

**Prioritization:
Chemicals Identified for Consultation
with the Carcinogen Identification Committee**

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**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 five chemicals for review by the Carcinogen Identification Committee (CIC), using the prioritization process endorsed by the CIC and adopted by OEHHA in 2004. These chemicals (see Table 1 below) 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 by the CIC at a future meeting.

Introduction

OEHHA's 2004 "Process for Prioritizing Chemicals for Consideration under Proposition 65 by the "State's Qualified Experts" (available at <http://oehha.ca.gov/media/downloads/proposition-65/document/finalpriordoc.pdf>), describes the process utilized to identify chemicals for CIC consultation. Briefly, OEHHA identifies chemicals with evidence of cancer hazard *and* potential human exposure in California as candidate chemicals. Hazard data screens are applied to the results of focused literature searches conducted on candidate chemicals. Chemicals that pass at least one of the applied data screens are then subjected to a preliminary toxicological evaluation. The preliminary toxicological evaluation entails consideration of the available overall evidence of carcinogenicity (*i.e.*, epidemiology, animal bioassay, other relevant information), but is of necessity an initial, abbreviated appraisal of the information identified through screening-level literature searches. Based on this preliminary evaluation, OEHHA identifies chemicals for consultation with the CIC.

In this most recent prioritization effort, OEHHA has applied both a human and an animal data screen to candidate chemicals in the tracking database. OEHHA has identified five chemicals (See Table 1 below) for committee discussion, advice, and possible preparation of hazard identification materials for consideration at future CIC meetings.

This document, which is the subject of a public comment period that ends on October 24, 2016, presents these five chemicals. For each of the chemicals, OEHHA has compiled a separate summary of the relevant studies that were identified during the preliminary toxicological evaluation. The information for each of the five chemicals is presented in the Appendix.

At its next meeting on November 15, 2016, the CIC will provide advice and consultation regarding possible development of hazard identification materials on these chemicals, as described in “Next Steps” below. The following is a description of the process OEHHA conducted in applying these data screens.

Chemicals Screened

Under this process, only candidate chemicals are 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.

Chemicals that are candidates for listing via an administrative listing mechanism were not screened. OEHHA has applied both a human and an animal data screen to candidate chemicals present in the tracking database as of October 2014. Chemicals meeting either the human epidemiology or animal data screen are subjected to preliminary toxicological evaluation (see below).

Applying the Epidemiology Data Screen

The epidemiology data screen was applied to candidate 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 to identify studies 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 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 cancer effect might be attributed to the chemical with some confidence.

For each chemical, the steps used in applying the epidemiology data screen 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/pubmed>). 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.

Applying the Animal Data Screen

Subsequent to the epidemiology data screen, OEHHA applied the animal data screen to candidate chemicals (or chemical groups). The animal data screen is based on "positive" bioassays and involved finding relevant animal cancer bioassays through a literature search and evaluating them with regard to the screening criteria. A positive animal cancer bioassay is a study in which a treatment-related increase in the incidence of malignant or combined malignant and benign tumors is observed in a given tissue or organ, or for a given type of tumor (e.g., hemangiosarcoma). An increased incidence is either statistically significant ($p < 0.05$) by pairwise comparison with controls, or biologically significant (e.g., an increased incidence of a rare tumor type).

The animal screen identified chemicals with:

- Two or more positive animal cancer bioassays;
- One positive animal cancer bioassay with findings of tumors at multiple sites or with malignant (or combined malignant and benign) tumors occurring to an unusual degree with regard to incidence, site, type of tumor or age at onset;

- One positive animal cancer bioassay and evidence from a second animal cancer bioassay of benign tumors of a type known to progress to malignancy.

For each chemical, the steps used in applying the animal data screen were as follows:

1. The chemical identifiers were used in a search of the literature, using PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>). 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). Searches of TOXNET and other databases were also conducted, as appropriate.
2. Animal cancer bioassays were identified from the titles retrieved in the online search.
3. Abstracts of the identified articles were reviewed. The full article was retrieved if the abstract indicated that animal cancer bioassay findings were presented or discussed in the article. For articles lacking abstracts, copies of those with titles suggesting possible relevance were requested for review.
4. All articles identified as potentially relevant were considered in assessing whether the animal data screen employed in this round of prioritization had been met for the chemical (or chemical group) in question.

