IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

STYRENE INFORMATION AND RESEARCH CENTER, INC., *et al.*,	)	
Plaintiffs,	)	
v.	)	**Civil Action No. 1:11-cv-01079-RBW**
KATHLEEN SEBELIUS, *et al.*,	)	
Defendants.	)	

PLAINTIFFS' MEMORANDUM IN SUPPORT OF ITS MOTION FOR SUMMARY JUDGMENT

Dated: May 18, 2012

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Statutes

Federal Regulations

Federal Register

Cases

Secondary Sources

I. PRELIMINARY STATEMENT

Secretary Sebelius acted illegally when she listed styrene as "reasonably anticipated to cause cancer in humans" in the Congressionally mandated 12th Annual Report on Carcinogens ("RoC"). *See* 42 U.S.C. § 241(b)(4)(A). The Secretary's conclusion went beyond findings of both the World Health Organization's ("WHO") International Agency for Research on Cancer ("IARC") and the European Union as well as the Secretary's own Agency for Toxic Substances and Disease Registry ("ATSDR"). The Secretary reached her conclusion primarily by rejecting the conclusions of a 1979 National Cancer Institute mouse study that had been reviewed, and accepted, by every other governmental review and by rejecting the conclusions of a 2006 epidemiology study of workers in the synthetic rubber industry. Secretary Sebelius' actions were arbitrary, capricious and contrary to law. First, in making her listing decision, the Secretary relied on internal memoranda responding to issues she raised about the listing that misstated, mischaracterized and omitted information that was relevant to the Secretary's decision. These staff-prepared synopses so distorted the record that the Secretary's decision was based on inaccurate and incomplete information rendering her action arbitrary and capricious. *See National Small Shipments Traffic Conference, Inc. v. Interstate Commerce Commission*, 725 F.2d 1442, 1450-51 (D.C. Cir 1984). Second, the National Toxicology Program ("NTP") did not follow its own procedures in recommending that the Secretary list styrene in the RoC. Third, the listing criteria applied by the Secretary and NTP to styrene are contrary to law because they allow for the listing of a substance based on mere suspicion or the possibility that the substance is a human carcinogen, standards which are contrary to the statutory direction of Congress.

The Secretary's listing process does not confirm to the requirements of the Information Quality Act ("IQA"), 44 U.S.C. § 3516 note. This failure further demonstrates that the

Secretary's process was arbitrary and capricious. The IQA required that the RoC be " prepared following procedures that maximized the quality, objectivity, utility, and integrity of the information contained in the report." RoC at 7, Administrative Record ("AR") 2471. But HHS ignored the twin standards of objectivity and utility by generating a document that does not rely on the best available science, presents an inaccurate and unreliable characterization of styrene's carcinogenic potential, and fails to document or properly publish its new studies. HHS also violated the IQA's standard of utility by publishing a document that deprives the public of the ability to make an informed judgment about the carcinogenicity of styrene. Such action demonstrates the arbitrary and capricious nature of the Secretary's action.

II. FACTUAL BACKGROUND

A. Styrene and Related Products

1. Styrene is a clear, colorless liquid that is a component of materials used to make thousands of everyday products for home, school, work and play. *See* RoC AR 2457-2963, at 387, AR 2851. Styrene is used in a wide variety of everyday goods, including foodservice containers, agricultural shipping and storage containers, bicycle helmets, refrigerators, microwave ovens, computers, televisions, trucks, cars, boats, carpets and other home furniture. *Id*.

2. Styrene is manufactured synthetically in petrochemical plants. It also occurs naturally in the environment and is present at low levels in common foods, such as fruits, vegetables, nuts, beverages and meats. *See id*.; ATSDR Toxicological Profile of Styrene ("ATSDR Tox. Profile") AR 3155-3436,k at 3, AR 3177.

3. Styrene is a $28-billion dollar industry, comprising hundreds of companies with thousands of facilities throughout the country. *See e.g*., Letter to John Burklow from Jack Snyder (October 26, 2009) ("Burklow Letter") at 11, AR 2312. Nearly 128,000 workers are employed in the U.S. styrene industry in more than 5,000 plants with an annual payroll that exceeds $4 billion. *Id.*

B. Evaluations of Styrene By Other Governmental Entities

4. Styrene is approved by the United States Food and Drug Administration as a flavoring additive to food and styrene polymers are widely used in food packaging. *See* 21 C.F.R. § 172.515; RoC at 387, AR 2312.

5. United States and European government agencies have reviewed the carcinogenicity of styrene, including the ATSDR, an agency of Health and Human Services ("HHS"); the WHO's International Agency for Research on Cancer ("IARC"); and the government of the United Kingdom on behalf of the European Union ("EU"). These reviews found no causal link between styrene and cancer in humans. ATSDR Tox. Profile, AR 3155 – 3436; IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Styrene (2002) ("IARC 2002"), AR 7521-7634; European Union Risk Assessment Report on Styrene ("EU RAR") (June, 2008) ("EU RAR"), AR 14276 – 14684. They concluded that styrene was not carcinogenic to humans or, at most, is a possible human carcinogen, but the evidence they identified, by their own characterization, is weak. The scientific literature upon which these evaluations were based is essentially the same literature reviewed by NTP in conducting its assessment of styrene for the RoC.

6. ATSDR is a public health agency of HHS. *See* Answer ¶ 18; *see also* http://www.atsdr.cdc.gov. ATSDR is part of the Centers for Disease Control and Prevention ("CDC"). *Id.* CDC describes itself as "one of the major operating components" of HHS. *See* http://www.cdc.gov/about/organization/cio.htm.

7. According to its website, "ATSDR is directed by congressional mandate to perform specific functions concerning the effect on public health of hazardous substances in the environment. These functions include . . . health consultations concerning specific hazardous substances, health surveillance and registries, . . . applied research in support of public health assessments, information development and dissemination, and education and training concerning hazardous substances." http://www.atsdr.cdc.gov/about. *See* Answer (Docket No. 23), ¶ 19. On the issue of accountability, ATSDR ensures "that our research and our services are based on sound science and meet real public needs to achieve our public health goals." http://www.atsdr.cdc.gov/about/mission_vision_goals.html.

8. On November 30, 2010, ATSDR published a notice of availability for an updated Toxicological Profile For Styrene which is a peer-reviewed document. *See* 75 Fed. Reg. 74,053 (Nov. 30, 2010). *See also* ATSDR Tox. Profile, AR 3155 - 3436; Answer ¶ 20. According to the ATSDR, the toxicological profile "[s]uccinctly characterizes the toxicologic and adverse health effects information for the hazardous substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies." ATSDR Tox. Profile at Foreword, AR 3159. The profile "reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed." *Id.*

The profile was reviewed by staffs of the CDC and other federal scientists. Finally, the profile was peer-reviewed by a nongovernmental panel and was made available for public review. *Id.*

9. ATSDR concluded that "[t]aken together, the animal and human data indicate that styrene may possibly be a weak human carcinogen." *Id.* at 133, AR 3307. This peer-reviewed finding by an HHS agency can, at most, be characterized as a possible carcinogen evaluation. As reflected in ATSDR's Cancer Policy Framework, a possible carcinogen classification does not support the inclusion of styrene in the RoC as reasonably anticipated to be a human carcinogen. *See* ATSDR Cancer Policy Framework, Appendix A: Classification of Carcinogens (1993), AR 7521-7634, *also available at* http://www.atsdr.cdc.gov/cancer.html.

10. IARC, part of the World Health Organization, evaluated the potential carcinogenicity of styrene in 1978, 1987, 1994, and 2002. IARC 2002 at 437, AR 7521. Like HHS, IARC classifies the carcinogenic potential of substances based on an assessment of the sufficiency of the scientific information from peer-reviewed publications using a tiered classification system. IARC first classified styrene as "possibly carcinogenic," Category 2B, in 1987. *See IARC* Monographs on the Evaluation of Carcinogenic Risks to Humans, at pages 345-47 (1987), *available at* http://monographs.iarc.fr/ENG/Monographs/suppl7/index.php. Through subsequent reviews, this classification has remained unchanged. IARC 2002 at 437, AR 7521.

11. The evidentiary basis for a Group 2B classification is not sufficient to support listing styrene in the RoC as reasonably anticipated to be a human carcinogen. This is reflected in HHS' failure to list styrene on the RoC between 1987 and 2011, and explained by ATSDR's

Cancer Policy Framework. Only IARC Group 1 or Group 2A support a listing on the RoC.[1] ATSDR equates IARC's Group 2A (probably carcinogenic to humans) with NTP's "reasonably anticipated to be a carcinogen." IARC's Group 2B (possibly carcinogenic to humans), which includes styrene, does not meet the sufficiency of evidence necessary for listing. The Department of Labor, through the Occupational Safety and Health Administration, also differentiates between the IARC 2A and 2B categories.[2]

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[1] This is demonstrated by Table 1, shown below, which comprises Appendix A to ATSDR's Cancer Policy Framework, *available at* http://www.atsdr.cdc.gov/cancer.html.

Table 1. Classification of carcinogens

EPA	IARC	NTP	OSHA
(Group A) Human Carcinogen	(Group 1) Carcinogenic to Humans	Human Carcinogen	Category I
(Group B1, B2) Probable Human Carcinogen	(Group 2A) Probably Carcinogenic to Humans	Reasonably Anticipated to be a Carcinogen	Category II
(Group C) Possible Human Carcinogen	(Group 2B) Possibly Carcinogenic to Humans		
(Group D) Not Classifiable as to Human Carcinogenicity	(Group3) Not Classifiable as to Human Carcinogenicity		
(Group E) Evidence of Non-Carcinogenicity for Humans			

[2] The Occupational Safety and Health Administration's Hazard Communication Standard ("HCS") differentiates obligations based on IARC 2A and 2B classifications. *See* 29 C.F.R. § 1910.1200. Under the HCS Inspection Procedures, an IARC 2B classification triggers MSDS

12. In June 2008, the United Kingdom published the draft EU Risk Assessment Report on Styrene ("RAR") and submitted it to the European Chemicals Agency ("ECHA"). ("EU RAR"), AR 14276 - 14684. The EU RAR was agreed to by the EU's Technical Committee for New and Existing Substances in 2008 and underwent independent peer review by the EU's Scientific Committee on Health and Environmental Risks ("SCHER").[3] The EU RAR found that "there is no clear and consistent evidence for a causal link between specific cancer mortality and exposure to styrene." *Id*. at AR 14532. In support of that finding, the EU RAR stated:

> The increased risks for lymphatic and haematopoietic neoplasms observed in some of these studies are generally small, statistically unstable and often based on subgroup analyses. These findings are not very robust and the possibility that the observations are the results of chance, bias or confounding by other occupational exposures cannot be ruled out. In the styrene-butadiene rubber industry, several studies have pointed to an increased risk of cancer of the lymphatic and haematopoietic systems. However, detailed analysis of these data, together with the general toxicological picture for styrene and butadiene (see butadiene EU RAR), suggests that where increases are due to occupational exposure, it is butadiene, not styrene, that is the more likely causative agent. In conclusion, based on human studies, there is no clear and consistent evidence for a causal link between specific cancer mortality and exposure to styrene.

Id.

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requirements but not labeling requirements. *See* OSHA Directive Number: CPL 02-02-038, Inspection Procedures for the Hazard Communication Standard (1998), *available at* http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_id=1551&p_table=DIRECTIVES (Table A1).

[3] The EU RAR was never formally "finalized" because the legislation under which it was published was repealed and replaced by REACH (Registration, Evaluation and Authorization of Chemicals). *See* AR 2301j. However, the Annex XV Transitional Dossier for styrene cites to the EU RAR as providing "[a] summary of the carcinogenicity of styrene." Transitional Dossier at 18; http://echa.europa.eu/documents/10162/13630/trd_uk_styrene_en.pdf. At the time of the NTP listing, styrene was not classified as a cancer risk in the EU. *See* AR 2301j.

13. The EU RAR also commented on the animal carcinogenicity studies. The EU RAR rejected the applicability to humans of the finding of lung tumors in mice. The EU RAR discussed the likely "most plausible toxicological mechanism for the mouse lung tumors" and found that mechanism is less operative in the rat, where no lung tumors were found, and "even less operative in humans." *Id*. at AR 14532-33. Furthermore, "[t]here is no evidence from extensive epidemiological investigations that long term exposure to styrene has produced lung damage or lung cancer in humans." *Id*. at AR 14533. The RAR concluded that

> Hence, overall, the weight of evidence appears to indicate that the consequences of long term exposure to styrene in mouse lung cannot be replicated in the human situation at relevant levels of exposure. . . . [I]t is reasonable to conclude that the lung tumors seen in mice are unlikely to be of any relevance for human health.

Id. This conclusion is consistent with the finding of IARC that "the proposed mechanism involving metabolism of styrene to styrene 7,8-oxide in mouse Clara cells is not operative in human lungs to a biologically significant extent." *Id*. at 14534.

14. The EU RAR then disagreed with the IARC finding that "based on the observations in human workers regarding blood styrene 7,8-oxide, DNA adducts and chromosomal damage, it cannot be excluded that this and other mechanisms are important for other organs." *Id*. The RAR found this IARC conclusion to be "highly speculative." *Id.*

15. On May 6, 2008, the Scientific Committee on Health and Environmental Risks ("SCHER") of the EU Health & Consumer Protection Directorate-General published its opinion reviewing the EU RAR on styrene ("SCHER Report"). *See* AR 14269 – 14275. EU SCHER found that "[t]he most relevant studies and publications are all included in the EU RAR." *Id*. at 5, AR 14273. EU SCHER generally agreed with the conclusions in the EU RAR. *Id.*

16. More particularly, EU SCHER agreed "with the overall conclusion that '[t]here is no convincing evidence that styrene possesses significant mutagenic/clastogenic potential *in vivo*' from the available data in experimental animals." *Id.* at 6, AR 14274.

