March 14, 2022

Submitted Electronically

Tyler Saechao
Office of Environmental Health Hazard Assessment
1001 I Street
P. O. Box 4010, MS-12B
Sacramento, California 95812-4010

Re: Request for Relevant Information on the Carcinogenicity of Bisphenol A (BPA)

Dear Mr. Saechao:

Please find attached written comments from the Polycarbonate/BPA Global Group of the American Chemistry Council[1] in response to OEHHA's Request for Relevant Information on the Carcinogenicity of Bisphenol A (BPA).[2] The Polycarbonate/BPA Global Group consists of the leading global manufacturers of bisphenol A (BPA) and polycarbonate plastic, which for many years have supported and conducted scientific research to understand whether BPA has the potential to cause health or environmental effects and to support scientifically sound public policy. Our comments are limited to information relevant to assess the carcinogenicity of BPA.

Based on the extensive scientific data and previous reviews available, BPA does not meet the OEHHA Carcinogen Identification Committee (CIC) guidance criteria for identifying chemicals

[1] The American Chemistry Council (ACC) represents the leading companies engaged in the multibillion-dollar business of chemistry. ACC members apply the science of chemistry to make innovative products, technologies and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health, safety and security performance through Responsible Care®; common sense advocacy addressing major public policy issues; and health and environmental research and product testing. ACC members and chemistry companies are among the largest investors in research and development, and are advancing products, processes and technologies to address climate change, enhance air and water quality, and progress toward a more sustainable, circular economy.

[2] https://oehha.ca.gov/proposition-65/crnr/request-relevant-information-carcinogenicity-bisphenol-bpa

for listing as "known to the State to cause cancer."[3] As detailed in the attachment, this conclusion is based on the following key points:

- Low Exposure and Efficient Metabolism Indicate Low Potential for Carcinogenicity
- Comprehensive Reviews Find Little Concern for Carcinogenicity
- NTP 2-Year Bioassays Find No Compelling Evidence for Carcinogenicity
- CLARITY-BPA Produced Little Evidence that Bisphenol A Could Be Carcinogenic
- Epidemiologic Studies are Inadequate to Demonstrate a Causal Link between Bisphenol A (BPA) and Carcinogenesis
- Mechanistic "Key Characteristics" Do Not Overcome Results of Lifetime Studies that Demonstrate Bisphenol A is Not Carcinogenic
- Extensive Weight of Evidence Indicates that Bisphenol A is Not Genotoxic
- Co-Carcinogenicity and Xenograft Studies Are of Limited Relevance to Human Health

Please do not hesitate to contact me at Alexandra_Peck@americanchemistry.com if I can be of further assistance to clarify any of the information provided or if additional information is needed.

Regards,

Alexandra Peck
Manager
Polycarbonate/BPA Global Group

Attachment

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

**ATTACHMENT**

# Comments on the Request for Relevant Information on the Carcinogenicity of Bisphenol A (BPA)

**Submitted to the**
**Office of Environmental Health Hazard Assessment**
**California Environmental Protection Agency**

**from the**
**Polycarbonate/BPA Global Group**
**American Chemistry Council**

**March 14, 2022**

## 1. Overview

Bisphenol A (BPA), a chemical building block used primarily to make polycarbonate plastic and epoxy resins, does not meet the OEHHA CIC guidance criteria for identifying chemicals for listing as "known to the State to cause cancer." This conclusion is based on the weight of evidence from an extensive scientific database, as well as numerous comprehensive reviews of the scientific evidence that have concluded BPA is not a significant carcinogenic hazard or risk. Specifically, scientific studies show that:

- After ingestion, which is by far the predominant route of human exposure, BPA is efficiently converted to biologically inactive metabolites (i.e., conjugates) that are rapidly eliminated from the body. Therefore, BPA does not bioaccumulate and is thus unlikely to cause long-term human health effects;

- Recent studies conclude that little unconjugated BPA is found in human blood even after high dietary exposures;

- Numerous biomonitoring studies, most notably the National Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control and Prevention (CDC), demonstrate human exposure to BPA is very low;

- Standard National Toxicology Program (NTP) 2-year bioassays do not support a finding of carcinogenicity with BPA exposure in rodent models;

- The CLARITY-BPA Core study produced little evidence that BPA could be carcinogenic in rats;

- Epidemiologic studies are inadequate to demonstrate a causal link between BPA and carcinogenesis.

- Mechanistic "Key Characteristics" do not overcome results of lifetime studies that demonstrate BPA is not carcinogenic;

- The weight of evidence indicates that BPA is not genotoxic; and

- Co-carcinogenicity and xenograft studies are of limited relevance to human health based on inappropriate routes of administration, non-physiologic animal models and conflicting results from the oral exposure studies.

## 2. What Is Bisphenol A and How It Is Used?

BPA is a chemical building block used primarily (i.e., approximately 94% of BPA produced) to make polycarbonate plastic and epoxy resins. Products made from these materials have a long safety track record, more than 50 years, and an equally long history of testing. The unique attributes of these materials make them ideal for use in a wide array of products, many of which improve the health and safety of consumers.

Polycarbonate is a lightweight, highly shatter-resistant plastic with optical clarity comparable to glass. Common products made from polycarbonate include eyeglass lenses, sports safety equipment (e.g., helmets, visors, goggles), critical components of medical devices (e.g., kidney dialyzers, blood oxygenators), electronic equipment housings, protective shields, and automobile components (e.g., headlamp lenses, mirror housings, bumpers).

Epoxy resins have an exceptional combination of toughness, chemical resistance and adhesion. Common products made from epoxy resins include corrosion resistant coatings for metals (e.g., steel pipes/fittings, structural steel, concrete reinforcement bar), printed circuit board laminates, automobile primer coatings, and fiber reinforced composites.

