



Styrene Information and Research Center (SIRC)  
910 17th Street NW #500-B, Washington, DC 20006  
Phone: 202-787-5996 www.styrene.org

*This Document Delivered By Electronic Delivery*

2 Apr 2013

James J. Reisa, Ph.D.  
Director, Environmental Studies and Toxicology  
National Research Council  
Keck Center of the National Academies  
500 Fifth Street, NW  
Washington, DC 20001

**Follow-up Submission for NRC Review of Styrene**

Dear Dr. Reisa and Members of NRC Styrene Review Committee:

SIRC appreciated the opportunity to provide oral comments at the March 19, 2013 Public Session of the Joint Meeting of the NRC Committees charged with reviewing the styrene and formaldehyde assessments in the NTP 12<sup>th</sup> *Report on Carcinogens (RoC)*.

This follow-up submission supplements SIRC's February 20, 2013 written comments in response to several questions raised by members of the Styrene Review Committee as well as comments made by NTP and others who spoke at the Joint Meeting.

SIRC believes this additional information will help to clarify a few scientific points and further support the conclusion that **an evidence-based interpretation of the toxicology and human data, including a mode of action evaluation, strongly indicates that styrene is not a human carcinogen.** As you know, this contrasts with the views expressed by the NTP in the *RoC* and at the March 19 Public Meeting.

If it would be helpful to the Styrene Review Committee, SIRC would be pleased to assist the NRC staff in arranging for in-depth discussions with the authors of key papers and/or those individuals who provided comments at the Joint Meeting.

Sincerely,

A handwritten signature in black ink that reads "Jack Snyder". The signature is written in a cursive style.

Jack Snyder, Executive Director  
Styrene Information and Research Center

## FOLLOW-UP SUBMISSION FOR NRC STYRENE REVIEW

---

SIRC's follow-up submission addresses the following topics raised during the Public Meeting of the March 19, 2013 Joint Meeting of the NRC Committee to Review the Styrene Assessment in the NTP 12<sup>th</sup> RoC and the NRC Committee to Review the Formaldehyde Assessment in the NTP 12<sup>th</sup> RoC:

- Brief reprise of SIRC's hypothesis-based research program and its conclusions, provided for the Committee's convenience;
- Animal data - clarification of the International Agency for Research on Cancer's (IARC) basis for listing styrene in its 1994 and 2002 *Monographs*.
- Human data - address questions related to the Collins *et al.* paper.
- Misrepresentation of the status of the *European Risk Assessment for Styrene*.

### Animal Data

#### Evolution of Hypotheses Related to Styrene's Potential Carcinogenicity

The following reprise is drawn from SIRC's February 20, 2013 written comments to the Styrene Review Committee.

Beginning in the late 1990s, SIRC began to sponsor research that was intended to address gaps in the scientific data related to the possible effects on human health of exposure to styrene.

Following the publication of SIRC-sponsored rodent inhalation studies in 1998<sup>1</sup> and 2001,<sup>2</sup> which found that mouse lung tumors were the only tumor of concern, **SIRC's default hypothesis at that time was that styrene may cause mouse lung tumors via its main metabolite styrene oxide (SO).**

This is also the hypothesis of the NTP relies on to list styrene in the RoC.

SIRC initially investigated if the mode of action (MoA) for mouse lung tumors was associated with the major metabolite of styrene, styrene-7,8-oxide (SO), which is produced primarily by the actions of the enzyme CYP2E1 on styrene's vinyl side-chain. However, the data did not support that hypothesis even though styrene is metabolized to SO via the vinyl side-chain.

About the same time the mouse study was published in 2001, data challenging the SO-associated default hypothesis were identified, and a growing body of contrary evidence began to emerge. These data indicate various chemicals\* which are structurally similar to styrene cause lung tumors in mice but not in rats, and several of these substances were also metabolized by CYP2F2 in mouse lung.<sup>2</sup> Importantly, Clara cells, which are the primary target cell for styrene mouse lung toxicity, also are the cell type in which styrene is metabolized by CYP2F2.<sup>3</sup>

---

\* Substances that cause lung tumors in mice but not in rats include styrene, naphthalene, ethylbenzene, cumene (isopropylbenzene), alpha-methylstyrene, divinylbenzene, benzofuran and coumarin.