17. After observing that styrene had been found to induce lung and stomach tumors in mice, EU SCHER stated its agreement "with the proposed non-genotoxic mechanism of tumour induction in mice and the notion that this mechanism, . . ., is not operational in human lungs to any significant extent. This agrees with the conclusion of IARC (2002)." *Id*.

18. EU SCHER further observed that "although the EU RAR clearly describes the metabolic formation of the genotoxic and carcinogenic styrene oxide, its possible contribution to the carcinogenic risk of styrene exposure in other organs than lung is also considered negligible. This is insufficiently justified. Therefore, EU SCHER agrees with the conclusion of IARC (2002), that, based on the observations in human workers regarding blood styrene 7,8-oxide, DNA adducts and chromosomal damage, it cannot be excluded that this and other mechanisms are important for other organs." *Id*.

19. The ATSDR Tox. Profile, the IARC classification, and the EU Risk Assessment Report conflict with and do not support the inclusion of styrene in the RoC as a substance reasonably anticipated to be a human carcinogen. These contrary determinations demonstrate that the errors made by HHS in preparing the RoC with regard to styrene were outcome determinative, arbitrary, capricious, an abuse of discretion, and *ultra vires*.

20. In December 2010, California Environmental Protection Agency published its Public Health Goals for Chemicals in Drinking Water, Styrene ("OEHHA Report"). AR 14685 – 14979.

21. The OEHHA Report "provides a comprehensive review of the toxicology and epidemiology literature on styrene and its primary reactive metabolites and degradation products. The potential of styrene to induce cancer and non-cancer effects is described." *Id*. at 1, AR 14695.

22. In its summary, OEHHA stated that it concurred with IARC's assessment of styrene. *Id.* OEHHA also concurred with NTP's conclusion "that there is sufficient evidence that styrene causes cancer in animals," *Id*. at 2, AR 14696, but disagreed with the conclusions about human carcinogenicity data. According to OEHHA, "[w]hile several epidemiological studies of styrene and cancer in workers exposed in reinforced plastics and other industries have been published, the data do not show proof of carcinogenicity in humans." *Id.* Thus, although appearing to agree with NTP, OEHHA adopted a different view of the substantiality of the toxicological evidence related to styrene's potential carcinogenicity. *Id.*

C. Report on Carcinogens

1. The Regulatory Framework

23. The Report on Carcinogens ("RoC") is mandated by Congress. 42 U.S.C. § 241(b)(4)(A). According to the statute, the Secretary of Health and Human Services ("HHS") shall publish a biennial report that contains, in relevant part, "a list of all substances (i) which either are known to be carcinogens or may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed." *Id.* Under the statutory scheme, substances that have only suggestive evidence of carcinogenicity should not be listed at all. That is, HHS has not been directed to list "possible" or "suspected" carcinogens. *See id.*

24. The mandate from Congress to HHS was clear on this point: "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." 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).

2. Development of the Report on Carcinogens Generally

25. The preparation of the 12th RoC consisted of the following steps:

a. The nomination of substances by the National Toxicology Program ("NTP") for review, public comment, and finalization of the list of substances for review;
b. The publication of a draft background document for each substance followed by an opportunity for public comment;
c. Review of the draft background document by an expert panel;
d. Publication of an expert panel report, which was supposed to contain the panel's peer review of the draft background document and a listing recommendation;
e. Opportunity for comment on the expert panel report;
f. Finalization of the draft background document based on the expert panel's report and any public comments;
g. Preparation and opportunity for comment on a draft substance profile that is, in essence, a chapter in the RoC containing an abbreviated discussion of the substance's toxicology and listing status;
h. Preparation of the draft RoC by NTP; and,
i. Final approval of the RoC by the Secretary of HHS.

RoC at 8-10, AR 2472-74.

26. Under NTP policy, the information in a background document's sections discussing human cancer studies, studies of cancers in experimental animals, and other relevant

data "must come from publicly available, peer-reviewed sources. . . . [In addition, f]or each study cited in the background document from the peer-reviewed literature, information on funding sources (if available) and the authors' affiliations are provided in the reference section." Final Report on Carcinogens Background Document for Styrene (Sept. 29, 2008) ("Final Background Document") at i, AR 1194; RoC at 8, AR 2472.

27. Peer review of "influential scientific information" that is disseminated by the federal government is required under the OMB's "Final Information Quality Bulletin for Peer Review." The more important scientific assessments disseminated by the federal government require "more intensive" peer review. *Id.* at 2665.

3. Prior NTP Work on Styrene-7,8-Oxide

28. NTP had previously listed styrene-7,8-oxide in 2002 as reasonably anticipated to be a human carcinogen. The NTP listing was based on studies in experimental animals. RoC at 391, AR 2855.

29. The styrene-7,8-oxide studies relied upon by NTP involved the direct placement of styrene-oxide into the stomach of either rats or mice. *Id.* Cancer of the forestomach developed in both mice and rats. *Id.* There were also liver tumors in male mice only. *Id.* There were no experimental carcinogenicity studies in which styrene-oxide was administered by the inhalation route. Final Report on Carcinogens Background Document for Styrene-7,8-oxide ("Final Background Document on Styrene-7,8-oxide") at p. 21; http://ntp.niehs.nih.gov/ntp/newhomeroc/roc10/SO.pdf.

30. NTP noted that "[n]o epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to styrene-7,8-oxide." RoC at 391, AR 2855.

31. In discussing the existing studies of workers in the styrene industry as part of the background document on styrene-7,8-oxide, NTP noted that

> In summary, IARC (1994b) concluded that there was *inadequate evidence* in humans for the carcinogenicity of styrene. Studies published since then have provided some additional evidence in humans that styrene is carcinogenic, but it remains difficult to disentangle exposures to styrene and butadiene in many of the cohorts studies. Further studies in the reinforced plastics industry may help resolve this issue.

Final Background Document for Styrene-7,8-oxide at 16 (emphasis in original).

D. Development of the 12th Report on Carcinogens Relating to Styrene

1. Nomination of Styrene and Announcement of NTP's Procedures

32. On May 19, 2004, NTP announced the nomination of styrene for consideration for the 12th RoC with a 60-day comment period. 69 Fed. Reg. 28940-44 (May 19, 2004). *See also* 69 Fed. Reg. 62276-79 (Oct. 25, 2004). On October 18, 2005, NTP solicited public comments on an updated list of nominations, including styrene. 70 Fed. Reg. 60548-53 (Oct. 18, 2005).

33. On April 16, 2007, NTP announced in the Federal Register that it had added two "important elements in the RoC review process." For the 12th RoC, the review process would include: "(1) the public peer review of draft background documents by an *ad hoc* scientific expert panel and (2) the public peer review of draft substance profiles by the NTP Board of Scientific Counselors." 72 Fed. Reg. 18999 (Apr. 16, 2007). NTP further stated that it would prepare a response to public comments for the 12th RoC on a "trial basis." *Id.*

34. On May 9, 2007, NTP published a request for nominations of Scientific Experts to "serve on expert panels" as part of the review process for the 12th RoC. 72 Fed. Reg. 26394 (May 9, 2007). As noted by NTP, "[t]he NTP will convene an *ad hoc* expert panel to peer review the draft background document at a public meeting and make a recommendation to the NTP on the candidate substance's listing status for the RoC." *Id.*

2. The Background Document on Styrene, the Expert Panel Review, and Ad Hoc Science

35. On May 20, 2008, NTP announced the availability of the Draft Background Document for Styrene. 73 Fed. Reg. 29139-40 (May 20, 2008). (The Draft Background Document is at AR 419-854). NTP solicited public comments on the draft by July 7, 2008. *Id*. NTP further announced that the Styrene Expert Panel would be meeting on July 21-22, 2008. *Id.*

36. In preparing the Draft Background Document, NTP developed a new study by comparing data from a 1979 National Cancer Institute ("NCI") animal study titled "Bioassay of Styrene for Possible Carcinogenicity (Technical Report Series No. 185, 1979)," ("1979 NCI Study"), AR 9022 -9129, with new data outside of that study. Draft Background Document at 164-65, AR 612-13. Based on this newly-invented comparison, NTP reached conclusions different from the authors of the paper. The 1979 NCI Study examined rats and mice for adverse health effects from styrene. 1979 NCI Study at vii, AR 9030. NCI stated in the report's summary that "*no convincing evidence for the carcinogenicity of the compound was obtained in Fischer 344 rats or B6C3F1 mice of either sex*." *Id.* at viii, AR 9031 (emphasis added). While accepting the rat study, NTP substituted a different set of animal controls for those originally used in the mouse part of the study, and based on this novel and non-peer reviewed approach,

proceeded to find "sufficient evidence" of a link between styrene and tumors in the mice. Draft Background Document at 164-65, AR 612-13.

37. The new data and statistical analysis created by NTP did not constitute a "publicly available peer reviewed" source as required by NTP practice and procedure. Final Background Document at Foreword, AR 1194. In addition, substituting a different set of control animals from another laboratory as a basis of comparison conflicted with prior NTP peer-reviewed recommendations against this approach. *See* Haseman, et al., Use of historical control data in carcinogenicity studies in rodents, 12 Toxicol Pathol 126-135 (1984); Keenan, et al., Best Practices for Use of Historical Control Data of Proliferative Rodent Lesions, 37 Toxicol Pathol 679-693 (2009).

38. The Draft Background Document did not consider the peer-reviewed paper by Dr. Delzell and colleagues, *An Updated Study of Mortality Among North American Synthetic Rubber Industry Workers*, Health Effects Institute Research Report Number 132 (2006) ("Delzell 2006"), AR 5088-5160, about workers in the synthetic rubber industry. *See* AR 5088-5160. According to the paper, workers in the synthetic rubber industry were exposed to three significant chemicals: 1,3-butadiene ("BD"), styrene and dimethyldithiocarbamate ("DMDTC"). After controlling for effects of BD, the authors found no consistent exposure-response relation between styrene and all leukemias, chronic myelogenous leukemia, or chronic lymphocytic leukemia. AR 5088. According to the paper's authors, the data from this study indicate that employment in the synthetic rubber industry is related causally to leukemia; however, uncertainty remains about the specific agent or agents responsible for that association. *Id.* According to the authors, the carcinogenic mechanisms through which BD, styrene, or DMDTC

could cause leukemia in humans have not been established and epidemiologic support for a leukemogenic role is limited for these agents. *Id.* While the study reported an association between styrene exposure and non-Hodgkin Lymphoma ("NHL"), and with CLL-NHL, the author found that " these associations did not display consistent exposure – response trends and were due in part to a lower than expected number of deaths among unexposed subjects in comparison with external referenced populations." AR 5137. Additionally, the authors found no "[e]xternal support for this relation" reported from other epidemiologic studies. *Id.* at 5088. In fact, the authors noted that the NHL and CLL-NHL finding is "inconsistent with other research. Notably, studies of occupational groups exposed to concentrations of styrene higher than those found in the synthetic rubber industry have not reported any consistent increase in NHL deaths or incident cases." *Id.* at AR5136.

39. Commenting on NTP's reliance on her research, Dr. Delzell stated that her study did not constitute "strong evidence of a causal relation" between NHL and styrene. According to her, the results for styrene and NHL were "unconvincing." Comments on the RoC Background Document for Styrene and Related Documents dated October 10, 2008, AR 1722-26 at 1723.

40. According to a Commentary on the Delzell Paper published by the Health Effects Institute Health Review Committee, "[n]o clear association was found between any of the three agents [butadiene, DMTDTC or styrene] and non-Hodgkin lymphoma, multiple myeloma, or colorectal cancer. AR 5155. This is consistent with the observations of EU RAR. *See* ¶ 12 *supra*.

41. On July 21-22, 2008, the NTP Styrene Expert Panel ("Expert Panel") met for the purpose of conducting a "peer review" of the Draft Background Document on Styrene and to

recommend whether, and at what level, styrene should be included in the 12th RoC. NTP added this Expert Panel step for the 12th RoC process, doing so "to enhance the scientific development of the report and address guidance in the Office of Management and Budget's 'Final Information Quality Bulletin for Peer Review' ("OMB 2004")." RoC at 4, AR 2468. According to OMB, peer review is:

> a form of deliberation involving an exchange of judgments about the appropriateness of methods and the strength of the author's inferences. Peer review involves the review of a draft product for quality by specialists in the field who were not involved in producing the draft. [4]

70 Fed. Reg. 2664, 2665 (Jan. 14, 2005).

42. The Expert Panel was charged with determining whether the information in the Draft Background Document was "presented in a clear and objective manner, to identify any missing information from the body of knowledge presented in the document, and to determine the utility of the body of knowledge in the background document for drawing conclusions about the carcinogenicity of a candidate substance and for applying the RoC criteria for listing." Styrene Expert Panel Report, Part A, AR 1110-1149, at 1, AR 1110; *see also*, NTP Response to Expert Panel's Peer-Review Comments on Background Documents, AR 1150-76, at 2, AR 1153.

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[4] The OMB Guidelines further state:

> The peer reviewer's report is an evaluation or critique that is used by the authors of the draft to improve the product. Peer review typically evaluates the clarity of hypotheses, the validity of the research design, the quality of data collection procedures, the robustness of the methods employed, the appropriateness of the methods for the hypotheses being tested, the extent to which the conclusions follow from the analysis, and the strengths and limitations of the overall product.

Id.