The manufacturing processes to make polycarbonate plastic and epoxy resins convert virtually all BPA into the plastic or resin, leaving behind only trace levels of residual BPA, typically less than 100 parts per million (<0.01% by weight), in the finished materials. Consumers frequently benefit from products made from these materials but come into contact with very little BPA from use of these products.

### 3. Low Exposure and Efficient Metabolism Indicate Low Potential for Carcinogenicity

As described above, the amount of residual BPA remaining in polycarbonate plastic and epoxy resins is very low, typically less than 100 ppm, which limits the potential for human exposure. These materials currently have very limited use in food packaging applications and various other consumer products that contact food. The result is little potential for human exposure to BPA from the limited use of these materials in contact with food.

Until recently, epoxy resins had commonly been used as the protective coating on food and beverage cans. However, the can industry has reported that epoxy resins have largely been replaced by alternative coatings that do not contain BPA. As a result, products that contact food are not expected to be a significant source of human exposure to BPA.

Similarly, BPA had been used as a component of the thermally reactive coating applied to paper to make thermal paper products such as cash register receipts. It is unlikely that BPA is significantly used in these products any longer in the U.S. market. Consequently, thermal paper products are unlikely to be a significant source of human exposure to BPA.

In recent years, large-scale urine biomonitoring studies conducted by the CDC have documented human exposure to BPA in the US population. These studies confirm that exposure to BPA from all sources is extremely low, typically less than 100 nanograms/kg-day. For example, based on CDC's 2011-2012 data, median daily intake for the overall population (age 6 and above) is approximately 25 nanograms/kg-day.[1]

This median value has declined further in more recent CDC datasets due to the replacement of BPA based epoxy resins as the protective coating on food and beverage cans and the replacement of BPA in thermal paper products. Both of these products were considered to be a significant source of human exposure to BPA.

Of more importance than the magnitude of exposure is the disposition of BPA after ingestion. The metabolism and pharmacokinetics of BPA have been the subject of numerous studies on laboratory animals and humans. While a complete review of this subject is beyond the scope of these comments, key findings from high-quality studies funded and conducted by federal government laboratories are summarized below. These findings are generally consistent with the many previous studies that have been conducted, all of which demonstrate that BPA is efficiently metabolized and rapidly eliminated by adults, children and infants.

- **BPA is Efficiently Metabolized and Rapidly Eliminated in Adult Humans; Unlikely to Cause Health Effects**

  Two published studies monitored the metabolism and elimination of BPA that was orally administered at relatively high doses (30 or 100 mg/kg-bw). The most recent study[2] was conducted by NTP and included participation by researchers with the Food and Drug Administration (FDA). The second study[3] was conducted by the Pacific Northwest National Laboratory and included participation by FDA researchers.

  Both studies confirmed that BPA is efficiently converted to biologically inactive conjugates after ingestion, which are then rapidly eliminated from the body in urine. In both of the human studies, the amount of unconjugated BPA found in the blood was <1% of the administered dose. The data from both studies indicate that conjugation of BPA is rapid and nearly complete. Previous studies have shown that the conjugated forms of

[1] LaKind, J. S. and Naiman, D. Q. 2015. Temporal trends in bisphenol A exposure in the United States from 2003-2012 and factors associated with BPA exposure: Spot samples and urine dilution complicate data interpretation. Environmental Research. 142:85-95.
[2] Thayer, K. A., Doerge, D. R., Hunt, D., Schurman, S. H., Twaddle, N. C., Churchwell, M. I., Garantziotis, S., Kissling, G. E., Easterling, M. R., Bucher, J. R., and Birnbaum, L. S. 2015. Pharmacokinetics of bisphenol A in humans following a single oral administration. Environment International. 83:107-115.
[3] Teeguarden, J. G., Twaddle, N., Churchwell, M. I., Yang, X., Fisher, J. W., Seryak, L. M., and Doerge, D. R. 2015. 24-Hour human urine and serum profiles of bisphenol A: Evidence against sublingual absorption following ingestion in soup. Toxicology and Applied Pharmacology. 288(2):131-142.

BPA (i.e., BPA-glucuronide,[4] BPA-sulfate[5]) are not estrogenic and have no known biological activity.

In an EPA-funded study conducted at the Pacific Northwest National Laboratory, with participation from FDA and CDC laboratories, Teeguarden *et. al.* conducted a clinical exposure study and monitored the metabolism and elimination of BPA from 20 adult human volunteers.[6] The study further confirmed that BPA is efficiently converted to conjugates, which are then rapidly eliminated from the body in urine. As noted above, previous studies have shown that the conjugated forms of BPA are not estrogenic and have no known biological activity.

With an atypically high exposure level and a sensitive analytical method, BPA was not detected in blood at any time point in the study. Only the inactive conjugates of BPA were transiently found at low levels before rapid elimination from the body in urine.

The results of these studies, along with the similar results of numerous other human and laboratory animal studies, indicate that, because of the way it is processed in the body, it is very unlikely that BPA could cause health effects at any foreseeable exposure.

