From: "emgray@mindspring.com" <emgray@mindspring.com>
To: <coshita@oehha.ca.gov>
Date: 2/14/2010 7:40 AM
Subject: publication from NHEERL, ORD, USEPA Gray Lab on BPA
Attachments: ryan et al highlight.pdf; Howdeshell et al 2008. Tox Sci 102 2.pdf; Ryan et al EE2 BPA sex behavior Tox Sci ONLINE 2010 LEGjr .pdf

I am attaching our two recent papers on the transgenerational effects of EE2 and BPA in the rat for inclusion in your evaluation of BPA.

I also am attaching a review of the most recent paper (Ryan et al, 2010) by Dr R Sharpe, MRC, UK which discussed the significance of our recent publication

Let me know if you have any questions about the work.

Sincerely

Dr Leon Earl Gray Jr
emgray@mindspring.com

--- Scanned by M+ Guardian Messaging Firewall ---

HEALTHY BUILDING NETWORK

Cynthia Oshita
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-19B
Sacramento, California 95812-4010

April 27, 2010

Dear Ms. Oshita and OEHHA:

We write on behalf of the Healthy Building Network to affirm OEHHA's recognition of bisphenol A (BPA) as a reproductive and developmental toxicant under a Proposition 65 authoritative body listing.

While many are aware of the reproductive health concerns associated with BPA in baby bottles and/or food can liners, few are aware that BPA is a chemical component of epoxy resins used in building materials, including in high performance coatings (paints) and adhesives, which are widely used in buildings throughout the state of California. As an authoritative body, NTP-CERHR considered the emerging science regarding occupational exposure to epoxy resins made from BPA linking it to reproductive health concerns in humans. The NTP-CERHR listing makes clear that Proposition 65 labeling is warranted to inform users of potential hazards.

The Healthy Building Network support OEHHA's listing of BPA as a developmental and reproductive toxicant under Proposition 65 so that consumers can make informed choices about their potential exposure to this harmful chemical.

If you have any questions or concerns, please do not hesitate to contact us.

Sincerely,

Julie L. Silas

Julie Silas, J.D.
Director, Health Care Projects
Healthy Building Network

Tom Lent
Policy Director
Healthy Building Network

California Department of Public Health
MEMORANDUM

OFFICE OF ENVIRONMENTAL HEALTH
HAZARD ASSESSMENT

MAY 06 2010

Received
SACRAMENTO

DATE: April 30, 2010

TO: Cynthia Oshita
Office of Environmental Health Hazard Assessment
1001 I Street, IMS A-23
MS 19B

FROM: Donald O. Lyman, M.D., Chief
Division of Chronic Disease and Injury Control
California Department of Public Health
(916) 449-5700

SUBJECT: Bisphenol-A (BPA)

This memorandum is in response to the Office of Environmental Health Hazard Assessment call for public comments on BPA. I appreciate the opportunity to submit comments relevant to the proposed consideration of BPA for listing under the Safe Drinking Water and Toxic Enforcement Act of 1986, Health and Safety Code Section 25249.5 et seq., known as Proposition 65.

Dental sealants are an important public health strategy to prevent dental decay and the high prevalence of caries (cavities) among California's children. Sealants have been extensively studied and are recognized as one of the most effective methods for preventing tooth decay thereby decreasing the need for restorations. Dental sealants do not contain BPA, but some products release small amounts in the hour after application which may contribute to very low-level BPA exposure. [1,2,3]

Good oral health is a basic necessity for children's overall health. Dental disease is an infectious disease, preventable by simple measures such as fluoride and dental sealants. When left untreated, dental disease can become debilitating and can lead to other serious infections and even death. Infection, sleep deprivation, nutrition problems, tooth loss, attention deficit, and slower social development are a few issues caused by dental decay.

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[1] Joskow, R et al., Exposure to bisphenol A from bis-glycidyl dimethacrylate-based dental sealants, JADA , March 2006; 137:353-62.

[2] Center for the Evaluation of Risks to Human Reproduction, National Toxicology Program U.S. Dept. of Health and Human Services. NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A, November 26, 2007

[3] Council on Scientific Affairs Statement, American Dental Association, November 2008.

Children's oral health problems come at a considerable cost to their overall health, as well as their education; children cannot focus on learning when they are in pain. Additionally, California students miss an estimated 874,000 school days annually due to dental problems. These absences cost local school districts approximately $28.8 million.

According to the 2006 California Smile Survey, An Oral Health Assessment of California's Kindergarten and Third Grade Children:

- By the time children enter kindergarten, more than 50 percent already have dental decay, 19 percent have rampant decay and 28 percent have untreated decay
- By third grade, over 70 percent of the children have a history of tooth decay
- 28 percent, approximately 750,000 children, have untreated tooth decay
- 4 percent, approximately 138,000 children, need urgent dental care because of dental pain or infection.

Promoting children's oral health is good for children's overall well-being and makes good financial sense for California. For every dollar spent on prevention, as much as $50 is saved on restorative and emergency oral health procedures.

Healthy People 2010 Oral Health Objective 21-8 calls for 50 percent of 8 and 14 year-old children to have sealants on their permanent molar teeth. According to the 2006 California Smile Survey, only 28 percent of California's third graders have sealants.

For 30 years, the California Children's Dental Disease Prevention Program (CCDDPP), a school-based program serving low-income children, operated in schools providing sealants as one of five required program components: sealants, fluoride, oral health education, and brushing and flossing instructions. This program served more than 300,000 children each year and provided dental sealants to more than 9,000 children annually. Unfortunately, the 2009 budget cuts eliminated funding for CDDPP leaving many low-income, high-risk children without the benefit of this public health program.

