

EVIDENCE ON THE CARCINOGENICITY OF
1,2,4-TRICHLOROBENZENE

FINAL

September 2005



**Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency**

PREFACE

The Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65, California Health and Safety Code 25249.5 *et seq.*) requires that the Governor cause to be published a list of those chemicals “known to the state” to cause cancer or reproductive toxicity. The Act specifies that “a chemical is known to the state to cause cancer or reproductive toxicity ... if in the opinion of the state’s qualified experts the chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer or reproductive toxicity.” The lead agency for implementing Proposition 65 is the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency. The “state’s qualified experts” regarding findings of carcinogenicity are identified as the members of the Carcinogen Identification Committee of the OEHHA Science Advisory Board (Title 22 Cal. Code Regs. §12301).

1,2,4-Trichlorobenzene (1,2,4-TCB) was assigned a final priority of “high” carcinogenicity concern and placed on the Final Candidate list of chemicals for Committee review on March 12, 2004. A public request for information relevant to the assessment of the evidence on the carcinogenicity of this chemical was announced on March 12, 2004, in the *California Regulatory Notice Register*. No information was received as a result of this request. These hazard identification materials were compiled to provide the Committee with the available scientific evidence on the carcinogenic potential of this chemical, and were released on May 13, 2005 for a 60-day public comment period.

At their August 12, 2005 meeting, the Committee, by a vote of two in favor and four against, did not find that 1,2,4-TCB had been “clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.” Accordingly, 1,2,4-TCB was not placed on the Proposition 65 list of chemicals known to the state to cause cancer.

The following are the hazard identification materials that were discussed by the Committee at their August 2005 meeting.

SUMMARY OF AVAILABLE INFORMATION

1,2,4-TCB is used as a solvent and as an intermediate in the production of chemicals. Manufacture in or import into the U.S. of greater than one million pounds has led to its listing in the U.S. Environmental Protection Agency’s High Production Volume Challenge Program.

As discussed in more detail in the Attachments, long-term studies have shown that male and female mice treated in diet with 1,2,4-TCB develop a high incidence of hepatocellular adenomas and carcinomas. Similar studies in rats showed no evidence of carcinogenic effects. A limited skin painting study in mice also produced no evidence of carcinogenicity. While tests for genotoxicity have generally been negative, dose-related increases in micronuclei have been observed in bone marrow cells of mice treated intraperitoneally with 1,2,4-TCB. In addition, 1,2,4-TCB produced cell transformation in rat liver epithelial cells *in vitro*. Mizutani and Miyamoto (1999) conducted experiments in mice that suggest that intraperitoneally administered 1,2,4-TCB may produce reactive quinone metabolic intermediates.

No additional studies relevant to the carcinogenicity of 1,2,4-TCB, other than those reviewed in or included as Attachments I-V were identified in an April 2005 search of the published scientific literature.

ATTACHMENTS

In order to provide the Committee with the scientific evidence on the carcinogenic potential of 1,2,4-TCB, attached are:

Attachment I. The document supporting OEHHA's Public Health Goal for 1,2,4-Trichlorobenzene in Drinking Water (February 1999), which includes a summary of the scientific studies investigating the carcinogenic and genotoxic effects of 1,2,4-TCB that were available at that time (See sections entitled Genetic Toxicity, p. 7, and Chronic Toxicity and Carcinogenicity, p. 9). This document reviews initial reports of two sets of bioassays conducted in rats and mice that were submitted to the U.S. Environmental Protection Agency (U.S. EPA) by the Chemical Manufacturers Association. OEHHA has since obtained copies of the final reports of these bioassays, and these final reports appear below as Attachments II and III.

Attachment II. Relevant sections of a final report submitted to the U.S. EPA on long-term bioassays in male and female B6C3F₁ mice that were sponsored by the Chemical Manufacturers Association and performed by Hazleton Washington, Inc., entitled "104-Week Dietary Carcinogenicity Study with 1,2,4-Trichlorobenzene in Mice" (Final Report with cover letter dated 6/15/94).

Attachment III. Relevant sections of a final report submitted to the U.S. EPA on long-term bioassays in male and female F-344 rats that were sponsored by the Chemical Manufacturers Association and performed by Hazleton Washington, Inc., entitled "104-Week Dietary Carcinogenicity Study With 1,2,4-Trichlorobenzene in Rats" (Final Report with cover letter dated 6/15/94).

Attachment IV. An additional research paper not reviewed in Attachment I, which provides information potentially relevant to a carcinogenic mode of action for 1,2,4-TCB (Mizutani T, Miyamoto Y 1999 Modulation of halobenzene-induced hepatotoxicity by DT-diaphorase modulators, butylated hydroxyanisole and dicumarol: evidence for possible involvement of quinone metabolites in the toxicity of halobenzenes. *Toxicology Letters* **105**:25-30).

Attachment V. Data submitted under the Toxic Release Inventory program for the years 1999 to 2002 showing air releases of 1,2,4-TCB in California ranging from approximately 500 to 4300 pounds per year.