

PROCESS FOR PRIORITIZING CHEMICALS FOR CONSIDERATION UNDER PROPOSITION 65 BY THE "STATE'S QUALIFIED EXPERTS"

**Office of Environmental Health Hazard Assessment
California Environmental Protection Agency**

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BACKGROUND

The Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65, California Health and Safety Code section 25249.5 *et seq.*) requires the Governor to publish a list of chemicals known to cause cancer or reproductive toxicity. One of the mechanisms by which a chemical is placed on this list is a finding by the "state's qualified experts" that a chemical "has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer or reproductive toxicity" (Health and Safety Code section 25249.8(b)). As the lead agency for the implementation of Proposition 65, the Office of Environmental Health Hazard Assessment (OEHHA) has formed the Science Advisory Board (SAB), which includes two committees of independent scientists and health professionals that serve as the state's qualified experts. These committees are the Carcinogen Identification Committee (CIC) and the Developmental and Reproductive Toxicant Identification Committee (DART IC).

This document describes the process used by OEHHA staff to identify chemicals for evaluation by the CIC and DART IC. The process is designed to ensure that the efforts of these committees are focused on chemicals that may pose significant hazards to Californians. As with the previous process (OEHHA, 1997), this process includes multiple opportunities for public input.

The CIC, at its December 2002 meeting, asked OEHHA to develop this process as an alternative to the random prioritization process that had been in use since 1997. The CIC specifically asked for an alternative process that could better take into account the level of exposure in California, the population potentially affected by various chemicals being reviewed by OEHHA, as well as the degree and extent of potential harm posed by the chemical. The CIC also asked OEHHA to address the deficiencies in the existing process and the costs of an alternative process. Deficiencies noted in the existing process included the significant length of time needed to conduct prioritizations, the considerable staff resources expended, and the public health importance of chemicals reaching the committees for consideration. The Chair of the CIC requested that two of its members informally assist OEHHA in developing an alternative procedure.

Since the prioritization process also affects the work of the DART IC, after consultation with the Director of OEHHA, the Chair of the DART IC asked that members of the DART IC also be involved in developing an alternative prioritization process. An informal workgroup comprised of OEHHA staff and a few members of the DART IC and CIC assisted OEHHA in this effort. The process laid out in this document is the result of a two-year proceeding. The workgroup developed a draft prioritization process following input from the DART IC, CIC and the public. Two public comment periods and a public workshop were held and finally the prioritization process outlined here was discussed and endorsed by the CIC at their November 1, 2004 public meeting and the DART IC at their November 4, 2004 public meeting, following additional public comment.

This prioritization process replaces the existing one described in OEHHA's 1997 document, "Procedure for Prioritizing Candidate Chemicals for Consideration under Proposition 65 by the 'State's Qualified Experts'" and is posted on the OEHHA Web site.

The goals of this process is to more quickly and efficiently prioritize chemicals for development of hazard identification materials for subsequent CIC and DART IC review.

The prioritization process is based on a preliminary appraisal of the evidence of hazard for the purpose of identifying chemicals for possible hazard identification materials preparation and committee review. The cost in staff resources and time required to conduct the proposed process are not expected to exceed those of the previous process.

The prioritization process described here is the primary method by which a chemical can reach the CIC or DART IC for consideration. As has always been the case, the Director of OEHHA at his or her discretion may decide to abbreviate or modify the process. For example, a member of the public or a committee member may petition OEHHA to abbreviate the process to respond to new information or an emerging public health issue. Following consultation by the Director with the appropriate committee chair, a chemical may be placed on the agenda for discussion at the next scheduled committee meeting. In all such cases, OEHHA will post public notices of any such action in the *California Regulatory Notice Register* and on its Web site, with appropriate notice periods.

In addition, a chemical may be referred to the CIC or DART IC by OEHHA when it is found not to meet the criteria for listing by the authoritative bodies mechanism subsequent to the issuance by OEHHA of a Notice of Intent to List as provided in regulation (Title 22, Cal. Code of Regs. §12306). Finally, as appropriate, chemicals will be brought to the relevant committees that are listed in Title 22, Cal. Code of Regs. § 14000 (Health and Safety Code section 25249.8(c)) because they are required by State or Federal law to be tested for carcinogenicity or reproductive toxicity, once the required testing has been completed. If the resulting tests on a chemical provide data with strong evidence of cancer or reproductive toxicity, the chemical will typically be brought to the relevant committee for consideration.

PRIORITIZATION PROCESS

The following lays out the steps that OEHHA uses in selecting chemicals for consideration by the CIC and DART IC. This prioritization process is conducted on a periodic basis, with no set interval, and it is rerun as needed. Figure 1 is a flow chart of the prioritization process.

