November 14, 2022

Esther Barajas-Ochoa
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-12B
Sacramento, CA 95812-4010

RE: Carcinogen Identification Committee Meeting Scheduled for December 14, 2022 to Consider Possible Listing of Bisphenol A under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65)

Dear Ms. Barajas-Ochoa:

The American Chemistry Council (ACC) submits the following comments relative to OEHHA's Hazard Identification Document (HID) on the carcinogenicity of Bisphenol A (BPA). Our comments demonstrate that the scientific evidence in the HID does not meet the standard for listing in the statute and the Carcinogen Identification Committee (CIC) "Guidance Criteria for Identifying Chemicals for Listing as 'Known to the State to Cause Cancer.'"

Health and Safety Code § 25249.8 states "[a] chemical is known to the state to cause cancer … if in the opinion of the state's qualified experts it has been clearly shown through scientifically valid testing *according to generally accepted principles* to cause cancer." (emphasis added). The CIC guidance criteria further provide that:

> a "weight-of evidence" approach shall be used to evaluate the body of information available for any given chemical. The body of evidence shall include all evidence bearing on the issue of carcinogenicity shown through scientifically valid testing according to generally accepted principles…. Thus 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.[1]

As outlined below and in the attached scientific comments, the weight of scientific evidence does not clearly show that BPA causes cancer in humans or animals.

[1] https://oehha.ca.gov/media/downloads/crnr/revcriteria.pdf

Based on review of the HID prepared by the OEHHA Reproductive and Cancer Hazard Assessment Branch, the attached scientific comments conclude:

- The epidemiology studies contain many important limitations affecting the final conclusions. The major limitation centers around the measurement of BPA in biological samples collected from study participants at only one point in time, which does not reflect long-term exposure levels during the critical period of cancer development. Even without considering the limitations, the epidemiology studies do not provide clear and compelling evidence that BPA causes invasive cancer due to a lack of consistency in the direction or statistical significance of the results.
- Most of the animal studies reviewed have significant methodological limitations and are of limited utility for assessing BPA carcinogenicity. In contrast, the CLARITY BPA core study provides reliable evidence consistent with a lack of BPA carcinogenicity even when subjected to additional statistical analysis by OEHHA. The evidence from the chronic animal bioassays, as well as the other experimental animal studies, does not demonstrate clear and consistent evidence that BPA causes cancer in experimental animals.
- OEHHA provides some evidence, particularly from *in vitro* studies, that BPA exhibits the "10 key characteristics of carcinogens" (KCCs), but these characteristics are also shared by many non-carcinogenic substances and the relevance of the KCC to cancer development in humans is unclear. The KCC are not supported by the results of the epidemiology and experimental animal studies of BPA, which do not provide clear or consistent evidence that BPA induces invasive cancer in humans or animals by any mechanism.

BPA does not meet the standard for listing set forth in Health and Safety Code § 25249.8 and the CIC guidance criteria. OEHHA failed to include "all evidence bearing on the issue of carcinogenicity" in the HID by excluding certain CLARITY-BPA core study results.

Moreover, the use of KCCs cannot meet the standard of "scientifically valid testing according to generally accepted principles." OEHHA has failed to demonstrate the predictive ability of these mechanistic assays including assay relevance, reproducibility/reliability, specificity, and domain of applicability and predictivity. In fact, a 2017 analysis of high-throughput screening results for over 200 substances that have been reviewed by the U.S. Environmental Protection Agency for carcinogenic potential found that the use of the KCCs approach was "no better than chance" in predicting cancer.[2] OEHHA staff have indicated that

[2] Becker RA *et al.* How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data? *Reg Toxicol Pharma* 90:185-196 (2017). http://doi.org/10.1016/j.yrtph.2017.08.021

use of the KCCs has been of "limited value for cancer hazard identification."[3] Therefore, reliance on this approach, in the absence of evidence of the ability to predict carcinogenic potential, is lacking in evidentiary support.

Finally, BPA has not been identified as a carcinogen by a body considered by OEHHA to be authoritative[4] and no U.S. state or federal government has required it to be identified as causing cancer. In fact, the results of the CLARITY-BPA core study published by National Toxicology Program and the U.S. Food and Drug Administration, do not show clear or consistent increases in cancer due to exposure to BPA in rodents. Further, no other jurisdiction outside the US has listed BPA as a carcinogen nor has it been regulated on such a basis anywhere.

Taken together with the lack of consistent and clear results throughout the studies, the weight of the evidence does not support the listing of BPA as a carcinogen. The CIC should conclude that BPA should not be listed under Proposition 65 as a chemical known to the state of California to cause cancer.

Please feel free to contact me at (202) 249-6604 or Lee_Salamone@americanchemistry.com if you have any questions or wish to discuss this information further.

Regards,

Lee Salamone

Lee Salamone

Senior Director

Attachment: Gradient Comments on OEHHA Hazard Identification Document Prepared for ACC

[3] Sandy MS. Integrating information from multiple toxicity testing approaches in cancer hazard identification. Presentation at National Toxicology Program Converging on Cancer Workshop. April 29-30, 2019. https://ntp.niehs.nih.gov/events/webinars-workshops/2019/coc/presentations/index.html

[4] *See* Cal. Code Regs. tit. 27, § 25306(m).

Comments on the OEHHA Hazard Identification Document for Consideration of Listing Bisphenol A as a Chemical Known to the State of California to Cause Cancer Under Proposition 65

Prepared for
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Executive Summary

The Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency prepared a hazard identification document that reviews the available epidemiology, experimental animal, and mechanistic studies evaluating potential associations between bisphenol A (BPA) exposure and cancer outcomes in preparation for a possible inclusion of BPA on the list of chemicals known to the State of California to cause cancer under Proposition 65. The studies reviewed in the hazard identification document do not provide clear or consistent evidence that BPA causes invasive cancer in humans or animals; thus, they do not support a listing of BPA by OEHHA, and this is supported by the following points.

- The epidemiology studies have many important limitations that restrict their ability to be informative regarding whether BPA exposure is a causal factor in the development of cancer in humans. Many of the limitations can lead to potentially biased results, and the hazard identification document often states that this bias would be toward the null, implying that associations would likely be stronger if the sources of the bias were not present. This is not necessarily the case, however, as the study limitations result in considerable uncertainties that render the study results unreliable and cannot be assumed to universally bias risk estimates toward the null. The potential for bias away from the null should also be considered when interpreting these studies.
- The major limitation across most of the epidemiology studies is the measurement of BPA in biological samples collected from study participants at only one point in time, which does not reflect long-term exposure levels during the critical period of cancer development. Although a lack of BPA measurements during the critical exposure period for cancer development could result in causal effects (if there are any) being missed, it cannot be determined whether the studies would have reported positive associations with cancer if the authors had measured BPA levels from multiple samples collected prior to and during cancer development. Because of the ubiquitous nature of BPA exposure, it is expected that all study participants had at least some exposure to BPA throughout their life, but there is no way to know the magnitude of that exposure and whether it would contribute to the development of cancer because information on BPA exposures at earlier time points does not exist.
- Even despite their severe limitations, the epidemiology studies of BPA do not provide clear or compelling evidence that BPA causes invasive cancer in humans. There is no consistency in the direction or statistical significance of results across studies for any cancer type or across all cancers in general. The inconsistent results are more likely explained by the inadequate exposure assessment and other methodological limitations that can bias the results in either direction than by causation. Overall, there is no evidence in the epidemiology literature to support the plausibility of BPA as a carcinogen.
- Most of the experimental animal studies have significant methodological limitations and are of limited utility for assessing BPA carcinogenicity, though the chronic rodent bioassay conducted by the National Toxicology Program (NTP) (1982) and the Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) core study (NTP, 2018) have fewer limitations and are much more useful for evaluating BPA carcinogenicity over a wide range of doses. The NTP (1982) study used very high doses of BPA, investigated all target organs in detail, and reported remarkably few tumor types with an increased incidence only in male rodents and not in more than one species, except for leukemias (which the study authors concluded were not clearly

