

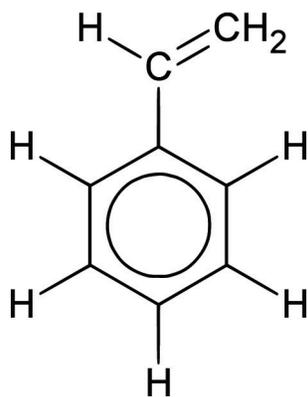
## Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens

### Why Did the National Research Council Do This Study?

In 2011, the National Toxicology Program listed styrene as “reasonably anticipated to be a human carcinogen” in its 12th Report on Carcinogens (RoC). Congress directed the Department of Health and Human Services to request the National Academy of Sciences to review independently the substance profile of styrene and its listing in the 12th RoC. This report presents the findings and conclusions of the committee formed in response to the congressional request.

### Key Finding

After conducting a scientific review of the styrene assessment presented in the National Toxicology Program 12th RoC, the committee finds that the overall conclusion reached by the National Toxicology Program in 2011, that styrene is “reasonably anticipated to be a human carcinogen” is appropriate.



**Figure 1.** The structure of the styrene molecule

### WHAT IS THE REPORT ON CARCINOGENS?

The Report on Carcinogens (RoC), published by the National Toxicology Program, is a summary of substances judged to meet two criteria: that the substance is known or reasonably anticipated to be a human carcinogen on the basis of RoC listing criteria and that a significant number of people living in the United States are exposed to the substance. The assessment of chemicals for listing in the RoC constitutes a hazard assessment, not a risk assessment.

### WHAT IS THE DIFFERENCE BETWEEN A HAZARD ASSESSMENT AND A RISK ASSESSMENT?

A hazard assessment focuses on the identification of substances that may pose a hazard to human health, and it makes a classification about toxicity, for example, whether a chemical is “carcinogenic to humans” or “likely to be carcinogenic to humans”. A risk assessment quantitatively evaluates the likely degree of adverse effects caused by exposure to a substance. It requires much more information, including completion of a hazard identification, dose–response analysis, exposure quantification, and quantitative characterization of risk.

### WHAT IS STYRENE?

Styrene is an organic chemical that is a component of polystyrene and several other polymers. Sources of environmental exposures include food (from the migration of styrene from polymer packaging materials), cigarette smoke, vehicle exhaust, and other forms of combustion and incineration of styrene polymers. Occupational exposure can occur during the industrial production and use of styrene. Styrene is used to create a broad spectrum of products, including latex paints and coatings, synthetic rubbers, and packaging.

### HOW DID THE COMMITTEE CARRY OUT ITS TASK?

The committee first conducted a peer review of the styrene substance profile and listing in the National Toxicology Program 12th RoC, considering literature available up to June 10, 2011, when the 12th RoC was published. The committee then conducted an independent hazard assessment of styrene, using evidence published both before and after the 12th RoC, and made a listing recommendation using the RoC listing criteria.

## WHAT DID THE REPORT FIND?

### The Listing Criteria

The committee's evaluation of the evidence was guided by the RoC listing criteria (see Box 2). The committee's task stated that "the NRC's assignment does not also include a separate review of the National Toxicology Program's listing criteria." Therefore, while the report does not contain an evaluation of the listing criteria, the committee did clarify several pertinent issues.

The information needed to fulfill the criterion for sufficient evidence in animals is clear; however, the National Toxicology Program did not explain how it defined the terms *limited* or *sufficient* in the context of the epidemiology evidence.

Given the lack of explicit guidance in the RoC listing criteria, the committee used its professional judgment to develop and apply a set of factors to evaluate the credibility of epidemiologic evidence on the carcinogenicity of styrene. Those factors were:

- high estimates of relative risks or their surrogates
- exposure–response relationships for any reliably established exposure metric
- consistency of observations among at least two independent cohort studies of the reinforced-plastics industry or between cohort and case–control studies

### Box 1 What is the National Toxicology Program?

The National Toxicology Program is an interagency program of the National Institute of Environmental Health Sciences, the administrative lead and a part of the National Institutes of Health; the National Institute for Occupational Safety and Health, a part of the Centers for Disease Control and Prevention; and the National Center for Toxicological Research, a part of the Food and Drug Administration. The National Institutes of Health, the Food and Drug Administration, and the Centers for Disease Control and Prevention are all agencies under the U.S. Department of Health and Human Services.

