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Dr. Linda S. Birnbaum
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Re: NTP Report on Carcinogen Process Failures on the Use of Publicly Available, Peer-Reviewed Evidence

Dear Dr. Birnbaum:

I am writing to bring to your attention a **major failure** on the part of the National Toxicology Program (NTP) to follow the NTP policy enunciated in your letters of September 30, 2009, to the Honorable Rick Boucher and the Honorable Mike Thompson.

This failure strikes at the heart of NTP's flawed draft justification for recommending the listing of styrene in the *12th Report on Carcinogens (RoC)*. We request that this serious failure be corrected. A new Background Document on styrene should be prepared and reviewed in accordance with NTP policies.

Failure to Follow NTP Policy

In your letters you state **"Per NTP policy, the scientific evidence cited in support of the NTP's policy decision must come from publicly available, peer-reviewed sources."** As you know, the NTP staff's recommendation to classify styrene as "reasonably anticipated to be a human carcinogen" was based almost entirely on its **re-interpretation** of two key scientific studies, namely, the epidemiology study by Delzell *et al*., "An updated study of mortality among North American synthetic rubber industry workers (*Res. Rep. Health Eff. Inst*., 2006) and the NCI animal study entitled "Bioassay of Styrene for Possible Carcinogenicity (*Technical Report Series No. 185*, 1979).

As shown below, in each case, NTP staff justified its recommendation regarding styrene by using **findings not found in the original papers**, and which have never appeared in the peer-reviewed literature. Without these two novel re-interpretations, the NTP staff would not have been able to make a case for listing styrene in the *RoC.* **This reliance on non-peer reviewed evidence for two of the three key criteria that support the NTP staff recommendation appears to us to be in direct contradiction to your statement regarding NTP Policy.**

Study	Authors' conclusions	NTP staff's re-interpreted conclusions	Use in NTP staff's draft styrene profile
Delzell, *et al.,* 2006	NHL (non-Hodgkin's lymphoma), was associated most strongly with styrene ppm-years, but the data for this agent did not indicate clear trends and were not statistically significant.	There was an exposure-response relationship for NHL and NHL plus CLL (chronic lymphocytic leukemia) that was not attenuated by control for butadiene and only mildly attenuated by control for dimethyldithiocarbamate (DMDTC).	"Limited" evidence in humans
NCI, 1979	"No more than suggestive evidence" and "no evidence" of tumors.	"Sufficient" evidence (after NTP staff substituted *different* historical controls)	"Sufficient" evidence in animals

The NTP Policy would be rendered meaningless if it were interpreted to mean that NTP must merely begin with a published study and can re-interpret it to conclude something entirely different from what the original peer-reviewed study found, and then **not** have this new conclusion validated in a publicly available, peer-reviewed source. Because these two re-interpretations represent two of the three key criteria that support the proposed listing of styrene, in order to be consistent with the NTP policy, NTP staff must subject its new conclusions to an independent peer review.

While one might argue that these re-interpretations were "peer reviewed" by the Expert Panel and by the Board of Scientific Counselors (BSC), these "peer reviews" should not be considered valid under the NTP policy. In the case of the Expert Panel, which originated these two new re-interpretations, the Panel cannot legitimately peer review its own work. In the case of the BSC's review, the staff did not highlight the novel nature of the two re-interpretations, nor did it fully describe them in a way that would allow meaningful peer review by the BSC. In addition, if this NTP policy that the "scientific evidence cited in support of the NTP's policy decisions come from publicly available, peer-reviewed sources" could be fulfilled simply by a BSC review, then the policy would be meaningless. By this reasoning, NTP staff

could have any non-peer-reviewed assertion validated as "publicly available and peer reviewed" simply by including it in the submission to the BSC. If this were allowed, then what is the purpose of stating that NTP must rely on peer-reviewed sources to support its decisions?