associated with BPA treatment). A statistically significant decrease in adrenal tumors reported in rats suggests that the large number of tissues and endpoints examined in this study, as well as the multiple statistical tests used, may have led to statistically significant findings in either direction. Thus, the results of the NTP (1982) study demonstrate that there is no clear or convincing evidence that high doses of BPA are carcinogenic in rats or mice, which is consistent with the study authors' conclusion.

- The CLARITY-BPA core study (NTP, 2018) is the largest study of BPA toxicity ever conducted, with two study arms that include dosing during the perinatal period and a wide range of tested doses, including doses that are far lower than those in the NTP (1982) study. The CLARITY-BPA core study also did not show any clear or consistent treatment-related increases in any cancer type (including leukemias), even when additional statistical analyses of the underlying data were conducted by OEHHA authors and presented in the hazard identification document. OEHHA authors also compared tumor incidence in three historical control data sets to tumor incidence in the CLARITY-BPA core study, but these data sets are inappropriate for such a comparison and do not allow for a reliable evaluation of rare *vs*. spontaneous tumor types. These comparisons only highlight the variability observed in rare tumor types across study arms, time points, and doses, suggesting that they are spontaneous tumors and not related to BPA treatment. The hazard identification document discusses a few issues with the CLARITY-BPA core study, but there is no evidence that these issues limited the ability of the study to detect potential carcinogenic effects of BPA. Thus, the CLARITY-BPA core study provides reliable evidence consistent with a lack of BPA carcinogenicity in rats.
- The hazard identification document presents the experimental animal evidence in a manner that is not systematic and appears to be aimed toward a conclusion of carcinogenicity for BPA regardless of whether the available evidence supports it. The OEHHA authors selectively reported the statistically significant results of statistical tests that they conducted rather than the results of the analyses reported by the study authors (which were not always statistically significant), with no rationale as to why the additional statistical analyses were conducted. The OEHHA authors also used inappropriate historical control data to identify rare tumors in the CLARITY-BPA core study and imply that they are associated with BPA treatment when it is more likely that they are spontaneous tumors. The hazard identification document excluded studies with a duration of less than 1 year if they did not observe tumors but included studies of a similar duration if they had positive tumor results. The document also did not report any evidence supporting a lack of BPA carcinogenicity, including when statistically significant decreases in the incidence of malignant tumors were reported by study authors.
- The experimental animal studies that evaluated exposures to BPA alone, which include the NTP (1982) bioassay and CLARITY-BPA core study, as well as several other studies with significant methodological limitations, are consistent in showing no statistically significant associations with the induction of any type of malignant tumor in rodents. The studies in which BPA was evaluated as a tumor promoter after exposure to known carcinogenic agents were limited in number and not relevant to humans but showed that BPA does not promote tumor induction in the animal systems tested. In studies in which BPA exposure was followed by exposure to known carcinogenic agents, BPA did not enhance susceptibility to most tumor types, but there is evidence that BPA exposure may enhance susceptibility to dimethylbenzanthracene (DMBA)-induced mammary gland tumors. The exposure to DMBA that was required to observe these effects is not a relevant exposure scenario for humans. Overall, there is no clear and consistent evidence that exposure to BPA causes malignant cancers in experimental animals unless the BPA exposure is followed by exposure to the known rodent carcinogen, DMBA, which is not a relevant exposure scenario for humans.
- The hazard identification document reports that there is some evidence that BPA exhibits the "10 key characteristics of carcinogens" (KCCs), but much of this evidence comes from *in vitro*

studies for which the effects of BPA and the concentrations of BPA required to induce the effects are not easily extrapolated to whole animals or humans. Just because a substance can induce certain effects in cultured cells that are consistent with mechanistic pathways associated with carcinogenesis, this does not provide strong evidence of carcinogenicity. Though BPA may have been shown to exhibit some effects consistent with these characteristics in certain studies, the characteristics are also shared by many non-carcinogenic substances. Expert judgment is needed to evaluate and weigh the evidence for or against these characteristics to determine if they are plausible and associated with mechanisms for BPA carcinogenicity. There are many different mechanisms proposed for BPA carcinogenicity, through interactions with a variety of receptors and other cellular molecules and activation of many signaling pathways. The relevance of these mechanisms to cancer development in humans is unclear, and the mechanisms are not supported by the results of the epidemiology and experimental animal studies, which do not provide clear or consistent evidence that BPA acts as a carcinogen by any mechanism.

1 Introduction

The Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency selected bisphenol A (BPA) for consideration on the Proposition 65 list of chemicals known to the State of California to cause cancer. In preparation for a possible listing, OEHHA conducted an extensive review of the literature and prepared a hazard identification document titled "Evidence on the Carcinogenicity of Bisphenol A (BPA)" (CalOEHHA, 2022). This document is referred to herein as the "hazard identification document." The hazard identification document reviews the available epidemiology, experimental animal, and mechanistic studies evaluating potential associations between BPA exposure and cancer outcomes. The Carcinogen Identification Committee (CIC) will use this document, along with guidance criteria for identifying chemicals for listing as "known to the State to cause cancer" (CalOEHHA, 2001), to assess whether BPA should be listed. BPA may be listed if the evidence from scientifically valid studies *clearly* shows that BPA causes *invasive* cancer in humans or animals (CalOEHHA, 2001).

The comments below discuss the strengths, limitations, and results of the available studies relevant to BPA carcinogenicity that were reviewed in the hazard identification document, as well as issues with the interpretation of the study results in the hazard identification document. Upon review of the totality of the evidence and considering the strengths and limitations of the studies, it cannot be concluded that the evidence clearly shows that BPA causes invasive cancers in humans or experimental animals.

2 Epidemiology Evidence

The OEHHA hazard identification document reviews the available epidemiology studies examining associations between BPA exposure and risks of various cancers and identifies multiple limitations of the studies. Many of the limitations can lead to potentially biased results, and the hazard identification document often states that this bias would be toward the null, implying that associations would likely be stronger if the sources of the bias were not present. This is not necessarily the case, however, as the study limitations result in considerable uncertainties that render the study results unreliable, but do not necessarily bias the results toward the null. As such, the results of the epidemiology studies do not provide clear evidence as to whether BPA is a human carcinogen. The epidemiology study limitations and their impact on the interpretation of the results are described below.

2.1 Lack of longitudinal BPA exposure measurements is a major limitation of the epidemiology studies and does not allow for reliable interpretation of their results.