- **Tracking database.** OEHHA maintains tracking databases of chemicals that have come to OEHHA's attention for DART or carcinogenicity evaluation. Chemicals may come to OEHHA's attention through literature searches or suggestions from the CIC or DART IC, other state organizations, the scientific community or the general public. A chemical may be grouped with other, similar chemicals at various stages in the prioritization process. For example, groupings may result from similarity in chemical structure, mechanistic considerations, or the production of the same or similar proximate active dissociation products or metabolites. Examples of chemical groupings that have been reviewed by the CIC or DART IC are: aflatoxins and polychlorinated biphenyls (similarity of chemical structure and mechanism), inorganic oxides of arsenic (same active dissociation product), alcoholic beverages (same set of proximate carcinogens), and radionuclides (similarity of mechanism and active agent).
- **Candidate Chemicals.** Chemicals entered into the tracking database are investigated for the existence of relevant toxicity data and the potential for human exposure. Those with data suggesting they cause reproductive toxicity or cancer and have exposure potential in California become candidate chemicals.

The toxicity evaluation at this stage involves the identification of one or more studies suggesting cancer or reproductive effects in animals or humans. The evaluation of exposure potential in California is qualitative and does not involve prediction of levels of exposure. Production, use, or monitoring data provide qualitative evidence of exposure potential. In the absence of information specific to California, data on production, use and environmental levels at the national level is generally assumed to reflect that in California. Examples of evaluations of exposure potential in California are given in OEHHA (2004).

- **Proposed Chemicals for Committee Consideration.** Candidate chemicals are screened using a focused literature review. All candidate chemicals initially undergo an epidemiology data screen. This involves the identification of those chemicals with epidemiological evidence suggesting they cause cancer or reproductive toxicity. The type of literature review screen will change over time. The literature review is typically based upon original research articles, literature compilations, or reviews. A chemical that does not pass this screen remains a candidate chemical, and will be reevaluated using future screens based upon other relevant criteria such as evidence from animal studies at a later time. This and future screens will be applied to all candidate chemicals. In

conducting the initial epidemiology screen, if OEHHA becomes aware of a chemical with very strong evidence from animal studies, that does not meet the epidemiology screen, but nevertheless poses a potentially significant hazard, that chemical will be proposed for committee consideration as well.

Chemicals selected by the screen undergo preliminary toxicological evaluation to determine whether they should be proposed for committee consideration for possible preparation of hazard identification materials. At this stage of the prioritization process, the overall evidence of carcinogenicity or reproductive toxicity of the chemical is considered, including epidemiologic, animal bioassay, and other relevant information (e.g., on pharmacokinetics, chemical structure, maternal toxicity, genotoxicity), as appropriate. This preliminary overall evaluation is typically based on original research articles, and literature compilations or reviews. Both positive and negative studies will be considered.

Factors considered in weighing the epidemiological evidence include the type of epidemiological study (e.g., case-control), study population, exposure situation, endpoint (e.g., tumor type, developmental effect), dose-response, possible roles of bias and confounding, and overall study quality. Greater weight will be given to analytical studies, and less weight to descriptive studies and case reports. Factors considered in weighing evidence from animal studies include the number of experiments, species tested, routes of administration, frequency and duration of exposure, numbers of test animals, and dose-response. Other relevant data such as from genotoxicity, pharmacokinetic and mechanistic studies, and maternal toxicity will also be considered in weighing the evidence. In accordance with guidelines of the U.S. Environmental Protection Agency (1991, 1996), adverse developmental effects that co-occur with maternal toxicity, and reproductive effects that co-occur with systemic toxicity are considered evidence of reproductive toxicity unless these toxicities are severe enough to preclude interpretation of the study. In animal data evaluations, effects are assumed to be relevant to humans, unless OEHHA determines there is sufficient evidence to the contrary.

It is unlikely that chemicals will be proposed for CIC or DART IC review that have been recently reviewed by an authoritative body and found to have insufficient evidence of carcinogenicity or reproductive toxicity, respectively. Exceptions to this generalization may occur, for example, if an authoritative body has evaluated a chemical but failed to review all relevant data, or compelling new data have become available since the evaluation. Also, a chemical may be taken to the CIC or DART IC if an authoritative body finds adequate evidence of carcinogenicity or reproductive toxicity but the evidence or formal identification does not meet the criteria for listing in regulation (Title 22, section 12306).

Public comment and submission of chemical list to the relevant committee. The list of chemicals proposed by OEHHA for CIC or DART IC consideration for potential preparation hazard identification materials is released to the public for comment, along

with the rationale for the selection. A notice identifying OEHHA's list of chemicals proposed for potential preparation of hazard identification materials is published in the *California Regulatory Notice Register* and posted on OEHHA's Web site. This begins a 60-day public comment period. The public may then comment on the scientific evidence pertaining to the selection of the chemical for prioritization. OEHHA then compiles public comments and sends them to the relevant committee for review, along with the list of chemicals proposed for potential preparation of hazard identification materials and related rationale.