- **Laboratory Animal Studies Confirm that BPA is Efficiently Metabolized At All Age Groups**

  A series of studies on monkeys and rats conducted in the FDA laboratory confirm that BPA is efficiently metabolized not only in adults, but also in pregnant animals, neonates and the fetus.[7,8,9,10] Notably, the ability of monkeys only a few days after birth to metabolize BPA is equivalent to that of adult monkeys. In rats, the developing fetus also has the ability to metabolize BPA. In addition, the amount of BPA that could reach the

[4] Matthews, J.B., Twomey, K., and Zacharewski, T.R. 2001. In vitro and in vivo interactions of bisphenol A and its metabolite, bisphenol A glucuronide, with estrogen receptors alpha and beta. Chemical Research in Toxicology. 14(2):149-157.
[5] Shimizu, M., Ohta, K., Matsumoto, Y., Fukuoka, M., Ohno, Y., and Ozawa, S. 2002. Sulfation of bisphenol A abolished its estrogenicity based on proliferation and gene expression in human breast cancer MCF-7 cells. Toxicology in Vitro. 16(5):549-556.
[6] Teeguarden, J. G., Calafat, A. M., Ye, X., Doerge, D. R., Churchwell, M. I., Gunawan, R., and Graham, M. 2011. Twenty-four hour human urine and serum profiles of bisphenol A during high-dietary exposure. Toxicological Sciences. 123(1):48-57.
[7] Doerge, D. R., Twaddle, N. C., Woodling, K. A., and Fisher, J. W. 2010. Pharmacokinetics of bisphenol A in neonatal and adult rhesus monkeys. Toxicology and Applied Pharmacology. 248(1):1-11.
[8] Doerge, D. R., Twaddle, N. C., Vanlandingham, M., and Fisher, J. W. 2010. Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats. Toxicology and Applied Pharmacology. 247(2):158-165.
[9] Doerge, D. R., Twaddle, N. C., Vanlandingham, M., Brown, R. P., and Fisher, J. W. 2011. Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague-Dawley rats. Toxicology and Applied Pharmacology. 255(3):261-270.
[10] Doerge, D. R., Vanlandingham, M., Twaddle, N. C., and Delclos, K. B. 2010. Lactational transfer of bisphenol A in Sprague-Dawley rats. Toxicology Letters. 199(3):372-376.

fetus is extremely low due to the efficient metabolism of BPA by the mother, which protects the fetus from exposure. Similar to the studies above on human adults, these studies indicate that BPA is unlikely to cause health effects at any age with any foreseeable exposure. In addition, because of differences noted between rats and monkeys, health effect studies in rodents are likely to over-predict the potential for health effects in primates, including humans.

- **Results From Metabolism and Pharmacokinetic Studies Especially Relevant for Epidemiology Studies**

  As noted above, numerous pharmacokinetic and metabolism studies demonstrate that BPA, in particular by the oral route of exposure, is efficiently metabolized and rapidly eliminated from the body. This is particularly important for epidemiology studies that aim to associate exposure BPA with chronic health effects, for example carcinogenic effects.

  In the case of BPA, a valid association is likely to require measurement of exposure before the health effect is present since BPA is so rapidly eliminated from the body after exposure. This may not often be done since the long timeframe of many chronic effects, coupled with rapid elimination of BPA after exposure, will significantly lengthen the timeframe of epidemiology studies. It is likely to be more common to measure exposure when, or even after, a carcinogenic effect is found.

  In addition, valid measurement of exposure for individuals is likely to require multiple biomonitoring measurements over a long period of time since BPA levels will vary significantly over short periods of time. This is due to the rapid elimination of BPA from the body, and the need for multiple biomonitoring measurements has been demonstrated in several studies.

  A further complication for epidemiology studies is that BPA is efficiently metabolized after exposure. Since the conjugated metabolites are not bioactive, measurement of the much lower level of unconjugated BPA is necessary to achieve a valid measure of exposure.

## 4. Comprehensive Reviews Find Little Concern for Carcinogenicity

Numerous government and scientific bodies worldwide have examined the scientific evidence supporting the safety of BPA. In every case, the assessments of these bodies support the conclusion that BPA is not a risk to human health at the extremely low levels to which people might be exposed.

Many of these assessments comprehensively examined the potential carcinogenicity of BPA. Consistent with the CIC guidance criteria for identifying carcinogens, each of these assessments applied a "weight-of-evidence" approach to evaluate the body of information available for BPA.

As detailed below, these assessments consistently determined that BPA is not a carcinogenic hazard or risk to humans. No other government or scientific body has reached a different conclusion. In addition, no authoritative body recognized under Proposition 65 to identify chemicals as causing cancer has listed or taken action on BPA. Several key evaluations of BPA are briefly summarized below along with their overall conclusions regarding the potential carcinogenicity and mutagenicity/genotoxicity of BPA.

### a. European Union Risk Assessment

Under the European Union (EU) Existing Substances Directive, the EU conducted a comprehensive risk assessment of BPA that was initially published in 2003 and updated in 2008.[11] These assessments comprehensively evaluated studies on the toxicity, metabolism and pharmacokinetics, and exposure of BPA. The overall conclusions for carcinogenicity and mutagenicity from the 2003 report and 2008 updates are presented below.

Carcinogenicity Conclusions

> "Taking into account all of the animal data available the evidence suggests that BPA does not have carcinogenic potential." (2003)
>
> "Overall, therefore, the new information on the potential carcinogenic and/or promoting effects of BPA in prenatal and neonatal rat models supports the original conclusion from the published report that BPA does not possess any significant carcinogenic potential." (2008)

Mutagenicity Conclusions

> "Considering all of the available genotoxicity data, and the absence of significant tumour findings in animal carcinogenicity studies, it does not appear that BPA has significant mutagenic potential *in vivo*." (2003)
>
> "Therefore, the original conclusion from the published assessment that BPA has no significant mutagenic potential *in vivo*, is still valid." (2008)

### b. European Food Safety Authority

[11] European Union Risk Assessment Report – 4,4'-isopropylidenediphenol (Bisphenol-A). Available at Addendum 2008 + RAR 2003 (europa.eu) (combined 2003 full report and 2008 update).

The European Food Safety Authority (EFSA) conducted a detailed scientific assessment of BPA that was released in 2015.[12] The evaluation focused on exposure and toxicity to support a risk conclusion.

A Weight of Evidence (WoE) approach was applied to reach conclusions on hazards associated with a variety of health effects. Of particular relevance here, the assessment included a review of available data on mutagenicity and carcinogenicity. The overall conclusions for carcinogenicity and mutagenicity are presented below.