As a champion of public health strategies to prevent disease, I support the use of dental sealants. Please consider the public health benefits of dental sealants as you consider BPA as part of your assessment.

cc: Richard Kreutzer, M.D.
Division Chief
Environmental and Occupational Disease Control
California Department of Public Health

Can Manufacturers Institute

1730 Rhode Island Avenue, N.W.
Suite 1000

Washington, D.C. 20036

T. 202-232-4677
F. 202-232-5756

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-19B
Sacramento, California 95812-4010

Re: CMI PROP 65 COMMENTS TO OEHHA FOR BISPHENOL-A (BPA) BEING CONSIDERED FOR LISTING BY THE AUTHORITATIVE BODIES MECHANISM

Dear Ms. Oshita:

The Can Manufacturers Institute (CMI) appreciates the opportunity to submit these comments on the Office of Environmental Health Hazard Assessment for BPA being considered for listing by the Authoritative Bodies Mechanism. CMI is the national trade association of the metal can manufacturing industry and its suppliers in the United States. CMI members account for over 86 percent of annual domestic production of 135 billion food, beverage and general line metal cans; together they employ some 35,000 people with plants in 36 states. CMI member companies have more plants, 26, and more employees, 3650, in the state of California than in any other state in the nation.

CMI fully endorses the comments submitted to you on this matter by the Grocery Manufacturers Association.

CMI is commenting today to inform you its opposition to the listing of bisphenol-A ("BPA") under Proposition 65. An unwarranted label on food and beverage cans could greatly disrupt the manufacture of metal cans and significantly reduce the availability of food and beverage products in California and hinder consumer ability to find nutritious, valuable and shelf stable foods and beverages, which represents about total canned edibles are 20% of unit sales for total edible categories, especially in these difficult times.

BPA has been used for over 40 years and is a key ingredient of the epoxy resins used in metal food packaging to prevent spoilage and contamination. The can coatings are produced by coating suppliers that use FDA approved materials. The Obama Administration and FDA say BPA is safe for current uses. FDA's position on the safety of BPA concurs with the European Union, Canada, Australia, New Zealand, Japan and even California (for now).

Because adequate alternatives are not currently available, actions such as a Prop 65 listing, would severely impact an exceptionally wide range of canned, glass and other packaged food, from fruits and vegetables to soft drinks and beer.

FDA has begun working with the food industry to reduce or eliminate BPA exposure.

This important partnership should be encouraged to help reinforce the research efforts underway. The Prop 65 activity would undermine the authority of the FDA and Obama Administration to effectively regulate the safety of food, including packaging. FDA is expected to complete a safety assessment within the next 18 to 24 months. In addition, the National Institutes of Health has devoted $30 million in 'stimulus' money to study the safety of BPA. Our industry welcomes FDA and NIH scientific review of BPA.

In its January 2010 BPA statement, both the HHS/NIH and the FDA urged consumers, including infants, not to change dietary behaviors because nutritional benefits outweigh any potential risk from BPA exposure.

A Prop 65 warning label that would be imposed by this Office would undermine FDA's goal of limiting warnings on food labels to only those deemed necessary to protect the public health, based on credible scientific evidence. The Prop 65 warning label would convey a threat to human health that is unsupported by appropriate scientific evidence and is not supported by the conclusions about the safety of BPA drawn by FDA and other federal and international public health bodies.

Furthermore, any renewed efforts to restrict or malign the use of BPA in food can linings would undermine broader federal and state public health goals relating to food safety and encouraging a diet rich in fruits and vegetables. Cans are the most tamper-resistant and traceable food packaging, and are readily traceable throughout the distribution system. Canning sterilizes food and therefore avoids the risks of *listeria*, *E. coli*, or other pathogens of public health concern that may be found in fresh produce. Canned food also offers the lowest cost, most efficient means of delivering fruits and vegetables to the U.S. population, helping citizens meet the fruit and vegetable intake goals advised by the USDA/HHS Dietary Guidelines for Americans. These nutritional goals remain a priority for FDA, which, as noted above, emphasized that it is currently taking steps regarding BPA only as a "precaution" and is not recommending industry or consumer changes in food packaging or consumption.

Inexpensive and nutritious canned foods have become even more important in the current economic climate, with sales of canned foods increasing as Americans on tight budgets look to feed their families well at lower cost. The Prop 65 listing would mandate an erroneous warning on canned foods that is not supported by appropriate scientific studies, but could scare consumers away from these important and affordable sources of nutrition. The action would thereby frustrate the federal and state objectives of not changing consumption of fruits and vegetables, and ensuring the safety and affordability of a wholesome food supply.

The Metal Can Industry is an Important Part of California's Economy

California companies that manufacture metal cans are an important part of the state's economy. Manufacturers of cans along with the companies that provide supplies and materials for the cans provide well paying jobs in California and pay significant amounts in tax to the State and Federal governments.

Companies that manufacture metal cans employ approximately 3,650 people in the state and generate an additional 22,000 jobs in supplier and ancillary industries. These include jobs in companies supplying goods and services to can manufacturers.

These are good jobs, paying an average of $53,470 in wages and benefits. And today, every job is important. In fact, in California the unemployment rate has reached over 12 percent. This means that there are already 2.2 million people trying to find jobs in the state, and collecting unemployment benefits.

Not only does the manufacture of cans create good jobs in California but the industry also contributes to the economy as a whole. In fact, in 2008 the metal can industry was responsible for as much as $5.7 billion in total economic activity in the state. The broader economic impact flows throughout the economy, generating business for firms seemingly unrelated to cans. Real people, with real jobs, working in industries as varied as banking, retail, accounting, metalworking, even printing all depend on the metal can industry for their livelihood.

Not only does the metal can industry create jobs, it also generates sizable tax revenues. In California the industry and its employees pay over $97.2 million in taxes including property, income, and sales based levies.

In sum, we are very concerned that a Prop 65 rule to needlessly list BPA in products would severely impact consumer confidence and severely restrict the wide range of canned (and glass) food and beverages available to consumers; shut down our facilities and put workers out of jobs in your state and the nation.

Please contact me at 202-232-4677 or gcullen@cancentral.com with any questions.

