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 39 chemicals for review by the Carcinogen Identification Committee (CIC) under Proposition 65,[1] 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 is the development of hazard identification materials by OEHHA followed by consideration of the chemical for listing by the CIC at a future meeting.

Introduction

OEHHA has screened several hundred chemicals in the OEHHA tracking database for evidence of cancer hazard as well as potential human exposure in California. This initial screening follows the procedure described in the 2004 "Process for Prioritizing Chemicals for Consideration under Proposition 65 by the "State's Qualified Experts," which is available at http://www.oehha.ca.gov/prop65/CRNR_notices/state_listing/pdf/finalPriordoc.pdf. Chemicals with data suggesting they cause cancer and with potential human exposure in California become candidate chemicals.

OEHHA applied both a human and an animal data screen to all of the candidate chemicals in the tracking database. These screens were discussed at the November 17, 2007 and November 5, 2008 meetings of the CIC, and are described below. Chemicals that passed either of these hazard screens were 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 identified the 39 chemicals in Table 1 for committee discussion, advice,

[1] Health and Safety Code section 25249.5 et seq.

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 September 20, 2011, presents these 39 chemicals. For each of the chemicals, OEHHA has compiled a separate summary of the relevant studies that were identified during the preliminary toxicological evaluation. This information for each of the 39 chemicals is in the Appendix.

At its next meeting, 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, OEHHA screened 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 all of the other chemicals in the database. In 2009 OEHHA brought 38 chemicals to the CIC for review and consultation. In 2010 OEHHA brought 27 chemicals to the CIC for review and consultation. Now OEHHA is bringing an additional 39 chemicals (see Table 1) identified through this screening process for CIC review and consultation.

Applying the Epidemiology Data Screen

OEHHA first applied the epidemiology data screen 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. 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. OEHHA reviewed the studies 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 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/sites/entrez). 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/sites/entrez). 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).
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

A preliminary toxicological evaluation was made 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 Proposed for CIC Consideration

OEHHA identified the 39 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 Wednesday and Thursday, October 12 and 13, 2011.

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

- Abacavir and Its Salts
- Acetaminophen
- Bisphenol A
- Butyl Benzyl Phthalate
- Butylated Hydroxytoluene
- C.I. Disperse Yellow 3
- Chloroalkyl Ethers
- Chloropicrin
- Clodinafop-Propargyl
- Coumarin
- Dapsone
- Dibenzanthracenes and Dibenz[*a,c*]anthracene
- 3,3'-Dichlorobenzidine-Based Compounds Metabolized to 3,3'-Dichlorobenzidine
- 2,4-Dichlorophenoxyacetic acid (2,4-D) and Its Salts and Esters
- Dicloran
- Dinitroaniline Pesticides and Prodiamine and Trifluralin
- Entecavir
- Flonicamid
- Fluazinam
- Hexythiazox
- Hydralazine and Its Salts
- Isophosphamide
- Metofluthrin
- Mixtures Containing Pentabromochlorocyclohexane
- N-Methyl-N-Nitroso-1-Alkylamines and N-Methyl-N-Nitroso-1-Octanamine, N-Methyl-N-Nitroso-1-Decanamine, N-Methyl-N-Nitroso-1-Dodecanamine, and N-Methyl-N-Nitroso-1-Tetradecanamine
- N-Nitroso-N-Methylaniline
- N-Methylpyrrolidone
- 6-Nitrobenzimidazole
- Pentachloronitrobenzene
- Pimecrolimus and Tacrolimus
- Pivalolactone
- Pyraflufen Ethyl
- Raloxifen and Its Salts
- Stavudine
- Thiophanate Methyl
- Topoisomerase II Inhibitors
- Triazole Antifugal Agents
- 2,4,6-Trimethylaniline and Its Salts
- Tris(2-Ethylhexyl) Phosphate

For each of the chemicals, OEHHA has compiled a separate summary of the relevant studies that were identified during the preliminary toxicological evaluation. This information for each of the 39 chemicals is in the Appendix.

Chemicals for CIC Consultation October 12 and 13, 2011

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	Analytical: mixed / poorly defined exposure	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
Abacavir and Its Salts		x							x					x		x		
Acetaminophen	x				x				x				x	x				x
Bisphenol A	x								x				x	x			x	x
Butyl Benzyl Phthalate	x								x				x	x			x	x
Butylated Hydroxytoluene	x								x				x	x		x		
C.I. Disperse Yellow 3	x								x					x		x		
Chloroalkyl Ethers	x				x			x	x				x	x		x		
Chloropicrin	x										x			x				
Clodinafop-Propargyl	x								x					x		x		x
Coumarin	x								x					x	x			
Dapsone		x			x			x	x				x	x		x		
Dibenzanthracenes and Dibenz[a,c]anthracene	x								x				x	x	x	x		
3,3'-Dichlorobenzidine-based Compounds Metabolized to 3,3'-Dichlorobenzidine			x				x		x					x	x	x		x
2,4-Dichlorophenoxyacetic acid and Its Salts and Esters	x				x				x					x			x	x
Dicloran	x										x			x		x		
Dinitroaniline Pesticides and Prodiamine and Trifluralin	x				x				x					x		x	x	
Entecavir		x							x					x		x		
Flonicamid	x								x					x		x		x

Chemical Name	Exposure				Human Data				Animal Data					Other Relevant Data				
	Widespread	High in frequent consumers	Limited / occupational	High in infrequent consumers	Analytical	Descriptive	Analytical: mixed / poorly defined exposure	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
Fluazinam	x								x					x				
Hexythiazox	x										x			x				
Hydralazine and Its Salts		x			x			x	x					x				x
Isophosphamide		x							x					x		x		
Metofluthrin				x					x					x		x		x
Mixtures Containing Pentabromochlorocyclohexane	x										x			x				
N-Methyl-N-Nitroso-1-Alkylamines and four individual compounds	x								x					x		x		
N-Nitroso-N-Methylaniline	x								x					x		x		
N-Methylpyrrolidone	x								x					x				
6-Nitrobenzimidazole			x						x					x		x		
Pentachloronitrobenzene	x								x					x				
Pimecrolimus and Tacrolimus		x			x			x	x					x				x
Pivalolactone			x						x					x		x		
Pyraflufen Ethyl	x								x					x				
Raloxifen and Its Salts		x			x				x					x		x		
Stavudine		x							x					x		x		
Thiophanate Methyl	x								x					x		x	x	
Topoisomerase II Inhibitors				x	x			x	x					x		x		x
Triazole Antifungal Agents	x								x					x		x		x
2,4,6-Trimethylaniline and Its Salts	x								x					x		x		
Tris(2-Ethylhexyl)Phosphate	x								x					x		x		

Next Steps

With the release on July 22, 2011 of the 39 chemicals proposed for CIC consideration, OEHHA opens a public comment period that closes on September 20, 2011.

The CIC will consider the chemicals in Table 1 at its October 12-13, 2011 meeting, providing advice and consultation regarding possible development of hazard identification materials by OEHHA. Written public comments received by OEHHA by September 20, 2011, will be provided to the CIC for consideration. The public is also given the opportunity to comment on the chemicals being proposed for hazard identification materials preparation at the CIC meeting.

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 following preparation of hazard identification materials.

Hazard identification materials summarizing the available scientific evidence on the carcinogenic potential of the selected chemicals will be prepared following an exhaustive search and evaluation of the scientific literature. OEHHA will provide these materials to the CIC and release them for public comment prior to the public meeting at which the CIC will consider the chemical's listing. 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