Appraisals of the evidence to support a proposal for potential preparation of hazard identification materials for a given chemical for review by the CIC or DART IC is qualitative. This initial evaluation by its nature is abbreviated and is not as intensive or thorough as a hazard evaluation. It is simply a preliminary appraisal for the purpose of identifying chemicals for further evaluation, preparation of hazard identification materials and potential committee review. The in-depth review of toxicological data would occur at the later stage, when hazard identification materials are developed.

- ***Committee Consultation on Chemicals for Review.*** During the CIC and DART IC meetings, OEHHA will receive advice and consultation from the committees on the list of chemicals proposed for hazard identification materials preparation and eventual committee consideration. That is, the committee advises OEHHA on the chemicals that should undergo the development of hazard identification materials, committee review and eventual listing decision. The CIC advises OEHHA concerning chemicals for carcinogenicity hazard identification, and the DART IC advises OEHHA concerning chemicals for reproductive toxicity hazard identification. The committees may also suggest other chemicals that should undergo hazard identification materials preparation. At the committee meeting, the public is given the opportunity to comment on chemicals being proposed for hazard identification materials preparation and eventual committee consideration. The committees can vote on recommendations or provide less formal advice to OEHHA concerning which chemicals should be brought back for their consideration following preparation of hazard identification materials.
- ***OEHHA Selection of Chemicals for Preparation of Hazard Identification Materials.*** OEHHA selects the chemicals for the development of hazard identification materials. After receipt of committee advice and public comment, OEHHA will select those chemicals that appear to have evidence of reproductive toxicity or carcinogenicity sufficiently strong to warrant the development of hazard identification materials and subsequent CIC or DART IC review for possible listing.

The prioritization process ends with the selection of chemicals by OEHHA for the development of hazard identification materials. The next steps in the process, described below, are those of hazard identification for the purposes of Proposition 65.

- ***Data Call-In.*** OEHHA solicits information on the evidence for carcinogenicity or reproductive toxicity on chemicals selected for review. A "data call-in" notice published

in the *California Regulatory Notice Register* and posted on OEHHA's Web site requests information relevant to the preparation of hazard identification materials on the chemicals selected for review.

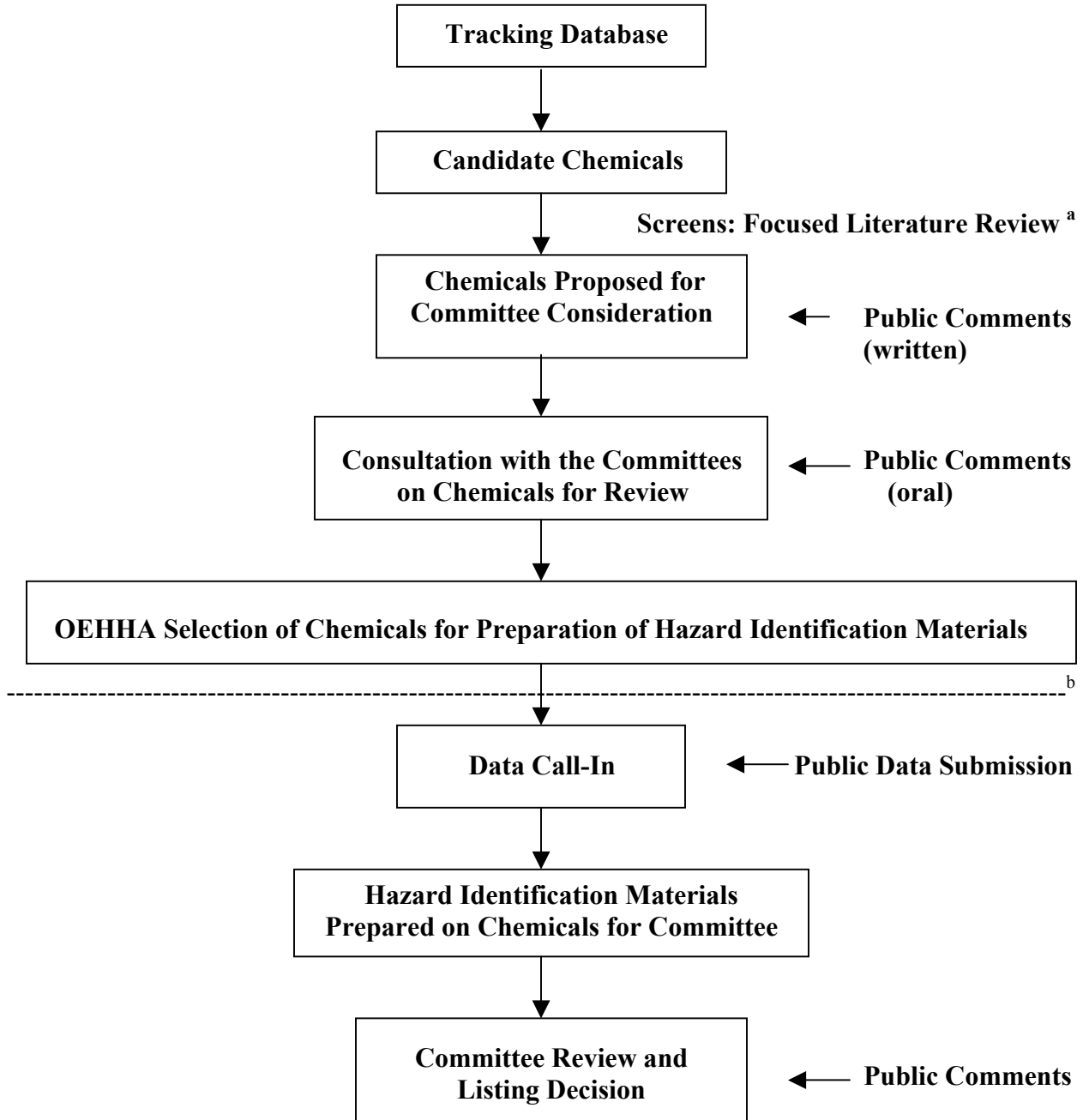
- ***Hazard Identification Materials on Chemicals for Committee Review.*** Hazard identification materials are prepared for CIC or DART IC consideration and released to the public for comment. OEHHA decides the order in which these materials are prepared based on committee advice, staff resources, and public health considerations. The public is invited to comment on the hazard identification materials during a 60-day public comment period. Approximately two weeks before the public meeting of the respective committee, the public comments are collated and sent to the committee for consideration along with the hazard identification materials developed by OEHHA.
- ***Committee Review and Decision on Listing.*** The CIC or DART IC holds a public meeting to deliberate on whether the chemical has been clearly shown to cause cancer or reproductive toxicity. The hazard identification materials and the public comments received during the 60-day comment period are considered at the meeting. The public has a further opportunity to comment at the meeting. At the conclusion of the deliberations, the committee generally will render an opinion as to the developmental or reproductive toxicity or carcinogenicity of a chemical, as appropriate. In considering groups of chemicals, the committee may make findings for individual members of the group, or the group as a whole (e.g., arsenic [inorganic oxides]).