Sincerely,

Geoffrey Cullen
Vice President of Government Relations

From: <Alerts@FreeEats.com>
To: <coshita@oehha.ca.gov>
Date: 5/10/2010 7:03 PM
Subject: Comments Regarding The Proposal Spend Addtional Tax Dollars on BPA

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-19B
Sacramento, California 95812-4010

(submitted electronically)

Dear Ms. Oshita:

I am a resident of California, and was recently contacted by the Institute for Liberty, a national advocacy organization focused on limiting the expansion of government power. IFL informed me about an attempt by the State of California to limit my choices as a consumer, through your agency's efforts to halt the use of a particular plastic resin, Bisphenol A (BPA). I am submitting these comments in response to this proposal.

Last July, the California Development and Reproductive Toxicant Identification Committee (DART-IC) investigated the safety of the plastic resin Bisphenol A (BPA) and determined that it was safe and should not be classified it as a toxicant under our strict safe drinking laws. The determination was made based on research provided by the National Toxicology Program, the Environmental Protection Agency, the Centers for Disease Control, and investigative scientific bodies in Canada, Australia, Japan and the EU, all of which found BPA to be safe. Immediately after the DART-IC determination and in an effort to promote its own political agenda, a radical environmental group (the Natural Resources Defense Council) requested that another arm of the California government hold yet another hearing on BPA.

Our state is suffering serious financial woes. Tax dollars are spread thin already, and we have little money to spend on redundant public hearings or unreasonable requests from special interests groups trying to further their own agendas but leave us paying the price. The original DART-IC process was necessary to investigate the safety of BPA, but was very expensive for Californian taxpayers. The NRDC's use of the California government as a private army for its own special interests will cost us even more. BPA has been proven safe by multiple private and governmental agencies both in the U.S. and abroad for use in products that use plastics. It poses no harm to our drinking water. But BPA manufacturing and its associated industries does generate $6.B in wages and 100,000 jobs in the U.S. They also produce tax revenue from sales, property and income taxes.

The science is clear on BPA - it is safe. In our present economic circumstances, California cannot allow special interests to dictate high cost administrative procedures as we have no financial resources left to deal with imaginary threats to health and safety. Banning BPA will limit consumer choices, hurt the state's small businesses, and ultimately cost the state's residents sorely needed jobs.

I urge you to immediately halt any more costly, redundant and completely unnecessary state action on BPA.

Sincerely,

S E GERRARD

REDLANDS, CA 92373

Comment collected by the Institute for Liberty on May 10 2010 9:03PM

COMMENTS ON THE PROPOSED LISTING OF BISPHENOL A

AS A REPRODUCTIVE OR DEVELOPMENTAL TOXICANT

UNDER PROPOSITION 65

Submitted by

Anthony R. Scialli, M.D.
Senior Scientist
Tetra Tech Sciences
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May 12, 2010

Anthony R. Scialli, M.D.

Qualifications
I am an obstetrician-gynecologist and reproductive toxicologist with specific expertise in the evaluation of the medical and scientific literature concerning reproductive and developmental toxicology and concerning teratology. I am Adjunct Professor of Obstetrics and Gynecology and of Biochemistry and Molecular Biology at Georgetown University, where I teach and Clinical Professor of Obstetrics and Gynecology at George Washington University, where I teach and provide clinical services. I am employed by Tetra Tech Sciences, a health and environmental consulting firm. I am also Director of the Reproductive Toxicology Center, A Non-Profit Foundation. The Reproductive Toxicology Center operates a data base called REPROTOX®, which is a reference source for information on the reproductive and developmental effects of chemical and other agents on all aspects of reproduction. REPROTOX® is used by physicians, genetic counselors, industry scientists, and government agencies in the US and in other countries.

I am the founding editor of the peer-reviewed journal *Reproductive Toxicology*, which is published by Elsevier Science. I was Editor-in-Chief of *Reproductive Toxicology* for 17 years. I continue to serve as a reviewer for articles submitted to *Reproductive Toxicology* as well as for articles submitted to other scientific journals including *Birth Defects Research*, *Obstetrics and Gynecology*, *the New England Journal of Medicine*, and the *American Journal of Obstetrics and Gynecology*, among others.

From 1983 to 2004, I was a full-time faculty member at Georgetown University School of Medicine, achieving the ranks of Professor of Obstetrics and Gynecology and Professor of Biochemistry and Molecular Biology. I was also Director of the Residency Program in Obstetrics and Gynecology at Georgetown University Hospital.

I have served as an advisor or consultant on the subject of developmental toxicology and reproductive medicine for organizations such as the US Food and Drug Administration (FDA), the World Health Organization, the Environmental Protection Agency (EPA), and the Occupational Safety and Health Administration, among others. My activities at the FDA include teaching a course for medical officers on the interpretation and use of developmental toxicity data and service as a consultant to the Pregnancy Labeling Task Force, the purpose of which was to revise the pregnancy portion of the medication labeling to make it more useful and understandable for clinicians.

I have been active in national and international professional societies concerned with reproductive medicine and toxicology. These societies include the Teratology Society, of which I am a past president, the Organization of Teratology Information Specialists, the Society of Toxicology, of which I am a member of the Reproductive and Developmental Toxicology Specialty Section, the American College of Obstetricians and Gynecologists, and the American Society for Reproductive Medicine.

I have counseled men and women about the reproductive effects of exposures to chemicals and other agents and have authored, coauthored, or edited original scientific studies, review articles, book chapters, and books in reproductive medicine, including reproductive and developmental toxicology. I have been a regular contributor to the scientific literature on the effects of chemicals and other agents on reproduction. I am

very familiar with methods of risk assessment in reproductive and developmental toxicology and with the interpretation of findings that are confounded by parental or adult toxicity.

During 2004–2007, I was Principal Investigator on the National Toxicology Program (NTP) Center for Evaluation of Risks to Human Reproduction (CERHR) contract held by my employer. In this capacity, I organized and supported the writing of Expert Panel reports. I am very familiar with the goals of CERHR and the methodology used in the development of Expert Panel reports.

Purpose

It is my understanding that a petition has been submitted seeking the listing of bisphenol A as a known reproductive and developmental toxicant under Proposition 65. The basis of this petition is the purported determination by NTP through CERHR that bisphenol A is a reproductive and developmental toxicant. This determination was described by the petitioner as being based on the results of studies conducted at parentally/adult toxic bisphenol A exposure levels.