Based on this, **as an alternative to an SO-mediated MoA, SIRC next hypothesized that styrene causes mouse lung tumors via ring-oxidized cytotoxic metabolites\* generated by mouse lung CYP2F2.**

The results of a series of investigations supported this hypothesis and helped provide the evidence upon which SIRC's current hypothesis about styrene related mouse lung tumors is based: **Styrene-induced mouse lung tumors are not quantitatively, and likely qualitatively, relevant for human risk.**

Please see SIRC's February 20, 2013 written comments<sup>4</sup> to the Styrene Review Committee for more details regarding the evolution of SIRC's hypothesis.

### Scientific Basis for Styrene's Listing in IARC Monographs

A comment submitted to the Styrene Review Committee states "*The overall evidence from animal studies was considered "sufficient" by the ROC, consistent with the previous IARC reviews.*"<sup>5</sup>

This is incorrect.

The International Agency for Research on Cancer (IARC) has reviewed styrene on three occasions, in 1987,<sup>6</sup> 1994<sup>7</sup> and 2002.<sup>8</sup> In each of these reviews, the animal data are classified by IARC as "limited," not "sufficient."

## Human Data

### Questions Related To Collins *et al.*, 2013

Comments submitted to the Styrene Review Committee challenged some of the conclusions of a recently-published update<sup>9</sup> of a cohort of reinforced plastics (RPC) workers.<sup>10</sup> Several specific points raised in these comments points are addressed below.

- **Comment:** "*The attempt by the Dow authors to blame smoking for the observed excess risk of cancer is pure speculation, when in fact the cancer findings are supported by some previous workplaces [sic] studies that have reported elevations in kidney cancer and other cancers.*"<sup>5</sup>

**Response:** Collins *et al.* provided specific evidence for why smoking may be related to increased risk of lung and other cancers, *e.g.*, kidney cancer, in the RPC worker study:<sup>9</sup> "A previous nested case-control study of this group of workers, which collected data on smoking habits, concluded that smoking was the cause for the excess of lung cancer.<sup>11</sup> In that study, 83% of the control group reported they had ever smoked in 1977, compared with 33% of current or occasional smokers in a national survey in 1978-1980.<sup>12</sup> Although these two surveys are not directly comparable, they do indicate a higher smoking prevalence in the styrene workers."

An unexpected finding of Collins *et al.* was an association of cumulative and peak styrene exposures with kidney cancer. However, other studies of styrene-

---

\* The metabolites include 4-hydroxystyrene, 3,4-dihydroxystyrene and possibly 4-hydroxystyrene oxide.

exposed workers have not found increased kidney cancer risk,<sup>13, 14, 15</sup> and the excess risk of smoking-related cancers in the Collins study indicated that part of the excess in this cancer is probably because of smoking. This finding is likely due to chance because the exposure-response pattern is weak, no increased risk is observed in the other studies of styrene workers, and there is potential confounding with smoking.

- **Comment:** “Both the recent Dow study and the earlier European multi-plant cohort reported that the elevated pancreatic cancer risk was associated with increasing cumulative exposure (Kogevinas et al 1993, 1994; ROC 2011), making the Dow study consistent with other scientific reports.”<sup>5</sup>

**Response:** Collins *et al.* performed multiple tests for significance levels and trends with styrene exposure and pancreatic cancer. Table 2<sup>9</sup> reports no increased pancreatic cancer rates in the study population overall (Standardized Mortality Ratio, or SMR=0.96, 95% CI 0.73-1.22) or among workers with 15 or more years of latency (SMR=0.90, 95% CI 0.67-1.17). As summarized in Table 3,<sup>9</sup> the authors examined both cumulative exposure by exposure category and proportional hazards model for continuous exposure. No trend of pancreatic cancer with exposure category was observed in the study. Additionally, the proportional hazards model revealed a poor model fit for pancreatic cancer but a weak positive relation with cumulative exposure. However, the analysis of peak styrene exposure (Table 4<sup>9</sup>), reported no trend with peak category. Interpreting results across analyses in a single study requires judgment on whether the differences are true or random, and the authors concluded that styrene exposure was not related to increased pancreatic cancer risk.