As noted in the hazard identification document, exposure to BPA was assessed in the epidemiology studies most often by measurement of BPA concentrations in biological samples (*i.e.*, urine, blood, or tissue), as well as through questionnaire or job-exposure matrix (JEM). BPA concentrations were measured in biological samples collected from the adult study participants at one point in time, and for many of the studies this was at the time of cancer diagnosis or treatment. This is a major limitation that does not allow for a reliable interpretation of the results. Given the short half-life of BPA in the body (*i.e.*, less than 6 hours), a BPA measurement at one point in time does not reflect long-term exposure levels. In addition, measurement of BPA near the time of cancer diagnosis or treatment does not reflect BPA exposure during the critical period of cancer development, given the long latency periods of most cancers.

Although a lack of BPA measurements during the critical exposure period for cancer development could result in causal effects (if there are any) being missed, it cannot be determined whether the studies would have reported positive associations with cancer if the authors had measured BPA levels from multiple samples collected prior to and during cancer development. To surmise that the studies would have reported such associations is purely speculation and assumes that BPA does indeed cause the types of cancer evaluated and that the participants had sufficient exposures to induce those cancers. The epidemiology studies that measured BPA in biological samples do not allow for a determination one way or another whether BPA causes cancer because they cannot establish temporality between the BPA exposure level and the disease. Because of the ubiquitous nature of BPA exposure, it is expected that all study participants had at least some exposure to BPA throughout their life, but there is no way to know the magnitude of that exposure and whether it would be correlated with the induction of cancer, because information on BPA exposures at earlier time points does not exist.

2.2 Other limitations of the epidemiology studies can bias their results in either direction.

The hazard identification document discusses several other key limitations of the epidemiology studies, particularly with respect to BPA exposure assessment, and often states that the limitations can lead to non-differential exposure misclassification that may bias risk estimates toward the null. This is not always the case, however, as discussed below.

There are two primary types of misclassification: differential and non-differential. It is widely accepted that differential misclassification, which occurs when the probability of misclassifying the exposure differs between two groups (diseased and non-diseased, for example), can result in bias in the study risk estimate in either direction (toward or away from the null). Non-differential misclassification, which occurs when the probability of misclassification is equal between two groups, is frequently assumed to result in risk estimates biased toward the null (Gordis, 2009). However, the assumption of bias in the direction of the null, even in instances of non-differential misclassification, is not always true in reality (Yland *et al*., 2022; Dosemeci *et al*., 1990; Jurek *et al*., 2005, 2008; Sorahan and Gilthorpe, 1994; Greenland and Gustafson, 2006), and it can actually result in bias away from the null, as shown in a considerable proportion of simulated scenarios (Yland *et al*., 2022; Dosemeci *et al*., 1990; Sorahan and Gilthorpe, 1994).

While non-differential misclassification theoretically occurs when misclassification is equal between diseased and non-diseased groups, in practice, the true proportion misclassified within each outcome group is likely to be differential due to random variation within the study (Yland *et al*., 2022; Jurek *et al*., 2005, 2008), which can result in bias in either direction. Even in instances where there often would be an assumption of bias toward the null, such as non-differential misclassification of a binary variable (*e.g*., exposed to BPA/not exposed to BPA), there is always a chance of deviation from that expectation due to random variation within the study itself. Studies that are small (*e.g*., the study of BPA and breast cancer by Keshavarz-Maleki *et al*. [2021]) and studies with low sensitivity (*e.g*., another BPA-breast cancer study by Lopez-Carrillo *et al*. [2021]) are more likely to be impacted from misclassification that deviates from expectations and can bias the results in either direction.

A few of the BPA epidemiology studies used a questionnaire or JEM to estimate BPA exposures. As noted in the hazard identification document, use of these methods for exposure assessment is a significant limitation, as questionnaire responses do not correlate well with urinary BPA levels, and a JEM is of limited utility because of widespread non-occupational exposure to BPA. Thus, the estimates from using these methods likely do not reflect actual individual BPA exposure levels. The hazard identification document states that use of a questionnaire can result in non-differential exposure misclassification, and that this may bias risk estimates towards the null. However, case-control studies in which exposures are captured *via* questionnaire can be impacted by recall bias, resulting in differential misclassification bias, if cases recall their exposures differently than non-cases. The case-control study examining the association between BPA and prostate cancer (Tse *et al.*, 2017), which reported a statistically significant elevated risk, estimated BPA exposures using questionnaire-based data, which can lead to a risk of bias in either direction.

Very few of the epidemiology studies noted assessing or controlling for contamination of samples. The hazard identification document notes that contamination could result in non-differential misclassification and that this could bias risk estimates toward the null. As noted above, however, truly equal probabilities of misclassification of exposure between outcome groups is unlikely, and this deviation from expectation can result in bias in either direction (Yland *et al*., 2022; Jurek *et al*., 2005, 2008).

The hazard identification document states that exposure characterization that relies upon a single spot sample of BPA could result in non-differential misclassification that may result in bias toward the null. As noted above, a sample at a single point in time does not accurately characterize historical or longitudinal exposures. Due to factors such as the short half-life of BPA in the body, intraindividual variability in BPA metabolism, and random variability in the sample itself, it is not possible to predict what the true long-term exposure levels were, and this uncertainty leads to results that are unreliable. Because the true long-term BPA exposure levels could be higher or lower than the exposure level estimated from a spot sample, it cannot be assumed that reliance on a spot sample for BPA exposure would bias risk estimates toward the null.

It has been demonstrated that non-differential misclassification of a continuous variable does not guarantee non-differential misclassification of the categorized variable (Yland *et al*., 2022). Most of the BPA epidemiology studies analyzed levels of BPA that were measured in biological samples on a continuous scale by using a categorical approach. If categorization results in misclassification that is no longer non-differential, it can be much more difficult to predict the direction of any potential bias, and it cannot be assumed to be toward the null (Gordis, 2009).

The hazard identification document notes the inconsistency with which studies adjusted for urinary concentrations of BPA; some studies reported creatinine-adjusted values and others reported unadjusted values, while few reported both. The hazard identification document states that the studies that only reported unadjusted values could introduce bias. However, while creatinine adjustment is a commonly used method to adjust chemical concentrations to account for urine dilution, there is no universally accepted method to control for dilution (LaKind *et al*., 2019). Further, it has been shown that adjustment for creatinine can lead to results that are difficult to interpret, and it has been suggested that without a better understanding of how to control for urine dilution, studies should provide estimates that are both unadjusted and adjusted for creatinine (or specific gravity) for comparison (LaKind *et al*., 2019).

Overall, the impact of the potentially misclassified BPA exposures in the epidemiology studies reviewed in the hazard identification document cannot be assumed to universally bias risk estimates toward the null. Even with the assumption of non-differential misclassification, which in and of itself may not be a fair assumption, the resulting bias can be away from the null. Thus, the potential for bias away from the null should also be considered when interpreting these studies.

2.3 Despite their limitations, the epidemiology study results do not clearly support an association between BPA and invasive cancer in humans.

