

**Prioritization of Chemicals for
Carcinogen Identification Committee Review:**

**Proposed Chemicals for Committee Consideration
August 2007**

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

Summary

The Office of Environmental Health Hazard Assessment (OEHHA) is proposing three chemicals for review by the Carcinogen Identification Committee (CIC) under Proposition 65, using the process endorsed by the CIC and adopted by OEHHA in 2004. These chemicals are: dimethylformamide; marijuana smoke; and 2,4,6-trinitrotoluene. The chemicals are not proposed for listing at this time. OEHHA is seeking public comment and the CIC's consultation regarding which of these chemicals should proceed to the next stage of the listing process. The next stage would be the development of hazard identification materials by OEHHA and the consideration of a chemical for listing at a future CIC meeting.

Introduction

In 2002, the CIC asked OEHHA to improve its process for prioritizing chemicals for review and potential listing. Leads from the CIC were identified to provide consultation to OEHHA in developing the improved process. Subsequently, the Chair of the Developmental and Reproductive Toxicant Identification Committee (DART IC) identified leads from that committee to also provide consultation to OEHHA. The CIC suggested that an improved process should more fully reflect exposure in California to chemicals under consideration, populations exposed, and the degree and extent of potential harm. In consultation with members of the DART IC and CIC, OEHHA undertook development of the improved process. There were two thirty-day public comment periods on the draft prioritization process document, from May 28, 2004 until June 28, 2004, and from September 3, 2004 until October 4, 2004. During the first of these, a public workshop was held on June 16, 2004, at which additional comments were accepted. The prioritization process document was revised based upon the public comments received and upon input from members of the DART IC and CIC, and the proposed revised prioritization process was presented to the DART IC at a public meeting on November 4, 2004, and to the CIC at a public meeting on November 1, 2004. After opportunity for additional public comment at each of these meetings, the proposal was discussed and endorsed by both committees. Accordingly, on December 17, 2004,

OEHHA adopted this streamlined prioritization process that it now uses to select chemicals for DART IC and CIC and review.

In accordance with the 2004 prioritization process, OEHHA used a focused literature review to conduct a preliminary appraisal of exposure potential and evidence of hazard on candidate chemicals in its database. The evidence of hazard used in this round of prioritization was an epidemiologic data screen, as described below. The chemicals that passed the screen were then subjected to preliminary toxicological evaluation. In the next step, OEHHA will release the results of the evaluation for public comment. At its next meeting, the CIC will provide advice and consultation regarding possible development of hazard identification materials on the chemicals being considered for listing under Proposition 65, as described in “Next Steps” below. The following is a description of the process OEHHA conducted in 2005-2007 to screen potential chemicals and select chemicals for consideration by the CIC.

Chemicals screened

All candidate chemicals were screened. These are chemicals in the tracking database with data suggesting that they cause cancer and have exposure potential in California. The evaluation of exposure potential is qualitative, based primarily on production, use or monitoring data. Candidate chemicals were not screened if they had already been assigned a final priority under OEHHA’s former prioritization process or if they were candidates for listing via an administrative listing mechanism.

Applying the epidemiology data screen

The epidemiology data screen was applied to 235 chemicals (or chemical groups). The screen entails the identification of chemicals with epidemiological studies suggesting evidence of carcinogenicity. The screen involved finding relevant epidemiology studies through a literature search and evaluating them. Applying the screen required identification of epidemiology studies of the chemical reporting an association between exposure to the chemical and increased cancer risk. More weight was given to analytical studies, and less weight to descriptive studies and case reports. Single case reports were not sufficient to satisfy the screen. For those chemicals with studies available, the studies were examined in some detail. Studies were reviewed to determine whether there was a positive finding of cancer associated with exposure to the chemical. The studies were further reviewed to determine whether the effect might be attributed to exposure to the chemical of concern with some confidence.

For each chemical, the steps were as follows:

1. The chemical's Chemical Abstracts Service (CAS) registry number and synonyms were identified using TOXLINE (<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE>).
2. The chemical identifiers were used in a search of the literature, using PubMed (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>). The search included a standardized search term (cancer [sb]) in the PubMed lexicon. Further refinement of the search was performed if necessary (e.g., enormous volume of articles returned).
3. Epidemiological studies were identified from the titles retrieved in the online search.
4. Abstracts of epidemiological articles were reviewed for relevance to the possible finding of cancer in humans exposed to the chemical. The full article was retrieved if the study appeared relevant upon review of the abstract. For articles lacking abstracts, copies of those with titles suggesting possible relevance were requested for review.
5. All articles identified as potentially relevant were considered in assessing whether evidence existed of human cancer related to exposure to the chemical.

Preliminary toxicological evaluation

A preliminary toxicological evaluation was made of chemicals identified through application of the epidemiology data screen. Further search of the literature was performed to identify animal bioassays and studies on genotoxicity, mechanism of action, metabolism and pharmacokinetics. This additional information was used in conducting a preliminary evaluation of the overall evidence of carcinogenicity for each of the chemicals identified by the epidemiology data screen. Chemicals for which a preliminary evaluation of the overall evidence indicated that carcinogenicity may be a concern have been proposed here for CIC consideration.

Chemicals proposed for CIC consideration

The above process yielded three chemicals:

- dimethylformamide
- marijuana smoke
- 2,4,6-trinitrotoluene

Epidemiological studies and other data relevant to the carcinogenicity of these chemicals are provided in papers and other materials listed in the Appendix.

Next Steps

With the publication of this document on September 7, 2007, OEHHA opened the public comment period on the chemicals proposed for CIC consideration. The comment period closes on November 6, 2007.

The CIC will deliberate on the three chemicals proposed for their consideration at an upcoming meeting, and provide advice and consultation regarding possible development of hazard identification materials. Written public comments received by OEHHA by November 6, 2007, will be provided to the CIC for consideration.

The CIC may also suggest other chemicals for which hazard identification materials should be prepared. At the CIC meeting, the public is given the opportunity to comment on the chemicals being proposed for hazard identification materials preparation. The CIC can vote on recommendations or provide less formal advice to OEHHA concerning which chemicals should be brought back for their consideration for listing following preparation of hazard identification materials.

Hazard identification materials summarizing the available scientific evidence on the carcinogenic potential of the selected chemicals would be prepared following an exhaustive search and evaluation of the scientific literature. These materials will be provided to the CIC, and released for public comment, prior to the public meeting of the CIC at which a listing decision would be deliberated upon.

Further details on prioritization, the development of hazard identification materials and committee consideration of the listing of chemicals under Proposition 65 are given in OEHHA (2004).

Reference

Office of Environmental Health Hazard Assessment (OEHHA, 2004). *Process for Prioritizing Chemicals for Consideration under Proposition 65 by the "State's Qualified Experts."* California Environmental Protection Agency, OEHHA, Sacramento, CA, December. Available online at:
www.oehha.ca.gov/prop65/CRNR_notices/state_listing/pdf/finalPriordoc.pdf