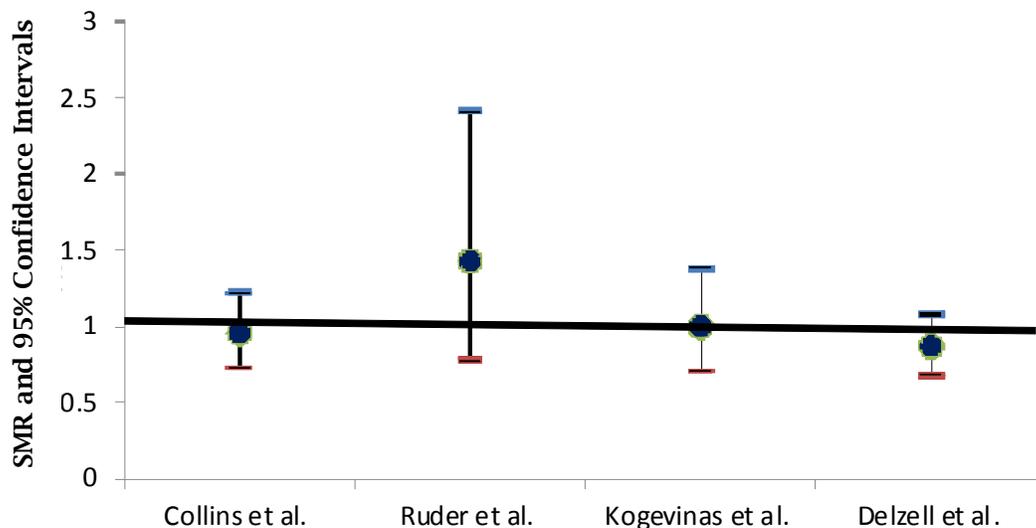
Pancreatic cancer outcomes reported for Collins *et al.* (2013),<sup>9</sup> the NIOSH study,<sup>11</sup> the European industry-wide study,<sup>16</sup> and styrene-butadiene rubber industry<sup>14</sup> are depicted in [Figure 1](#). The findings of the Kolstad Danish cohort<sup>17</sup> are not included in [Figure 1](#) since the workers\* were included in the European industry wide study.<sup>16</sup> The SMR for pancreatic cancer presented in Table 4 for the Danish study, however, was 1.20 (95% CI 0.86-1.63).<sup>17</sup> Also, the SMR for the highest exposed workers in the European industry-wide study was 1.48 (95% CI 0.76-2.58) and the SMR for the highest exposed workers in the NIOSH study was 1.88 (95% CI 0.51-4.81). In the European study, the SMRs were the highest 20 or more years after first exposure (SMR=2.05, 95% CI 0.58-7.29) and increased with cumulative exposure (p-value = 0.068).

Regarding pancreatic cancer rates for these studies overall, the NIOSH study reported pancreatic cancer rates slightly greater than expected, while all other studies were at or below expected levels. Importantly, none of these key epidemiology studies identified a significantly elevated SMR for pancreatic cancer.

---

\* Kogevinas *et al.* included 13,000 workers at companies who were estimated to be than 50% involved in RPC, but excluded 20,000 with <50% involvement; all of these workers were included in the Kolstad cohort.

Figure 1. Standardized Mortality Ratios (SMR) and 95% Confidence Intervals (CI) for Pancreatic Cancers among Workers in the Reinforced Plastics Industry and Styrene-Butadiene Rubber Industry.



