

**BEFORE THE UNITED STATES  
DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**STYRENE INFORMATION AND  
RESEARCH CENTER, INC.**

910 17<sup>th</sup> Street, N.W., 500B  
Washington, DC 20006

*Petitioner*

*Filed with:*

**KATHLEEN SEBELIUS,**

in her official capacity as  
Secretary of the United States  
Department of Health and Human Services  
200 Independence Avenue, S.W.  
Washington, D.C. 20201

March 8, 2013

**PETITION TO ANNOTATE THE LISTING OF STYRENE  
IN THE *REPORT ON CARCINOGENS***

The Styrene Information and Research Center, Inc. (“SIRC” or “Petitioner”) petitions the Secretary of the U.S. Department of Health and Human Service (“DHHS”) to temporarily annotate the web page listing of styrene in the National Toxicology Program’s (“NTP”) Report on Carcinogens (“RoC”) pending completion of the ongoing review of the scientific basis for NTP’s listing by the National Research Council of the National Academy of Sciences (National Academy).

This temporary annotation could be accomplished through a short statement on the RoC web page listing of styrene to the effect that DHHS has commissioned a National Academy review of the RoC listing of styrene, which has begun. SIRC is not requesting that the Secretary suspend, withdraw or vacate the RoC listing under the present circumstances.

Adding a simple statement to the RoC webpage will help DHHS fulfill its duty to keep the public informed. Whatever duty the Secretary has to inform the public of hazards carries a companion duty not to mislead or misinform the public. From Petitioner’s perspective, the public is misinformed or misled when DHHS continues to proclaim, in an unqualified fashion, that styrene is “reasonably anticipated to be a human carcinogen” when DHHS has commissioned a National Academy of Sciences review of the science underlying the listing decision, and evolving science further puts that determination in question.

This Petition is further supported by several interrelated and cumulative factors, primarily:

- Appropriate respect and comity for the ongoing National Academy of Sciences' review of the RoC styrene listing;
- Avoiding premature administrative actions prompted by the RoC listing;
- Consideration of new scientific evidence, which will also be considered by the National Academy, that further questions the propriety of the NTP listing; and
- Mitigating unjustified economic impact.

## **I. Statutory Authority and Petitioner**

Pursuant to the Right to Petition Government Clause contained in the First Amendment of the United States Constitution<sup>1</sup> and the Administrative Procedure Act,<sup>2</sup> the undersigned Petitioner hereby submits this citizen's petition seeking the DHHS to annotate the listing of styrene as "reasonably anticipated to be a human carcinogen" in the RoC.<sup>3</sup>

SIRC is a non-profit trade association whose membership includes major producers and users of styrene monomer and downstream products. Collectively, SIRC's membership represents approximately 95% of the North American styrene monomer industry. SIRC serves as a liaison between industry, federal and state governments, and international agencies on health-issues involving styrene. SIRC's mission is to evaluate existing data on potential health effects of styrene, and to develop additional data where it is needed. During the past 25 years, SIRC has supported extensive scientific investigation of the potential human health effects of exposure to styrene. Prior to the June 2011 publication of NTP's listing of styrene in the RoC, SIRC-sponsored research was reported in over 55 peer-reviewed publications, with five additional peer-reviewed studies being published between June 2011 and the present.<sup>4</sup>

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<sup>1</sup> "Congress shall make no law...abridging...the right of the people...to petition Government for a redress of grievances." U.S. Const., amend. I. The right to petition for redress of grievances is among the most precious of the liberties safeguarded by the Bill of Rights. *United Mine Workers of America, Dist. 12 v. Illinois State Bar Association*, 389 U.S. 217, 222 (1967). It shares the "preferred place" accorded in our system of government to the First Amendment freedoms, and has "a sanctity and a sanctions not permitting dubious intrusions." *Thomas v. Collins*, 323 U.S. 516, 530 (1945). The Supreme Court has recognized that the right to petition is logically implicit in, and fundamental to, the very idea of a republican form of government. *United States v. Cruikshank*, 92 U.S. (2 Otto) 542, 552 (1875). Certainly, the right to petition extends to all departments of the Government, including administrative agencies. *California Motor Transport Company v. Trucking Unlimited*, 404 U.S. 508, 510 (1972).

<sup>2</sup> 5 U.S.C. § 553(e) (2005) (declaring that agencies must provide all interested parties the "right to petition" for the issuance, amendment, or repeal of a rule). The RoC is a rule or interpretative rule subject to the APA.

