion of the proposed listing for ethylene oxide at 354-56 ("Dr. Bucher: [W]e cannot use unpublished information in these background documents, nor can unpublished information be considered by this panel during their deliberations. Chairman Brown: I think that is a longstanding rule we have abided by . . . .")