- Comment:** *“It is odd that the Dow study failed to report on whether or not esophageal cancers were elevated, because deaths from this type of cancer were elevated in the earlier study of the same cohort (SMR= 1.92, 95% CI = 1.05-3.22; 14 exposed deaths; Wong et al 1994). Dow authors report on all digestive cancer and peritoneum (which includes esophageal cancer), but do not break out the esophageal cancers in their report.”<sup>5</sup>*

**Response:** Indeed, Collins *et al.* did not report the standardized mortality ratio (SMR) or 95% confidence intervals (95%CI) for esophageal cancer.<sup>9</sup> The stated purpose of this study, based on the authors’ review of the literature, was to “determine if styrene exposure is related to increased cancer risk especially for cancers of the lymphatic and hematopoietic systems, lung and pancreas (page 195).”<sup>9</sup>

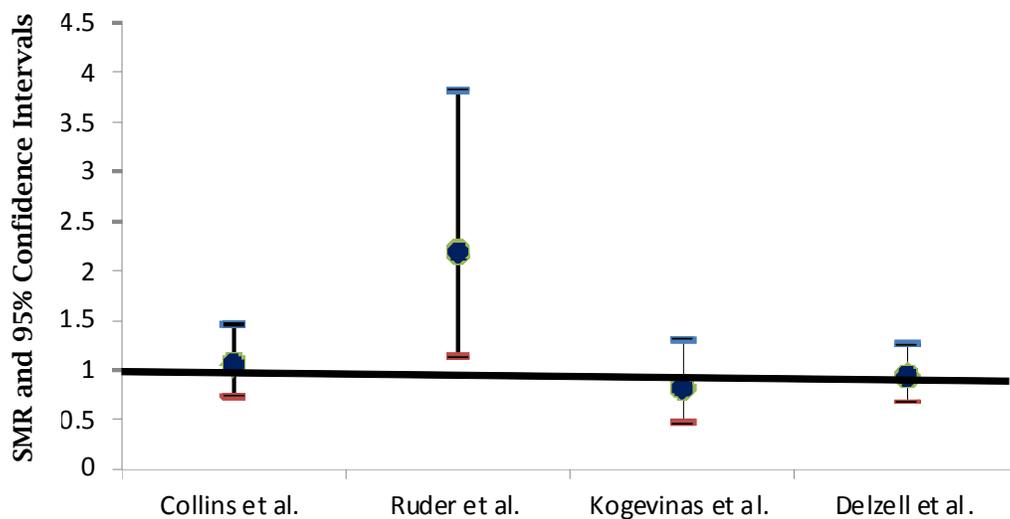
Some information was not included in the published paper in order to reduce the size and number of tables, including the SMR for esophageal cancer. However, in the extended report provided to the NRC Styrene Review Committee on March 20, 2013, Table 2 presents the SMR and 95% CIs for each part of the digestive organs and peritoneum. The SMR for esophageal cancer for males and females combined, based on 36 deaths, is 1.06 (95% CI 0.74-1.46). These findings were also presented during Dr. Collins’, presentation at the Joint Meeting on March 19<sup>th</sup>.

The SMRs and 95% CIs for esophageal cancer for the Collins study,<sup>9</sup> the NIOSH study,<sup>11</sup> the European industry-wide study,<sup>16</sup> and styrene-butadiene rubber industry<sup>14</sup> are shown in [Figure 2](#). As with pancreatic cancer, [Figure 2](#) does not include the results of the Danish reinforced plastics industry study<sup>17</sup> since the workers in the Kolstad cohort were included in the European industry wide

study.<sup>16</sup> The SMR for esophageal cancer for the Danish study, however, was 0.92 (95% CI 0.50-1.57).

Additionally, the European industry-wide study reported an SMR for laminators, typically the highest of the exposed workers, of 1.81 (95% CI 0.87-2.84). While the NIOSH study reported esophageal cancer rates greater than expected, the confidence limits were wide and all the other studies reported SMRs consistent with no increased cancer risk.

Figure 2. Standardized Mortality Ratios (SMR) and 95% Confidence Intervals (CI) for Esophageal Cancers among Workers in the Reinforced Plastics Industry Studies and Styrene-Butadiene Rubber Industry.