43. The Expert Panel was composed of eleven scientists. Only one scientist came from industry; a pathologist, retired from Pfizer. Six scientists came from academia, one from the California EPA, one from the American Cancer Society and one, Peter F. Infante, was a consultant who retired from the government and who has testified as a plaintiff's expert in toxic tort personal injury cases. *See* Styrene Expert Panel Report, Part A, at 1, AR 1110. *See also*, *Henricksen v. Conocophillips Co.*, 605 F.Supp.2d 1142 (E.D. Wash. 2009)(Dr. Infante testified as an expert for plaintiff at trial).

44. The Expert Panel divided into subgroups to conduct its initial review of the Draft Background Document. The subgroup assigned to review the human carcinogenicity section was chaired by Dr. Matanoski with Dr. Infante and a scientist from the American Cancer Society.[5] No statistician participated in this review. The subgroup recommended that the Dezell 2006 paper be added to the Background Document and provided a two page discussion to be included in the Document. Styrene Expert Panel Report, Part A at 7-9, AR 1116-8. In that discussion the epidemiological subgroup conducted their own analysis of the data and drew different conclusions from those of Dr. Delzell's and her five colleagues. *See e.g.*, Answer, ¶ 39 ("during the Expert Panel's public meeting, Dr. Matanoski suggested another way of looking at certain data"); Transcript of July 21-22, 2008, Meeting of the NTP Styrene Expert Panel at Part 25 starting at 4:00; Styrene Expert Panel Report, Part B – Recommendation for listing status for "styrene" in the Report on Carcinogens and Scientific Justification for the Recommendation ("Styrene Expert Panel Report, Part B"), AR 1696-1701, at AR 1697 (the Expert Panel made its

[5] A fourth scientist, Dr. Suzanne Snedeker, was listed in the subgroup as primarily assigned to section 5, the section dealing with "other relevant data." *See* AR 15525-26.
Dr. Snedeker holds a Ph.D. in Nutrition.

recommendation after "additional recommended inclusions and some re-analysis of published date"). Dr. Matanoski acknowledged this at the Expert Panel meeting when she described the new analysis of the Delzell 2006 paper. Dr. Matanoski stated: "[i]f you recombine the groups as we've done in looking at the tables we've recombined these that say have five groups into three groups you find a nice monotonic linear exposure. So it has to do with grouping to some extent." Transcript of July 21-22, 2008, Meeting of the NTP Styrene Expert Panel at Part 25. Based on this facially-biased review using newly-created but unwritten data that departed from the Delzell 2006 Paper's conclusions, the Expert Panel then found an association between styrene and non-Hodgkin Lymphoma ("NHL"). In later comments

Dr. Delzell and her colleagues found this association "unconvincing." RoC Background Document for Styrene, Elizabeth Delzell, Sc.D., (October 10, 2008) at AR 1723. Nonetheless, this newly created relationship between styrene and NHL was subsequently incorporated by HHS in the Substance Profile for styrene, but was never included in the peer-reviewed literature. RoC at 384, AR 2848.

45. In the Draft Background Document, NTP concluded that workers in the reinforced plastics industry—rather than workers in the synthetic rubber industry—were the most relevant study population for epidemiology studies of styrene exposure. Draft Background Document at 133, AR 581. But the Expert Panel rejected this conclusion. Instead, the Expert Panel focused primarily on the synthetic rubber industry studied by Drs. Delzell and Matanoski. Styrene Expert Panel Report, Part A at pp. 7-9, AR 1116-8.

46. Based on the inclusion of the Delzell 2006 study and its re-analyzed data, the Expert Panel recommended that styrene be listed in the 12th RoC as "reasonably anticipated to

be a human carcinogen," based on "limited" evidence in human data. *See* Expert Panel Report, Part B, AR 1697. ("Following a discussion of the draft document, together with additional recommended inclusions and some re-analysis of published data, the expert panel reviewed the RoC listing criteria and made its recommendation for the listing status of styrene in the RoC."). The Expert Panel has recommended listing styrene based on "sufficient" evidence in animals is reliant, in significant part, on the reanalyzed NCI study.

47. Further, participation in the Expert Panel by Dr. Genevieve Matanoski violated the OMB Peer Review Bulletin's requirement of independence and presented an appearance of bias. The lack of independence arose from her having been asked to peer review her own work, which the Bulletin flatly prohibits. *See, e.g.*, Draft Background Document at 94-96, 104, AR 542-544, AR 552; 70 Fed. Reg. at 2669 ("In its narrowest sense, independence in a review means that the reviewer was not involved in producing the draft document to be reviewed.") . The appearance of bias arose because the Delzell 2006 Paper was an update of an earlier 1987 study that Dr. Matanoski initially conducted but was not hired to update. In addition, Dr. Matanoski is referenced as the primary author of five studies upon which the Background Document rests. Final Background Document, AR 1192-2691, at 423-424, AR 1652-53.

48. The creation of a new study by manipulating the tabular data in the Delzell 2006 Paper is undocumented and in violation of the Information Quality Act; nothing showing the recombined groups appears in either the Final Background Document or the Expert Panel materials and the analysis was not provided by NTP in response to a request submitted by SIRC under the Freedom of Information Act. HHS NIH NIEHS FOI Case No. 35461.

49. The new study developed by the Expert Panel did not constitute peer-review of the NTP Draft. Also, the new analysis by the Expert Panel is not "from the peer-reviewed literature" as required by NTP policy. NTP Report on Carcinogens Review Process at 2, AR 45.

50. On September 8, 2008, NTP "invited" public comment on Part B of the Expert Panel's report, that is, its recommendation "on the listing status for styrene in the 12th RoC and the scientific justification for the recommendation." 73 Fed. Reg. 52059-60 (Sept. 8, 2008). Comments were due to be submitted by October 23, 2008. *Id*.

51. Both Part A (the Expert Panel's "peer review" comments on the Draft Background Document) and Part B of the Expert Panel Report were signed and finalized on August 26, 2008, prior to the close of the public comment period. *See* Styrene Expert Panel Report, Part B at 4, AR 1699; Expert Panel Report Part A at 33, AR 1142.

52. On September 29, 2008, nearly a month before the close of the comment period on the Expert Panel Report recommendations, NTP finalized the Draft Background Document and published its Final Report on Carcinogens Background Document for Styrene. *See* Final Background Document, AR 1192-1693. According to the Final Background Document, the Draft Background Document was "finalized based on the peer-review recommendations of the expert panel and public comments received on the draft document." *Id*. at Foreword, AR 1194. Although HHS appears to segregate the Draft Background Document development from the Expert Panel's listing recommendation, as shown below, the Expert Panel's listing recommendation is based on nothing other then the Background Document that the Expert Panel modified.

3. The Styrene Substance Profile

53. According to the NTP process, once the Background Document and Expert Panel recommendation are finalized, NTP drafts a substance profile for each substance. ROC at 9, AR 2473. The substance profiles are short documents summarizing NTP's classification of the substance and information about carcinogenicity, properties, use, production, exposure, regulations and guidelines. The compiled substance profiles constitute the RoC. *Id*.

54. On December 22, 2008, NTP announced the availability of the draft Substance Profile for styrene and that the NTP Board of Scientific Counselors ("NTP BSC") would be meeting on February 24, 2009. 73 Fed. Reg. 78364-65 (Dec. 22, 2008). According to the announcement, the NTP BSC is a "federally-chartered, external advisory group . . . that provides primary scientific oversight to the NTP and evaluates the scientific merit of NTP's intramural and collaborative programs." *Id.* at 78364. The NTP BSC was charged with "[d]etermin[ing] whether the scientific information cited in the draft substance profile for a candidate substance is technically correct, clearly stated, and supports the NTP's preliminary policy decision regarding its listing in the RoC. . . ." Summary Minutes of February 24, 2009, Meeting of NTP Board of Scientific Counselors AR 1844-1880, at 6, at AR 1850. However, the NTP did not ask the NTP BSC to comment on the policy decision to list a chemical on the RoC. *Id.*

55. After the peer review of the Draft Substance Profiles, NTP prepares a draft RoC. ROC at 9, AR 2473. The draft RoC is then submitted first to the Director of NTP and then to the Secretary of HHS to transmit to Congress and the public. *Id*.

56. On October 22, 2009, SIRC provided the Director of NTP with two newly published papers relevant to the NTP's consideration. *See* Letter from Jack Snyder to Dr. Linda

S. Birnbaum (October 22, 2009), AR2199-2218. The first paper was Boeffetta et al, *Epidemiological Studies of Styrene and Cancer: A Review of the Literature,* which was scheduled to be published in the Journal of Occupational and Environmental Medicine. The second paper was Cruzan et al, *Mouse Specific Lung Tumors From CYP2F2-mediated Cytotoxic Metabolism: An EndpointToxic Response Where Data From Multiple Chemicals Converge to Support a Mode of Action.* 55 Regulatory Tox. & Pharm. 205 (2009). *See* AR 2205-2218.[6]

57. The Boffeta paper authors were clear and direct. After a review of the published literature "[w]e found no consistent increased risk of any form of cancer among workers exposed to styrene. A large study of reinforced plastic workers reported an association between average estimated styrene exposure and non-Hodgkin lymphoma (NHL, P = 0.05) but no trend with increasing duration of exposure. Other studies of styrene exposure and NHL found no increased risk. In two US studies of reinforced plastic workers, esophageal cancer mortality was increased, but these findings were generated in a background of multiple comparisons. Results for other cancers were unremarkable. The available epidemiologic evidence does not support a causal relationship between styrene exposure and any type of human cancer."

58. The Cruzan paper concluded that the likely mode of action that produced cancerous tumors in the lungs of mice exposed to styrene is "highly unlikely" to occur in humans. AR 2216. The EU SCHER came to the same conclusion even before the Cruzan paper. AR 14274 ("EU SCHER agrees with the proposed non-genotoxic mechanism of tumour

[6] The Boffetta paper was not included in the administrative record can be found at http://ntp.niehs.nih.gov/files/20081216SIRCattach.pdf.

induction in mice and the notion that this mechanism, . . . is not operational in human lungs to any significant extent.").

AR 2133.

59. On October 5, 2010, SIRC submitted to the Director of NTP the initial findings of a study of CYP2F2-Knock-Out Mice being exposed to styrene *See* Letter from Marcy Banton *et al*. to Dr. Linda S. Birnbaum (October 5, 2010), AR 2219-25. According to the report, "[t]his preliminary study clearly demonstrates that styrene toxicity in mouse lung is totally dependent on metabolism of CYP2F2. Since humans have very small amounts of CYP2F, lung toxicity and tumors are not expected from styrene in humans." *Id.* at AR 2223.

60. On December 2, 2010, Linda Birnbaum, Director, National Institute of Environmental Health Sciences and National Toxicology Program wrote a memo to Secretary Sebelius titled: "Follow-up Information on the *Report on Carcinogens, Twelfth Edition*." ("Dec. 2 Memo."), AR 2301h-l.

61. In her memo, the Director downplayed the importance of an NTP listing. She told the Secretary that "[l]isting in the *Report* as either a *known* or *reasonably anticipated* carcinogen requires no action under the Public Health Service Act, nor does listing result in any restrictions on use, or establish any specific exposure limits or guidelines." *Id*. at 2, AR 2301i (emphasis in original). She noted, however, that "[c]ertain regulatory agencies have chosen to base certain of their regulatory actions on a listing of a substance in the *Report on Carcinogens*, but this is at their volition." *Id.* (emphasis in original).

62. Director Birnbaum summarized evaluations of styrene by the EU and other groups. After acknowledging that the EU RAR for styrene "concluded that styrene is not a cancer risk," Director Birnbuam discounted that finding. *Id*. at 3, AR 2301j. According to Dr. Birnbaum:

> The EU Scientific Committee on Health and Environmental Risks (SCHER), an external peer review group, disagreed with the EU RAR conclusion . . ., and agreed with the conclusion of the World Health Organization's International Agency for Research of Cancer (IARC 2002) that metabolism of styrene in the human body and resultant genetic damage indicates a possible carcinogenic risk to humans.

Id. She then noted that the EU RAR did not include the Delzell 2006 study "or an analysis of genetic damage across many studies of exposed workers, which are included in the NTP evaluation and add evidence to the NTP conclusions." *Id*. She then added, without any context, that "[t]he metabolite styrene-7,8-oxide, identified in exposed workers in the United States, is listed in the *11th Report as reasonably anticipated to be a human carcinogen*." *Id*. (emphasis in original).

63. The Director further disparaged the EU evaluation in contrast to NTP. After noting that "evaluation of occupational epidemiology studies is critical to the assessment," the Director informed the Secretary that "[u]nlike the EU evaluation, the process for preparation of the *12th Report* involved extensive scientific expertise in human epidemiology studies." *Id*. at 4, AR 2301k.

64. The Director further asserted that "NTP was careful to manage interactions with affected parties, such as industry, to prevent a potential or real conflict of interest" without any stated basis for the implication that the EU did not. *Id*.

65. The Director did admit that "[b]oth the EU RAR and the NTP concluded that the relationship between exposure to styrene and cancer is not causal." *Id*. at 5, AR 2301l. She attempted to discount this finding by stating "[h]owever, unlike the NTP, the EU RAR did not conclude that genetic damage caused by a major metabolite of styrene (styrene-7,8-oxide) found in the blood of workers exposed to styrene was likely to contribute to the carcinogenicity of styrene." *Id*.

66. The Director further noted that the EU RAR "concluded that styrene caused lung tumors in mice but determined that the evidence for mouse lung tumors was not relevant for humans." *Id*. According to the Director, NTP disagreed and found sufficient evidence based on animal studies. She claims that "such study results have indicated potential carcinogenicity in humans for other chemicals even though the tumor sites in humans and animals differed." *Id*.