Carcinogenicity Conclusions

> "BPA was not carcinogenic in two standard oral cancer bioassays in rats and mice exposed (from 6-8 weeks of age) for 2 years. New results do not provide convincing evidence that BPA is carcinogenic in animals when exposed during their adult life or when exposed perinatally."
>
> "Using a WoE approach, the CEF Panel assigned a likelihood level of "unlikely to - as likely as not -" to carcinogenic effects of BPA. Since the likelihood level for this endpoint is less than "as likely as not" (see Appendix A), this endpoint was not taken into account in the evaluation of uncertainty for hazard characterisation and risk characterisation."

Mutagenicity Conclusions

> "In summary, BPA is not mutagenic (in bacteria or mammalian cells), or clastogenic (micronuclei and chromosomal aberrations)."

The recently updated Draft Opinion (issued December 15, 2021 by EFSA) includes a new assessment of carcinogenicity data, but only based on studies published between January 1, 2013 and October 15, 2018, that were not previously considered by EFSA.[13] This limited assessment based on the restricted timeframe does not represent a WoE approach, and therefore, should not be considered as a comprehensive review of the scientific evidence for carcinogenicity of BPA. Once finalized, however, the updated EFSA Opinion report on BPA may be useful as part of a WoE assessment (for at least that specific timeframe) for BPA and cancer.

[12] Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: PART II - Toxicological assessment and risk characterization. EFSA Journal 2015;13(1):3978.
[13] EFSA. 2021. Draft Scientific Opinion: Re-evaluation of the risks to public health related to the presence of bisphenol (BPA) in foodstuffs. Issued December 15, 2021.

### c. U.S. Food and Drug Administration

The U.S. Food and Drug Administration (FDA) issued a comprehensive draft report in 2008 finding that BPA remains safe in food contact materials.[14] Similar to the EU Risk Assessment, FDA's draft report comprehensively evaluated studies on the toxicity, metabolism and pharmacokinetics, and exposure of BPA. The overall FDA conclusion for carcinogenicity was:

> "As part of this safety assessment, CFSAN's Cancer Assessment Committee (CAC) evaluated BPA based on the available bioassay data and recent peer-reviewed publications on BPA, specifically those that reported evidence of pre-neoplastic and neoplastic changes in animal models that were administered BPA orally at various dose levels. The CAC concluded that the findings reported in the 1982 NTP study on BPA do not provide any evidence that BPA is carcinogenic to F344 rats or B6C3F1 mice of either sex as tested under the conditions of this bioassay."

> "Because of these limitations [referring to limitations of the recent peer-reviewed publications referenced above], the CAC concluded that the totality of the information contained in these reports is of questionable usefulness for a determination of potential enhancement of neoplastic effects of BPA on the rodent prostate and mammary gland."

However, in 2008, a subcommittee of FDA's science board raised questions about whether this review had adequately considered the most recent scientific information available. Therefore, FDA experts from across the Agency completed a four-year review of more than 300 scientific BPA studies in 2014. In the final report to the FDA Chemical and Environmental Science Council, the BPA Joint Review Working Group (JRWG)[15] summarized findings from three interim reviews of the BPA literature conducted in 2011, 2012, and 2014. In this final report, the JRWG did not identify carcinogenesis as a potential hazard.[16] In the more detailed memorandum of the 2014 interim review, the JRWG concluded the following for carcinogenicity studies:

> "The negative findings in the carcinogenicity [*sic*] do not support mammary gland carcinogenicity as a potential hazard. The negative findings in prostate histopathology do not support prostate carcinogenicity as a potential hazard."[17]

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[14] Draft Assessment of Bisphenol A for use in Food Contact Applications. Draft 2008 report available http://wayback.archive-it.org/7993/20180126150108/https://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-0038b1_01_02_FDA%20BPA%20Draft%20Assessment.pdf

[15] Bisphenol A (BPA) Joint Emerging Science Working Group (2014). Final report for the review of literature and data on BPA memorandum sent to US FDA Chemical and Environmental Science Council. Available at https://www.fda.gov/media/90546/download.

[16] Ibid.

[17] Bisphenol A (BPA) Joint Emerging Science Working Group (2014). 2014 Updated Review of Literature and Data on Bisphenol A (CAS RN 80-05-7). (p. 113). Memorandum to FDA Chemical and Environmental Science Council. Available at https://www.fda.gov/media/90582/download.

### d. Japanese National Institute for Advanced Industrial Science and Technology

In 2005, the Japanese National Institute for Advanced Industrial Science and Technology (AIST) issued a comprehensive risk assessment of BPA, with an English translation made available in 2007.[18] A thorough update of the assessment, which considered research published since the original 2005 report, was released in July 2011.[19] The AIST assessments evaluated studies on toxicity, metabolism and pharmacokinetics, and exposure of BPA. The overall AIST conclusions for carcinogenicity and genotoxicity from the 2005 report and 2011 update are presented below.

Carcinogenicity and Genotoxicity Conclusions

> "Carcinogenicity studies in F344 rats and B6C3F1 mice both produced negative results (NTP 1982). Results of cell transformation assays using cultured cells (*in vitro* carcinogenicity tests) were negative too (see, for example, Jones *et al*. 1988, European Commission 2003)." (2005)
>
> "Following a weight-of-evidence approach recommended by IARC and US EPA, Haighton *et al.* (2002) concluded that BPA is not likely to be a human carcinogen. We consider that this conclusion is appropriate." (2005)
>
> "Overall, taking the above results into account, it does not appear that BPA has positive genotoxic potential" and "BPA is unlikely to have genotoxic or carcinogenic potential." (2005)
>
> "Following a weight-of-evidence approach, it has been concluded that BPA is not likely to be carcinogenic to humans (Haighton, 2002). This was due to the fact that a) BPA did not cause gene mutations or chromosomal aberrations in bacteria/fungi/mammalian cells in standard in-vitro genetic tests; b) BPA was negative in in-vivo chromosomal aberrations tests; and c) BPA was negative in all of the bone-marrow micronucleus tests in mice, dominant lethal tests in rats, and carcinogenicity study in rats and mice. None of the new information supported overturning this conclusion." (2011)