It is my purpose in this commentary to correct the misunderstanding that these studies demonstrate the reproductive or developmental toxicity of bisphenol A. Moreover, it is not the case that CERHR determined that bisphenol A is a reproductive or developmental toxicant, nor would CERHR make such a determination. I will explain how CERHR did its business and what determinations were made by CERHR.

The Effect of Systemic Toxicity on Reproduction

The reproductive system in mammals is sensitive to stress induced by general toxicity. The function of the ovaries and testes depends on appropriate stimulation by the pituitary gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The pituitary gonadotropins are released in response to pulsatile release of gonadotropin-releasing hormone (GnRH) by the arcuate nucleus in the hypothalamus. There are a number of neural inputs to the arcuate nucleus that can modify or eliminate GnRH production. One such system, for example, is the opioidergic system, which turns off the arcuate nucleus in response to stress (Yen et al., 1985). In addition, a recently identified group of gonadotropin-inhibiting substances have been identified. These hormones are produced by the adrenal gland in response to stress and inhibit the gonadotropic system through direct action on the pituitary and hypothalamus (Tsutsui 2009).

Embryo development has been known for decades to be sensitive to the effects of maternal toxicity. Khera (1984) reviewed teratology studies performed in mice, rats, hamsters, and rabbits and determined that resorptions and embryo death were common end points associated with maternal toxicity. Chernoff et al. (1990) showed that toxicant-induced maternal toxicity can be associated with resorptions and decreased fetal weight. Inadequate maternal nutrition, which can be due to inappetence or inefficient processing of ingested feed, can produce deficits in fetal body weight and viability. Feeding restriction studies in rats have shown effects on pup weight and function that persist well

after birth (Chernoff et al., 2009). Human experience from famines has confirmed that inadequate maternal dietary intake can produce impairments in fetal growth and postnatal function (Stein et al., 2004; Kyle and Prichard, 2006). In clinical obstetrics, it is axiomatic that the best environment for growing a healthy baby is a healthy mother.

Because maternal/adult toxicity can confound the results of reproductive and developmental toxicology studies, recommendations for study design include the selection of a dose range that does not cause excessive parental/adult toxicity. For example, the Guidelines for Developmental Toxicity Risk Assessment of the US EPA (1991) state with respect to dose selection:

"The high dose is selected to produce some minimal maternal or adult toxicity (i.e., a level that at the least produces marginal but significantly reduced body weight, reduced weight gain, or specific organ toxicity, and at the most produces no more than 10% mortality). At doses that cause excessive maternal toxicity (that is, significantly greater than the minimal toxic level), information on developmental effects may be difficult to interpret and of limited value."

More recently, the Organisation for Economic Cooperation and Development (2007) published similar guidelines for developmental neurotoxicity studies, specifying:

"Unless limited by the physico-chemical nature or biological properties of the substance, the highest dose level should be chosen with the aim to induce some maternal toxicity (*e.g.,* clinical signs, decreased body weight gain (not more than 10%) and/or evidence of dose-limiting toxicity in a target organ)."

Therefore, decreases weight of body weight gain of more than 10% are considered to represent dose levels higher than the maximum tolerated dose (MTD).

The CERHR Approach

CERHR adopted an evaluative process that differs fundamentally from the Proposition 65 process. While Proposition 65 entails consideration of whether a chemical should be listed as a reproductive or developmental toxicant based on effects that occur as a result of prenatal exposure, CERHR characterizes the conditions under which reproductive or developmental toxicity occur and determines a level of concern for human exposure based on a comparison of anticipated human exposure conditions and those represented in experimental studies. The guidelines for the CERHR approach have been published (Shelby, 2005). The statement template set forth in these guidelines is:

"There is (sufficient, insufficient) evidence in (animals and/or humans) that (chemical X) (does or does not) cause (developmental, reproductive) toxicity when exposure is (route, dose, timing, duration). The data are (relevant, assumed relevant, irrelevant) to human risk."

As indicated in the Shelby paper, this template was taken from a National Research Council Report published in 2001. I was a coauthor of that report. There was a distinct intention to avoid a prescription for list-making by the members of the committee that

generated the National Research Council Report and, consequently, determined the basis of the CERHR process. The CERHR process by its design could not have listed bisphenol A as a reproductive or developmental toxicant because it does not create lists.

As is discussed amply in the CERHR report on the relevant bisphenol A studies, the context of the reproductive and developmental effects associated with bisphenol A experiments included high dose level exposures with consequent maternal toxicity. I will review each of these studies.

The Studies

In each of the six studies that have been identified as showing reproductive or developmental toxicity after treatment with bisphenol A, parental or adult toxicity explains the reproductive or developmental effects that were described. The studies are presented in chronological order except for a 2002 study that is placed after the 1985 study that it attempted to reproduce.

NTP (1985)

This report describes a mouse reproduction study performed by continuous breeding and using dietary dosing with bisphenol A. This type of study design was developed by the National Toxicology Program and consists of four tasks. Task 1 was intended to identify an appropriate high dose at which there would be some impairment of body weight gain but not excessive toxicity. Task 2 was the fertility study in which male and female mice were placed on test diets for a 7-day pre-cohabitation period followed by a 98-day cohabitation period and a 21-day separation period (to permit birth of the last litter). Diets contained 0, 0.25, 0.5, or 1.0% bisphenol A resulting in estimated ingestion of 0, 437.5, 875, or 1750 mg/kg bw/day. Litters were removed from dams after birth to permit continued breeding. Task 3 was a cross-over trial in which animals in the high dose group were mated with animals in the control group. Task 4 was a mating trial of F_1 offspring that had been exposed via their dams during pregnancy and lactation and directly in the diet between weaning and sexual maturity.