There is, of course, a reason for the NTP policy. No chemical substance should be listed in the *RoC* on the basis of the opinions of NTP staff (or anyone else, for that matter) that differ from those of the underlying study authors, when those opinions have not been subjected to peer review in a rigorous process independent of the NTP listing process. This policy is necessary not only to ensure a sound scientific procedure that greatly decreases the possibility of error, but also to protect the credibility and objectivity of this important *RoC* process.

Because the two re-interpreted studies are **fundamental** to the staff's justification for its recommended listing of styrene as "reasonably anticipated," it is essential that this major failure to follow NTP policy be corrected and the carcinogenicity of styrene reassessed accordingly. Our conviction on this matter is reinforced by the fact that both the European Union and the International Agency for Research on Cancer (IARC) have come to fundamentally different conclusions than the NTP staff (i.e. – EU provisional conclusion *not* to list styrene as a carcinogen and IARC "possible" carcinogen classification).

Special Care is Required with the NTP Classification Scheme

Because of the structure of its classification scheme, we believe that the NTP has an obligation to be especially meticulous in applying its criteria for listing. As you know, the other major "listing" organization in the cancer assessment field, besides NTP, is IARC. Unlike NTP, however, IARC has a three-category classification scheme, including a category for "possible" carcinogens. This scheme imposes upon IARC the necessity to make careful distinctions on the basis of the strength of the evidence between substances that are only "possible" based on the strength of the evidence, and those for which there is more certainty. NTP, with only two categories in its scheme, needs to be especially careful not to place chemicals in the NTP category of "reasonably anticipated" that have only suggestive evidence of carcinogenicity. Instead, under the NTP scheme, these chemicals should not be listed at all; NTP has not been directed to list "possible" carcinogens. The mandate from Congress to NTP was clear on this point, and in light of the proposed classification of styrene, we believe this mandate is worth repeating: The Joint House-Senate Comparative Summary on the legislation that authorized the *RoC* stated that

> "…the phrase 'suspected carcinogens' [was replaced] with 'substances…reasonably anticipated to be carcinogens', in order to make it absolutely clear in the statute that there must be

> reasonable grounds for designating a substance as a putative carcinogen."[1]

NTP has an obligation to follow this congressional guidance and inform its staff and its peer-review panels accordingly.

In short, we do not believe that the justification for the recommended classification of styrene as "reasonably anticipated to be a human carcinogen" is consistent with the NTP policy as you have enunciated it in your recent letters. In addition, as **we have repeatedly pointed** out to NTP, **the Background Document does not even mention, much less address, a large portion of the scientific evidence** related to styrene. This exclusion is not consistent with the NTP policy of considering "the body of scientific evidence" as you indicated in your letters. I will not repeat the numerous concerns in this regard that we have transmitted to you and others in NTP over the past many months, except to mention the third major criterion used by the NTP staff to justify its recommended listing—genotoxicity. In that particular case, the NTP's assessment of the styrene mode of action data does not address an increasingly large body of data that contradict the conclusions it reached, including data that indicate that styrene-7,8-oxide is <u>not</u> relevant for mouse lung tumors from styrene exposure, and that genotoxicity assays of styrene in laboratory animals are almost universally negative.

What is a Reasonable Remedy?

Because styrene was the first major chemical to go through the new process designed for the *12th RoC*, it is not surprising that there were start-up difficulties. Unfortunately, styrene was the victim of these early mistakes, and it would be wrong to ignore this injustice. We believe the appropriate remedy is for NTP to develop a corrected Background Document that reflects these and the other problems identified and then conduct a new scientific review using a procedure that actually provides the transparency and checks and balances promised when the new *RoC* process was announced. If this re-review should require NTP to delay its decision on styrene until the *13th RoC*, that would not be unprecedented; NTP has often delayed a chemical from one report to the next in order to accommodate workload and other problems.