67. The Director also discounted the IARC conclusions because it did not include the Delzell 2006 paper. *Id*. at 2301j.

68. The Director also discussed the California Environmental Protection Agency, Office of Environmental Health Hazard Assessment (OEHHA) DRAFT Assessment Public Health Goal for Drinking Water (February 2010). She noted that the draft "concludes that there is suggestive evidence for the carcinogenicity of styrene in humans." *Id.* The Director did not remind the Secretary that suggestive evidence is not sufficient to support a listing.

69. On April 7, 2011, Director Birnbaum wrote a second memorandum to the Secretary to supplement the earlier memo. ("April 7 memo."), AR 2301b-g. The purpose of the second memorandum was "to provide additional follow-up information . . . in response to questions that have been raised in the course of your review of the 12th RoC and, in particular,

the proposed RoC listing of styrene as *reasonably anticipated to be a human carcinogen*." *Id*. at AR 2301b (emphasis in original).

70. In her April 7 memorandum, the Director claimed that the findings of the CA OEHHA Review were "consistent with the proposed RoC listing." *Id*. at 4, AR 2301e.

71. The Director discounted the importance of the ATSDR findings. First, she claimed that "a toxicology or 'tox' profile serves a different purpose than a listing in the RoC . . . The tox profiles are summaries of ATSDR's evaluations concerning whether and at what levels of exposure adverse health effects occur and levels at which no adverse effects occur." *Id*. at 4-5, AR 2301e-2301f. She then stated that "[w]ith regard to potential carcinogenicity, in particular, ATSDR officials have indicated that a tox profile is not intended to provide a comprehensive review or assessment of existing cancer research for a particular substance." *Id.* at 5, AR 2301f.

72. The Director further informed the Secretary that "[t]he conclusion that styrene 'may be'(as opposed to 'may possibly be') carcinogenic arguably represents very little difference from the RoC proposed listing, particularly given the different purposes of the two documents, not to mention the different processes used in their development." *Id*.

73. The Director cited language in the ATSDR report that "acknowledges that 'DHHS' has 'not evaluated the carcinogenic potential of styrene.'" *Id*. She added her "understanding that ATSDR defers to NTP as the appropriate agency to speak for the Department with respect to a substance's carcinogenicity. Thus, the above-quoted text is not intended to represent the Department's definitive position on the matter." *Id.* Finally, the Director stated that "if the proposed styrene listing is approved and the 12th RoC is published, we

understand that ATSDR intends to prepare an addendum to the Styrene Tox Profile acknowledging the RoC listing." *Id.*

74. The Director provided the Secretary with the NTP's analysis of Boffetta et al., *Epidemiologic Studies of Styrene and Cancer: A Review of the Literature*." *Id*. at 5-6, AR 2301f-g. In so doing, the Director informed the Secretary that Dr. Boffetta was the co-author of a subsequent paper that "identified findings supportive of NTP's proposed listing." *Id*. at 6, AR 2301g. According to the Director, the paper "concludes that '[r]isk of follicular lymphoma significantly increased with three independent metrics of exposure . . . to styrene ($p=1x10^{-5}$)' and that '[s]ignificant upward trends were observed for [B-cell non-Hodgkin's lymphoma (B-NHL)] with styrene exposure . . . .'" *Id.*

75. The paper to which the Director referred is, P. Cocco et al., *Occupational Exposure to Solvents and Risk of Lymphoma Subtypes: Results from the Epilymph Case-Control Study*, 67 Occupational & Envtl. Med. 341 (2010), AR 14980-87. The paper's conclusion was that "[t]his analysis . . . confirms a role of occupational exposure to solvents in the aetiology of B-NHL, and particularly, CLL. It is suggested that benzene is most likely implicated, but we cannot exclude the possibility of a role for other solvents in relation to other lymphoma subtypes, such as follicular lymphoma. No association with risk of T-cell lymphoma and Hodgkin's lymphoma was shown." *Id*. at AR 14981.

76. The Director of the ATSDR also wrote the Secretary in support of the styrene listing. *See* May 6, 2011 Memorandum, AR 2301a. In his memorandum, the ATSDR Director took it upon himself to speak for the agency in interpreting the meaning of the Tox Profile for Styrene and to state the agency's opinion of the NTP recommendation. *Id.* According to the

ATSDR Director, "[n]either NTP nor ATSDR view" the statement that "studies suggest that styrene may be a weak human carcinogen" and styrene is "reasonably anticipated to be a human carcinogen" as "inconsistent." AR 2301a. In so stating, he ignored the extensive review process that the agency went through in adopting its report, the agency's Cancer Guidelines and the process through which ATSDR reaches conclusions about the toxicology of a substance.

77. The Secretary approved the listing of styrene in the 12th RoC and the report was made available to the public on June 10, 2011. 76 Fed. Reg. 36924 (June 23, 2011).

E. SIRC's Information Quality Act Request for Correction

78. The Information Quality Act ("IQA"), 44 U.S.C. § 3516 note, and implementing guidelines issued by OMB,[7] HHS,[8] and NIH[9] apply to the RoC because it is information disseminated by a federal agency. The IQA requires that influential scientific information disseminated by a government agency be of appropriate "quality," which encompasses utility, objectivity and integrity. OMB, Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies, 67 Fed. Reg. 8452-60, 8459 (Feb. 22, 2002) ("OMB Guidelines").[10] As such, it must be "accurate [and]

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[7] Office of Management and Budget, Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies; Republication, 67 Fed. Reg. 8452-60 (Feb. 22, 2002).

[8] Guidelines for Ensuring the Quality of Information Disseminated to the Public, *available at* http://aspe.hhs.gov/infoquality/guidelines/part1.shtml.

[9] Guidelines for Ensuring the Quality of Information Disseminated to the Public, *available at* http://aspe.hhs.gov/infoquality/guidelines/NIHinfo2.shtml.

[10] OMB defines "influential" information as that which "has a clear and substantial impact on important public policies or private sector decisions." 67 Fed. Reg. at 8460. It is clear that NIH regards the RoCs as "influential;" *see* NIH IQA Guidelines, n.12, *supra*, at § V.2.d ("One of

reliable," contain "the best available . . . science," and present information in a "complete and unbiased manner . . . within the proper context." *Id*. at 8457, 8459. NTP is also required to incorporate a "high degree of transparency about the data and methods to facilitate the reproducibility of such information by qualified third parties." *Id*. at 8460.

79. On October 26, 2009, SIRC submitted to NIH a Request for Correction under the IQA seeking corrections to the Final Background Document for Styrene. *See* Request for Correction, AR 2302-2411. This 100-page document contained: (a) detailed descriptions of the portions of the Final Background Document that require correction; (b) the specific reasons why those portions do not comply with IQA requirements; (c) suggested recommendations for revising the Final Background Document; and, (d) an explanation of how the Final Background Document affected and will affect SIRC and its members. Despite its stated policy of responding to IQA correction requests in 60 days, NTP did not provide a substantive response until December 23, 2010 - 14 months after SIRC submitted the request. *See* NTP Response to RFC, AR 2412-2436.

80. Although NTP recognized the need to make roughly a dozen corrections to the Final Background Document and to provide some additional clarifications, it responded to the majority of SIRC's comments with formulaic statements to the effect that it had followed its procedures and thus, the Final Background Document must be correct. *See, e.g.*, AR 2412-14. NTP's response reflected a fundamental misunderstanding of the objectivity criterion under the

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our most visible publications is the Report on Carcinogens . . . ."). Finally, in its responses to SIRC's Request for Correction and SIRC's appeal of that request, NIH has never disputed the characterization of the RoC as "influential." *See* Interim Responses to RFC, AR 2411a-f; NTP Response to RFC, AR 2412-2436; HHS Response to Request for Reconsideration, AR 2453-2456.

IQA, as demonstrated in SIRC's IQA Appeal of February 11, 2011, which was denied in a letter dated June 8, 2011, shortly before the RoC was issued.[11] For the Final Background Document to comply with the IQA criterion, it must be "accurate [and] reliable," contain "the best available . . . science," and present that information in a "complete and unbiased manner . . . within the proper context." OMB Guidelines, 67 Fed. Reg. 8452-60. It does not. The Final Background Document also violates the "utility" criterion of the IQA because it does not enable a reader to make an informed judgment about the carcinogenicity of styrene.

F. The Impact of Listing Styrene in the Report on Carcinogens

81. The listing of styrene in the NTP triggered new labeling requirements under the Occupational Safety and Health Administration's ("OSHA") Hazard Communication Standard ("HCS"). "A chemical is considered to be a carcinogen [for purposes of the HCS] if: (b) it is listed as a carcinogen or potential carcinogen in the Annual Report on Carcinogens published by the National Toxicology Program (NTP) (latest edition)," 29 C.F.R. § 1910.1200(d)(1) at Appendix A to § 1910.1200, even if the substance is only listed as "reasonably anticipated." *See* OSHA's 1998 Directive entitled "Inspection Procedures for the Hazard Communication Standard," *available at* http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_id=1551&p_table=DIRECTIVES (Table A1). Written hazard communications required of employers for carcinogens include labels and other forms of warning, material safety data sheets, and employee information and training.

[11] *See* Request for Reconsideration (Information Quality Act Appeal) Styrene Background Document Submitted by SIRC, Feb. 11, 2011, AR 2437-2452. *See also* HHS Response to Request for Reconsideration, June 8, 2011, AR 2453-2456.

III. LEGAL BACKGROUND

A. Standard of Review

The Administrative Procedure Act ("APA") permits individuals suffering a legal wrong because of final agency action to seek judicial review thereof. 5 U.S.C. § 702. Our Court of Appeals has held that publication of the RoC constitutes a reviewable final agency action. *Tozzi v. U.S. Dep't of Health and Human Servs.*, 271 F.3d 301, 310 (D.C. Cir. 2001).

"Under the APA, the Court must 'hold unlawful and set aside agency action, findings, and conclusions' that are 'arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.'" *Stuttering Found. of Am. v. Springer*, 498 F.Supp.2d 203, 207-08 (D.D.C. 2007)(quoting 5 U.S.C. § 706(2)(A)). In conducting this analysis, the court "is to determine whether or not as a matter of law the evidence in the record permitted the agency to make the decision it did." *Gentiva Healthcare Corp. v. Sebelius*, No. 11-438, --- F.Supp.2d ----, 2012 WL 1142450, at *5 (D.D.C. Apr. 6, 2012)(internal quotations omitted). Specifically, the Court must "ensure that the deciding body 'has examine[d] the relevant data and articulate[d] a satisfactory explanation for its action including a rational connection between the facts found and the choices made.'" *Loma Linda Univ. Med. Ctr. v. Sebelius*, 684 F.Supp.2d 42, 51 (D.D.C. 2010)(quoting *Kennecott Greens Creek Mining Co. v. Mine Safety & Health Admin.*, 476 F.3d 946, 952 (D.C. Cir. 2007)). *See also Fund for Animals v. Babbitt*, 903 F. Supp. 96, 105 (D.D.C. 1995), *amended on other grounds*, 967 F.Supp. 96, 105 (D.D.C. 1995)(A reviewing court must consider "whether the agency has explained its decision, whether the facts on which the agency purports to have relied have some basis in the record, and whether the agency considered the relevant factors.")(Internal citations omitted.).

Although this standard is deferential, the Court's review must be "searching and careful." *Marsh v. Oregon Natural Res. Council,* 490 U.S. 360, 378 (1989). Courts "do not hear cases merely to rubber stamp agency actions. To play that role would be 'tantamount to abdicating the judiciary's responsibility under the Administrative Procedure Act.'" *NRDC, Inc. v. Daley*, 209 F.3d 747, 755 (D.C. Cir. 2000)(quoting *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1491 (D.C. Cir. 1995)).

"Summary judgment is the proper mechanism for deciding, as a matter of law, whether an agency action is supported by the administrative record and consistent with the APA standard of review." *Am. Fed. of Gov't Emps., AFL-CIO, Local 3669 v. Shinseki*, 821 F.Supp.2d 337, 345 (D.D.C. 2011)(quoting *Loma Linda Univ. Med. Ctr.*, 684 F.Supp.2d at 52).

B. The Public Health Service Act Does Not Authorize Listing a "Possible Carcinogen" on The Report on Carcinogens.

The statute which authorizes the RoCs, the Public Health Service Act, instructs the Secretary of HHS to publish reports listing "all substances (i) which either are known to be carcinogens or may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed." 42 U.S.C. § 241(b)(4)(A). The statute does not authorize the Secretary to list substances that have only suggestive evidence of carcinogenicity; *i.e.*, that are "possible" or "suspected" carcinogens. "[T]here must be reasonable grounds for designating a substance as a putative carcinogen." 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).

C. The Information Quality Act Requires Objectivity and Utility

The Information Quality Act ("IQA"), 44 U.S.C. § 3516 note, requires that information disseminated by federal agencies meet the IQA's twin standards of objectivity and utility. The RoC is subject to the most demanding requirements of OMB's, HHS's and NIH's IQA Guidelines because it is "influential scientific . . . information" that involves "analysis of risks to human health." OMB Guidelines, 67 Fed. Reg. at 8460.[12] To be objective, the RoC must be "accurate, reliable and unbiased," *id.* at 8549, and based on "the best available . . . science . . . conducted in accordance with sound and objective scientific practices . . . ." *Id.* at 8457. It must also incorporate a "high degree of transparency about data and methods to facilitate the reproducibility of such information by qualified third parties." *Id.* at 8460. Objectivity must also be reflected in the way that information is presented: to be objective, information must be "presented in an accurate, clear, complete and unbiased manner," which includes presentation in the proper context. *Id.* at 8459. Influential scientific information bearing on assessing health risks—like the RoC—must present "each significant uncertainty identified in the process" and "peer-reviewed studies . . . that fail to support any estimate of risk." *Id.* at 8457-58 (internal quotations omitted). Finally, the IQA also aims to ensure the "utility" of information; *i.e.*, that it be useful to its intended users, including the public. *Id.* at 8459; *cf.* 44 U.S.C. § 3504(e)(1)(B).