The many limitations of the epidemiology studies preclude their ability to provide evidence as to whether BPA exposure is associated with human cancers. The results across analyses of specific cancer types are inconsistent and do not support an association with BPA exposure. For example, of the 13 studies evaluating breast cancer that are reviewed in the hazard identification document, the majority reported no associations with BPA; there were some associations in the negative direction in certain analyses and in the positive direction in other analyses. Only a few of the breast cancer studies reported statistically significant, positive associations, but these are most likely due to chance or bias, given the severe limitations in exposure assessment discussed above that render the exposure estimates as uncertain and the study results as unreliable, as well as other limitations that can bias the results in either direction.

The results of studies of other cancer types reviewed in the hazard identification document are also inconsistent or otherwise do not provide clear evidence of associations with BPA exposure. The few studies of prostate cancer reported statistically significant associations with BPA exposure in some analyses, but there was no exposure-response relationship in fully adjusted models (Tarapore *et al*., 2014; Tse *et al*.,

2017; Salamanca-Fernández *et al*., 2021). The two studies of thyroid cancer were cross-sectional in design and cannot be used to establish causation; one of these studies reported a non-statistically significant increased risk of thyroid cancer (Marotta *et al*., 2019), while the other reported a statistically significant increased risk (Zhou *et al*., 2017), though neither study adjusted for any potential confounders or other covariates. There were no associations reported for several cancers examined in only one study each: endometrial cancer (Sarink *et al*., 2021), lymphoma (Costas *et al*., 2015), uveal melanoma (Behrens *et al*., 2012), extrahepatic biliary tract cancer (Ahrens *et al*., 2007), and all cancer sites combined (Bao *et al*., 2020). Statistically significant associations were reported for the individual studies that evaluated osteosarcoma (Jia *et al*., 2013), lung cancer (Li *et al*., 2020), and meningioma (Duan *et al*., 2013); however, Duan *et al*. (2013) evaluated risks of only benign meningiomas, most of which do not progress to malignant tumors (Di Nunno *et al*., 2022). In addition, the results of the studies of osteosarcoma and lung cancer are subject to confounding bias, as they did not adequately adjust for key risk factors for these cancer types. The results for osteosarcoma and lung cancer are also from only one study each and need to be confirmed in additional studies with better designs before they can be used as evidence of carcinogenicity. As with the breast cancer studies, the statistically significant associations reported in only certain analyses of a few other types of cancer are likely due to chance or bias, given the limitations of the studies with respect to exposure assessment and other methodological issues.

Overall, the epidemiology studies reviewed in the hazard identification document do not clearly show that BPA causes invasive cancer in humans. There is no consistency in the direction or statistical significance of results across studies for any cancer type or across all cancers in general. The inconsistent results are more likely explained by the inadequate exposure assessment and other methodological limitations that can bias the results in either direction than by causation. Most importantly, the studies do not evaluate long-term exposures prior to cancer induction and thus cannot establish the magnitude of BPA exposure during the critical period of cancer development. Given these important limitations, the epidemiology studies of BPA exposure and cancer are uncertain, leading to unreliable results that cannot be used as evidence for or against causation. Even despite their limitations, the studies do not provide clear or consistent evidence that BPA can cause any type of cancer in humans, and as such, there is no evidence in the epidemiology literature to support the plausibility of BPA as a carcinogen.

3 Animal Evidence

The OEHHA hazard identification document reviews experimental animal studies of BPA exposure and tumor-related endpoints, with most of these studies having significant methodological limitations such as short (*i.e*., less than lifetime) study durations, a small number of animals per dose group with no power calculation to justify the small group size, and lack of reporting regarding whether researchers were blinded to the exposure status of the animals. Many of the experimental animal studies also did not confirm the purity of the BPA administered and did not randomize animals into the different dose or vehicle groups, and some did not report the statistical methods used or even conduct statistical analyses. Because of these limitations, these studies are of limited utility for assessing BPA carcinogenicity.

In contrast, the two chronic rodent carcinogenicity studies of BPA with exposure *via* the diet (NTP, 1982) or oral gavage (NTP, 2018; Camacho *et al*., 2019) are well-conducted studies of high quality and, therefore, are more useful for evaluating BPA carcinogenicity over a wide range of doses. The NTP (1982) dietary bioassay in rats and mice was conducted according to NTP guidelines for carcinogenicity bioassays in small rodents and in compliance with Good Laboratory Practice (GLP). NTP (2018) and Camacho *et al.* (2019) reported the results of the core study of the Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) research program, which involved academic and regulatory scientists in the study design and provided animals and biological samples to National Institute of Environmental Health Sciences (NIEHS)-funded academic scientists to conduct hypothesis-driven studies of various endpoints to address controversies over the potential toxicity of BPA. The CLARITY-BPA core study was conducted in rats in compliance with United States Food and Drug Administration (FDA) GLP for the conduct of nonclinical laboratory studies (Camacho *et al*., 2019). The NTP (1982) bioassay and the CLARITY-BPA core study do not provide clear or consistent evidence of BPA carcinogenicity in rodents, as discussed below.

3.1 The 1982 NTP bioassay does not provide clear or consistent evidence of BPA carcinogenicity in rodents at high doses.

The NTP (1982) bioassay exposed rats and mice to BPA *via* the diet for 2 years at doses that are at least six orders of magnitude higher than typical estimated human intakes. For example, the lowest dose to rats in this study was 74 mg/kg-day BPA, whereas median daily intakes of BPA from all sources for the general US population are estimated to be approximately 20 ng/kg-day (LaKind *et al*., 2019). NTP (1982) reported statistically significant differences in the incidence of a few types of tumors in male animals treated with these high doses of BPA compared to controls. These differences do not provide strong evidence for BPA carcinogenicity, however. None of the tumors with a statistically significant increased incidence were observed in more than one sex or more than one species, except for leukemias, which were observed in male rats and male mice. The leukemias and other tumors with increased incidence were not clearly associated with BPA treatment, as explained below.

In male F344 rats, BPA exposure was associated with an increased incidence of leukemia (not otherwise specified) at the highest dose tested in at least one of the statistical tests (46% *versus* 26%; $p = 0.03$) and the dose trend was statistically significant ($p = 0.021$) (NTP, 1982). When life table analysis was conducted, neither the high-dose effect nor the dose-response trend was statistically significant. No statistically significant increases in the incidence of leukemia were reported for female rats. The leukemia incidence rates were within the range of historical control data for F344 rats, so it is likely that the increased incidence

of leukemias in the high-dose male rats was not related to BPA treatment (Haighton *et al*., 2002). Consistent with this, NTP (1982) concluded that the increased incidence of leukemia in male rats was not clearly associated with BPA administration, and it is not considered to be convincing evidence of carcinogenicity.

In male B6C3F1 mice, BPA exposure was associated with a statistically significant increased incidence of all lymphomas in at least one of the statistical tests in the low dose group (16% *versus* 4%; $p = 0.049$) but not the high dose group, and no increase in all lymphomas was reported for female mice (NTP, 1982). A statistically significant increase in the incidence of lymphomas and leukemias combined was also reported in male mice in the low dose group (18% *versus* 4%; $p = 0.028$) but not the high dose group (and not in female mice). This increase was driven by the lymphoma results, as there was only one animal with leukemia in the low dose group. The level of significance for these results did not meet the Bonferroni inequality criterion, however, and NTP (1982) stated that the increased incidence cannot be associated unequivocally with the administration of BPA. In addition, the types of lymphohematopoietic tumors observed in the mice were typical of those that occur spontaneously in the studied strain, and the incidence rates were within the range of historical controls for the strain (Haighton *et al*., 2002). NTP (1982) concluded that the increased incidence of leukemias and lymphomas in mice were not convincing evidence of carcinogenicity.