<sup>3</sup> U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, *Report on Carcinogens, Twelfth Edition* (2011).

<sup>4</sup> More information on SIRC can be found at <http://www.styrene.org>.

## II. Report on Carcinogens

The Public Health Service Act requires the DHHS Secretary to publish a list of all substances known or reasonably anticipated to be carcinogens.<sup>5</sup> Pursuant to this statutory directive, the NTP prepares periodic revisions of the Report on Carcinogens that are transmitted to the Secretary for approval.<sup>6</sup>

On May 19, 2004, NTP nominated the chemical styrene for listing in the 12<sup>th</sup> RoC.<sup>7</sup> After preparing a background document and subsequent proceedings, NTP drafted a final Styrene Substance Profile. On June 10, 2011, DHHS Secretary Kathleen Sebelius signed the final 12<sup>th</sup> RoC, which included the listing of styrene as “reasonably anticipated to be a human carcinogen.”

## III. Basis for Request

### A. Review by the National Academy

The Secretary should promptly annotate the listing of styrene in the RoC while the National Academy completes its scientific peer review of the styrene assessment presented in the 12<sup>th</sup> RoC. Under the Consolidated Appropriations Act of 2012, Pub. Law No. 112-74 (H.R.2055), enacted on December 23, 2011, DHHS contracted with the National Academy of Sciences for a scientific peer review of the RoC listing of styrene.<sup>8</sup> The National Academy of Sciences is fulfilling its obligations through the National Research Council. The members of the National Academy committee have been named, and the committee’s first meeting was held on February 19, 2013.<sup>9</sup> A subsequent meeting is scheduled for March 19-20, 2013.<sup>10</sup> A final report on the scientific validity of this NTP listing decision is expected in approximately 24 months.

The National Academy describes the project scope as follows:

A committee of the National Research Council will conduct a scientific peer review of the styrene assessment presented in the National Toxicology Program (NTP) 12th Report on Carcinogens (RoC). The committee will identify and evaluate relevant, publicly

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<sup>5</sup> 42 U.S.C. § 241(b)(4).

<sup>6</sup> See National Toxicology Program (NTP); Report on Carcinogens Review Process for the *12th Report on Carcinogens (RoC)*, 72 *Fed. Reg.* 18,999 (Apr. 16, 2007).

<sup>7</sup> National Toxicology Program; Call for Public Comments on 21 Substances, Mixtures and Exposure Circumstances Proposed for Listing in the *Report on Carcinogens, Twelfth Edition*, 69 *Fed. Reg.* 28,940 (May 19, 2004).

<sup>8</sup> See H.R. Rep. No. 112-331, at 1145 (December 15, 2011) (“In addition, the conference agreement includes \$1,000,000 for the Assistant Secretary for Health to contract with the National Academy of Sciences to conduct a scientific peer review of the 12<sup>th</sup> Report on Carcinogens determinations related to...styrene. Included in the review should be all relevant, peer-reviewed research related to...styrene.”).

<sup>9</sup> See <http://www8.nationalacademies.org/cp/committeevview.aspx?key=49511>; and <http://www8.nationalacademies.org/cp/meetingview.aspx?MeetingID=6480>.

<sup>10</sup> See <http://www8.nationalacademies.org/cp/meetingview.aspx?key=49511&MeetingId=6481>.

available, peer-reviewed literature, with particular emphasis on literature published as of June 10, 2011, the release date of the 12th RoC. The committee will document its decisions for inclusion or exclusion of literature from its evaluation and will identify the set of information deemed most critical to the evaluation. The committee will apply independently the NTP's established RoC listing criteria to the scientific evidence from studies in humans, experimental animals, and other studies relevant to mechanisms of carcinogenesis and make independent level-of-evidence determinations with respect to the human and animal studies. The committee will integrate the level-of-evidence conclusions, and considering all relevant information in accordance with the RoC listing criteria, make an independent listing recommendation for styrene and provide scientific justification for its recommendation.

Note: The NRC has an agreement with the Department of Health and Human Services to undertake a scientific peer review of the determinations concerning formaldehyde and styrene in the National Toxicology Program's 12th Report on Carcinogens (RoC). The expert committees appointed by the Academy for this assignment will follow standard Academy practices in carrying out their independent scientific reviews, which may include consideration of any and all issues that the committees and the Academy decide are necessary to carry out credible, independent, scientific evaluations of the two determinations, potentially including the criteria for the determinations. The statements of task for these two peer reviews were recently modified to make it clear that the NRC's assignment does not also include a separate review of the National Toxicology Program's listing criteria.