D. The Court Can Consider Information Outside the Administrative Record

Judicial review of agency action under the Administrative Procedure Act is generally limited to the administrative record. *Texas Rural Legal Aid, Inc. v. Legal Servs. Corp.*, 940 F.2d

[12] *See supra* n.12.

685, 698 (D.C. Cir. 1991). This general rule is weaker for challenges to the procedural soundness of agency action. *Esch v. Yeutter*, 876 F.2d 976, 991 (D.C. Cir. 1989).

The D.C. Circuit recognizes four "well established" exceptions to the general rule. *Amfac Resorts, L.L.C. v. United States Dep't. of the Interior*, 143 F.Supp.2d 7, 11 (D.D.C. 2001). "First, a court may look beyond the record if there was such a failure [by the agency] to explain administrative action so as to frustrate effective judicial review. Second, courts have looked beyond the record when it is necessary to determine whether the agency considered all the relevant factors. Third, non-record review is merited when the agency may have deliberately or negligently included documents that may have been adverse to its decision. Finally, non-record review is also permissible in situations where there is a strong showing of bad faith or improper behavior on the part of the agency." *Id.* at 11-12 (internal quotations and citations omitted).

E. NTP Must Comply With Its Own Procedural Requirements

Federal agencies are "bound to the standards by which [they] profess [their] action[s] to be judged." *Lopez v. Fed. Aviation Admin.*, 318 F.3d 242, 246 (D.C. Cir. 2003) (citing *SEC v. Chenery Corp.*, 318 U.S. 80, 87-88 (1943)). Thus, agencies must "follow their own rules, even gratuitous procedural rules that limit otherwise discretionary actions." *Steenholdt v. FAA*, 314 F.3d 633, 639 (D.C. Cir. 2003). In the case of an alleged violation of an agency procedure designed to provide the agency with information it needs to reach an informed decision, the complaining party must show that the agency violation caused it to suffer substantial prejudice. *Lopez*, 318 F.3d at 247. However, no special showing is necessary if the agency rule is intended primarily to provide procedural benefits to individuals in the face of otherwise unfettered agency discretion. *Id.*

IV. ARGUMENT

The decision to list styrene as "reasonably anticipated to cause cancer in humans" in the RoC was arbitrary, capricious and contrary to law. First, NTP failed to follow its own procedures. Rather than relying on the peer-reviewed literature as required, NTP reanalyzed and developed new conclusions for two studies, each of which is crucial to the listing decision. Second, the memoranda upon which the Secretary relied in approving the listing of styrene misled her and failed to provide her with all the information relevant to her decision, rendering her action arbitrary and capricious. Third, HHS failed to fulfill its obligations under the Information Quality Act. *See National Small Shipments Traffic Conference, Inc. v. Interstate Commerce Commission*, 725 F.2d 1442, 1450-51 (D.C. Cir 1984). Finally, the criteria that NTP used to list styrene were contrary to the Congressional mandate that a substance not be listed merely because it is suspected to be a carcinogen.

The errors made by HHS led to the wrong decision. The body of peer-reviewed literature that NTP has cited in the RoC is substantially the same body of literature that was reviewed just the year before by NTP's sister agency ATSDR. Interpreting the literature in November 2010, ATSDR issued a peer-reviewed Toxicological Profile for Styrene which concludes that the studies of styrene "suggest" that it "may possibly be a weak human carcinogen." *See* ATSDR Tox. Profile, AR 3155-3436, at 133, AR 3307. ATSDR's conclusion about styrene is not consistent with a listing in the RoC since it, as best, identifies styrene as a "suspect" carcinogen. Additionally, two international agencies and one state agency also have evaluated the relevant literature and come to the same conclusion as ATSDR. Both EU SCHER, EU RAR and IARC came to conclusions that do not support a listing of styrene. *See* EU SCHER at 6, AR 14274; EU

RAR at AR 14532; IARC 2002 at 522, AR 7606. ATSDR's Cancer Policy Framework clearly indicates that this IARC conclusion (Group 2B - possibly carcinogenic to humans) does not meet the NTP classification of "reasonably anticipated" to be a human carcinogen. *See* ATSDR – Cancer Policy Framework, Appendix A, Table 1, *supra*, n.1. Finally, the State of California in its OEHHA Report did not agree with NTP's conclusions about the pivotal epidemiology study upon which NTP relied. The conclusions of ATSDR, the EU, IARC and OEHHA demonstrate that NTP has acted arbitrarily and capriciously. NTP has thus exceeded its statutory authority and the RoC's listing of styrene cannot stand.

A. The Listing of Styrene Was Arbitrary and Capricious Because NTP Failed to Follow Its Procedures

NTP has established three bases for listing a substance as "reasonably anticipated" to be a human carcinogen in the RoC:

> (1) limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded; or
>
> (2) sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset; or
>
> (3) there is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

RoC at 4, AR 2468. *See* also, April 7 memo. at 2, AR 2301c. NTP further notes that "[c]onclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment with consideration given to all relevant information." RoC at 4, AR 2468. The criteria are not cumulative or additive; a substance merely has to satisfy one of the criteria to be listed.

The RoC listed styrene as "*reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of carcinogenicity from studies in experimental animals, and supporting data on mechanisms of carcinogenesis." RoC, at 383, AR 2847 (emphasis in original). These "findings" were described to the Secretary as providing "at least two independent bases" for the listing. *See e.g.*, Apr. 7 memo. at 3, AR 2301d ("the evidence was determined to satisfy the established criteria for the RoC listing on at least two independent bases."). Mechanistic data was not cited as an independent basis for listing.

The NTP listing is based on the Final Background Document. According to NTP the Final Background Document reports only relevant publicly available, peer-reviewed studies. NTP Report on Carcinogens Review Process at 1, AR 44. The section on human cancer studies "summarizes traditional cancer epidemiology studies" and the section on experimental animals, "summarizes experimental animal studies." *Id*. Nowhere in its published materials does NTP assert that it will conduct a new analysis or re-analysis of data reported in peer-reviewed studies. But that is exactly what happened. The Background Document contains a reanalysis of both the NCI 1979 study and the Delzell 2006 study, rejects the conclusions of the authors of each and

draws new conclusions from each study that purportedly support the listing of styrene in the RoC.

Second, the Expert Panel did not limit itself to conducting a peer review of the Draft Background Document as required by NTP procedure. *See* NTP Report on Carcinogens Review Process at 2, AR 45 (the Expert Panel is to "peer review the background document.") Rather, the Expert Panel rejected the substantive conclusions of the Background Document, developed new information, and invented its own science. A subcommittee of the Expert Panel, chaired by Dr. Matanowski, proposed the inclusion of Dr. Delzell's 2006 paper in the Background Document and provided a two page insertion to be included as well. Styrene Subgroup Report for Section 3: Human Cancer Studies, AR 15526-32, at 1-3, AR 15526-28. In drafting their conclusion, the subcommittee improperly reanalyzed Dr. Delzell's data, rejected her analysis and concluded that Dr. Delzell's study demonstrated a link between styrene exposure and Non-Hodgkin's Lymphoma ("NHL"). The reanalysis, and new conclusions, were adopted by the NTP in violation of its procedure. First, the reanalysis and new "conclusions" from Delzell 2006 do not appear in the peer reviewed literature as required by NTP's own procedures. Second, the Expert Panel's reanalysis did not constitute a peer review of the Draft Background Document but rather represented new work that itself was never peer reviewed as required by NTP.

The actions of the subcommittee and NTP were pivotal to the recommendation to list styrene. According to the RoC, "[t]he limited evidence for the carcinogenicity of styrene in humans is based on studies of workers exposed to styrene that showed (1) increased mortality from or incidence of cancer of the lymphohematopoietic system and (2) increased levels of DNA adducts and genetic damages in lymphocytes from exposed workers." RoC at 383, AR 2847.

The finding was based, in significant part, on Dr. Delzell's 2006 paper. *See* AR 2853 (citing *Res Rep Health Eff Inst* (132): 1-63, 65-74). In fact, the NTP Director pointed to the lack of consideration of the Delzell study as a reason that other expert bodies had not come to the same conclusion as NTP on styrene in her briefing of the Secretary. *See* Dec. 2 memo at 2, AR 2301j. Furthermore, the Subcommittee's actions were disputed. Dr. Delzell rejected the conclusions that the Expert Panel drew and so informed the NTP. *See* Letter to Dr. Ruth M. Lunn (October 23, 2008), AR 1705-26 (Dr. Delzell's comments were attached to the letter to Dr. Lunn, *see* AR 1722-26). Additionally, OEHHA's review of Delzell 2006 did not adopt the reanalysis done by the Expert Panel and did not reach the same conclusions. *See* OEHHA Report at 183, AR 14877. Without reliance on the Delzell study, a finding related to human carcinogenicity, cannot stand.

The basis for the listing based on animal studies was the purported development of lung tumors in several strains of mice by two routes of exposure. RoC at 385, AR 2849.[13] In order to support its conclusion based on animal studies, NTP combined some data from the 1979 National Cancer Institute Study with new data from a different set of animals from a different laboratory, thereby creating a new study and ignoring thirty years of global acceptance of the study authors' peer-reviewed conclusions; conclusions that had been accepted by IARC, the EU RAR, ATSDR and OEHHA. *See* IARC 2002 at 475, AR 7559; OEHHA Report at 112, AR 14806. As with Delzell 2006, the 1979 NCI Study concluded that there was no firm conclusion of styrene carcinogenicity. NTP rejected that conclusion. Rather, NTP asserted that in light of

[13] Audio of February 24, 2009 NTP Board of Scientific Counselors Meeting at Part at 1 starting at 58:10. There were three studies: two gavage studies (NCI 1979) and Ponomarkov and Tomatis 1978) and one inhalation study – (Cruzan 2001). IARC's comment on the Ponomarkoff study was that: " The Working Group noted the high treatment-related toxicity and mortality early in the study." IARC 2002, AR 7521-7643, at 477, AR 7561.

substituted historical control animals from a different laboratory, the study found a link between styrene exposure and cancer; "[t]he incidence of lung tumors in control male mice in the NCI (1979a) study was not unusually low and support the finding that lung tumors as a result of styrene exposure are statistically significant." Final Background Document at p. 197, AR 001426. The reanalysis violated NTP's procedure in two ways. First, NTP's conclusions do not appear in the peer-reviewed literature as required. Second, the substitution of a different set of control animals from a different laboratory conflicts with NTP's best practices as described by NTP authors in peer-reviewed publications. *See* Haseman, et al. Use of historical control data in carcinogenicity studies in rodents, 12 Toxicol Pathol 126-135 (1984); Keenan, et al., Best Practices for Use of Historical Control Data of Proliferative Rodent Lesions, 37 Toxicol Pathol 679-693 (2009). Without the NCI study, NTP does not satisfy the two study requirement for listing styrene as a carcinogen in the 12th RoC.

Furthermore, NTP relied on a study conducted by Dr. Cruzan and colleagues ("Cruzan 2001"), AR 4931 – AR 4942) as the other animal study. Here again, NTP rejected a key finding in order to support its conclusion. Dr. Cruzan concluded that his finding of lung tumors in mice was not applicable to humans. Id. at AR 4940. That essential finding was rejected by NTP.

Additionally, NTP finalized the Draft Background Document nearly a month before the end of the public comment period on the Expert Panel's recommendations regarding the appropriate cancer classification of styrene and the scientific justification for that listing status. *See* Final Background Document; *compare* 73 Fed. Reg. 52059 at AR 1694 (stating that comments regarding the RoC Expert Panel's recommendation on the listing status for Styrene in the 12th ROC must be received by October 23, 2008). The Expert Panel's recommendations

resulted in NTP dramatically reshaping the Background Document to conform to those recommendations. Public comments on the Expert Panel's report could—and should—have directly impacted the form of the Final Background Report. But HHS precluded that possibility when it shortcut the process and finalized the Background Report almost a month before the end of the public comment period on the Expert Panel report.[14]

This failure by NTP to follow its own procedure fatally compromised the integrity of the process and the legitimacy of its conclusions and rendered the styrene listing invalid as taken "without observance of procedure required by law." 5 U.S.C. § 706(2)(D).