In the NTP (1982) study, BPA exposure was also associated with a statistically significant increase in testis interstitial cell tumors in male rats in both the low ($p = 0.001$) and high ($p = 0.003$) dose groups. The Cochran Armitage test for linear trend was also statistically significant ($p = 0.001$). However, NTP did not consider the increase in testicular interstitial cell tumors to be treatment-related based on historical control data for F344 rats at the NTP facility, and there is a high incidence (>90%) of interstitial cell testicular tumors in aging F344 male rats (NTP, 1982).

The NTP (1982) study also reported a statistically significant linear trend in the incidence of pituitary chromophobe carcinomas male mice when using the Cochran Armitage test ($P_{trend} = 0.016$). In male rats, no statistically significant increases in pituitary adenoma/carcinoma or cortical adenoma/carcinoma were observed (NTP, 1982), so this study does not provide strong or consistent evidence for an association between BPA and pituitary tumors.

Finally, the NTP (1982) study reported a statistically significant *decrease* in pheochromocytomas of the adrenal gland in male rats in both the low ($p = 0.035$) and high ($p = 0.049$) dose groups compared with controls. In addition, the Cochran Armitage test for linear trend was statistically significant in the negative direction ($p = 0.031$). There were no statistically significant changes in incidence of adrenal pheochromocytomas in BPA-treated female rats compared to controls.

Overall, the NTP (1982) study examined multiple cancer endpoints across male and female rodents of two species, yet reported very few cancer types, with an increased incidence observed only in male animals and not in more than one species, except for leukemias, for which a statistically significant increase was observed in male rats and a combined incidence of one leukemia with lymphomas was increased in male mice. The hazard identification document does not discuss that the study authors concluded that these tumors, as well as the testicular interstitial cell tumors observed in male rats, were not clearly associated with BPA treatment. The leukemias and testicular tumors were also not observed in rats in the high-quality CLARITY-BPA core study, as discussed below, which provides support for the increased incidence of these cancer types being chance findings or due to common spontaneous tumor types in aging male rats. The increased trend in pituitary tumors in male mice was not observed in other species or sexes, and the statistically significant decrease in adrenal tumors in rats suggests that the large number of tissues and endpoints examined in this study, as well as the multiple statistical tests used, may have led to statistically significant findings in either direction due to lack of adjustment for multiple comparisons. Thus, the results of the NTP (1982) study do not provide clear or consistent evidence of BPA carcinogenicity in rats or mice

at dietary exposure levels that are far higher than typical human exposures, which is consistent with the conclusions of the NTP (1982) study authors.

3.2 The CLARITY-BPA core study provides reliable evidence consistent with a lack of BPA carcinogenicity in rats.

The CLARITY-BPA core study, as reported by NTP (2018) and Camacho *et al*. (2019), used much lower doses of BPA and over a wider dose range than the NTP (1982) bioassay and exposed Sprague Dawley rats *via* oral gavage during the perinatal period (*i.e*., the stop-dose arm), as well as up to 1 or 2 years of age (*i.e*., the continuous-dose arm). The study involved the evaluation of many endpoints across two study arms (stop-dose and continuous-dose), each with five dose levels of BPA (ranging from 2.5 to 25 mg/kg-day) and vehicle controls, as well as two doses of the positive control ethinyl estradiol (EE2) (only in the continuous-dose arm). NTP (2018) reported very few statistically significant increases in the incidence of malignant tumors in BPA-treated animals compared to controls, and only in those sacrificed at 2 years of age in the stop-dose arm of the study. Specifically, there was a statistically significant increase in mammary gland adenomas and adenocarcinomas combined in female rats at the lowest BPA dose tested (2.5 μg/kg-day), a statistically significant increase in malignant lymphoma of the prostate gland in male rats at the highest BPA dose tested (25 mg/kg-day), and a statistically significant increased trend for malignant lymphomas at all sites in male rats.

3.2.1 The few positive results for malignant tumors are likely the result of chance fluctuations in incidence or false positive findings due to a lack of adjustment for multiple comparisons.

The statistically significant, non-dose-dependent increase in female mammary gland adenomas and adenocarcinomas combined was only observed at the 2-year sacrifice in the stop-dose arm of the study at the lowest dose tested and not at the 1-year sacrifice for this arm or at either the 1- or 2-year sacrifice in the continuous-dose arm (NTP, 2018). Exposure to the higher dose (0.5 μg/kg-day) of the EE2 positive control also resulted in a statistically significant increase in mammary adenocarcinomas. The statistically significant result at only the lowest BPA dose in only the stop-dose arm should be interpreted with caution, as there is evidence that the results are likely a chance fluctuation in incidence (Camacho *et al*., 2019). For example, there were no statistically significant increases in nonneoplastic mammary lesions that may be precursors for adenocarcinoma at any BPA dose in the stop-dose arm. In addition, the authors compared incidences of many neoplastic and nonneoplastic lesions between treatment groups at multiple doses and in different study arms, but did not adjust for multiple comparisons, so the statistically significant increase in mammary gland tumors may be a false positive finding.

The increase in malignant lymphoma of the prostate gland and the increased trend for malignant lymphoma at all sites reported for males in the stop-dose arm of the study should also be interpreted with caution. As with the increased mammary gland tumor incidence, these results may be chance findings or false positives due to multiple comparisons. It is also not plausible that BPA exposure during only the perinatal period would induce mammary gland tumors or lymphomas at a specific dose but not when exposure to the same dose of BPA occurred during both the perinatal period and up to 2 years of age in another arm of the study. This is consistent with the conclusions of the CLARITY-BPA core study authors that while there were some statistically significant differences in treated rats compared to vehicle controls, the effects did not show a coherent or plausible pattern consistent with treatment-related lesions, particularly given the low stringency statistical tests that were applied (NTP, 2018).

3.2.2 The OEHHA authors conducted additional statistical analyses of the CLARITY-BPA data, with no rationale for doing so, and selectively reported their statistically significant results.

The hazard identification document does not provide the conclusions of the CLARITY-BPA core study authors, and instead reports the results of statistical tests for the study tumor data that were conducted by the authors of the hazard identification document at OEHHA. These additional statistical tests conducted by OEHHA authors found statistically significant increasing trends in hepatocellular carcinomas in male rats in the continuous-dose arm at the 2-year sacrifice and in clitoral gland adenomas and carcinomas combined that the CLARITY-BPA core study authors did not report. The hazard identification document provides no rationale as to why additional statistical analyses were conducted by OEHHA authors for the CLARITY-BPA study, such as whether the OEHHA authors disagree with the statistical tests used by the CLARITY-BPA core study authors. In fact, it is only in the footnotes of the various tables of results for this study that it is specified in the hazard identification document that the statistical analyses were conducted by OEHHA authors and not the study authors. Thus, the OEHHA authors conducted additional statistical analyses of the results and selectively reported those that produced statistically significant results. This practice results in "*p*-hacking" (*i.e.*, selective reporting) and can lead to the reporting of false positive results (Head *et al.*, 2015).