### e. Joint FAO/WHO Expert Meeting

In November 2010, the World Health Organization (WHO) and the UN Food and Agriculture Organization (FAO) jointly organized an Expert Meeting to assess the safety of BPA. The full

[18] Bisphenol A Risk Assessment Document. English version available at https://riss.aist.go.jp/results-and-dissemin/1169/

[19] Updated Hazard Assessment of Bisphenol A. English version available at https://riss.aist.go.jp/en/research-outcomes/356/

report from the meeting was released in September 2011.[20] The overall conclusions for carcinogenicity and genotoxicity are presented below.

Carcinogenicity Conclusion

> "In the traditional rodent cancer bioassay (NTP, 1982), BPA at doses of approximately 75–150 mg/kg bw per day gave, at best, weak evidence of carcinogenic activity, but it is questionable whether the chemical was adequately studied. The United States National Toxicology Program (NTP) bioassay did not include exposures during the perinatal period, which would appear to be a critical window of exposure. Studies that included perinatal (gestational and/or lactational) exposures to BPA (oral doses to the dam from ~10 to 250 μg/kg bw per day) have reported, among other lesions, proliferation of mammary ductal epithelium and squamous metaplasia of prostatic epithelium in offspring, conditions thought by many to predispose to neoplasia (Timms et al., 2005; Moral et al., 2008). Additional treatments with initiating or promoting agents have led to earlier onset of mammary tumours (Jenkins et al., 2009) or prostatic intraepithelial neoplasia (Prins et al., 2011).
>
> However, the studies that included exposures to BPA during the appropriate periods all suffered from one or more deficiencies in design or execution that prevent a definitive evaluation of its potential as a carcinogen. These include 1) lack of consideration of litter effects, 2) small numbers of animals, 3) insufficient study duration to determine whether developmental conditions thought to enhance cancer susceptibility actually did so and 4) additional treatment with a strong initiating or additional promoting agent(s). In the absence of additional studies addressing these deficiencies, there is currently insufficient evidence on which to judge the carcinogenic potential of BPA."

Genotoxicity Conclusion

> "In conclusion, BPA is not a mutagen in in vitro test systems, nor does it induce cell transformation. BPA has been shown to affect chromosomal structure in dividing cells in in vitro studies, but evidence for this effect in in vivo studies is inconsistent and inconclusive. BPA is not likely to pose a genotoxic hazard to humans."

### f. Haighton et al., Regulatory Toxicology and Pharmacology (2002)

A seminal evaluation of the potential carcinogenicity of BPA was published in 2002 by Haighton et al.[21] The evaluation included carcinogenicity and genotoxicity studies, along with

[20] Toxicological and Health Aspects of Bisphenol A. Report of Joint FAO/WHO Expert Meeting. See https://apps.who.int/iris/handle/10665/44624 for full documentation on the meeting.
[21] Haighton, L.A., Hlywka, J.J., Doull, J., Kroes, R., Lynch, B.S., and Munro, I.C. 2002. An evaluation of the possible carcinogenicity of bisphenol A to humans. Regulatory Toxicology and Pharmacology. 35:238-254.

various other toxicity, metabolism and exposure studies, and followed weight-of-evidence guidelines for assessment of carcinogenicity from the International Agency for Research on Cancer (IARC) and the U.S. Environmental Protection Agency. The overall conclusion of this evaluation was:

> "Following a weight-of-evidence approach as recommended by IARC and U.S. EPA, it was concluded that BPA is not likely to be carcinogenic to humans. The bases for this conclusion included: (a) the results of an NTP study which provided no substantive evidence to indicate that BPA is carcinogenic to rodents; (b) the lack of activity of BPA, at noncytotoxic concentrations, in standard *in vitro* genetic toxicity tests; (c) the lack of genotoxic activity of BPA in a GLP-compliant *in vivo* mouse micronucleus assay; and (d) the results of metabolism studies showing BPA is rapidly glucuronidated without evidence of formation of potentially reactive intermediates, except possibly at high doses that could saturate detoxication pathways."

## 5. NTP 2-Year Bioassays Find No Compelling Evidence for Carcinogenicity

NTP evaluated the carcinogenic potential of BPA in 2-year feeding studies in F344 rats and B6C3F1 mice.[22] Each study included two BPA dose groups along with a control group.

In rats, a higher incidence of leukemias was observed only in high-dose male rats. However, all incidence values were well within the historical control data range for the F344 rat strain, and statistical analyses revealed that the higher incidence was an incidental non-treatment related finding. Similarly, the higher incidence of interstitial-cell tumors was not considered treatment related since these tumors occur spontaneously at a very high, but variable, incidence rate in aging F344 male rats, and the observed incident rates were all within the historical control levels for the testing facility. Fibroadenomas of the mammary gland in male rats were observed in greater, but not statistically significant, proportions in the high-dose group. However, the incidence was within the historical range for this tumor type in male rats.

In the mouse study, male mice in the low-dose group exhibited a significantly higher combined incidence of lymphomas and leukemias, but with no dose-response relationship and no such effect in females. The types of hemopoietic tumors observed were typical of those that occur spontaneously in aging B6C3F1 mice and the incidence values were within the range of historical control data for malignant lymphoma in this strain and species. The incidence of multinucleated giant hepatocytes was significantly higher in male, but not female, mice but there

[22] NTP Technical Report on the Carcinogenesis Bioassay of Bisphenol A in F344 Rats and B6C3F1 Mice (Feed Study). 1982. National Toxicology Program, U.S. Department of Health and Human Services, Public Health Service, National Institute of Health.

were no increased incidences of liver tumors in either sex. The occurrence of multinucleated giant hepatocytes is a common non-neoplastic phenomenon in aging mice.