B. The Listing of Styrene Was Arbitrary and Capricious Because the Secretary's Decision Was Based On Misleading and Incomplete Information

The Secretary of HHS is mandated by Congress to issue the RoC. 42 U.S.C. § 241(b)(4). Thus, by law, and in fact, Secretary Sebelius decided to include styrene in the 12th RoC. Although the Secretary did not document the basis for her decision, the Record demonstrates that the decision was based upon three "briefings" she received from the Director of the National Toxicology Program, Dr. Linda Birnbaum, and a letter from the head of ATSDR, Dr. Christopher Portier. The first Birnbaum briefing was apparently oral and is undocumented. The

[14] In response to SIRC's IQA request for correction, NTP argued that it had not sought comment on the Expert Panel's peer review comments on the Draft Background Document (Part A of its report), but only on Part B (the Expert Panel's proposed cancer classification and scientific justification therefore). It may be, as a matter of procedural formality, that "conclusions reached by the expert panel and reported in the Expert Panel Report, Part B, are independent of the Background Document." NTP Response to Request for Correction, AR 2412-2436, at p. 6, AR 2417. In reality, however, that statement is demonstrably false. The conclusions set out in the Expert Panel's scientific justification for listing are woven throughout the Expert Panel's peer review comments, which are self-evidently constructed to maximize apparent support for those conclusions. This can be readily seen by comparing the two at any corresponding points. *Compare*, *e.g.*, the discussion of Delzell *et al.* in the Styrene Expert Panel Report, Part A, at pp. 7-8, 12, AR 1116-17, 1121 with the discussion in Part B, at p. 2, AR 1697.

second and third Birnbaum "briefings" were memoranda on December 2, 2010 and April 7, 2011. Dec. 2 memo., AR 2301h-l; April 7 memo., AR 2301b-g. Dr. Birnbaum's briefings were not objective; rather, they were designed to encourage the Secretary to include styrene in the RoC. To that end, Dr. Birnbaum's briefings were slanted and contained inaccurate and incomplete information. Similarly, Dr. Portier misled the Secretary about the meaning and effect of the ATSDR's work on styrene. There is no doubt that the Secretary relied on the information provided to her by Dr. Birnbaum and Dr. Portier.[15] The Secretary's reliance on such skewed synopses "breach[ed her] . . . statutory duty to accord 'consideration' to relevant comments submitted for the record by interested parties." *National Small Shipments Traffic Conference, Inc. v. Interstate Commerce Commission*, 725 F.2d 1142, 1450-51 (D.C.Cir. 1984) (quoting 5 U.S.C. 533 (c)). Since the Secretary's decision was based on that inaccurate and incomplete information, the decision was arbitrary and capricious and must be reversed. *See id.*

1. Mischaracterization and Omissions Related to California's Office of Environmental Health Hazard Assessment (OEHHA) Report

In both of her written communications, Dr. Birnbaum cited the California Drinking Water Standard for Styrene as support for the inclusion of styrene in the RoC. Dec. 2 memo. at 3, 2301j; Apr. 7 memo. at 4, 2301e. Dr. Birnbaum failed to inform the Secretary that California's decision was based on a single mouse study, a basis that would not support an RoC listing and that, furthermore, California did not find support in the key studies relied upon by NTP.

[15] Secretary Sebelius' biography indicates that she does not have formal training nor work experience in scientific matters. The Secretary holds a Bachelor of Arts degree from Trinity Washington University and a Masters of Public Administration from the University of Kansas. http://www.hhs.gov/secretary/about/biography/index.html. She served in the Kansas House of Representatives, as the Kansas Insurance Commissioner and as Governor of Kansas before being appointed as Secretary. *Id.*

Additionally, Dr. Birnbaum failed to inform the Secretary of California's reliance on the Draft Background Document on Styrene which makes HHS' reliance on California's OEHHA Report circular.

In December, Dr. Birnbaum told the Secretary that California's draft report "concludes that there is suggestive evidence for the carcinogenicity of styrene in humans." Dec.2 memo. at 6, AR 002301j. Dr. Birnbaum failed to tell the Secretary that suggestive evidence is insufficient to support the listing of styrene in the RoC. *See supra,* Section III.B. In April, Dr. Birnbaum found the final report to be much more supportive. She told the Secretary:

> In California, the OEHHA has now finalized its document, Public Health Goal for Styrene in Drinking Water (Dec. 2010). Among other purposes, this document describes the adverse health effects of styrene in humans. California's findings with regard to styrene's carcinogenicity are consistent with the proposed RoC listing: "Overall OEHHA concludes that there is sufficient evidence that styrene causes cancer in animals and limited evidence in humans. For these reasons, it is prudent to assume carcinogenicity for the purposes of risk assessment."

Apr. 7 memo. at 4, AR 2301e.

Dr. Birnbaum's failed to tell the Secretary that California's action was based on a single rodent study. According to OEHHA, "[t[he PHG is based on a chronic inhalation study by Cruzan *et al*. (2001) in mice, in which there were significant dose-related increases in bronchioloalveolar adenomas and combined adenomas and carcinomas." OEHHA Report, Summary, at 1, AR 14695. A single animal study demonstrating carcinogenicity is insufficient to support a listing in the RoC; two such studies are required. RoC p. 4, AR 2468.

Second, Dr. Birnbaum failed to inform the Secretary that the quoted OEHHA language is ultimately just a statement of agreement with NTP and an incomplete thought as well. OEHHA's complete statement was:

> An NTP expert panel (NTP, 2008b) recently recommended that styrene should be listed in the NTP Report on Carcinogens as "reasonably anticipated to be a human carcinogen based on limited evidence of carcinogenicity in humans and sufficient evidence in animals." OEHHA concurs that there is sufficient evidence that styrene causes cancer in animals. While several epidemiological studies of styrene and cancer in workers exposed in reinforced plastics and other industries have been published, the data do not show proof of carcinogenicity in humans.
>
> * * *
>
> Overall OEHHA concludes that there is sufficient evidence that styrene causes cancer in animals and limited evidence in humans. For these reasons, it is prudent to assume carcinogenicity for the purposes of risk assessment.

OEHHA, Summary, at 2, AR 14696. Thus, the situation is circular. Dr. Birnbaum refers the Secretary to OEHHA's report as support for the NTP conclusions when, in fact, OEHHA relied on NTP's conclusions to support its own. Also undisclosed was the fact that Lauren Zeise, Chief, Reproductive and Cancer Hazard Assessment of OEHHA, was a member of the NTP Expert Panel, which demonstrates interdependence and neither independent agency action nor unbiased peer review.

Finally, Dr. Birnbaum did not inform the Secretary of OEHHA's ultimate conclusion reflected in its discussion of human carcinogenicity:

> OEHHA concurs with the IARC (2002) finding of "limited" evidence of carcinogenicity for styrene in humans. That is, there is suggestive evidence that occupational exposures to styrene have increased the risk of cancer, but data are limited for making a definitive evaluation. In summary, the epidemiological data along

> with the supporting data described in other sections of this document justify concern about carcinogenicity of styrene.

OEHHA at 190, AR 14884. The IARC classification is insufficient to support an NTP listing.

The Director failed to provide the Secretary with a vital piece of analysis in the OEHHA study, the discussion of Delzell 2006 that formed the cornerstone of the NTP finding of "limited evidence" in humans. OEHHA did not adopt NTP's new analysis of that study. Instead, OEHHA stated that, "Delzell *et al.* (2006) . . . *provided no evidence to support any carcinogenic effects of styrene*." OEHHA at 183, AR 14877 (emphasis added).

Nor did the Director's briefing memoranda for the Secretary report that Dr. Delzell had filed comments expressing her disagreement with the reinterpretation of the study for which Dr. Delzell was the primary author. . *See* Letter to Dr. Ruth M. Lunn (October 23, 2008), AR 1705-26 (Dr. Delzell's comments were attached to the letter to Dr. Lunn, *see* AR 1722-26).

Mischaracterization of the EU RAR and the EU SCHER

Dr. Birnbaum also provided the Secretary with misleading information about the EU RAR on styrene. Dr. Birnbaum told the Secretary that:

> The EU SCHER peer reviewed the November 2007 draft EU RAR in May 2008. [EU] SCHER disagreed with the EU RAR conclusion that styrene was of no concern for human carcinogenicity and agreed with the conclusion of WHO's IARC that the findings of the genotoxic and carcinogenic metabolite (styrene-7,8-oxide) and genetic damage in the blood of styrene-exposed workers indicates a possible carcinogenic risk to humans.

December 2nd memo, at p. 5, AR 2301L. EU SCHER makes no statement of agreement that styrene is a "possible carcinogenic risk to humans" as stated. In fact, the report stated:

> [A]lthough the RAR clearly describes the metabolic formation of the genotoxic and carcinogenic styrene oxide, its possible contribution to the carcinogenic risk of styrene exposure in other

> organs than lung is also considered negligible. This is insufficiently justified. Therefore [EU] SCHER agrees with the conclusion of the IARC (2002) that, based on the observations in human workers regarding blood styrene 7,8-oxide, DNA adducts and chromosomal damage, it cannot be excluded that this and other mechanisms are important for other organs.

EU SCHER Report at 6, AR 14274.

The Director further mischaracterized the findings of the EU RAR making them more supportive of the NTP listing than they were. Although the Director acknowledged that the EU RAR "determined that evidence of mouse lung tumors was not relevant for humans," she did not tell the Secretary about the strength of that finding. *See* Dec. 2 memo. at 5, AR 2301L; EU RAR at 276, AR 014114. The EU SCHER found:

> No causal association between occupational styrene exposure and lung cancer have been demonstrated in a variety of epidemiological studies. Styrene was not carcinogenic in rats (five oral studies, two inhalation studies), but induced lung tumours in mice in one inhalation study and in two out of four gavage studies. [EU] SCHER agrees with the proposed non-genotoxic mechanism of tumour induction in mice and the notion that this mechanism, . . ., is not operational in human lungs to any significant extent. This agrees with the conclusion of IARC (2002).

EU SCHER Report at 6, AR 014274. The Director did not tell the Secretary that this conclusion contradicts NTP's conclusion that "[a]lthough styrene differs quantitatively among species, no qualitative differences between humans and experimental animals have been demonstrated that contradict the relevance of cancer studies in rodents for evaluation of human hazard." RoC at 386, AR 2850. Nor did Dr. Birnbaum tell the Secretary that this assertion was further called into question by Dr. Cruzan's post Expert Panel work which also called into question the applicability to humans of the lung tumor finding in mice. *See* Cruzan 2009, AR 2204-2218.

Additionally, the Director sought to discount and disparage the contrary findings of the EU RAR. After telling the Secretary that "evaluation of occupational epidemiology studies is critical to the assessment," the Director informed the Secretary that "[u]nlike the EU evaluation, the process for preparation of the 12th Report involved extensive scientific expertise in human epidemiology studies." Dec. 2 memo. at 4, AR 2301k. The Director did not reveal how many epidemiologists participated in the NTP process but the record only reveals three – the members of the Expert Panel subcommittee. Neither the NTP Director nor the Director of the Report on Carcinogens Group at NTP have degrees in epidemiology.[16] Moreover, epidemiology studies are only relevant to the consideration of whether there is a basis for listing as a result of cancer in humans. The epidemiology studies were not relied on to support either the animal studies or the mechanistic analysis since the cancers found in each were not found in the human studies.

Dr. Birnbaum told the Secretary that "NTP was careful to manage interactions with affected parties, such as industry, to prevent a potential or real conflict of interest." AR 2301k. Dr. Birnbaum's insinuation – without evidence or explanation – of impropriety in the EU evaluation is wholly improper and since without factual support, misleading. It is also surprising since one of the primary animal studies cited by NTP was funded, in part, by the styrene industry and the industry fully participated in providing public comment in the NTP process. *See e.g.*, at

[16] Dr. Birnbaum is a microbiologist. http://www.niehs.nih.gov/about/od/director/index.cfm. Dr. Lunn, the Director, Report on Carcinogens Group, has degrees in microbiology, immunology and environmental sciences. http://www.niehs.nih.gov/research/atniehs/dntp/roc/staff/lunn/index.cfm. Dr. Janke is a veterinarian with a degree in biochemistry. http://www.stjude.org/stjude/v/index.jsp?vgnextoid=e19b0b9d9b545210VgnVCM1000001e0215acRCRD&vgnextchannel=01a813c016118010VgnVCM1000000e2015acRCRD.

197, G. Cruzan, Chronic Toxicity/Oncogenicity Study of Styrene in CD-1 Mice by Inhalation Exposure for 104 Weeks, *J. Appl. Toxicol.* 21, 185-198 (2001), AR 4917-30 at 197, AR 4929.

2. Mischaracterization of the ATSDR Findings

HHS' ATSDR, in its peer-reviewed toxicological profile of styrene concluded that "[t]aken together, the animal and human data indicate that styrene may possibly be a weak human carcinogen." *ATSDR* Tox. Profile at 133; AR 3307. The Director mischaracterized the nature and importance of that ATSDR finding.

The first assertion made by Dr. Birnbaum is that ATSDR's Toxicological Profile serves a different purpose than a listing in RoC. "The tox profiles are summaries of ATSDR's evaluations concerning whether and at what levels of exposure adverse health effects occur and levels at which no adverse effects occur." Apr. 7 memo. at 4-5, AR 2301e-f. She further noted that the Tox Profiles "include information on multiple health outcomes" and that the "profile" is "not meant to be an exhaustive document." *Id.* at 5, AR 2301f. She then states that "[w]ith regard to potential carcinogenicity, in particular, ATSDR officials have indicated that a tox profile is not intended to provide a comprehensive review or assessment of existing cancer research for a particular substance." Apr. 7 memo. at 4, AR 2301e. According to Dr. Birnbaum, this contrasts with NTP which only examines carcinogenicity, using "experts specific to this topic to inform its reviews, and classifies carcinogenicity hazards using established criteria." *Id.*

As usual, Dr. Birnbaum failed to fully inform the Secretary. First, Dr. Birnbaum failed to acknowledge that the RoC listing also is not an exhaustive document. The only "exhaustive" document published by NTP is the Final Background Document which, in relevant part, summarizes the peer-reviewed published literature. *See* NTP Report on Carcinogens Review

Process at 1, AR 44. "The Background Documents do not contain any opinion regarding the listing status for the candidate substance." *Id.* Actually, the ATSDR Tox Profile's discussion of carcinogenicity is not significantly shorter than that of the NTP Substance Profile. The Tox Profile discussion includes five pages on cancer as a result of inhalation; one page on cancer by ingestion and four pages on genotoxicity and 14 pages on toxicokinetics and seven pages on mechanism of action compared to the NTP Substance Profile which is four double columned pages in its entirety.

Furthermore, Dr. Birnbaum failed to inform the Secretary that the ATSDR was peer-reviewed by "experts [who] collectively have knowledge of styrene's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans." ATSDR Tox. Profile at xi, AR 3165.

The Director at ATSDR did not perform a thorough review and did not say that no such review occurred, but implied it. In fact, Dr. Birnbaum mischaracterized ATSDR's work. According to ATSDR:

> The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

ATSDR Tox. Profile at Foreword, AR 3159.