The project is sponsored by the Department of Health and Human Services.

The approximate start date for the project is 09/10/2012.

A final report will be issued at the end of the project in approximately 24 months.<sup>11</sup>

The National Academy project scope expressly directs the committee to identify and evaluate all relevant scientific literature, apply independently the NTP's established RoC listing criteria, make independent level-of-evidence determinations with respect to the human and animal studies, and develop a listing recommendation for styrene together with a scientific justification for the committee's decision. Given the fact that DHHS has commissioned this review of the NTP styrene listing and the Committee's broad mandate, the Report on Carcinogens listing of styrene should be annotated.

For DHHS to maintain an active listing with full knowledge of this important review that DHHS has commissioned is, at minimum, confusing and is potentially misleading to the public. Moreover, the continued listing may cause actions to be taken by the public and companies without knowledge of the on-going review of the HHS listing and may prove later to be based on scientific decisions criticized or deemed invalid by the National Academy. NTP has repeatedly stated its intent to honor the science, and DHHS can maintain this promise of scientific

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<sup>11</sup> Available at: <http://www8.nationalacademies.org/cp/projectview.aspx?key=49511>.

impartiality by annotating the listing. In the interim, NTP's listing decision and all the supporting documentation remain available for public review. Thus, granting the Petition will not deprive any citizen of the knowledge of the nature of the Secretary's June 2011 decision or the related work product. This surely serves to fulfill the public information and education legislative goals underlying the Report on Carcinogens while maintaining DHHS' scientific credibility, its obligations to keep the public informed, and demonstrating its due respect for the National Academy.

Accordingly, the listing of styrene as "reasonably anticipated to be a human carcinogen" in the RoC should be annotated pending completion of the National Academy styrene review.

### **B. New Scientific Information Undermines the Basis of NTP's Listing Decision**

DHHS is authorized to list substances in the RoC only when it concludes that they are known or reasonably anticipated to be a human carcinogen.<sup>12</sup> Under the statutory scheme of the Public Health Service Act, substances that have only suggestive evidence of carcinogenicity should not be listed at all. The NTP has not been directed to list "possible" or "suspected" carcinogens.

This Petition is not a vehicle for seeking a science review by DHHS; that is the task already before the National Academy. Rather, we are informing DHHS of new science that will be considered by the National Academy because this information brings into question the scientific basis for NTP's listing decision. That scientific uncertainty warrants the temporary annotation of the RoC listing of styrene.

NTP found that styrene is 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. NTP's finding of limited evidence in humans, based primarily on a finding of an alleged relationship between styrene and non-Hodgkin's lymphoma, is highly questionable in light of a recently

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<sup>12</sup> A substance is "reasonably anticipated to be a human carcinogen" when:

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 factors, could not adequately be excluded; or

There is 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

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.

published update of the U.S. reinforced plastics and composites (“RPC”) epidemiology cohort.<sup>13</sup> The updated and more robust human study shows that no increase in non-Hodgkin’s lymphoma was detected based on either cumulative or average exposure, despite more than 30 years of follow-up for at least 85% of the members. Although two of the three earlier RPC cohort studies (including this one) suggested an increased incidence of pancreatic and esophageal cancer, an increase in esophageal or pancreatic cancer was not detected in the follow-up study. When all three RPC studies are combined, there is no evidence of an increase in any type of cancer.<sup>14</sup>

Similarly, recent mode of action (MoA) data confirms that NTP erred. NTP’s Styrene Substance Profile relies on a styrene-7,8-oxide (“SO”) mode of action, with styrene-7,8-oxide being a primary metabolite of styrene. The RoC relies, in two ways, on the metabolism of styrene to styrene-7,8-oxide as justification for listing; both approaches are contradicted by the data. First, NTP claimed that, because styrene-7,8-oxide is listed in the 10<sup>th</sup> RoC, and because SO is a styrene metabolite, styrene should be listed. The new data, however, completely negate this association. SO-induced rodent forestomach tumors are likely related to a mode of action that is unrelated to styrene mouse lung tumors from styrene exposure.