Further Reasons Why a Revised Background Document and New Review are Necessary

The current Background Document does not reflect two important new publications that are directly related to key elements of the NTP staff's recommended listing of styrene,

[1] Joint House-Senate Comparative Summary and Explanation of Title II of H.R. 12460 and H.R. 12347, as Reported by the Committee on Interstate and Foreign Commerce, the Senate Bill, S. 2450, and the House Amendment in the Nature of a Substitute. 124 CONG. REC. H38657 (1978) (statement of Rep. Rogers).

both of which NTP has been advised of regarding their pending publication status. The first of these is the Boffetta *et al.* report "Epidemiological Studies of Styrene and Cancer: A review of the Literature," which we have been informed will be published in the November issue of the *Journal of Occupational and Environmental Medicine*. This step represents publication of the report that NTP received in December of 2008 from a blue-ribbon panel of epidemiologists who had reviewed **all** the styrene epidemiological studies, **as well as** the NTP Expert Panel's report on styrene, and concluded that "The available epidemiologic evidence does not support a causal relationship between styrene exposure and any type of human cancer." This is the same report that the NTP staff reviewed and inexplicably concluded did not "contradict" their classification of styrene as "reasonably anticipated to be a human carcinogen." **In essence, this is a published peer-review of the Expert Panel's work on which the NTP staff subsequently relied, and this work fails to pass peer review by this panel of internationally-recognized epidemiologists.**

The second publication is "Mouse specific lung tumors from CYP2F2-mediated cytotoxic metabolism: An endpoint/toxic response where data from multiple chemicals converge to support a mode of action" by Cruzan *et al.,* just published by *Regulatory Toxicology & Pharmacology* (*Regulatory Toxicology and Pharmacology*, Volume 55, Issue 2, November 2009, Pages 205-218). A copy of this paper is being provided to you as an enclosure with this letter. This publication documents the **extensive evidence for styrene's non-genotoxic mode of action** in causing lung tumors in mice.

Both of these publications are key to a re-written Background Document because they address the NTP staff's fundamental justifications for the listing of styrene.

Further, we would like to inform you that SIRC has commissioned an updating of Dr. Otto Wong's epidemiology study of reinforced plastic workers. The update will add at least 15 years of follow-up to the members of the cohort who were still alive in 1989 when the last update was conducted. Publication of the results is expected in the 2011 timeframe. This update should make the years at risk roughly comparable to the Kogevinas *et al.,* 1994 study and will have roughly 35 years of follow-up. This long follow-up should provide adequate years at risk to evaluate whether there were increases in lymphomas. This will be a very important addition to the peer-reviewed literature on styrene epidemiology. If the NTP's schedule allows, these new results from the updated Wong study should also be incorporated into the NTP styrene review.

In addition, in order to facilitate the re-drafting of the Background Document on styrene, we are submitting under separate cover an extensive Request for Correction of the Background Document under the Information Quality Act. In this 100-page detailed request, we spell out the numerous serious scientific deficiencies of the Background Document and suggest specific rewording that will bring that document into conformity with the broad

scientific database for styrene. We trust that NTP will review this submission very carefully and act on it expeditiously. It is because these deficiencies are so extensive and fundamental to the justification previously put forward by the NTP staff for a listing of "reasonably anticipated" that a full re-review of styrene's possible carcinogenicity is necessary, once the Background Document is revised.

Finally, by now you undoubtedly will have received a copy of a submission we made to Dr. Francis Collins, in response to his recent call to constituents to identify problems within NIH. In that response, we requested that NIH undertake a review and revision of the current NTP review process for the *RoC*. We plan to present Dr. Collins with a more detailed petition related to this needed revision, along with specific recommendations for changes, and we will provide you with a copy when it is submitted. We hope that you will find these specific recommendations helpful in your own review of the process which you have indicated you plan to undertake.

Thank you for your consideration of these issues of great concern. As with previous SIRC correspondence on this matter, we ask that this letter please be included in the *12th Report on Carcinogens* on-line public docket file for styrene.

Very truly yours,

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Cc: Dr. Ruth Lunn, NTP

Enclosure