The hazard identification document also does not state whether the OEHHA authors conducted their own statistical analyses for all tumor endpoints in the study or only certain endpoints, nor does it provide a methodology section that states the specific statistical methods used. The table footnotes indicate that a Fisher pairwise comparison with controls and an "Exact trend test" was conducted for several endpoints, but there is no explanation as to exactly which type of trend test this is. There is also no mention of whether there was adjustment for multiple comparisons. If OEHHA authors conducted their own statistical analyses for the large number of tumor types observed in at least one animal in the CLARITY-BPA core study, it is very possible that the two statistically significant increased trends not reported by the study authors are false positive findings due to multiple comparisons.

3.2.3 OEHHA used historical control data sets that were inappropriate for identifying rare tumors in the CLARITY-BPA animals.

The hazard identification document includes an analysis of three sets of historical control data by OEHHA authors to identify rare tumor types observed in rats in the CLARITY-BPA core study that are found in less than 1% of historical control animals. The hazard identification document states that the most appropriate historical control data are from studies of animals of the same strain, colony, laboratory, diet, test substance administration, and housing conditions, and that were conducted within 2-3 years of the current study. However, the OEHHA authors acknowledged that there are no historical control databases that meet these criteria for the CLARITY-BPA core study, and the hazard identification document stresses that such inappropriate historical control data should be used only with extreme caution. Despite this, the OEHHA authors used three historical control data sets that are inappropriate to compare to the CLARITY-BPA core study data. One set was also used by NTP (2018), which included animals of the same strain, colony, and laboratory, but NTP (2018) acknowledged that the studies in this data set were conducted more than 5 years prior to the CLARITY-BPA core study and used dietary exposure rather than oral gavage. The other two data sets were from studies conducted in the same rat strain but different colonies, and most of the studies in these data sets were conducted more than 3 years prior to initiation of the CLARITY-BPA core study (CalOEHHA, 2022). When the OEHHA authors inappropriately compared these three historical control data sets to the CLARITY-BPA core study data, they identified a wide variety of rare tumor types observed

in one or a few animals, with an incidence that exceeds or is similar to the mean incidence in each historical control data set.

Given the uncertainties in the appropriateness of the historical control data sets, as stated in the hazard identification document, they should not be used to evaluate the incidence of rare tumor types in the CLARITY-BPA study. The historical control data do not provide accurate information about spontaneous tumor incidence in the colony of rats used in the CLARITY-BPA study, so an analysis of rare tumor types using these data is moot and should not be relied upon for evaluating the carcinogenicity of BPA. Because the CLARITY-BPA core study is a 2-year bioassay, it is not uncommon to observe spontaneous tumors in animals during an evaluation of this duration. Consistent with this, the "rare" tumors identified in the hazard identification document are highly variable across study arms, time points (1 year *vs*. 2 years), and sexes as far as the tumor site and type, with no discernible dose-response relationships across the various tumor types. In addition, the number of rare tumor types observed is much higher in rats sacrificed at 2 years than those sacrificed at 1 year, increasing the likelihood that they are spontaneous tumors that occurred with increasing age of the animals. Thus, the reported low incidences of these tumors cannot be reliably attributed to BPA exposure.

3.2.4 The issues with the CLARITY-BPA study noted by OEHHA did not limit the study's ability to detect potential carcinogenic effects of BPA.

The hazard identification document notes that there are several issues associated with the CLARITY-BPA core study that may have limited its ability to detect carcinogenic effects. One is the concern regarding data from a pilot study of the CLARITY-BPA project in which it was shown that control animals had significant background contamination with BPA and the source of the contamination was not identified (Churchwell *et al*., 2014). The hazard identification document states that contamination is also a possibility in the core study, as it was not possible to identify the BPA source and effectively address the issue. The hazard identification document notes that the "high incidence of several rare tumors" in the vehicle control animals of the CLARITY-BPA core study (which were identified using inappropriate historical control data sets, as discussed above) "may result from the unexplained BPA contamination" (CalOEHHA, 2022). It is not plausible that the increased incidence of these tumor types is attributable to BPA contamination, however, as these tumor types were not observed with the higher and more continuous exposures to BPA in the actual BPA treatment groups. This argues against BPA contamination as a cause of the rare tumors and supports that they are more likely to be spontaneous tumors that occurred in aging animals.

However, NTP (2018) conducted sensitivity analyses to address whether BPA contamination would affect study outcomes. NTP (2018) reported that a subset of the study animals was housed for a short period of time in the same room as animals dosed with 250 mg/kg-day BPA and were potentially exposed to low levels of BPA above the dietary exposure, which could potentially lead to blood levels of BPA metabolites similar to those in the lowest dose group (2.5 μg/kg-day) (Heindel *et al*., 2015). NTP (2018) also noted that animals co-housed with those receiving 25 mg/kg-day BPA had no detectable BPA metabolites in their blood (Heindel *et al*., 2015). NTP (2018) conducted additional statistical analyses of each endpoint excluding the animals co-housed with animals receiving 250 mg/kg-day BPA (*i.e*., sensitivity analyses), and these did not show any consistent effects of BPA treatment that were not evident in the main analyses with all animals, indicating that any inadvertent BPA exposure during the co-housing with high-dose animals had minimal impact on the results of the statistical tests.

Another issue discussed in the hazard identification document is the potential insensitivity of the specific rat colony used in the CLARITY-BPA studies to known estrogenic chemicals, such as EE2. The CLARITY-BPA core study included two doses of EE2 (0.05 and 0.5 μg/kg-day) as positive controls in the continuous-dose arm, and NTP (2018) reported that the higher EE2 dose was associated with several strong

effects in female animals that were clearly interpretable and biologically plausible as estrogenic effects. For example, EE2 had a clear impact on the female mammary gland, inducing an increase in adenocarcinoma incidence, ductal and alveolar dilatation, and lobular hyperplasia (NTP, 2018). In addition, a 90-day toxicity study conducted under the same conditions and using animals from the same colony as the CLARITY-BPA core study reported multiple adverse effects in female rats dosed with 0.5 μg/kg-day EE2 that are consistent with effects observed in other rodent studies of EE2 (Delclos *et al*., 2014).

A third issue discussed in the hazard identification document is the lack of an unhandled control group that was not subjected to oral gavage of the vehicle, as oral gavage can create significant differences in potential stress-related endpoints relative to unhandled animals, and such stress may have diminished the power of the study to identify BPA-related effects. Oral gavage dosing was selected for the CLARITY-BPA core study, which included perinatal exposure, because of poor lactational transfer of BPA to rat pups and the need for efficient and consistent concentrations when dosing a large number of neonatal rats (Camacho *et al*., 2019). A study by Gear *et al*. (2017) that used siblings of the core study animals reported decreased body weights in continuous-dose arm males (gavaged for up to 2 years) compared to stop-dose arm males (only gavaged as pups for a brief duration) and stated that this was consistent with other studies showing prolonged postnatal stress decreases weight gain in male animals. Camacho *et al*. (2019) noted that the other studies cited by Gear *et al*. (2017) used methods of restraint that were very different than those used in the CLARITY-BPA core study (*i.e*., holding for 75 minutes per day in plastic restraints or an electric shock pad *vs*. manual holding for less than a minute in the core study). In addition, the 90-day toxicity study using animals from the same colony as the CLARITY-BPA core study animals and conducted under the same conditions reported no significant body weight differences between unhandled controls and vehicle controls dosed *via* gavage (Delclos *et al*., 2014). Further, Camacho *et al*. (2019) reported that in the core study, there were no significant differences between dosing arms for several potentially stress-related endpoints, such as body weight, adrenal weight, thymus weight, and white blood cell counts.