NTP also asserted that, because styrene-7,8-oxide is a genotoxic carcinogen, styrene causes mouse lung tumors via a genotoxic mode of action. Again, the new data completely negate this speculative association

Newly completed studies further reinforce the conclusion that the MoA for styrene-induced lung tumors in mice is related to a cytotoxic MoA involving ring oxidized metabolites and not a genotoxic MoA involving styrene-7,8-oxide.<sup>15</sup> CYP2F2-generated metabolites, not styrene oxide, are a key event mediating the mode of action of styrene-induced mouse lung tumors. This is further supported by data elucidating the modification of the metabolism and toxicity of styrene and styrene oxide in CYP2F2 deficient mice.<sup>16</sup>

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<sup>13</sup> Collins, J.J. *et al.*, Cancer Mortality of Workers Exposed to Styrene in the US Reinforced Plastics and Composite Industry, *Epidemiology*, v. 24, issue 2, pp. 195-203 (March 2013); *available at*: [http://journals.lww.com/epidem/Abstract/2013/03000/Cancer\\_Mortality\\_of\\_Workers\\_Exposed\\_to\\_Styrene\\_in.5.aspx](http://journals.lww.com/epidem/Abstract/2013/03000/Cancer_Mortality_of_Workers_Exposed_to_Styrene_in.5.aspx).

<sup>14</sup> SIRC can provide a more robust explanation of the new science, although we anticipate that NTP is aware of this and other work based on NTP’s review of the scientific literature.

<sup>15</sup> Cruzan, G., Bus, J., Hotchkiss, J., Harkema, J., Banton, M., Sarang, S. Cruzan, G. *et al.*, CYP2F2-generated metabolites, not styrene oxide, are a key event mediating the mode of action of styrene-induced mouse lung tumors, *Regulatory Toxicology and Pharmacology*, v. 62, issue 1, pp. 214–220, Feb. 2012; *available at* <http://www.sciencedirect.com/science/article/pii/S0273230011002005>; Carlson, G.P., Modification of the metabolism and toxicity of styrene and styrene oxide in hepatic cytochrome P450 reductase deficient mice and CYP2F2 deficient mice, *Toxicology*, v. 294, issues 2-3, pp. 104-108, 11 Apr 2012; *available at* <http://www.sciencedirect.com/science/article/pii/S0300483X12000480>.

<sup>16</sup> *Id.*

Recent mode of action work also demonstrates that this MoA is unlikely to function in humans.<sup>17</sup> Therefore, the observed mouse lung tumors are not quantitatively, or even more likely qualitatively, relevant to humans. This new work removes the uncertainty that NTP noted in the final substance profile.

Applying the same criteria employed by NTP, a 2013 weight-of-evidence analysis published in the peer review literature concluded that the NTP determination was “based on ... erroneous findings of [1] limited evidence of carcinogenicity in humans, [2] sufficient evidence of carcinogenicity in experimental animals, and [3] supporting mechanistic data.”<sup>18</sup> In summary:

- NTP based its finding of sufficient animal evidence on two mouse studies, but compelling mode of action data demonstrate that the observed mouse lung tumors are not relevant to humans quantitatively and, likely, qualitatively.
- NTP characterized cancer studies in humans as showing limited evidence, but the epidemiology studies show no consistent increased incidence of, or mortality from, any type of cancer. Thus, the causal association of human cancer and styrene exposure is demonstrably erroneous, particularly in light of recently published epidemiology data.
- There is no concordance of tumor incidence and tumor types among animals and humans, showing that no particular cancer has been consistently observed among all available studies.
- A comprehensive weight-of-evidence assessment confirms that, as a whole, the evidence does not support the characterization of styrene as either a “known carcinogen” under Proposition 65 or reasonably anticipated to be a human carcinogen under the NTP listing criteria.

The National Academy’s charter makes it evident that the National Academy Styrene Review Committee will consider the new data, as well as the data that was before NTP when it was forming its recommendation. The current state of the science further supports a temporary annotation of the RoC listing of styrene because the National Academies’ independent review is likely to find the NTP listing decision to be unsupported, if not with the data available to NTP at the time of the listing, then certainly based on the data now available.

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<sup>17</sup> Cruzan, G, Bus, J, Hotchkiss, J, Sura, R, Moore, C, Yost, G, Banton, M, Sarang, S., Studies of Styrene, Styrene Oxide and 4-Hydroxystyrene Toxicity in CYP2F2 Knockout and CYP2F1 Humanized Mice Support Lack of Human Relevance for Mouse Lung Tumors, *Regulatory Toxicology and Pharmacology*, in press (2013).