## EU Styrene Risk Assessment

### Status of EU Risk Assessment Misrepresented

A comment submitted to the Styrene Review Committee states “*One of the Congressional letters was written by Senator Richard Shelby (R-AL) and Mark Warner (D-VA). The Shelby/Warner letter was blatantly inaccurate in its assertions, which are almost identical to styrene industry talking points. The Shelby/Warner letter says that the NTP finding regarding styrene is “contrary” to two recent assessments: a report “conducted by the European Union” and a study by a “blue ribbon’ panel of epidemiologists.” The EU report is actually a draft Risk Assessment Report prepared by the U.K. which failed peer review by the EU’s Scientific Committee on Environmental Risk, and was never finalized.*”<sup>18</sup>

This statement misrepresents the status of the styrene risk assessment prepared by the U.K. Rapporteur on behalf of the European Union.

In fact, while the EU Styrene Risk Assessment remains unfinished, this is because the regulation it was prepared under was superseded, not because of issues related to peer review.

A brief timeline may be helpful in clarifying the status of this assessment:

- November 2007 - “Draft Risk Assessment Report, Styrene”<sup>19</sup> was provided by the U.K. lead Rapporteur to the Scientific Committee on Health and Environmental Risks (SCHER) of the European Commission for their review. The draft report was prepared under the then-current legislative framework for new and existing chemicals.<sup>20</sup>
- May 6, 2008 - SCHER completed its review and returned it to the Rapporteur. In this document, SCHER expressed support for the 2002 IARC classification as possibly carcinogenic to humans and stated that some of the draft styrene assessment’s discussion was “insufficiently justified.”<sup>21</sup>
- June 2008 - “European Union Risk Assessment Report, Styrene” was published by the U.K. Rapporteur; the cover page gives the document’s status as “Draft for publication, June 2008.” Additionally, the “DRAFT” watermark found in the November 2007 draft was removed in the June 2008 document.<sup>22</sup>
- The June 2008 assessment also includes a number of edits in response to the SCHER’s input. For example, see Table 1 for a comparison of the conclusions related to carcinogenicity that are found on pp. 276-277 of the November 2007 draft to pp. 273-274 of the June 2008 version.
- June 2008 - Regulation No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) came into force and replaced the regulations which authorized the styrene risk assessment.
- November 28, 2008 - The U.K. Rapporteur, in accordance with REACH, submitted an “Annex XV Transitional Dossier” to the European Chemicals Agency (ECHA). This dossier incorporated the results of the June 2008 styrene Risk Assessment verbatim.<sup>23</sup>
- 2009 - ECHA accepted the *Styrene Annex XV Transitional Report* as an appropriate reference guide for EU Member States, the European Commission and industry.<sup>24</sup>
- September 2011- Danish authorities, who were serving as the Rapporteur for a Classification and Labelling review of styrene, incorporated the summary discussion from the June 2008 styrene assessment regarding carcinogenicity verbatim.<sup>25</sup>

Thus, the June 2008 styrene Risk Assessment is currently serving as a basis for regulatory action in the EU, and any issues related to its discussion of carcinogenicity were addressed to the satisfaction of European authorities.