The committee considered evidence in humans to be limited if it is credible, but bias, chance, and confounding factors cannot be excluded; evidence was considered sufficient if it is credible and bias, chance, and confounding factors can be excluded.

### Peer Review

The committee determined that the National Toxicology Program had identified most of the relevant literature, had sufficiently described that literature in the background document, and had

### Box 2 Report on Carcinogens Listing Criteria

#### Known To Be Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans\*, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

#### Reasonably Anticipated To Be Human Carcinogen:

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.

\* This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to substances in question, which can be useful for evaluating whether a relevant cancer mechanism is operating in humans.

selected the most informative studies in making its listing determination. The National Toxicology Program appropriately concluded that there is sufficient evidence of carcinogenicity in experimental animal studies.

Based on its interpretation of the RoC listing criteria, the National Research Council committee concluded that the description and analysis of literature presented by the National Toxicology Program for experimental animal studies and for human studies support its classification of styrene as “reasonably anticipated to be a human carcinogen”.

### Independent Assessment

In its independent assessment of styrene carcinogenicity, the National Research Council committee integrated data from individual studies to determine whether the evidence in experimental animals and in humans was limited or sufficient for a causal conclusion.

In sum, the committee found compelling evidence to support a listing of styrene as, at a minimum, reasonably anticipated to be a human carcinogen. That conclusion is based on credible but limited evidence of carcinogenicity in traditional epidemiologic studies, on

sufficient evidence of carcinogenicity in animals, and on convincing evidence that styrene is genotoxic in exposed humans.

The RoC listing criteria state that a substance should be classified as known to be a human carcinogen if “there is sufficient evidence of carcinogenicity from studies in humans”. The footnote associated with that sentence states that “this evidence can include data derived from the study of tissues or cells from humans exposed to [styrene] that can be useful for evaluating whether a relevant cancer mechanism is operating in people”. The evidence of styrene genotoxicity in exposed humans is convincing, so a strong argument could be made to support the listing of styrene as a known human carcinogen if data derived from the study of tissues or cells are in and of themselves sufficient for making such a determination. The committee notes that there is ambiguity with respect to weighing the mechanistic evidence in applying the listing criteria. Further clarification and expanded guidance by the National Toxicology Program regarding the types and strength of mechanistic evidence and the use of that evidence in the context of the RoC listing criteria are warranted.

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**Committee to Review the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens:** Jane E. Henney (*Chair*), Kansas City, MO; John C. Bailar III, University of Chicago (*retired*), Mitchellville, MD; Arthur P. Grollman, State University of New York, Stony Brook; Judith B. Klotz, Drexel University School of Public Health, Lawrenceville, NJ; Xiaomei Ma, Yale University School of Public Health, New Haven, CT; John B. Morris, University of Connecticut, Storrs; Charles G. Plopper, University of California, Davis (*retired*), Chester, CA; Stephen M. Roberts, University of Florida, Gainesville; Ivan Rusyn, University of North Carolina, Chapel Hill; Elaine Symanski, University of Texas Health Science Center at Houston, TX; Weiqiang (John) Zhao, Ohio State University, Columbus; Heidi Murray-Smith, (*Project Director*), Keri Stoeber (*Research Associate*), Norman Grossblatt (*Senior Editor*), Mirsada Karalic-Loncarenovic (*Manager, Technical Information Center*), Radiah Rose (*Manager, Editorial Projects*), Ricardo Payne (*Program Coordinator*), National Research Council.

The National Academies appointed the above committee of experts to address the specific task requested by the Department of Health and Human Services. The members volunteered their time for this activity; their report is peer-reviewed and the final product signed off by both the committee members and the National Academies. This report brief was prepared by the National Research Council based on the committee’s report.

For more information, contact the Board on Environmental Studies and Toxicology at (202) 334-1434 or visit <http://dels.nas.edu/best>. Copies of *Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens* are available from the National Academies Press, 500 Fifth Street, NW, Washington, D.C. 20001; (800) 624-6242; [www.nap.edu](http://www.nap.edu).

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