Preliminary Toxicological Evaluation

OEHHA conducted a preliminary toxicological evaluation of chemicals identified through application of the human and animal data screens. OEHHA also performed a further search of the literature to identify additional information relevant to carcinogenicity, such as studies on genotoxicity, mechanism of action, metabolism and pharmacokinetics (and animal cancer bioassays for those chemicals identified through the epidemiology data screen). This additional information was used to conduct a preliminary evaluation of the overall evidence of carcinogenicity for each of the chemicals identified by the data screens. 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 previously brought for consultation are not brought back to the CIC unless additional human or animal data indicative of a carcinogenicity concern are identified.

Chemicals Proposed for CIC Consideration

OEHHA identified the five chemicals listed in Table 1 below for possible preparation of hazard identification materials. The CIC will provide OEHHA with advice on the prioritization of these chemicals for possible preparation of hazard identification materials at its next meeting on Tuesday, November 15, 2016.

Table 1. Chemicals Identified through Prioritization and Proposed for Consideration by the Carcinogen Identification Committee.

- Aspartame
- Asphalt and Asphalt Emissions Associated with Road Paving and Asphalt and Asphalt Emissions Associated with Roofing
- Methyl Chloride
- Type I Pyrethroids
- Vinyl Acetate

For each of the chemicals, OEHHA has compiled a separate summary of the relevant studies that were identified during the preliminary toxicological evaluation. The information for each of the five chemicals is presented in the Appendix.

Chemicals for CIC Consultation November 15, 2016

Exposure Characteristics and Types of Studies Providing Evidence of Carcinogenicity

Chemical Name	Exposure				Human Data			Animal Data				Other Relevant Data					
	Widespread	High in frequent consumers	Limited / occupational	High in infrequent consumers	Analytical	Descriptive	Case series / reports	Two or more studies	One study w/ unusual incidence, site/type, age at onset	One study and second study with benign tumors only	One study	Tumor initiation / promotion or co-carcinogenicity studies	Genotoxicity	Carcinogenic metabolites	Structural similarity with tumorigens or P65 carcinogens	Hormonal activity / disruption	Other mechanistic studies
Aspartame ¹	X	X			X	X		X					X	X			
Asphalt and Asphalt Emissions Associated with Road Paving and Asphalt and Asphalt Emissions Associated with Roofing			X		X			X				X	X	X	X ²		X
Methyl Chloride			X		X				X				X		X		
Type I Pyrethroids	X				X			X					X		X	X	X
Vinyl Acetate	X				X			X					X	X			

¹ Aspartame passed the animal data screen in 2009 and was brought to the CIC for consultation. In 2009 the CIC recommended that aspartame be placed at the bottom of the 'medium' priority group for development of hazard identification materials. Since 2009, additional epidemiology data, animal cancer bioassays, and genotoxicity data have become available. In 2016 aspartame passed both the human and the animal data screens, and is being brought back to the CIC for consultation.

² Asphalt and asphalt emissions are complex mixtures with individual constituents (e.g., benzo[a]pyrene and several other polycyclic aromatic hydrocarbons) found in some other complex mixtures, such as diesel engine exhaust and tobacco smoke, which are Proposition 65 carcinogens.

Next Steps

With the release on September 9, 2016 of the five chemicals proposed for CIC consideration, OEHHA opens a public comment period that closes on October 24, 2016.

The CIC will consider the chemicals in Table 1 at its November 15, 2016 meeting, providing advice and consultation regarding possible development of hazard identification materials by OEHHA. Written public comments received by OEHHA by October 24, 2016, will be provided to the CIC for consideration. The public is also given the opportunity at the CIC meeting to comment on the chemicals being proposed for hazard identification materials preparation.

The CIC may also suggest other chemicals for which hazard identification materials should be prepared. 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.

For chemicals that are brought to the CIC for listing consideration, OEHHA will prepare hazard identification materials summarizing the available scientific evidence on the chemicals' carcinogenic potential following a comprehensive 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 at which the CIC deliberates on a listing decision.

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 17, 2004. Available online at: <http://oehha.ca.gov/media/downloads/proposition-65/document/finalpriordoc.pdf>