Table 1

<p>“Summary of Carcinogenicity” (last 3 paragraphs) November 2007 SCHER Draft</p>	<p>“Summary of Carcinogenicity” (last 3 paragraphs) June 2008 Publication Draft</p>
<p>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. Although there are still some uncertainties in this postulated mode of action and in its relevance to humans, namely the lack of data on the relative rates of 4-VP metabolites detoxification in different species, no alternative modes of action that logically present themselves can be supported by as significant a body of evidence as the one presented in this assessment. Consequently, it is felt that the level of confidence in the postulated mode of action can be reasonably high and that, in view of the extensive negative lung epidemiology, it is reasonable to conclude that the lung tumours seen in mice are unlikely to be of any relevance for human health. A more detailed analysis (according to the IPCS framework for evaluating a mode of action in chemical carcinogenesis) of the evidence in support of the proposed mode of action and of its relevance for human health is presented in Annex A to this document.</p> <p>The carcinogenicity of styrene was evaluated by IARC in 2002. Styrene was considered <i>possibly carcinogenic to humans</i> (Group 2B). The Working Group concluded that based on metabolic considerations, it is likely 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. However, 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.</p>	<p>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. Although there are still some uncertainties in this postulated mode of action and in its relevance to humans, namely the lack of data on the relative rates of 4-VP metabolites detoxification in different species, no alternative modes of action that logically present themselves can be supported by as significant a body of evidence as the one presented in this assessment. Consequently, it is felt that the level of confidence in the postulated mode of action can be reasonably high and that, in view of the extensive negative lung epidemiology, it is reasonable to conclude that the lung tumours seen in mice are unlikely to be of any relevance for human health. A more detailed analysis (according to the IPCS framework for evaluating a mode of action in chemical carcinogenesis) of the evidence in support of the proposed mode of action and of its relevance for human health is presented in Annex A to this document.</p> <p>The carcinogenicity of styrene was evaluated by IARC in 2002. Styrene was considered <i>possibly carcinogenic to humans</i> (Group 2B). The Working Group concluded that based on metabolic considerations, it is likely 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. However, 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.</p>
<p>In the Rapporteur’s view, pointing to a carcinogenic potential of styrene in other organs is highly speculative as several large cohort and case-control studies of workers exposed to styrene have shown no evidence for a causative association between styrene exposure and cancer in humans at any site <del>and</del> no consistent evidence for styrene-induced toxicity in any organ has emerged from studies of exposed workers. <del>Furthermore</del>, the level of DNA damage found in workers exposed to styrene is very low (10-fold lower than that produced by endogenously-generated genotoxic substances such as ethylene oxide) and <del>generally</del> cannot be <del>taken as</del> the driving force for tumour formation. <del>This is highlighted by the lack of any relationship between</del> DNA adduct formation in mouse lung tissues and tumour development.</p>	<p>In the Rapporteur’s view, pointing to a <b>possible</b> carcinogenic potential of styrene in other organs is highly speculative as: <b>a)</b> Several large cohort and case-control studies of workers exposed to styrene have shown no evidence for a causative association between styrene exposure and cancer in humans at any site; <b>b)</b> No consistent evidence for styrene-induced toxicity in any organ has emerged from studies of exposed workers; <b>c)</b> The level of DNA damage found in workers exposed to styrene is very low (10-fold lower than that produced by endogenously-generated genotoxic substances such as ethylene oxide) and <b>thus cannot be considered to be of any relevance for subsequent tumour formation. Mechanistic studies have shown that styrene-oxide (SO) and its genotoxicity are not the driving force for lung tumour formation in mice, the only experimental tumour site observed so far. Furthermore, DNA adducts in animals after styrene exposure do not show any specific species or target organ relationship. For example, there is no excess of SO-adduct formation in tissues where SO is formed (e.g. in the liver) at high levels; d) Chromosomal damage caused by styrene exposure in humans is far away from being conclusive. Although 5 studies appear to present evidence that styrene may be weakly clastogenic in humans, there are 11 robust negative studies also. Together with a lack of evidence of a dose-response relationship and the negative response for induction of micronuclei when studied concurrently in two of the positive chromosome aberration studies, no clear conclusion on <i>in vivo</i> clastogenicity of styrene in humans can be made. Furthermore, at much higher exposures such effects were not observed in experimental animals.</b></p>