NTP concluded that the studies showed equivocal evidence of carcinogenicity in male rats, and no evidence of carcinogenicity in female rats and mice of either sex. Overall, the results of the bioassays did not provide any compelling evidence to indicate that BPA was carcinogenic in F344 rats or B6C3F1 mice.

## 6. CLARITY-BPA Core Study Produced Little Evidence that BPA Could Be Carcinogenic

The FDA recently conducted and published the CLARITY-BPA Core Study (Perinatal and Chronic Extended-Dose-Range Study of Bisphenol A in Rats).[23] The two-year toxicology study was conducted as part of the Consortium Linking Academic and Regulatory Insights on Bisphenol A Toxicity (CLARITY-BPA) and published in 2019.

The study was conducted on Sprague-Dawley rats and included five dose levels of BPA, ranging from 2.5-25,000 μg/kg, that were administered orally from gestation day 6 until termination at 1 or 2 years. The study also included a "stop-dose" arm in which dosing ended at post-natal day (PND) 21.

Regarding the observation of lesions, the study concluded "Neoplastic and nonneoplastic lesions diagnosed in both females and males were common age-associated lesions that were variable across control and BPA-treated groups. The lack of consistent responses within the continuous- and stop-dose arms within and across tissues brought into question the plausible relationship of most of these lesions to BPA treatment."

A slightly increased incidence of mammary gland lesions were observed only at the lowest dose tested and only in the "stop-dose" arm. Regarding this observation, the study concluded "Our interpretation of the overall evidence gathered in the study was that there is not a clear biologically plausible relationship between BPA exposure and female mammary gland adenoma/adenocarcinoma in this study, but rather that this was the result of chance fluctuation in incidences of a common rat neoplasm."

Although designed as a toxicity study rather than specifically as a carcinogenicity bioassay, the CLARITY-BPA core study produced little evidence that BPA could be carcinogenic over the lifetime of the exposed rats.

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[23] Camacho, L., Lewis, S. M., Vanlandingham, M. M., Olson, G. R., Davis, K. J., Patton, R. E., Twaddle, N. C., Doerge, D. R., Churchwell, M. I., Bryant, M. S., McLellen, F. M., Woodling, K., Felton, R. P., Maisha, M. P., Juliar, B. E., et al. 2019. A two-year toxicology study of bisphenol A (BPA) in Sprague-Dawley rats: CLARITY-BPA core study results. Food and Chemical Toxicology. 132:110728.

## 7. Extensive Weight of Evidence Indicates that Bisphenol A is Not Genotoxic

Genetic toxicity studies are of critical importance to the appropriate interpretation of animal carcinogenicity studies. Data from numerous *in vitro* and *in vivo* genotoxicity assays on BPA are available and should be examined in context with data from the NTP carcinogenicity bioassays discussed above. Both of the NTP bioassays provided no substantive evidence that BPA is carcinogenic, which is consistent with the largely negative genotoxicity data for BPA.

Evaluations of BPA in bacterial reverse mutation tests (Ames tests) have consistently produced negative (i.e., non-genotoxic) results.[24,25,26,27,28] Standard *in vitro* mammalian genotoxicity studies (including those conducted by OECD guidelines) of BPA have generally indicated a lack of mutagenic and clastogenic activity.[28,29,30,31]

Two studies reporting meiotic aneuploidy are cited in the "other relevant data" section of OEHHA's document on BPA.[32,33] Although an increase in aneuploidy metaphase II oocytes in mice was reported, there was not a significant increase in aneuploid embryos, indicating a lack of consistency between what should be concordant endpoints. In a subsequent study, the same researchers reported they could not replicate their initial findings, stating "After publishing our findings [Hunt et al., 2003], we initiated studies to assess the effect of long term BPA exposure on the growing follicle. To our surprise, levels of BPA that were sufficient to elicit an effect on meiotic chromosome dynamics during the previous two years of study suddenly produced little

[24] Dean, B. J. and Brooks, T. M. 1978. Toxicity tests with diphenylol propane (DPP): *In vitro* mutation studies. Shell Research Report TLGR.0111.78.
[25] Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., and Zeiger, E. 1983. Salmonella mutagenicity test results for 250 chemicals. Environmental Mutagenesis. Supplement 1:3-142.
[26] Takahata, J., Tamakawa, K., Takahaski, Y., Seki, T., Tsunoda, A., Nohmi, T., and Sofuni, T. 1990. Mutagenicity of environmental chemicals II, bisphenol A. Sendai-shi Eisei Kenkyushoho (Japan) 20:245-247.
[27] JETOC, 1996. Mutagenicity test data of existing chemical substances. Japan Chemical Industry Ecology-Toxicology & Information Center, Japan.
[28] Schweikl, H., Schmalz, G., and Rackenbrandt, K. 1998. The mutagenic activity of unpolymerized resin monomers in *Salmonella typhimurium* and V79 cells. Mutation Research. 415:119-130.
[29] Ivett, J. L., Brown, B. M., Rodgers, C., Anderson, B. E., Resnick, M. A., and Zeiger, E. 1989. Chromosomal aberrations and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. IV. Results with 15 chemicals. Environmental and Molecular Mutagenesis. 14(3):165-187.
[30] Myhr, B.C. and Caspary, W. J. 1991. Chemical mutagenesis and the thymidine kinase locus in L5178Y mouse lymphoma cells: Results for 31 coded compounds in the national toxicology program. Environmental and Molecular Mutagenesis. 18:51-83
[31] Hilliard, C. A., Armstrong, M. J., Bradt, C. I., Hill, R. B., Greenwood, S. K., and Galloway, S. M. 1998. Chromosome aberrations in vitro related to cytotoxicity of nonmutagenic chemicals and metabolic poisons. Environmental and Molecular Mutagenesis. 31(4):316-326.
[32] Hunt, P. A., Koehler, K. E., Susiarjo, M., Hodges, C. A., Ilagan, A., Voigt, R. C., Thomas, S., Thomas, B. F., and Hassold, T. J. 2003. Bisphenol A exposure causes meiotic aneuploidy in the female mouse. Current Biology. 13:546-553.
[33] Susiarjo, M., Hassold, T. J., Freeman, E., and Hunt, P. A. 2007. Bisphenol A exposure in utero disrupts early oogenesis in the mouse. PLoS Genetics. 3(1):1-8.