Adult toxicity was not systematically assessed in all dose groups due to the nature of the study design. Adult body weights were measured at specified intervals without regard to pregnancy status, making it difficult to identify possible treatment-related effects on body weight. Dam weight after pregnancy, which was reduced in the high-dose dams, was not adjusted for litter size, which was also reduced by treatment in the middle and high dose groups. It would be expected that the bearing of a smaller litter would be associated with an increase in postpartum maternal weight compared to control, and the lack of such an increase may represent adult toxicity. Necropsy weight at the end of the study was reduced 4% in the high-dose animals but was not reported for the other dose groups. It should be noted that in other rodent feeding studies (Tyl et al., 2002b, 2008), substantial weight decrements were seen in the first two weeks after onset of dosing; therefore, the 4% weight decrement at necropsy in this underestimates the degree of adult toxicity occurring with treatment. Organ weights and histopathology evaluations were obtained

only in high-dose animals and demonstrated significant toxicity, especially involving the liver and kidney.

Developmental toxicity in the high dose group included a reduction in number of litters per pair and number of live pups per litter. Based on the crossover matings, these effects appeared to be due to the female. The substantial adult toxicity in the high dose group was sufficient to cause the small decrease in litters per mating pair and live pups observed in these animals.

The magnitude of adult toxicity in the middle dose group, at which there was a small decrease in litters/pair and live pups/litter, cannot be assessed directly from Task II, but can be assessed from Task IV (mating of F_1 animals on the same diet as their parents). The middle dose group demonstrated liver and kidney toxicity in the experiment, characterized by alterations in organ weights and histologic abnormalities. In spite of this adult toxicity, there was no treatment effect on reproductive success in this single-mating study. The study authors concluded, "It is possible, therefore, that some or all of the adverse effects on reproductive performance observed in the present study may be secondary to the generalized toxicity of BPA." These effects were further investigated by Tyl et al. (2002a), discussed below.

Tyl et al., 2002a

This study was designed to further investigate the reproductive effects of bisphenol A as described in the 1985 NTP continuous breeding study. Adult male and female mice were given diets containing 0, 0.5%, or 1% bisphenol A, with estimated bisphenol A intake levels of 0, 1055, and 1988 mg/kg bw/day in females during the prebreeding period, and 0, 870, and 1716 mg/kg bw/day in females during pregnancy. These dietary concentrations are the same as in the NTP (1985) continuous breeding study. Exposure to the diet occurred during a 2-week prebreeding period and a 1-week breeding period. Body weights and food consumption were recorded periodically and dams in both dose groups underwent necropsy at the end of the study.

Weight gain was decreased during gestation by 16% in the low dose group and 19% in the high dose group. In both dose groups, hepatic and renal abnormalities were noted on histological examination and relative organ weights were increased. There was a 15% decrease in number of total pups and live pups per litter in the high dose group but no alteration in these end points in the low dose group. This study confirmed the developmental events reported by the NTP study with the 1% dietary bisphenol level but did not reproduce the developmental effects reported at the 0.5% level. The authors noted that the degree of maternal toxicity in both dose groups was considerable, and the developmental effects at the high exposure level were consistent with this maternal toxicity.

Morrissey et al. (1987)

This paper describes a standard developmental toxicity study in which pregnant rats and mice were treated with bisphenol A by gavage from gestation day 6 through 15. Dose

levels for rats were 0, 160, 320, 640, and 1280 mg/kg bw/day. Dose levels for mice were 0, 500, 750, 1000 and 1250 mg/kg bw/day. Pregnant animals were weighed at specified intervals during pregnancy and at termination on gestation day 20 (rats) or 17 (mice). Fetuses were counted, weighed, and examined using standard techniques for external, visceral, and skeletal abnormalities.

Maternal toxicity was prominent at all bisphenol A dose levels in both rats and mice. Maternal toxicity in rats was manifested as a decrease in body weight gain and a decrease in maternal carcass weight; that is, body weight excluding the pregnant uterus. The highest dose level produced a 14% decrease in maternal body weight gain over the course of the pregnancy. In spite of this substantial toxicity, there was no developmental toxicity at any dose in the rat.

Maternal toxicity in mice was more severe, resulting in deaths in all dose groups. In the three lower dose groups, there were one or two deaths among 29 to 34 dams. At the highest dose level, maternal mortality was 18% (6 deaths among 33 dams), which is considered excessive toxicity. Among survivors in the high dose group, maternal body weight was decreased 43%, which is also excessive. Fetal body weight per litter and resorptions per litter were increased in the high dose group, findings that are fully consistent with the degree of maternal toxicity produced at this excessive dose level. The authors concluded, "…post implantation exposure to BPA (gavage) did not cause external, visceral, or skeletal malformations at doses that caused significant maternal toxicity (rats) or mortality (mice)."

Kim et al., 2001

In this study, pregnant rats were treated from the day after evidence of mating through gestation day 20 with gavage doses of bisphenol A at 0, 100, 300, and 1000 mg/kg bw/day. Maternal body weight was assessed at standard intervals and food consumption was measured. Pregnant animals were killed on gestation day 21 and fetuses removed for external examination and for visceral or skeletal evaluation. Body weight gains in the middle and high dose group were decreased by 35 and 52%, respectively, well above the 10% decrease in body weight gain that is considered an appropriate degree of maternal toxicity. Some animals were reported to be emaciated. Fetal death and resorption were increased and fetal body weights were decreased 36% in the high dose group. Fetal body weight was decreased about 14% in male fetuses in the middle dose group. Skeletal ossification sites were decreased in the high dose group. The decrease in fetal weight and viability is typical for the degree of maternal toxicity produced in the high dose group. The decrease in skeletal ossification sites represents a delay in ossification rather than a developmental anomaly and is commonly due to maternal toxicity. Delayed ossification has been shown to be transient, resolving as delayed pups catch up during the lactation period (Carney and Kimmel, 2007).