LEGAL CONSIDERATIONS

The prioritization process is, and has always been, intended to be used by OEHHA as a general process for prioritization of chemicals for committee consideration. The Director may abbreviate or otherwise modify the process. For example, the public or a committee member may petition the Director to abbreviate the prioritization process to respond to new information or an emerging public health issue, and the chemical may consequently be placed on the agenda of an upcoming committee meeting for discussion. In all such cases, OEHHA will post public notices of any such action in the *California Regulatory Notice Register* and on its Web site, and provide appropriate notice and comment periods. The prioritization process does not now have, nor has it ever had, the force of a regulation. Based upon Health and Safety Code section 25249.8(e), the development and implementation of the prioritization process is not subject to the provisions of the Administrative Procedure Act.

This prioritization process will not generally be applied to chemicals contained only in prescription or over-the-counter medications with mandatory cancer or reproductive toxicity warnings approved by the federal Food and Drug Administration, based on the California Supreme Court decision in *Paul Dowhal v Smith-Kline Beecham Consumer Healthcare et al.* (2004) 12 Cal. Rptr. 3d 262; 4 Cal. Daily Op. Serv. 3259, 2004 Daily Journal D.A.R. 4601.

Figure 1. Prioritization Process



^a First screen based on epidemiological evidence; subsequent screens may be based on animal evidence.

^b Dotted line indicates where the prioritization process ends and hazard identification process begins.

REFERENCES

Office of Environmental Health Hazard Assessment (OEHHA, 1997). Procedure for Prioritizing Candidate Chemicals for Consideration under Proposition 65 by the “State’s Qualified Experts.” OEHHA, Reproductive and Cancer Hazard Assessment Section, Sacramento.

Office of Environmental Health Hazard Assessment (OEHHA, 2004). Final Prioritized Candidate Chemicals Under Consideration for Carcinogenicity Evaluation: Forty-five Batch #4 Chemicals, OEHHA, Reproductive and Cancer Hazard Assessment Section, Sacramento. (available at http://www.oehha.ca.gov/prop65/docs_state/pdf/bat4final45sums.pdf)

U.S. Environmental Protection Agency (U.S. EPA, 1991). Guidelines for Developmental Toxicity Risk Assessment. *Federal Register* 56(234): 63798-63826.

U.S. Environmental Protection Agency (U.S. EPA, 1996). Guidelines for Reproductive Toxicity Risk Assessment. *Federal Register* 61(212): 56274-56322.