or no effect. In an analysis of possible changes in experimental protocol, the only change identified was the lot of animal feed."[34] Two other subsequent *in vivo* studies from independent researchers attempting to replicate the original findings found no increase in aneuploid oocytes[35] or in aneuploid or diploid sperm[36] nor did either study find an increase in aneuploid embryos. In addition, in somatic cells, BPA was found to have a lack of genotoxic activity in a GLP compliant *in vivo* mouse micronucleus study, an assay which can detect both clastogenicity and aneuploidy.[37]

In the DNA adduct formation assay employing $^{32}$P post-labeling, two main adduct spots were observed in Syrian hamster embryos cells, but were not further characterized.[38] In another DNA adduct formation $^{32}$P post-labeling assay with purified rat DNA, positive responses were attributed to bisphenol-o-quinone, an oxidation product of BPA.[39] In subsequent testing, the formation of DNA adducts was inhibited by three known cytochrome P450 inhibitors indicating that activation of BPA to DNA-binding metabolite(s) is P450 dependent. A follow-up *in vivo* rat study (200 mg/kg body wt by gavage or by ip administration) reported the presence of DNA adducts characteristic of bisphenol-o-quinone.[40] The results of this study indicate that, at the high doses administered, BPA may be converted to a metabolite(s), possibly bisphenol-o-quinone, capable of DNA adduct formation. The lack of increased liver tumors in the NTP bioassays suggests that DNA adduct formation was either absent or not sufficient to elicit a response, even in mice, a species which is prone to liver tumors.

The German MAK Commission (1996), in evaluating Atkinson and Roy's data, calculated a covalent-binding index (CBI) of 0.01 for BPA. CBI is calculated as the micromole chemical bound per mole nucleotides divided by the millimole chemical administered per kg animal. These molar units allow a very rapid visualization of how many molecules are bound per million nucleotides after a theoretical dose of 1 mmole/kg. According to Lutz (1979, 1984, 1986), a CBI of <0.1 indicates that a substance has no tumorigenic activity and only very weak DNA binding capacity. As a result, the degree of DNA binding associated with this metabolite is minimal. In

[34] Muhlhauser, A., Susiarjo, M., Rubio, C., Griswold, J., Gorence, G., Hassold, T., and Hunt, P. 2009. Bisphenol A effects on the growing mouse oocyte are influenced by diet. Biology of Reproduction. 80(5):1066-1071.
[35] Eichenlaub-Ritter, U., Vogt, E., Cukurcam, S., Sun, F., Pacchierotti, F., and Parry, J. 2008. Exposure of mouse oocytes to bisphenol A causes meiotic arrest but not aneuploidy. Mutation Research/Genetic Toxicology and Environmental Mutagenesis. 651(1-2):82-92.
[36] Pacchierotti, F., Ranaldi, R., Eichenlaub-Ritter, U., Attia, S., and Adler, I.-D. 2008. Evaluation of aneugenic effects of bisphenol A in somatic and germ cells of the mouse. Mutation Research/Genetic Toxicology and Environmental Mutagenesis. 651(1-2):64-70.
[37] Gudi, R. and Krsmanovic, L. 1999. Mammalian erythrocytes micronucleus test. BioReliance AA12WJ.123.BTL.
[38] Tsutsui, T., Tamura, Y., Yagi, E., Hasegawa, K., Takahashi, M., Maizumi, N., Yamaguchi, F., and Barrett, J. C. 1998. Bisphenol-A induces cellular transformation, aneuploidy, and DNA adduct formation in cultured Syrian hamster embryo cells. International Journal of Cancer. 75:290-294.
[39] Atkinson, A. and Roy, D. 1995. *In vitro* conversion of environmental estrogenic chemical bisphenol A to DNA binding metabolite(s). Biochemical and Biophysical Research Communications. 210(2):424-433.
[40] Atkinson, A. and Roy, D. 1995. *In vivo* DNA adduct formation by bisphenol A. Environmental and Molecular Mutagenesis. 26:60-66.

the absence of evidence of genotoxic activity and carcinogenic potential, the MAK commission indicated that the toxicological significance of the DNA adduct formation is unclear. In any case, bisphenol-o-quinone does not appear to be a significant metabolite of BPA under in vivo conditions, at dose levels of 100 mg/kg-day, which is well in excess of potential human exposures (see Section 7 below).

Overall, the weight of evidence from the genotoxicity studies indicates that BPA is not genotoxic and this is especially true for *in vivo* studies that are more relevant for carcinogenic potential.

## 8. Co-Carcinogenicity and Xenograft Studies Are of Limited Relevance to Human Health

As summarized in OEHHA's compilation of studies identified during the preliminary toxicological evaluation provided to the CIC in September 2020, a small number of co-carcinogenicity and xenograft studies have been conducted on BPA. These studies and their limitations have been reviewed in various assessments of BPA; for example, the FAO/WHO Expert Meeting report and the Japanese AIST assessment, both described in Section 4 above. As noted in the FAO/WHO Expert Meeting report, all of these studies suffer from one or more deficiencies in design and execution, which makes them of limited value in assessing the potential carcinogenicity of BPA. In addition to the discussion in the various assessments, several key limitations are briefly summarized below.