- 
- <sup>1</sup> Cruzan, G. *et al.*, "Chronic Toxicity/Oncogenicity Study of Styrene in CD Rats by Inhalation Exposure for 104 Weeks," *Toxicological Sciences*, v. 46, issue 2, pp. 266-281, 1998; <http://toxsci.oxfordjournals.org/content/46/2/266.full.pdf>.
- <sup>2</sup> Cruzan, G. *et al.*, "Chronic toxicity/oncogenicity study of styrene in cd-1 mice by inhalation exposure for 104 weeks," *Journal of Applied Toxicology*, v. 21, issue 3, pp. 185-198, May/June 2001; <http://onlinelibrary.wiley.com/doi/10.1002/jat.737/abstract>.
- <sup>3</sup> Hynes, D.E. *et al.*, "Metabolism of styrene by mouse and rat isolated lung cells," *Toxicological Sciences*, v. 51, issue 2, pp. 195-201, Oct. 1999; <http://toxsci.oxfordjournals.org/content/51/2/195.full.pdf>.
- <sup>4</sup> SIRC's February 20, 2013 letter and comments to the NRC Styrene Review Committee are available at <http://www.styrene.org/news/pdfs/02-20-13-nas-response-letter.pdf>.
- <sup>5</sup> Sass, J. and Rosenberg, D., Comments Submitted by the Natural Resources Defense Council to the National Academies Review [sic] the Styrene Assessment in the NTP 12<sup>th</sup> ROC (DELS-BEST-12-05) and Review of the Formaldehyde Assessment in the NTP 12<sup>th</sup> ROC (DELS-BEST-12-04), p. 14- 16, March 19, 2013; [http://docs.nrdc.org/health/files/hea\\_13032001a.pdf](http://docs.nrdc.org/health/files/hea_13032001a.pdf).
- <sup>6</sup> International Agency for Research on Cancer (IARC), "Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42," Styrene (Group 2B), *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Supplement 7, p. 346; <http://monographs.iarc.fr/ENG/Monographs/suppl7/Suppl7-141.pdf>.
- <sup>7</sup> International Agency for Research on Cancer (IARC), "Some Industrial Chemicals, Styrene," *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, v. 60, p. 297, 1994; <http://monographs.iarc.fr/ENG/Monographs/vol60/mono60-11.pdf>.
- <sup>8</sup> International Agency for Research on Cancer (IARC), "Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene," *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, v. 82, p. 522, 2002; <http://monographs.iarc.fr/ENG/Monographs/vol82/mono82-9.pdf>.
- <sup>9</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, Mar. 2013; [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>10</sup> Wong, O. *et al.*, "An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry," *Occupational and Environmental Medicine*, v. 51, issue 6, pp. 386-396, June 1994; <http://oem.bmj.com/content/51/6/386.full.pdf>.
- <sup>11</sup> Ruder, A.M. *et al.*, "Mortality patterns among workers exposed to styrene in the reinforced plastics boatbuilding industry: an update," *American Journal of Industrial Medicine*, v. 45, issue 2, pp. 165-176, Feb. 2004; <http://onlinelibrary.wiley.com/doi/10.1002/ajim.10349/abstract>.
- <sup>12</sup> Nelson, D.E. *et al.*, "Cigarette Smoking Prevalence by Occupation in the United States: A Comparison between 1978 to 1980 and 1987 to 1990," *Journal of Occupational Medicine*, v. 36, issue 5, pp. 516-525, May 1994; abstract <http://journals.lww.com/joem/Abstract/1994/05000/>.
- <sup>13</sup> Matanoski, G.M. *et al.*, "Mortality of a Cohort of Workers in the Styrene-Butadiene Polymer Manufacturing Industry (1943-1982)," *Environmental Health Perspectives*, v. 86, pp.107-117, June 1990; <http://www.jstor.org/discover/10.2307/3430942>.