3.2.5 The CLARITY-BPA core study does not provide clear or consistent evidence of BPA carcinogenicity in rats.

Overall, the CLARITY-BPA core study did not show any clear or consistent treatment-related increases in any tumor type, even when additional statistical analyses of the underlying data were conducted by OEHHA authors. The use of inappropriate historical control data sets does not allow for a reliable evaluation of rare *vs*. spontaneous tumor types, and only highlights the variability in such tumor types across study arms, time points, and doses. There is no evidence that the issues with the CLARITY-BPA core study discussed in the hazard identification document limited the ability of the study to detect potential carcinogenic effects of BPA. Thus, the CLARITY-BPA core study provides reliable evidence consistent with a lack of BPA carcinogenicity in rats.

3.3 The hazard identification document provides a biased review of the experimental animal evidence.

The hazard identification document presents the experimental animal evidence in a manner that is not systematic and appears to be aimed toward a conclusion of carcinogenicity for BPA regardless of whether the available evidence supports it. As discussed above, the OEHHA authors conducted additional statistical analyses of the CLARITY-BPA core study data (without any justification for doing so) and used inappropriate and unreliable historical control data sets to identify rare tumor types in that study (but did not evaluate tumor incidence in additional historical control data sets for any other reviewed study). The hazard identification document also discusses the potential for BPA contamination of control animals and the potential insensitivity of the rat strain used in the CLARITY-BPA core study, but does not discuss these

issues for the other experimental animal studies reviewed in the document, despite the fact that these other studies have many significant methodological limitations and also cannot rule out potential BPA contamination. Thus, the hazard identification document provides a biased review of the overall evidence toward a conclusion of carcinogenicity, as it does not apply the same level of scrutiny to the other experimental animal studies as it does to the large and well-conducted CLARITY-BPA core study, which found reliable evidence consistent with a lack of BPA carcinogenicity in rats.

The OEHHA authors also conducted their own statistical analyses of some of the other experimental animal studies, but it is not clear exactly which studies and which endpoints in those studies were chosen for statistical reanalysis. There is also no methodology section in the hazard identification document to provide a rationale for why the additional statistical analyses were conducted and which data were selected to reanalyze, or an explanation of the statistical methods that were used. As noted above, conducting various statistical analyses until a statistically significant effect is produced and reported is a practice that results in "*p*-hacking" and can lead to the reporting of false positive results.

The hazard identification document also notes that studies with perinatal exposure to BPA and a study duration of less than 1 year are inadequate to assess BPA carcinogenic potential and were excluded from review *unless* tumors were observed in the studies. Exclusion of studies based on their results, whether positive or negative, goes against best practices for evaluating evidence for causality (Rhomberg *et al*., 2013), and if studies with such short durations are inadequate to assess BPA carcinogenicity, all such studies should be excluded based on this methodological limitation and not based on their results. The fact that tumors were observed in some studies with durations of less than 1 year indicates that such studies may indeed have the ability to detect treatment-related effects and should not be automatically excluded.

The hazard identification document does not report any evidence supporting a lack of BPA carcinogenicity. For example, when discussing the few statistically significant increases in tumor incidence reported in the NTP (1982) study, there is no mention of the statistically significant decrease in adrenal pheochromocytomas in male rats, which lends credence to the few statistically significant differences from controls in the study likely being attributable to chance or false positive results due to multiple comparisons. As another example, the hazard identification document discusses the statistically significant increased trend in incidence of uterine stromal polyps in females sacrificed at 1 year of age in the CLARITY-BPA core study continuous-dose arm, but does not mention that there was a statistically significant decreased incidence of these tumors at the highest dose tested and a statistically significant decreased trend in incidence of these tumors in females sacrificed at 2 years of age in the stop-dose arm of the study. If any statistically significant increase in tumor incidence is used as evidence that BPA causes cancer, then any statistically significant decrease in tumor incidence must be used as evidence that BPA exposure protects against cancer, but that cannot be done if the statistically significant results in the negative direction are not presented.

Another example of the biased review of the evidence is in the presentation of evidence from the CLARITY-BPA grantee study of mammary gland effects by Montevil *et al*. (2020). This 90-day study did not report any malignant mammary gland tumors in BPA-treated animals, but the hazard identification document provides a quote of the study authors' conclusions that "lower doses resulted in larger effects [than higher doses of BPA], consistent with the core study (NTP, 2018), which revealed a significant increase of mammary adenocarcinoma incidence in the stop-dose animals at the lowest BPA dose tested" (Montevil *et al*., 2020). This quotation is misleading, as it implies that the study by Montevil *et al*. (2020) reported an increased incidence in mammary gland adenocarcinomas, which it did not. The quotation refers to the non-neoplastic effects that were observed inconsistently across doses in the study at far less than a chronic exposure duration and were not necessarily "larger effects" at lower doses compared to higher doses.

3.4 The results of experimental animal studies as a whole do not provide clear evidence that BPA exposure causes malignant tumors.

The experimental animal studies that evaluated exposures to BPA alone are consistent in showing no statistically significant associations with the induction of any type of malignant tumor, whether in the chronic bioassays by NTP (1982, 2018) or the other studies reviewed in the hazard identification document that have multiple limitations, including a small number of animals and short study duration. Thus, there is no clear and consistent evidence that exposure to BPA alone causes malignant cancers in experimental animals.

Other experimental animal studies of BPA are not relevant to human exposures. Studies where a known carcinogen was administered in addition to BPA selected doses of the carcinogen based on an expectation that tumors would result independent of BPA exposure. Regardless, the studies in which BPA was evaluated as a tumor promoter after exposure to known carcinogenic agents were limited in number but showed that BPA does not promote tumor induction in the animal systems tested. BPA exposure was not associated with a statistically significant increase in mammary gland tumors in the study by Zhang *et al*. (2021), even though the hazard identification document states that it was. Zhang *et al*. (2021) did not report the statistical significance of the results for tumor incidence; they only reported the statistical significance of the results for tumor index (*i.e*., multiplicity, which quantifies the number of tumors per animal and not the ability to induce tumors). Two other studies did not report increases in thyroid tumors after exposure to a combination of three carcinogenic agents followed by exposure to BPA (Zhang *et al*., 2017; Takagi *et al*., 2001).