Tyl et al., 2002b

This paper describes a three-generation dietary study of bisphenol A in rats. Dose groups were 0, 0.015, 0.3, 4.5, 75, 750, and 7500 ppm resulting in ingestion of approximately

0.001, 0.02, 0.3, 5, 50, and 500 mg/kg bw/day bisphenol A. Parental animals (F_0) were exposed to the test diets for 10 weeks before mating, during mating, and, for females, during pregnancy and lactation. After weaning, the offspring (F_1) were exposed to the test diet for ten weeks prior to mating. The test diet was continued during mating and, for females, during pregnancy and lactation. Offspring of these matings (F_2) were treated in the same manner as their parents and mated after a ten week exposure period. Again, dietary treatment of females continued during pregnancy and lactation. Offspring of these matings (F_3) were examined at weaning or, after continued dietary exposure, at about 17 weeks of age. Standard methods were used including culling of litters on postnatal day 4, interval weighing, evaluation of pubertal landmarks, and necropsy of F_0, F_1, and F_2 adults.

Adult toxicity was seen at the highest two dose groups and consisted of decreases in body weights. Weaning weight in all generations was consistently decreased in the high dose group. There was a decrease in the number of pups per litter in the highest dose group, which could not be explained by post-implantation loss. It is possible that there was an increase in preimplantation loss or a decrease in the number of follicles that ovulated, both of which are expected consequences of adult toxicity, mediated by disruption of gonadotropins, which are necessary for ovulation, or suppression of prolactin, which is important in pregnancy maintenance in the rat. A decrease in ovarian weight in the highest dose group was noted, but ovarian histology was not compromised and the number of primary follicles was not altered by treatment. The decrease in ovarian weight is of uncertain significance, particularly given the known effects of stress on decreasing gonadotropin-releasing hormone and pituitary gonadotropins, thereby decreasing ovarian activity.

This study is remarkable for the lack of reproductive or developmental toxicity over three generations in the face of prominent adult toxicity in the high dose group. The authors concluded that bisphenol A should not be considered a selective reproductive or developmental toxicant.

Tyl et al., 2008

This paper describes a two-generation reproductive study in mice dosed with bisphenol A through the diet. Dietary levels were 0, 0.018. 0.18, 1.8, 30, 300, or 3500 ppm, and estimated bisphenol A intakes were 0, 0.003, 0.03, 0.3, 5, 50, or 600 mg/kg bw/day. Parental (F_0) animals were given treated feed for at least eight weeks prior to mating, during the mating period and, for females, throughout pregnancy and lactation. Offspring were continued on treated feed after weaning for at least eight weeks prior to mating and during mating, and females were continued during gestation and weaning. Their offspring (F_2) were evaluated and terminated at weaning after potential exposure through the dams during pregnancy and the lactation period and potential direct exposure to treated feed during the end of the lactation period. Standard methods were used to standardize litters on postnatal day 4.

There was no evidence of developmental toxicity in this study except for transient delay in testis descent in weanlings, attributed to maternal toxicity. Parental toxicity was prominent in the highest dose group, manifested as abnormal kidney and liver organ

weights and histopathology. The authors concluded that bisphenol A is not a selective reproductive or developmental toxicant.

Conclusions

Reproductive or developmental effects due to parental or adult toxicity do not warrant consideration of a chemical as a reproductive or developmental toxicant. Indeed, there is a well-established tradition in the field of avoiding excessive parental or adult toxicity in study design in order to avoid obtaining findings that cannot be interpreted. In the case of the six studies identified as showing reproductive or developmental effects, the effects occurred with exposure levels that produced clear parental/adult toxicity of a degree sufficient to explain the reproductive or developmental effects; moreover, the developmental effects were those expected to occur from adult toxicity. The CERHR Bisphenol A Expert Panel called attention to the parental/adult toxicity at high doses of bisphenol A. By design, the CERHR process does not result in a listing of chemicals as reproductive or developmental toxicants, and neither the CERHR Expert Panel nor the NTP listed bisphenol A as a reproductive or developmental toxicant. In my opinion, the data do not support the listing of bisphenol A as a reproductive or developmental toxicant under Proposition 65.

Disclosure

For the time spent in writing this commentary, my employer is being compensated by the American Chemistry Council.

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May 12, 2010

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-19B
Sacramento, CA 95812-4010

Re: Response to Request for Relevant Information on Bisphenol A

Dear Ms. Oshita,

Attached are my comments in response to the OEHHA Request for Information of February 12, 2010 (Request for Relevant Information on a Chemical Being Considered for Listing by the Authoritative Bodies Mechanism: Bisphenol-A). From this notice I understand that a petition has been submitted to OEHHA proposing to list bisphenol A (BPA) as a reproductive toxicant under Proposition 65. The basis for the petition is the NTP-CERHR report on BPA, which includes summaries of certain studies that report developmental toxicity at high levels of exposure.

I have reviewed the six relevant BPA studies, with a particular focus on the role of maternal toxicity on embryo-fetal/offspring toxicity. Notably, I am the first author and study director of three of these studies (one-, two- and three-generation reproductive toxicity studies on BPA and estradiol) and am a co-author on another of the studies (Morissey et al., 1987).

Based on my intimate knowledge of these studies and my review of other relevant studies, I conclude that BPA is not a selective reproductive or developmental toxicant. As detailed in the attached comments, reproductive or developmental effects occur only at very high BPA doses in the presence of profound maternal toxicity. At lower doses with less, but still significant, maternal toxicity, there are no reproductive or developmental effects. Based on other relevant studies, it is apparent that maternal toxicity is most likely the critical determinant of embryo-fetal/offspring toxicity observed at high doses of BPA. Consequently, BPA does not satisfy the criteria for listing under Proposition 65.

My review relies on my broad experience and recognized expertise, encompassing more than 40 years of experience in reproductive and developmental biology and toxicology. I am currently a Distinguished Research Fellow in Developmental and Reproductive Toxicology (DART) and

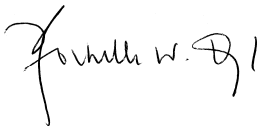
Principal Investigator of DART studies in the Center for Pharmacology and Toxicology at RTI International. I am also currently an Adjunct Professor in the Curriculum for Toxicology at the University of North Carolina at Chapel Hill. I have served as Study Director for more than 50 multigeneration studies in rodents and more than 150 developmental toxicity studies in rodents and rabbits, as well as numerous other related reproductive and developmental toxicity studies. I have authored or co-authored more than 100 peer-reviewed articles, 18 book chapters, more than 100 abstracts, and hundreds of study reports.