- 
- <sup>14</sup> Delzell, E. *et al.*, "An Updated Study of Mortality Among North American Synthetic Rubber Industry Workers," *Health Effects Institute Research Report Number 132*, Aug. 2006, 84 pp.; <http://pubs.healtheffects.org/view.php?id=263>.
- <sup>15</sup> Cox, D.R., "Regression Models and Life-Tables," *Journal of the Royal Statistical Society*, v. 34, no. 2, pp. 187-220, 1972; <http://www.jstor.org/discover/10.2307/2985181>.
- <sup>16</sup> Kogevinas, M. *et al.*, "Cancer mortality in a historical cohort study of workers exposed to styrene," *Scandinavian Journal of Work, Environment & Health*, v. 20, issue 4, p. 253, Aug. 1994; [http://www.sjweh.fi/show\\_abstract.php?abstract\\_id=1400](http://www.sjweh.fi/show_abstract.php?abstract_id=1400).
- <sup>17</sup> Kolstad H.A. *et al.*, "Exposure to styrene and chronic health effects: mortality and incidence of solid cancers in the Danish reinforced plastics industry," *Occupational and Environmental Medicine*, v. 52, issue 5, pp. 320-327, May 1995; <http://oem.bmj.com/content/52/5/320.full.pdf>.
- <sup>18</sup> Sass, J. and Rosenberg, D., Comments Submitted by the Natural Resources Defense Council to the National Academies Review [sic] the Styrene Assessment in the NTP 12<sup>th</sup> ROC (DELS-BEST-12-05) and Review of the Formaldehyde Assessment in the NTP 12<sup>th</sup> ROC (DELS-BEST-12-04), p. 7, March 19, 2013; [http://docs.nrdc.org/health/files/hea\\_13032001a.pdf](http://docs.nrdc.org/health/files/hea_13032001a.pdf).
- <sup>19</sup> European Union Risk Assessment Report, Styrene, CAS No: 100-42-5, EINECS No 202-851-5, Draft for submission to SCHER," prepared by the UK rapporteur on behalf of the European Union, November 2007, 430 pages.
- <sup>20</sup> *Council Regulation (EEC) No 793/93 of 26 March 1993 on the evaluation and control of the risks of existing substances*; <http://eur-lex.europa.eu/LexUriServ/site/en/consleg/1993/R/01993R0793-20031120-en.pdf>.
- <sup>21</sup> "Scientific Committee on Health and Environmental Risks opinion on: Risk Assessment Report on styrene Human Health Part," 7 pages, 6 May 2008; [http://ec.europa.eu/health/archive/ph\\_risk/committees/04\\_scher/docs/scher\\_o\\_095.pdf](http://ec.europa.eu/health/archive/ph_risk/committees/04_scher/docs/scher_o_095.pdf).
- <sup>22</sup> European Union Risk Assessment Report, Styrene, CAS No: 100-42-5, EINECS No 202-851-5, Draft for Publication," prepared by the UK rapporteur on behalf of the European Union, June 2008, 448 pages; [http://echa.europa.eu/documents/10162/13630/trd\\_rar\\_uk\\_styrene\\_en.pdf](http://echa.europa.eu/documents/10162/13630/trd_rar_uk_styrene_en.pdf).
- <sup>23</sup> European Chemicals Agency, "Styrene, CAS No: 100-42-5, EINECS No: 202-851-5," *Annex XV Transitional Report, Documentation of the work done under the Existing Substance Regulation (EEC) No 793/93 and submitted to the European Chemicals Agency according to Article 136(3) of Regulation (EC) No 1907/2006*, submitted by: UK Competent Authority, 134 pages, 28 Nov 2008; [http://echa.europa.eu/documents/10162/13630/trd\\_uk\\_styrene\\_en.pdf](http://echa.europa.eu/documents/10162/13630/trd_uk_styrene_en.pdf).
- <sup>24</sup> European Chemicals Agency, "Styrene, CAS No: 100-42-5, EINECS No: 202-851-5," *Annex XV Transitional Report Cover Page*, 3 pages, 2009; [http://echa.europa.eu/documents/10162/13630/trd\\_cover\\_page\\_styrene\\_en.pdf](http://echa.europa.eu/documents/10162/13630/trd_cover_page_styrene_en.pdf).
- <sup>25</sup> CLH report, Proposal for Harmonised Classification and Labelling, Based on Regulation (EC) No 1272/2008 (CLP Regulation), Substance Name: Styrene, submitted by Danish Environmental Protection Agency, 77 pages, September 2011; <http://echa.europa.eu/documents/10162/e7c7d1a1-b42a-410b-8afe-62b8ada88ca5>.