Route of exposure

The route of exposure is a major determinant of the pharmacokinetic profile of BPA in mammals, and consequently, is expected to influence any observed toxicologic outcome. Studies have clearly established the dramatic differences in bioavailability of unconjugated BPA resulting from oral ingestion, by which BPA is efficiently metabolized and rapidly eliminated, versus subcutaneous dosing, which bypasses the metabolism of BPA in the gut wall and liver. It is also well documented that oral ingestion is by far the predominant route of exposure for humans (e.g., see recent FAO/WHO report on BPA). Thus, studies in this section where BPA was administered by routes other than oral exposures, such as subcutaneous injection,[41] subcutaneously implanted pellets[42,43] and subcutaneously implanted infusion pumps,[44] are of limited relevance to assessment of the potential carcinogenicity of BPA in humans.

[41] Ho, S.-M., Tang, W.-Y., Belmonte de Frausto, J., and Prins, G. S. 2006. Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4. Cancer Research. 66(11):5624-5632.

[42] Weber Lozada, K. and Keri, R. A. 2011. Bisphenol A increases mammary cancer risk in two distinct mouse models of breast cancer. Biology of Reproduction. In Press.

Dose selection

Several investigators using the oral route of dosing have explicitly stated their rationale for dose selection as being environmentally relevant oral doses based on selected reports of ng/mL serum concentrations of unconjugated BPA. However, those studies as a basis for dose selection are no longer considered valid based on the more recent findings in human subjects of no detectable levels of unconjugated BPA in a population of subjects whose diet was enriched in BPA.[45] In this study, volunteers ingested a diet rich in BPA and their blood and urine were collected hourly over a 24-hour period. The average consumption of BPA was 21% greater than the 95$^{th}$ percentile of aggregate exposure for the US population, yet serum BPA was below the limit of detection in all 320 blood specimens collected and analyzed by the FDA and CDC.

Relevance of animal models to address public health concerns

In studies where BPA was administered via the oral route and the carcinogenic potential of BPA alone was assessed (no co-carcinogen exposure), no carcinogenic potential was found.[42,44,46,47] Where a known carcinogen was administered in addition to BPA, the dose of the carcinogen was selected on the basis of an expectation that tumors would result independent of BPA exposure. The relevance of such a model to public health risk is questionable. In fact, the study by Ichihara *et al.* (2003)[47] using the oral route of exposure for BPA and the administration of a carcinogen DMBA by subcutaneous injection did not result in any influence on the carcinogenic outcomes attributed to DMBA.

The studies employing xenografts[42,43] are also of limited relevance to an assessment of the carcinogenic potential of BPA. These studies used an immune-compromised strain of mice and, in addition, altered the normal physiology by castration or ovariectomization. These variations from a normal hormonal status and operant immunologic surveillance system render the reported results inappropriate for consideration in an assessment of the carcinogenic potential of BPA.

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[43] Wetherill, Y. B., Hess-Wilson, J. K., Comstock, C. E. S., Shah, S. A., Buncher, C. R., Sallans, L., Limbach, P. A., Schwemberger, S., Babcock, G., F., and Knudsen, K. E. 2006. Bisphenol A facilitates bypass of androgen ablation therapy in prostate cancer. Molecular Cancer Therapeutics. 5(12):3181-3190.

[44] Durando, M., Kass, L., Piva, J., Sonnenschein, C., Soto, A. M., Luque, E. H., and Munoz-de-Toro, M. 2006. Prenatal bisphenol exposure induces preneoplastic lesions in the mammary gland of Wistar rats. Environmental Health Perspectives. 115(1):80-86.

[45] Teeguarden, J. G., Calafat, A. M., Ye, X., Doerge, D. R., Churchwell, M. I., Gunawan, R., and Graham, M. 2011. Twenty-four hour human urine and serum profiles of bisphenol A during high-dietary exposure. Toxicological Sciences. 123(1):48-57.

[46] Yoshida, M., Shimomoto, T., Katashima, S., Watanabe, G., Taya, K., and Maekawa, A. 2004. Maternal exposure to low doses of bisphenol A has no effects on development of female reproductive tract and uterine carcinogenesis in Donryu rats. Journal of Reproduction and Development. 50(3):349-260.

[47] Ichihara, T., Yoshino, H., Imai, N., Tsutsumi, T., Kawabe, M., Tamaoa, S., and Inaguma, S., S. Suzuki, and Shirai, T. 2003. Lack of carcinogenic risk in the prostate with transplacental and lactational exposure to bisphenol A in rats. Journal of Toxicological Sciences. 28(3):165-171.

In addition, inconsistencies of outcomes between studies using comparable animal models further makes them of questionable relevance.[42,48] Both studies orally dosed Sprague Dawley rats during nearly comparable periods of gestation with identical doses of BPA. Weber Lozada and Keri[42] reported BPA treatment decreased time to onset of DMBA-related tumors whereas Betancourt *et al*.[48] reported that DMBA administered on PND 50 did not influence tumor incidence or tumor latency.

## 9. Conclusion

BPA is one the most thoroughly tested chemicals used today. Based on the extensive scientific evidence available, BPA does not meet the CIC guidance criteria for identifying chemicals for listing as "known to the State to cause cancer." This conclusion is based on the weight of evidence from an extensive scientific database, as well as numerous comprehensive reviews of the scientific evidence that have concluded BPA is not a carcinogenic hazard.

[48] Betancourt, A. M., Eltoum, I. A., Desmond, R. A., Russo, J., and Lamartiniere, C. A. 2010. In utero exposure to bisphenol A shifts the window of susceptibility for mammary carcinogenesis in the rat. Environmental Health Perspectives. 118(11):1614-1619.