I am currently an Editorial Board member for *Reproductive Toxicology*, have previously served as an Editorial Board member for *Fundamental and Applied Toxicology*, and am a manuscript reviewer for *Toxicological Sciences*, *Reproductive Toxicology*, *Birth Defects Research*, and other journals. I have also served in relevant professional society leadership positions including as President of the Reproductive and Developmental Toxicology Specialty Section of the Society of Toxicology (2007-2008), President of the Teratology Society (2003-2004), and as an elected member of the American College of Toxicology's Long-Range Planning Committee (2007-2009).

I have advised numerous governmental and private sector organizations on matters within my area of professional expertise. For the time spent in preparing my comments, my employer is being compensated by the American Chemistry Council.

Please feel free to contact me if I can be of further assistance in this matter.

Regards,



Rochelle W. Tyl, Ph.D., DABT
Distinguished Fellow

Comments on the Proposed Listing of Bisphenol A as a Reproductive Toxicant Under Proposition 65

Rochelle W. Tyl, Ph.D., DABT

May 12, 2010

I. Definition of Maternal Toxicity

Maternal systemic toxicity has been classically defined (U.S. EPA guidelines, 1991) as one or more of the following effects:

- Dose-related maternal mortality (no greater than 10%)
- Dose-related reduced body weight(s)
- Dose-related reduced body weight gain(s)
- Dose-related reduced feed and/or water consumption (especially if associated with reduced body weights)
- Adverse clinical observations or clinical observations known to be associated with adverse outcomes
- Necropsy observations such as changes in organ weights (increased or decreased), especially if there is confirmatory evidence of histopathology (e.g., liver, kidneys, adrenal glands, etc.), both absolute and relative to terminal body weight or brain weight, to correct for any confounding from changes in body weight (U.S. EPA Guidelines, 1991; pp. 7-9).

NOTE: Increased liver weight, due to increased cell sizes (hypertrophy) and/or increased cell numbers (hyperplasia), may be due (at least in part) to induction of metabolizing enzymes (Conney, 1967), and therefore an adaptive response rather than an adverse response.

II. Background

The attention to and concern for the role of maternal toxicity on embryo-fetal/offspring toxicity have a long history. Khera (1984 [mice], 1985 [rats and rabbits]) presented data and naively proposed that maternal toxicity was a “possible etiologic factor” in fetal malformations (in mice, rats, and rabbits) and in intra-uterine deaths and congenital malformations in humans (Khera, 1987a). Khera (1987b) also presented an overview of the role of maternal toxicity on fetal development in humans and animals. Many other noted developmental toxicologists weighed in on the role of maternal toxicity on embryo-fetal effects (e.g., Kavlock et al., 1985; Kimmel and Francis, 1987; Chernoff et al., 1989; Black and Marks, 1992; Chahoud et al., 1999; Chernoff et al., 2008; Beyer et al., 2010, etc.).

The current consensus is that maternal toxicity in toxicology studies is the major cause of embryo-fetal effects observed, including those effects which are adverse or those which are not. Some effects observed in offspring that are linked to maternal toxicity are: reduced fetal/offspring body weights, increased fetal variations, and delays in acquiring landmarks of pubertal development. Extreme maternal toxicity may result in embryo-fetal loss *in utero* (Carney et al., 2004). A variation on this theme is that maternal stress associated with maternally toxic doses of a test material "can be expected to result in associated, often transient, fetal abnormalities that may not be the result of deviant organogenesis…" "Sometimes, the toxicity toward the pregnant animal, including her embryos/fetuses… is severe enough to result in the resorption of the embryo or absorption of the fetus. Therefore, it is possible that embryo lethality and other indications of developmental toxicity, produced by some drugs and chemicals, may be the result of mechanism(s) other than selective toxicity toward the embryo" (Black and Marks, 1992). Also, alteration/disruption of maternal homeostasis can result in disruption of embryonic support and therefore fetal effects (e.g., toxicity, increased variations, etc.), but are not, in fact, due to the test chemical per se (Black and Marks, 1992). A review of the role of maternal gestational stress in enhancing developmental toxicity of chemicals (Hougaard and Hansen, 2007) confirmed the importance of maternal stress on developmental toxicity from chemical insult.

As Rogers (1987) and others (e.g., Schwetz and Moorman, 1987) have commented, the indicators of maternal toxicity in developmental toxicity studies are generally limited to "significant maternal mortality, dose-related weight loss, or obvious external observations" (see Section I above). It is possible that additional indicators of maternal toxicity are present but either not evaluated or missed. Better and more uniform assessment of maternal toxicity may aid in the interpretation of developmental toxicity and the role of maternal toxicity.

The argument that maternal toxicity is the major cause of developmental toxicity in many developmental reproductive toxicity studies is bolstered by two additional papers. A paper by Waalkens-Berendsen et al. (1990) evaluated a test chemical (Isomalt) in developmental toxicity studies of Wistar rats and NZW rabbits. They included an *ad libitum* negative control for both species and, in rats, a second control group was feed restricted to 80% of the *ad libitum* feed presented to the negative control group. What is germane is that the dams in the feed-restricted control group exhibited significantly reduced feed consumption (down to ~80% of the *ad libitum* negative control group), significantly reduced gestational weight gains, and reduced gravid uterine weights at term. This group also exhibited significantly increased postimplantation loss, increased numbers of small fetuses,

decreased fetal and placental weights, and significantly reduced skeletal ossification in cervical thoracic vertebral bodies. Therefore, clearly nonchemical-induced maternal toxicity caused the embryo-fetal toxicity.