<sup>18</sup> Rhomberg L, Goodman J, Prueitt R, The Weight of Evidence Does Not Support the Listing of Styrene as “Reasonably Anticipated to be a Human Carcinogen” in NTP’s Twelfth Report on Carcinogens, *Human & Ecological Risk Assessment* Volume 19, Issue 1, pp. 4-27 (2013). As the authors note, SIRC sponsored this review by independent researchers at Gradient.

### C. Avoiding Premature Administrative Actions

The RoC listing of styrene has already triggered derivative, administrative actions that are premature given the National Academy review and other developments. For example, the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment ("OEHHA") published its intent to list styrene (CASRN 100-42-5) as a chemical known to the State to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986, commonly referred to as Proposition 65.<sup>19</sup> OEHHA proposed to list styrene pursuant to the Labor Code mechanism contained in Health and Safety Code section 25249.8(a). Section 25249.8(a) incorporates California Labor Code sections 6382(b)(1) and 6382(d), and Labor Code section 6382(d) references chemicals or substances within the scope of the federal Hazard Communication Standard (HCS).<sup>20</sup>

OEHHA stated in its proposal that these "federal [HCS] regulations, in turn, identify the National Toxicology Program (NTP) as a source for identifying chemicals that cause cancer." Based on the RoC listing, OEHHA contended that styrene meets the requirements of Labor Code section 6382(d). SIRC and other interested parties have already expended time and resources to respond to the California proposal. While the initial proposal was recently withdrawn, OEHHA has informally indicated that it intends to re-propose listing, and we have every expectation that this will be based on the RoC's current listing of styrene.

Listings under Proposition 65 have immediate impact in the form of product deselection, well before any labeling requirement deadlines, and would be expected to have an adverse effect on product sales even if no labeling was required for a particular styrene-derived product.

The NTP recognizes that the listing of a substance in the RoC may prompt regulatory agencies to consider limiting exposures or uses of a substance. In fact:

The RoC is required to identify each of the listed substances for which no standard for exposure or release into the environment has been established by a Federal agency. The RoC addresses this requirement by providing in each profile a summary of the regulations and guidelines...that are likely to decrease human exposure to that substance.<sup>21</sup>

The NTP affirms that the listing of styrene would subject it to federal regulations by the Department of Transportation ("DOT"), Environmental Protection Agency ("EPA"), Food and Drug Administration ("FDA"), and Occupational Safety and Health Administration ("OSHA"), among others.

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<sup>19</sup> Cal. Health & Safety Code § 25249.5 *et seq.*

<sup>20</sup> 29 C.F.R. § 1910.1200.

<sup>21</sup> *Id.*, at 5.

Collectively, the potential for premature administrative action by other agencies warrants temporary annotation of the RoC listing of styrene.

#### **D. Avoiding Unwarranted Economic Impact**

One implication of the debate surrounding the scientific basis for NTP's listing decision is that adverse economic impact is not offset by demonstrable health and welfare benefits. Further, because the temporary annotation does not remove or permanently revoke the RoC listing for styrene, the public information goals of the RoC will continue to be met.

In weighing the equities in favor of the relief requested by this Petition, we ask the Secretary to carefully assess the role of adverse economic impact. Styrene plays a pivotal role in the manufacture and production of various consumer products. The two major markets of consumer-related goods include food-contact applications and reinforced plastics/composites. Businesses use styrene to make products that promote health, safety, and a higher standard of living. A few of these products include:

- Bicycle helmets
- Transport equipment for vaccines, transplant organs, and blood supplies
- Blood-analysis and dialysis machines
- Refrigerators, microwave ovens, and small kitchen appliances
- Insulating food-service containers
- Shipping and storage containers for produce, dairy, eggs, and other agricultural products
- Automotive tires
- Traffic-safety equipment

For many of these products, materials derived from styrene are preferred due to their favorable properties.

Deselection of products derived from styrene would harm not only those who produce and use styrenic packaging, but also the environment, consumers, and the public health. Styrenic containers reduce the consumption of fossil fuels and greenhouse gas emissions because these containers weight less than alternative materials, less fuel is consumed during transport. Styrene containers can be rinsed and recycled, unlike porous materials such as cardboard cartons, which can seldom be separated and effectively cleaned of food waste. Deselection pressure is not speculative. Companies marketing alternative materials reference the RoC listing of styrene as a marketing tool in promoting non-styrenic materials.<sup>22</sup>

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<sup>22</sup> See [http://www.chemweek.com/people\\_and\\_business/companies/36331.html](http://www.chemweek.com/people_and_business/companies/36331.html).