In studies in which BPA exposure was followed by exposure to known carcinogenic agents, BPA did not enhance susceptibility to most tumor types. One study reported a statistically significant increase in microinvasive, but not glandular, prostate tumors after exposure to BPA in combination with estradiol and testosterone (Prins *et al*., 2017), but two other studies did not report an enhanced susceptibility to prostate tumors after exposure to BPA in combination with either a high-fat diet (Facina *et al*., 2018) or exposure to the carcinogen 3,2'-dimethyl-4-aminobiphenyl (DMAB) (Ichihara *et al*., 2003). A statistically significant increased incidence of mammary gland tumors was reported in three studies in which BPA exposure (at oral doses ranging from 0.025 to 0.25 mg/kg-day, but not at a lower dose of 0.0025 mg/kg-day) was followed by exposure to DMBA (Betancourt *et al*., 2010; Leung *et al*., 2017; Varuzza *et al*., 2019), but not in another study where N-methyl-N-nitrosourea (MNU) was the tumor-inducing agent (Durando *et al*., 2007). Thus, while the tumor susceptibility studies provide evidence that BPA exposure may enhance susceptibility to DMBA-induced mammary gland tumors, the exposure to this potent rodent carcinogen that was required to observe these effects is not a relevant exposure scenario for humans.

The hazard identification document reviews several studies using xenograft or syngeneic mouse models, but these studies involve the injection of established cancer cells into animals and evaluation of the effects of BPA on their growth or volume, rather than the effects of BPA on inducing cells to become cancerous. As such, these studies do not provide evidence as to whether BPA can induce cancer.

Overall, there is no clear and consistent evidence that exposure to BPA causes malignant cancers in experimental animals unless the BPA exposure is followed by exposure to the known rodent carcinogen DMBA, which is not a relevant exposure scenario for humans.

4 Mechanistic Evidence

The OEHHA hazard identification document uses the "10 key characteristics of carcinogens" (KCCs) to organize information on the potential mechanisms of carcinogenesis for BPA. The 10 KCCs were proposed by the International Agency for Research on Cancer (IARC) as a set of mechanistic characteristics that are common to established human carcinogens (Smith *et al*., 2016). The 10 KCCs can be useful for organizing mechanistic evidence, but expert judgment is needed to evaluate and weigh the evidence for these characteristics to determine if they are plausible and associated with mechanisms for BPA carcinogenicity. This includes consideration of the quality of the mechanistic studies, the relevance of the evidence to human carcinogenicity, and how positive and negative findings from the mechanistic studies should be integrated with evidence from epidemiology and experimental animal studies to form conclusions regarding the likelihood that BPA has any of the 10 KCCs or causes cancer through any of them (Goodman and Lynch, 2017).

The hazard identification document indicates that there is at least some evidence that BPA has been shown to exhibit each of the 10 KCCs. However, much of this evidence comes from *in vitro* studies for which the effects of BPA and the concentrations of BPA required to induce the effects are not easily extrapolated to whole animals or humans. The hazard identification document focuses on providing any positive evidence for each of the 10 KCCs, but it does not weigh the evidence for or against each mechanism to evaluate whether it is a plausible mechanism for BPA carcinogenesis.

Just because a substance can induce certain effects in cultured cells that are consistent with mechanistic pathways associated with carcinogenesis, this does not provide strong evidence of carcinogenicity. Though BPA may have been shown to exhibit some effects consistent with the 10 KCCs in certain studies, the characteristics are also shared by many non-carcinogenic substances (Smith *et al*., 2021; Bus, 2017; Goodman and Lynch, 2017), particularly when tested at very high doses and/or in *in vitro* studies where positive (including false positive) results for a particular characteristic would be expected (Smith *et al*., 2021). Thus, the existence of evidence for one or more of the 10 KCCs for BPA does not automatically indicate that BPA is carcinogenic, and this cannot not be used to form conclusions about the potential carcinogenicity of BPA.

The key characteristics approach to evaluating mechanistic evidence for carcinogenicity is too broad to be used alone for an evaluation of the carcinogenic potential of a substance, which requires a comprehensive evaluation of the available epidemiology and toxicology evidence (Smith *et al*., 2021; Bus, 2017; Goodman and Lynch, 2017; Smith *et al*., 2016). There are many different mechanisms proposed for BPA carcinogenicity through interactions with a variety of receptors and other cellular molecules and activation of many signaling pathways (Cimmino *et al*., 2020; Cuomo *et al*., 2017; Dumitrascu *et al*., 2020; Khan *et al*., 2021; Wang *et al*., 2016), adding to the complexity of defining BPA's potential mode(s) of action for inducing various cancers, if indeed BPA is carcinogenic. The relevance of the mechanisms to cancer development in humans is not clear, however, as most of the studies in which the mechanisms are described are *in vitro* studies for which the effects are not easily extrapolated to humans. In addition, there is no support for these mechanisms among the epidemiology and experimental animal studies, which, as described above, do not provide strong and consistent evidence that BPA acts as a carcinogen by any mechanism.

5 Conclusions

The available epidemiology, experimental animal, and mechanistic studies evaluating potential associations between BPA exposure and cancer outcomes that were reviewed in OEHHA's hazard identification document do not provide clear or consistent evidence that BPA causes invasive cancer in humans or animals.

The epidemiology studies have many important limitations that restrict their ability to be informative regarding whether BPA exposure is a causal factor in the development of cancer in humans. Although the hazard identification document often states that these limitations would lead to risk estimates that are biased toward the null, this is not true, as many of the limitations can potentially lead to results that are biased in either direction. Despite their limitations, the epidemiology studies do not provide evidence that BPA causes invasive cancer in humans. There is no consistency in the direction or statistical significance of results across studies for any cancer type or across all cancers in general. Overall, there is no evidence in the epidemiology literature to support the plausibility of BPA as a carcinogen.

Most of the experimental animal studies also have significant methodological limitations and are of limited utility for assessing BPA carcinogenicity, except for two chronic bioassays that evaluated BPA carcinogenicity over a wide range of doses. The chronic bioassays reported very few tumor types with a statistically significant increased incidence that were likely attributable to chance fluctuations or multiple comparisons and, therefore, are not likely to be treatment related, which is consistent with the conclusions of the study authors. The hazard identification document presents the experimental animal evidence in a manner that is biased toward a conclusion of carcinogenicity by conducting additional statistical analyses of the study results with no rationale for doing so and selectively reporting the statistically significant results; using inappropriate historical control data sets to identify rare tumors and attribute these to BPA exposure; including studies of short duration with positive results but excluding such studies with null results; and failing to report any evidence that supports a lack of carcinogenicity, such as statistically significant decreases in tumor incidence. Despite this, it is clear from the evidence of the chronic bioassays, as well as the other experimental animal studies with significant limitations, that there is no clear and consistent evidence that BPA affects the incidence of malignant tumors in experimental animals unless the BPA exposure is followed by exposure to a known rodent carcinogen.

Although there is some evidence, particularly from *in vitro* studies, that BPA exhibits some mechanistic characteristics common to carcinogenic chemicals, these characteristics are also shared by many non-carcinogenic substances, and they do not provide strong evidence that BPA is a carcinogen. The relevance of the carcinogenic mechanisms to cancer development in humans is unclear, and they are not supported by the results of the epidemiology and experimental animal studies of BPA, which do not provide clear or consistent evidence that BPA induces invasive cancer in humans or animals by any mechanism.

The studies reviewed in the hazard identification document do not support a listing of BPA as a chemical known to the State of California to cause cancer.

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