ATSDR also stated that "[t]he carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data." *Id*. at Appendix B, B-1, AR 3421. As expected, ATSDR's conclusion is

well-grounded in the literature and the ATSDR report discusses most of the studies cited by NTP and others that NTP did not include. Thus, ATSDR's specific conclusion cites to 33 studies published between 1978 and 2005 including studies by Delzell, Kogevinas, Cruzan and NCI. ATSDR also discusses carcinogenicity of styrene based on inhalation and oral exposure. The clear purpose of those discussions is to inform the public health community about the carcinogenicity of styrene. To characterize the ATSDR's work as not a comprehensive assessment of existing research is to denigrate the report without foundation.

The Director further failed to note that the OEHHA report she promoted to the Secretary was a "Public Health Guide" designed to develop human exposure levels and potentially suffered from all the faults she assigned to the Tox Profile. The Director further informed the Secretary that "[t]he conclusion that styrene 'may be'(as opposed to 'may possibly be') carcinogenic arguably represents very little difference from the RoC proposed listing, particularly given the different purposes of the two documents, not to mention the different processes used in their development." Apr. 7 memo. at 5, AR 2301f. This assertion was supported by a letter from ATSDR's Director to the Secretary where, he too, made such a claim. AR 2301a. The NTP Director cited language in the ATSDR report that "acknowledges that 'DHHS' has not evaluated the carcinogenic potential of styrene." Apr. 7 memo. at 5, AR 2301f. She added her "understanding that ATSDR defers to NTP as the appropriate agency to speak for the Department with respect to a substance's carcinogenicity. Thus, the above-quoted text is not intended to represent the Department's definitive position on the matter." *Id.* Finally, the Director stated that "if the proposed styrene listing is approved and the 12th RoC is published, we

understand that ATSDR intends to prepare an addendum to the Styrene Tox Profile acknowledging the RoC listing." *Id.*

The language quoted by Dr. Birnbaum about HHS is merely meant to convey that NTP had not yet issued a final report on styrene. The ATSDR's Guidance for the Preparation of Toxicological Profiles instructs that if the substances had not been classified by other agencies, including "DHHS (NTP)," the report should so state. Guidance for the Preparation of Toxicological Profiles, at 20, http://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf. The statement is not meant to imply that ATSDR defers to NTP as "the appropriate agency to speak for the Department with respect to a substance's carcinogenicity" as Dr. Birnbaum stated. Even so, that fact would not denigrate the validity of ATSDR's conclusion nor the fact that it represents a statement by the DHHS that contradicts the RoC. In fact, ATSDR's practice of including any NTP's finding does not constitute an endorsement of that finding. ATSDR's practice is to report any conclusion by IARC, EPA and NTP. *Id.* at 198, 201.

Not only did the Director misrepresent ATSDR's findings, she did not tell the Secretary that ATSDR had several fundamental disagreements with NTP. First, in its discussion of cancer by inhalation, ATSDR stated that "[a]lthough there are several epidemiologic studies which suggest there may be an association between styrene exposure and an increased risk of leukemia and lymphoma, the evidence is generally inconclusive due to multiple chemical exposures and inadequate documentation of the levels and durations of exposure to styrene." ATSDR Tox. Profile at 72, AR 3246. Second, ATSDR opined that the glass-reinforced plastics manufacturing facilities should be the focus of analysis, not the synthetic rubber industry relied upon by NTP,

since workers there "are likely to be exposed to higher levels of styrene and have lower potential for exposure to other carcinogenic agents." *Id.* ADSTR's reliance was consistent with OEHHA. OEHHA Report at 187, AR 14881 ("[t]he results from the reinforced plastics worker studies are the most informative . . ."). Nor did the Director inform the Secretary that ATSDR had questions about the applicability of the animal testing to humans. ATSDR observed that "[t]he relevance of these tumors to humans has been questioned due to species differences in the metabolism of styrene in the lungs," *id*. at 77, AR 3251, in contrast to NTP which claimed there was no reason not to assume that animal data was predictive. *See* e.g., Dec. 2 memo. at 5, AR 2301l.

3. Mischaracterization of the Boffetta Paper

SIRC had provided NTP with an analysis by Boffetta et al. titled: *Epidemiologic Studies of Styrene and Cancer: A Review of the Literature*." AR 3979 – 3991. The Director gave the Secretary a copy of NTP's "analysis" of that study without also including the original study. Letter from Jack Snyder to Dr. Sam Wilson (Dec. 16, 2008), AR 15143 – 15188. In so doing, the Director informed the Secretary that Dr. Boffetta was the co-author of a subsequent paper that "identified findings supportive of NTP's proposed listing." Apr. 7 memo. at 6, AR 2301g. According to the Director, the paper "concludes that '[r]isk of follicular lymphoma significantly increased with three independent metrics of exposure . . . to styrene ($p=1x10^{-5}$)' and that '[s]ignificant upward trends were observed for [B-cell non-Hodgkin's lymphoma (B-NHL)] with styrene exposure . . .'". Apr. 7 memo. at 6, AR 2301g. Dr. Birnbaum cited only one aspect of the data discovered. She ignored, and failed to inform the Secretary, that the authors made no conclusion about a link between styrene and cancer.

The paper to which the Director referred was, P. Cocco et al., *Occupational Exposure to Solvents and Risk of Lymphoma Subtypes: Results from the Epilymph Case-Control Study*, 67 Occupational & Envtl. Med. 341 (2010), AR 14980-87. The paper concludes that its analysis "confirms a role of occupational exposure to solvents in the aetiology of B-NHL, and particularly CLL. It is suggested that benzene is most likely implicated, but we cannot exclude the possibility of a role for other solvents in relation to other lymphoma subtypes, such as follicular lymphoma. We did not show any association with risk of T-cell lymphoma and Hodgkin's lymphoma." AR 14981.

Furthermore, there is no evidence that Dr. Birnbaum had surveyed all the literature published since NTP completed the Draft Background Document and certainly she did not cite recent, negative studies to the Secretary that had been provided to her by SIRC.

In conclusion, the Secretary's decision was based on information provided to her that was incomplete, inaccurate and misleading. As a result her decision was arbitrary and capricious.

C. NTP Violated the IQA

NTP failed in its duties under the IQA in several ways, each of which is further evidence that HHS' action was arbitrary and capricious and not in accordance with the law under 5 U.S.C. § 706(2)(A). Science that is not the best available, or that is generated by practices that are chosen to produce a given effect, is not objective. As just discussed, NTP approached styrene in a result-oriented manner, intent on including it in the RoC. NTP actively chose not to consider all relevant evidence, but instead highlighted positive findings and omitted significant negative findings and conclusions. The 12th RoC's statements about the carcinogenicity of styrene in

humans or rodents are not accurate or reliable, given the improper ways in which they were derived. Nor are they presented in an unbiased way.

Additionally, the expert panel's undocumented re-analysis of Delzell 2006 violates the IQA's requirement of transparency. Nothing showing the recombined groups appears in either the Background Document or the expert panel materials, and the analysis was not produced in response to a request submitted by SIRC under FOIA. HHS NIH NIEHS FOI Case No. 35461.

Finally, the Background Document violates the "utility" criterion of the IQA because it does not enable a reader to make an informed judgment about the carcinogenicity of styrene. Rather, the reader and the public are left with a misleading conclusion that will lead to misinformed decisions. Already the public is being warned not to use any products made from styrene.

Plaintiffs do not seek to enforce the IQA. Rather, Plaintiffs assert that NTP's failure to fulfill its IQA obligations, obligations that have been recognized by NIH (NTP's parent agency) and embraced by HHS as embodied in the RoC, further demonstrates that NTP was acting arbitrarily and capriciously when it listed styrene in the RoC. Had NTP fulfilled its IQA obligations, this listing likely would not have happened. Thus, NTP's failure to comply with the IQA is further evidence that the RoC is arbitrary, capricious or otherwise not in accordance with the law.

D. NTP's Criteria for a Finding of "Reasonably Anticipated" Is Contrary to the Congressional Mandate That a Substance Not Be Used in the Report on Carcinogens Merely Because It Is Suspected To Be a Carcinogen

The decisional criteria applied by the Agency in listing styrene were contrary to the Congressional mandate that a substance be "reasonably anticipated to cause cancer in humans"

and not merely "suspected" of doing so. *See* 42 U.S.C. § 241(b)(4)(A). NTP allowed for the listing of styrene based on "limited evidence" in humans that could have been the result of chance which constitutes "suspicion" not "reasonable anticipation."

The legislative history clearly demonstrates that Congress intended the proof required to list a substance as "reasonably anticipated to cause cancer in humans" be greater than mere "suspicion." Congress required that materials "reasonably anticipated" to be carcinogens be reported, rather than those "suspected" of being carcinogens.

On December 1, 1977, Rep. Andrew Maguire introduced House bill 10190, also known as the "Cancer Prevention Act of 1978." H.R. 10190 contained, in relevant part, a provision requiring the NCI Director to publish an annual report containing "a list of all known or suspected carcinogens to which a significant number of persons residing in the United States are exposed . . . ."[17]

During March 1-3, 1978, the Health and Environment Subcommittee of the House Committee on Interstate and Foreign Commerce held a hearing on H.R. 10190 and two related bills. BRRTA Amendments Hearing. It was at this hearing that the concept of a comprehensive Annual Report was first presented publicly. On April 18, 1978, having considered the three related bills, the Subcommittee reported out a clean House bill, 12347.

H.R. 12347 proposed to amend The National Cancer Act of 1971 by requiring that the NCI Director publish an Annual Report on Carcinogens. H.R. REP. NO. 95-1192, at 53 (1978).

[17] *Biomedical Research and Research Training Amendments ("BRRTA Amendments") of 1978: Hearing on H.R. 10908, H.R. 10062, and H.R. 10190, Before the Subcomm. on Health and the Environment of the Comm. on Interstate and Foreign Commerce H.R.*, 95th Cong. 28 (1978), ("BRRTA Amendments Hearing") *available at* http://www.eric.ed.gov/ERICWebPortal/detail?accno=ED162544.

The Annual Report was to include, in relevant part, "a list of all 'known or suspected carcinogens' to which a significant number of persons residing in the United States are exposed . . . ."[18] *Id.* Senate Bill S. 2450 was adopted in lieu of H.R. 12347, and enacted as Public Law 95-622. Senate Rep. No. 95-838 (1978), reprinted in 1978 U.S.C.C.A.N. 9042 Unlike the House bill, the Senate bill added the Annual Report requirement to the Public Health Services Act, and assigned responsibility for the Annual Report to the Department of Health, Education, and Welfare. *See* BRRTA Amendments Hearing.

In relevant part, the Senate bill changed the House's reference to "suspected carcinogens" to "substances . . . reasonably anticipated to be carcinogens" to make it absolutely clear in the statue that there must be reasonable ground for designating a substance as a putative carcinogen.[19]

In 1991, NTP acknowledged that its classifications for the RoC were related to those adopted by IARC in 1982. Thus, the Sixth RoC stated:

> For the purpose of this report, the two categories anticipated to be carcinogens relate to the IARC criteria (as described in Supplement 4, IARC, 1982) . . . as follows:
>
> 1) Known to be carcinogens: . . .

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[18] *Biomedical Research and Research Training Amendments ("BRRTA Amendments") of 1978: Hearing on H.R. 10908, H.R. 10062, and H.R. 10190, Before the Subcomm. On Health and the Environment of the Comm. On Interstate and Foreign Commerce H.R.,* 95th Cong. 28 (1978), ("BRRTA Amendments Hearing") *available at* *http://www.eric.ed.gov/ERICWebPortal/detail?accno=ED162544.*

[19] 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).

> 2) Reasonably anticipated to be carcinogens:
>
> A. There is "limited evidence of carcinogenicity" from studies in humans, "which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded," or
>
> B. There is "sufficient evidence of carcinogenicity" from studies in experimental animals "which indicates that there is an increased incidence of malignant tumors: (a) in multiple species or strains, or (b) in multiple experiments (preferably with different routs of administration or using different dose levels), or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset. Additional evidence may be provided by data concerning dose-response effects, as well as information on mutagenicity or chemical structure."

Sixth Report on Carcinogens at 5, *available at* http://play.google.com/books/reader?id=C45UDuShU9gC&printsec=frontcover&output=reader&hl=en.

These criteria were adopted verbatim from IARC 1982's description of its Group 2 category, "[t]he chemical, group of chemicals, industrial process or occupations exposure is probably carcinogenic to humans" with two significant exceptions. [IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, IARC Monographs Supplement 4 ("IARC 1982") at 14 (definition of Group 2) & 12 (definitions of category of evidence in animals)(copies of the relevant pages are attached hereto as Appendix A)]. First, IARC divided the group in two subparts depending on the strength of the evidence and NTP did not. . According to IARC:

> "[t]o reflect this range [of almost "sufficient" to "inadequate"] the category was divided into higher (Group A) and lower (Group B) degrees of evidence. Usually, category 2A was reserved for exposures for which there was at least limited evidence of carcinogenicity to humans. The data from studies in experimental

> animals played an important role in assigning studies to category 2, and particularly those in Group B; thus the combination of "sufficient evidence in animals and inadequate data in humans usually resulted in a classification of 2B."

Id. at 14 (emphasis omitted). As noted, according to ATSDR, Group 2B is not equivalent to NTP's "reasonably anticipated" category. Factual Background, ¶ 11.

