Carcinogen Identification Committee
c/o Esther Barajas-Ochoa
Office of Environmental Health Hazard Assessment
Proposition 65 Implementation Office
1001 I Street
P. O. Box 4010, MS-12B
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November 14, 2022

RE: Consideration of bisphenol A (BPA) for possible listing under Proposition 65 based on carcinogenicity

Dear Carcinogen Identification Committee,

On behalf of the Natural Resources Defense Council, I appreciate the opportunity to submit comments on the proposal to list bisphenol A (BPA) as a carcinogen under Proposition 65. BPA is a public health threat due to its widespread occurrence and potential to cause health harms, including cancer. Biomonitoring data in California show that BPA is frequently detected in Californians.

OEHHA staff scientists have reviewed the available publications as of December 2021 - in addition to a data call-in period from January 2 to March 14, 2022, and have prepared thorough documentation demonstrating that BPA meets applicable criteria and should be listed as a carcinogen under Proposition 65.

A) Standards for CIC to recommend listing a chemical under Proposition 65

Pursuant to the regulations implementing Proposition 65, the Cancer Identification Committee (CIC) may "[r]ender an opinion . . . as to whether specific chemicals have been clearly shown, through scientifically valid testing according to generally accepted principles, to cause cancer." 27 Cal. Code Regs. § 25305(a). The criteria that guide the CIC's recommendations emphasize a "weight-of-evidence" approach and are "not intended to limit the scope of the Committee's consideration of appropriate scientific information, nor to limit its use of best scientific judgment."[1] However, they provide important indicators of the sufficiency of evidence that would support a recommendation for listing a chemical.

[1] OEHHA, *Guidance Criteria for Identifying Chemicals for Listing as "Known to the State to Cause Cancer"*. Revised March 2001.

According to the criteria, "if the weight of scientific evidence clearly shows that a certain chemical causes invasive cancer in humans, or that it causes invasive cancer in animals (unless the mechanism of action has been shown not to be relevant to humans), the committee will normally identify that chemical for listing."[2]

The CIC's guidance criteria outline various considerations for sufficiency of evidence for carcinogenicity in human and animal studies and includes general principles, such as General Principle F:

> "Whether evaluating the evidence for carcinogenicity in animals or humans, CIC members may make judgements utilizing other, more indirect, scientifically valid observations obtained using generally accepted methods and principles. Such information may derive from studies of genetic toxicology or DNA repair using in vitro methods, cultured mammalian cells, or living prokaryotes, lower eukaryotes, plants, or insects, although changes induced in whole mammals must be considered more pertinent."[3]

The causal relationship between exposure and cancer is judged on the weight of the evidence. Such a judgement is based on several details outlined in the CIC's guidance and include, for example, the route, schedule, and dosage of exposure, the species, strain, sex, and age of the animals, and the timing of appearance of and histological and anatomical description of tumors.[4]

The evidence for carcinogenicity presented by OEHHA meets these criteria, and therefore the CIC should recommend BPA for listing.

B) BPA is carcinogenic and should be listed under Proposition 65

OEHHA has clearly shown the weight-of-evidence supports listing BPA as a carcinogen under Proposition 65. The CIC guidance notes that the "body of evidence shall include all evidence bearing on the issue of carcinogenicity shown through scientifically valid testing according to generally accepted principles," including either human or animal data. There are two main categories of evidence relevant to the carcinogenicity of BPA.

The first is evidence of carcinogenicity in experimental animals, including, as specified in the CIC criteria, "an increased incidence of malignant tumors or combined malignant and benign tumors in multiple species or strains, in multiple experiments." This includes statistically significant increases in hepatocellular tumors, pituitary tumors, thyroid C-cell tumors, clitoral gland tumors, stromal polyps, testicular interstitial (Leydig) cell tumors, leukemia, lymphoma and fibroadenoma, adenocarcinoma and adenoma in mammary glands in long-term carcinogenicity studies of BPA across several strains of rats and mice. Additionally, several types of rare cancers were identified in rats and mice.

The second is mechanistic evidence of carcinogenicity, consistent with Principle F (above). The key characteristics of carcinogens were developed from a comprehensive review of the more

[2] Ibid.
[3] Ibid.
[4] Ibid.

than 100 agents known to cause cancer in humans.[5] The key characteristics approach provides a consistent, objective and systematic framework for identifying and evaluating mechanistic evidence and is consistent with General Principle F ("generally accepted methods and principles") as it is used by authoritative bodies, including IARC[6] and the Report on Carcinogens[7] to evaluate mechanistic evidence in the identification of carcinogens. OEHHA documents sufficient evidence for all ten of the key characteristics of carcinogens. Studies show that BPA:

1. is electrophilic or can be metabolically activated,
2. is genotoxic,
3. alters DNA repair or causes genomic instability,
4. induces epigenetic alterations,
5. induces oxidative stress,
6. induces chronic inflammation,
7. is immunosuppressive,
8. modulates receptor-mediated effects,
9. causes immortalization,
10. and alters cell proliferation, cell death, or nutrient supply.