NTP's activity leading up to the 12th RoC has already caused a negative impact on the styrene industry. In December 2010, OEHHA published its final Public Health Goal for Styrene in Drinking Water.<sup>23</sup> OEHHA cited the recommendation of the NTP Expert Panel to include styrene in the RoC, demonstrating that NTP's actions quickly influenced the decision making of other governmental agencies.

Additional business impacts from the RoC listing of styrene also appear in the form of increased liability insurance, potential for future increases of employee lawsuits, not to mention activities of the trial bar. Costs could drive companies to relocate operations outside the United States, resulting in decreased employment opportunities as well as lost revenue to the U.S. Treasury.

Whatever duty the Secretary has to inform the public of hazards carries a companion duty not to mislead or misinform the public. From Petitioner's perspective, the public is misinformed or misled when DHHS continues to proclaim that styrene is "reasonably anticipated to be a human carcinogen" when the evolving science put that determination in question and that very question is being reviewed by the National Academy under a review commissioned by DHHS.

To avoid unwarranted deselection of styrene products and adverse impacts on the styrene industry, Petitioner requests that the Secretary temporarily annotate the listing of styrene.

#### **IV. RELIEF REQUESTED**

Petitioner requests that the Secretary promptly annotate NTP's listing of styrene under the Report on Carcinogens until the National Academy review is completed. Several factors independently support the grant of this request and, collectively, present a compelling basis demonstrating that continued listing is contrary to the public interest and not supported by the Congressional intent that gave rise to the RoC. These factors include:

- The Department's duty to keep the public informed;
- Appropriate respect and comity for the National Academies' ongoing review of the RoC styrene listing;
- Avoiding premature administrative actions prompted by the RoC listing;
- Consideration of new scientific evidence, which will also be considered by the National Academy, that further questions the propriety of the NTP listing; and
- Mitigating unjustified economic impact.

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<sup>23</sup> Public Health Goal for Styrene in Drinking Water at 2. The announcement appears at <http://www.oehha.ca.gov/water/phg/122810styrene.html>, and this webpage has links to the full report.

Petitioner stresses that granting this Petition does not require the Secretary to withdraw, recall, or vacate the RoC listing of styrene. A temporary annotation can be accomplished by a simple annotation of the RoC web page listing for styrene.

Petitioner can provide additional information and can meet with the Secretary's representatives to provide DHHS with further information in relation to this Petition.

Respectfully submitted,

A handwritten signature in black ink that reads "Jack Snyder". The signature is written in a cursive style with a large, looped "S" at the end.

Jack Snyder  
Executive Director

**Enclosures**

- Carlson, G.P., Modification of the metabolism and toxicity of styrene and styrene oxide in hepatic cytochrome P450 reductase deficient mice and CYP2F2 deficient mice, *Toxicology*, v. 294, issues 2-3, pp. 104-108, 11 Apr 2012
- Collins, J.J. et al., *Cancer Mortality of Workers Exposed to Styrene in the US Reinforced Plastics and Composite Industry*, *Epidemiology*, v. 24, issue 2, pp. 195-203 (March 2013)
- Cruzan, G., Bus, J., Hotchkiss, J., Harkema, J., Banton, M., Sarang, S. Cruzan, G. et al., CYP2F2-generated metabolites, not styrene oxide, are a key event mediating the mode of action of styrene-induced mouse lung tumors, *Regulatory Toxicology and Pharmacology*, v. 62, issue 1, pp. 214-220, Feb. 2012
- Cruzan, G, Bus, J, Hotchkiss, J, Sura, R, Moore, C, Yost, G, Banton, M, Sarang, S., Studies of Styrene, Styrene Oxide and 4-Hydroxystyrene Toxicity in CYP2F2 Knockout and CYP2F1 Humanized Mice Support Lack of Human Relevance for Mouse Lung Tumors, *Regulatory Toxicology and Pharmacology*, in press (2013).

*Of Counsel*

Peter L. de la Cruz  
Keller and Heckman LLP  
1001 G Street N.W.  
Suite 500 West  
Washington, D.C. 20001