Furthermore, NTP has never adopted definitions of other possible categories to guide it and its reviewers on the full range of options and the differing levels of evidence that may or may not merit a listing. In contrast, IARC had defined "inadequate" in humans as that "which indicates that one of three conditions prevailed: (a) there were few pertinent data; (b) the available studies, while showing evidence of association, did not exclude chance, bias or confounding; (c) studies were available which do not show evidence of carcinogenicity." IRAC 1982 at 11. IARC defined "limited evidence" in animals as meaning

> Data [that] suggest a carcinogenic effect but are limited because (a) the studies involve a single species, strain, or experiment; or (b) the experiments are restricted by inadequate dosage levels, inadequate duration or exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) the neoplasms produced often occur spontaneously and, in the past, have been difficult to classify as malignant by histological criteria alone (e.g. lung and liver tumours in mice).

Id. at 12. EPA similarly has provided guidance on what constitutes "Suggestive Evidence of Carcinogenic Potential" and what constitutes "Inadequate Information to Assess Carcinogenic Potential." *See* EPA 2005 Guidelines for Carcinogenic Risk Assessment, http://www.epa.gov/ttn/atw/cancer_guidelines_final_3-25-05.pdf.

Importantly, in 1987, IARC changed its criteria and made two distinctions relevant to NTP's actions. First, substances found to be probably carcinogenic to humans generally required evidence of carcinogenicity in both humans and animals. Second, IARC made clear that Group 2B substances were only "possibly carcinogenic to humans." Thus, IARC identified the following criteria:

> Group 2A: The agent is probably carcinogenic to humans.
>
> This category is used when there is *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. Exceptionally, an agent may be classified into this category solely on the basis of limited evidence of carcinogenicity in humans or of sufficient evidence of carcinogenicity in experimental animals strengthened by supporting evidence from other relevant data.
>
> Group 2B: The agent is possibly carcinogenic to humans. This category is generally used for agents for which there is limited evidence in humans in the absence of sufficient evidence in experimental animals. It may be used when there is inadequate evidence of carcinogenicity in humans or when human data are nonexistent but there is sufficient evidence of carcinogenicity in experimental animals. In some instances, an agent for which there is inadequate evidence or no data in humans but limited evidence of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, (1987), at Preamble, *available at* http://monographs.iarc.fr/ENG/Monographs/suppl7/index.php.

NTP acknowledged IARC's new criteria but NTP's listing criteria remained unchanged. According to NTP, "[t]he Annual Report's 'Reasonably Anticipated' category does not distinguish whether the degree of evidence supporting a given listing corresponds to the IARC categories of either 'Probable' or 'Possible' carcinogens. The text entries for listed substances,

however, make clear whether the degree of evidence supporting the listing corresponds either to the 'Probable' or to the 'Possible' IARC category." 7th Annual Report on Carcinogens at 5, *available at* http://legacy.library.ucsf.edu/tid/nap40d00/pdf;jsessionid=04FAD5A572E21C7A8C303FB2BCE5471D.tobacco03.

Although NTP made some changes to its listing criteria prior to the publication of the 8th Annual Report in 1998, NTP still left "limited evidence" in humans and "sufficient evidence" in animals as separate and independent bases for listing. The primary changes were (1) to provide for a third basis for inclusion of a substance as "reasonably anticipated" and (2) to make clear that the conclusions are based on scientific judgment based on relevant information.[20] NTP continued to provide for the listing of substances as "reasonably anticipated" based solely on human data or animal data.

The NTP criteria violate the Congressional mandate because an association cannot be "reasonable anticipated" if chance cannot be eliminated. A conclusion that could be by chance is a "suspicion." Further, as IARC recognized, and amended its criteria to reflect, limited data in humans generally requires additional evidence such as animal data. U.S. EPA recently made the same observation in its 2005 Guidelines for Carcinogenic Risk Assessment, http://www.epa.gov/ttn/atw/cancer_guidelines_final_3-25-05.pdf. Without the additional data, the human evidence demonstrates a "possible" carcinogen and a "possible" carcinogen is only "suspect" not "reasonably anticipated." Finally, NTP did not fully define the choices involved in the listing process. NTP provided no criteria defining when the evidence was not sufficient as

[20] NTP also reworded the criteria for a finding of sufficient evidence in animal studies but did notmeaningfully change the criteria.

IARC and EPA have done. This failure means that there was no clear demarcation between what NTP believed to be acceptable for listing and what was not. NTP's failure to establish the correct criteria doomed its process.

The correct definition is important. For example, a review of the minutes of the Board of Scientific Counselors demonstrates that the counselors recognized that the NTP criteria were independent and different counselors found support for a listing based on different criteria. Summary Minutes February 24, 2009, NTB Board of Scientific Counselors, AR 1868-1876. That is, some supported listing based only on the purported human finding while other found support only on the purported animal finding. In fact, one found support in the mechanistic criteria which was not ever advanced by NTP. *Id*. at 1872-74. We do not know how the voting would have been affected had proper criteria been provided. In fact, one counselor even "questioned the definition of 'reasonably anticipated to be a human carcinogen' and found it to be self-contradictory, ambiguous, and difficult to implement in a transparent and objective way." *Id*. at 1871.

No court has reviewed the listing criteria on the basis raised here. Only one court has reviewed any aspect of the criteria. In *Synthetic Organic Chem. Mfrs. v. Secretary*, 720 F. Supp. 1244 (W.D. La. 1989) the District Court denied a preliminary injunction motion against the Fifth Annual Report on Carcinogens. The Court found that SOCMA was not likely to prevail on the merits of its claim that the Secretary was required to conduct a complete hazard analysis prior to listing a substance and that the Secretary improperly refused to use pharmacokinetic and mechanisms evidence in addition to the animal data in that case. *Id.* at 1256. SOCMA did not raise, and the court did not consider, whether the listing criteria for "reasonably anticipated"

improperly allowed for the listing of a suspect substance in violation of the clear statutory listing scheme.

In *Tozzi v. DHHS*, 271 F.3d 301 (D.C. Cir. 2001), our Court of Appeals addressed a limited challenge to the listing requirements as revised in 1996, after the SOCMA case. However, the *Tozzi* court addressed only the question of "whether the final, unindented paragraph [of the listing criteria] modifies both categories (as the Secretary interprets it) or only the 'reasonably anticipated' category (as appellants claim)." *Id.* at 306. *Tozzi* arose in the context of NTP's elevation of a substance from a "reasonably anticipated" to a "known" carcinogen to match a change that had been made by IARC. *Id*. Plaintiffs challenged the use of mechanistic rather than epidemiological evidence to support NTP's action based on their reading of the listing criteria to apply such data only in determining if a substance was "reasonably anticipated." *Id*. at 311. The Court of Appeal found that the challenge was to the Secretary's interpretation of an HHS regulation, to which deference was owed, rather than whether the regulation was consistent with the statutory mandate. The *Tozzi* decision dealt only with whether mechanistic evidence was relevant to the determination of known carcinogen and not whether HHS could rely on disparate criteria in finding "reasonably anticipated."

The statutory language "reasonably anticipated" does not include suspect or possible carcinogens. Even if there were doubt about the plain language of the statute, the short and pointed legislative history discussion of "reasonably anticipated" strongly supports the plain meaning interpretation. To the extent that HHS, through NTP, created classification definitions that encompass suspect or possible carcinogens, that action is arbitrary, capricious and *ultra vires*.

V. CONCLUSION

For the foregoing reasons, Plaintiffs respectfully request that the Court grant them summary judgment.

Dated: May 18, 2012

Respectfully submitted,

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APPENDIX

WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS

ON THE

EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

Chemicals, Industrial Processes and
Industries Associated with Cancer
in Humans
IARC Monographs, Volumes 1 to 29

IARC MONOGRAPHS SUPPLEMENT 4

IARC, LYON, FRANCE

OCTOBER 1982

METHODS

The data on each chemical were reviewed in detail before the meeting by selected members of the group: the animal studies and short-term test results were evaluated by experimentalists and the human studies by an epidemiologist. During the meeting of the Working Group these assessments were debated and adopted, and overall evaluations of carcinogenicity for humans were made on the basis of the combined evidence from humans and experimental systems (Table 1). Brief descriptions of the data on which the assessments and evaluations were based are given in the section on Results, together with references to the *Monographs* volumes in which they were evaluated previously and, when applicable, to papers published subsequently.

Assessment of evidence for carcinogenicity from studies in humans

Evidence of carcinogenicity from human studies comes from three main sources:

1. Case reports of individual cancer patients who were exposed to the chemical or process.
2. Descriptive epidemiological studies in which the incidence of cancer in human populations was found to vary in space or time with exposure to the agents.
3. Analytical epidemiological (case-control and cohort) studies in which individual exposure to the chemical or group of chemicals was found to be associated with an increased risk of cancer.

Three criteria must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias which could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance.

In general, although a single study may be indicative of a cause-effect relationship, confidence in inferring a causal association is increased when several independent studies are concordant in showing the association, when the association is strong, when there is a dose-response relationship, or when a reduction in exposure is followed by a reduction in the incidence of cancer.

The degrees of evidence for carcinogenicity from studies in humans were categorized as:

i. *Sufficient evidence* of carcinogenicity, which indicates that there is a causal relationship between the agent and human cancer.
ii. *Limited evidence* of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded.
iii. *Inadequate evidence*, which indicates that one of three conditions prevailed: (a) there were few pertinent data; (b) the available studies, while showing evidence of association, did not exclude chance, bias or confounding; (c) studies were available which do not show evidence of carcinogenicity.

Assessment of evidence for carcinogenicity from studies in experimental animals

These assessments were classified into four groups:

i. *Sufficient evidence* of carcinogenicity, which indicates that there is an increased incidence of malignant tumours: (a) in multiple species or strains; or (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site or type of tumour, or age at onset. Additional evidence may be provided by data on dose-response effects, as well as information from short-term tests or on chemical structure.

ii. *Limited evidence* of carcinogenicity, which means that the data suggest a carcinogenic effect but are limited because: (a) the studies involve a single species, strain, or experiment; or (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) the neoplasms produced often occur spontaneously and, in the past, have been difficult to classify as malignant by histological criteria alone (e.g., lung and liver tumours in mice).

iii. *Inadequate evidence*, which indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect; or that within the limits of the tests used, the chemical is not carcinogenic. The number of negative studies is small, since, in general, studies that show no effect are less likely to be published than those suggesting carcinogenicity.

iv. *No data* indicates that data were not available to the Working Group.

The categories *sufficient evidence* and *limited evidence* refer only to the strength of the experimental evidence that these chemicals are carcinogenic and not to the extent of their carcinogenic activity nor to the mechanism involved. The classification of any chemical may change as new information becomes available.

Assessment of data from short-term tests

Because of the large number and wide variety of short-term tests that may be relevant for the prediction of potential carcinogens, the data relative to each compound have been summarized in the form of tables. These indicate both the type of test used and the biological complexity of the test system. *'DNA damage'* includes evidence for covalent binding to DNA, induction of DNA breakage or repair, induction of prophage in bacteria, and a positive response in tests of comparative survival in DNA repair-proficient and DNA repair-deficient bacteria. *'Mutagenicity'* refers to induction of mutations in cultured cells or in organisms (e.g., heritable alterations in phenotype, including forward or reverse point mutations, recombination, gene conversion, and specific-locus mutation). *'Chromosomal anomalies'* refers to the induction of chromosomal aberrations, including breaks, gaps, rearrangements and micronuclei, sister chromatid exchange and aneuploidy. *'Other'* refers to various additional endpoints, including cell transformation (T), i.e., morphological transformation and colony formation in agar; dominant lethal (DL) tests; morphological abnormalities in sperm (SA); and mitochondrial mutation (Mt). The biological systems include: *'Prokaryotes'*, i.e., bacteria, in the presence or absence of an exogenous metabolic activation system, and cellular systems; *'Fungi and green plants'*; *'Insects'*, usually *Drosophila melanogaster*; *'Mammalian cells* (in vitro)',either rodent or human somatic cells or cell lines in culture; *'Mammals* (in vivo)', studies in which the test compound was administered to intact experimental animals; and *'Humans* (in vivo)', studies of cells from groups of individuals drawn from a population exposed to the substance in question.

Group 2

The chemical, group of chemicals, industrial process or occupational exposure is probably carcinogenic to humans. This category includes exposures for which, at one extreme, the evidence of human carcinogenicity is almost *'sufficient'*, as well as exposures for which, at the other extreme, it is inadequate. To reflect this range, the category was divided into higher (*Group A*) and lower (*Group B*) degrees of evidence. Usually, category 2A was reserved for exposures for which there was at least *limited evidence* of carcinogenicity to humans. The data from studies in experimental animals played an important role in assigning studies to category 2, and particularly those in Group B; thus, the combination of *sufficient evidence* in animals and inadequate data in humans usually resulted in a classification of 2B.

In some cases, the Working Group considered that the known chemical properties of a compound and the results from short-term tests allowed its transfer from Group 3 to 2B or from Group 2B to 2A.

Group 3

The chemical, group of chemicals, industrial process or occupational exposure cannot be classified as to its carcinogenicity to humans.

RESULTS AND CONCLUSIONS

The assessments of degrees of evidence for carcinogenicity to humans and in experimental animals and for activity in short-term tests, as well as the summary evaluations of carcinogenic risk to humans are given in Table 1.

Group 1: The Working Group concluded that the following 7 industrial processes and occupational exposures and 23 chemicals and groups of chemicals are causally associated with cancer in humans*.

Industrial processes and occupational exposures:

Auramine manufacture
Boot and shoe manufacture and repair
(certain occupations)
Furniture manufacture
Isopropyl alcohol manufacture
(strong-acid process)
Nickel refining
Rubber industry (certain occupations)
Underground haematite mining
(with exposure to radon)

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* This list does not include known human carcinogens such as tobacco smoke, betel quid and alcoholic beverages, since they have not yet been covered in the *Monographs* programme.