Both of these categories of data--relying on evidence of carcinogenicity in animals and on mechanistic evidence of carcinogenicity--are well-established and accepted scientific practice, consistent with the regulations' and the guidance's focus on generally accepted principles for assessing carcinogenicity, for example as expressed in Principle F. We agree with the limitations of the epidemiological studies that OEHHA outlined in the Evidence Document. However, there exists sufficient animal and mechanistic data for carcinogenicity of BPA, and therefore the CIC should recommend BPA for listing.

C) Additional studies for consideration

Of note, there are several papers that interrogate mechanistic changes in the mammary gland that may be relevant to the development of later life cancer in female and male mice exposed developmentally or perinatally to BPA that were not discussed in this document.[8,9,10,11] It is unclear at what point in the review process (literature searching or literature screening) these studies were excluded. At least one of these studies[12] would have been captured by the literature search described in Table B3 but was not discussed in the Evidence Document. Collectively, these studies indicate that early life exposure to BPA can alter the developmental

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[5] Smith, M.T., et al., *Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis.* Environ Health Perspect, 2016. **124**(6): p. 713-21.
[6] Samet, J.M., et al., *The IARC Monographs: Updated Procedures for Modern and Transparent Evidence Synthesis in Cancer Hazard Identification.* J Natl Cancer Inst, 2020. **112**(1): p. 30-37.
[7] Atwood, S.T., et al., *New Perspectives for Cancer Hazard Evaluation by the Report on Carcinogens: A Case Study Using Read-Across Methods in the Evaluation of Haloacetic Acids Found as Water Disinfection By-Products.* Environ Health Perspect, 2019. **127**(12): p. 125003.
[8] Vandenberg, L. N., et al., *Perinatal Exposure to the Xenoestrogen Bisphenol-A Induces Mammary Intraductal Hyperplasias in Adult CD-1 Mice*. Reproductive Toxicology, 2008. **26**: p. 210–19.
[9] Vandenberg, L. N., et al., *Exposure to Environmentally Relevant Doses of the Xenoestrogen Bisphenol-A Alters Development of the Fetal Mouse Mammary Gland*. Endocrinology, 2007. **148**(1): p. 116–127.
[10] Wadia, P. R., et al., *Perinatal Bisphenol A Exposure Increases Estrogen Sensitivity of the Mammary Gland in Diverse Mouse Strains*. Environmental Health Perspectives, 2007. **115**: p. 592–598.
[11] Vandenberg, L. N., et al., *The Male Mammary Gland: A Target for the Xenoestrogen Bisphenol A*. Reproductive Toxicology, 2013. **37**: p. 15–23.
[12] Ibid.

trajectory of the mammary gland tissue. Upon developmental exposure to environmentally relevant levels of BPA, intraductal hyperplasia characterized as proliferative structures that appeared as “beaded ducts” were observed. These studies may provide additional mechanistic support for the development of mammary gland tumors following exposure to BPA. OEHHA's Evidence Document failed to provide a description of why these studies were excluded.

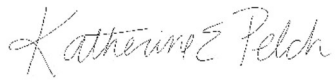
D) Additional transparency needed in the conduct of the systematic literature review

OEHHA reports using a systematic literature review approach based on The Office of the Report on Carcinogens (RoC) 2015 Handbook.[13] The literature search strategies appear well constructed. However, I note several areas of improvement in the conduct and reporting of the described approach. Firstly, how studies are screened and selected throughout the process is not clearly described. The inclusion and exclusion criteria that were used for study screening in SWIFT-Active Screener and HAWC (Health Assessment Workspace Collaborative) at both the title and abstract level and the full text level should be more explicitly stated either in Section 2.2 or Appendix B. Secondly, the parameters by which SWIFT-Active Screener is utilized should be more clearly described. An advantage of using SWIFT-Active Screener is that it iteratively predicts the point at which screening may stop,[14] and the selected cut-off point should be clearly stated. Thirdly, best practices in systematic review methodology recommend at least two reviewers be required to exclude studies at any point in the review process. The information provided in Appendix A suggests that studies could be excluded after only a single review. This contradicts information in Section 2.2 which states “two OEHHA scientists independently completed the screening for a decision to be made on each title and abstract, following predefined inclusion and exclusion criteria.” Finally, providing a link to the BPA literature tag tree in HAWC, would improve the transparency of the process and allow the public and others to quickly access and evaluate the lists of studies categorized within each tag.

Conclusion

OEHHA used scientifically supported systematic review methodology and generally accepted, scientifically sound criteria to arrive at the conclusion to list BPA as carcinogenic. Therefore, the CIC should determine that BPA has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.

Respectfully submitted,



Katherine E Pelch, PhD
Scientist
Natural Resources Defense Council

[13] NTP, *Handbook for Preparing Report on Carcinogens Monographs* Ofiffice of the Report on Carcinogens, 2015.

[14] Howard, B.E. et al., *SWIFT-Review: A Text-Mining Workbench for Systematic Review*. Systematic Reviews, 2016. **5**(1): p. 87.