A paper by Ryan et al. (2001) exposed SD rats to phenol at 0, 200, 1000, or 5000 ppm in the drinking water for a two-generation reproductive toxicity study and immunotoxicity screen. Phenol has been shown not be estrogenic in the E-SCREEN assay (Soto et al., 1995), so the effects observed in this study at high doses are not expected to be endocrine mediated. These effects with a known nonestrogen provide a useful comparison to assess whether the results from BPA, which is weakly estrogenic, in the same rat strain and study design are endocrine mediated or the result of maternal toxicity. In the phenol study, there were significant reductions in feed and water consumption and in body weights and weight gains at 5000 ppm (the top dose) in both sexes and both parental generations (F0 and F1). Acquisition of vaginal patency and preputial separation were both delayed in F1 animals at 5000 ppm, considered "secondary to the reduced F1 body weights." Litter survival of both F1 and F2 generations was also significantly reduced at 5000 ppm. Absolute uterine and prostate weights were significantly reduced in all dose groups for the F1 generation, with no underlying pathology and no functional deficit in any parameter of reproductive performance. Comparable parental and offspring findings were observed in the top dose of the SD rat, three-generation study of BPA (see Section III below), indicating they are also likely not endocrine mediated and more likely secondary to maternal toxicity.

III. Bisphenol A (BPA)

BPA is a monomer used in the manufacture of epoxy resins and polycarbonate plastics. Epoxy resins are corrosion resistant and are used in interior coatings of cans and drums, reinforced pipes, flooring, water main filters, dental sealants, and some food packaging materials. Polycarbonate plastic uses include disposable dishware, water bottles, compact discs, eyeglass lens, and electronics. In 2009, OEHHA in California issued a draft Hazard Identification Document (HID) from the Office of Environmental Health Hazard Assessment, entitled "Evidence on the Developmental and Reproductive Toxicity of Bisphenol A," with expressed concern that the offspring effects of BPA were not due to maternal toxicity. However, interest in BPA arose long before 2009.

Due to widespread occupational and consumer exposure, in the 1980s, the National Toxicology Program (NTP) undertook general toxicology and carcinogenicity studies of BPA in rats and mice (both types of studies were negative in both species). The reproductive and developmental toxicity studies

are most relevant to this discussion of maternal versus embryo-fetal/offspring toxicity. A reproductive assessment by continuous breeding (RACB) study of BPA in mice was performed (Reel et al., 1985) at dietary concentrations of 0, 0.25, 0.5, and 1.0%. Decreased numbers of litters per breeding pair and reduced numbers of live pups/litter were observed at 0.5 and 1.0%. A crossover mating trial (1.0% males x 0% females and 0% males x 1.0% females) indicated that reproductive processes of both male and female mice were adversely affected at this very high dose.

Morrissey et al. (1987) subsequently performed a standard developmental toxicity evaluation of BPA administered orally by gastric intubation on GD 6 through 15 to Sprague Dawley rats at 0, 160, 320, 640, and 1280 mg/kg/day and at 0, 500, 750, 1000, or 1250 mg/kg/day to CD-1 mice. The timed-pregnant females were sacrificed one day prior to expected parturition, and all term fetuses were evaluated for external, visceral, and skeletal effects. Maternal toxicity was also characterized. In **rats**, maternal weight gain during gestation, gestational weight gain corrected for gravid uterine weight (GUW), and weight gain during the treatment period were significantly reduced at all BPA doses. GUW and mean fetal body weight/litter were unaffected. There were maternal clinical signs of toxicity in all the BPA groups versus the control groups. There were no increased percentages of resorptions/litter or of malformed fetuses/litter.

In **mice**, maternal mortality occurred at all BPA doses reaching 18% at the top dose. Clinical signs of toxicity were also present at all BPA doses. There was a trend towards reduced maternal weight gain during gestation and the treatment period, with mice at the top dose gaining significantly less weight. Corrected weight gain (weight gain during gestation minus GUW) was unaffected across groups. There was a trend towards reduced GUW with increasing BPA dose; the high-dose GUW was significantly lower than the control group GUW. Maternal absolute liver weight was significantly increased at 500, 750, and 1000 mg/kg/day, and maternal relative liver weight (liver weight/body weight) was dose dependently and significantly increased at all doses. There were no differences among groups in the number of uterine implantation sites/litter, but the number of ovarian corpora lutea/dam (reflecting the number of eggs ovulated) was decreased in a dose-related pattern. The percent resorptions/litter increased at 1000 and 1250 mg/kg/day (the latter statistically significant). Seven litters in the high-dose group were totally resorbed. BPA had no effect on the number of live fetuses/litter (for litters with live fetuses) or on sex ratio.

Also in mice, there were dose-dependent decreases in average fetal body weight/litter with increasing BPA dose, with the value at 1250 mg/kg/day significantly less than the control group values.

There was no effect of BPA on the percentage of fetuses malformed/litter or on the percentage of litters with malformed fetuses. There were no significant treatment effects on any measure of teratogenicity. BPA exposure on GD 6 through 15 had no effect on the incidence of external, visceral, or skeletal malformations. BPA exposure was also not associated with any particular malformation or group of malformations in any dose group. In both rats and mice, the increased embryo-fetal response occurred only at maternally toxic doses at the higher end of the dose-response curve.

In a more recent paper, Kim et al. (2001) administered BPA by gavage at 0, 100, 300, and 1000 mg/kg/day to maternal female Sprague-Dawley rats once daily on GD 1 through 20 of gestation. The day of sperm in the vagina was designated GD 0, the dams were terminated on GD 21, and the fetuses were examined externally, viscerally, and skeletally. At 1000 mg/kg/day, there was significant maternal toxicity, including abnormal clinical signs, decreased maternal body weights and body weight gain, and reduced feed consumption. Also at this dose, there was an increase in pregnancy failure (in sperm-positive females), increased embryo deaths, increased postimplantation loss, reduced litter sizes, and reduced fetal body weights. In addition, at this dose there were decreased numbers of fetal ossification centers in several skeletal districts. There were no effects of BPA at any dose on the ovarian corpora lutea (number of eggs ovulated), on uterine implantation sites (i.e., preimplantation loss), or on fetal morphological findings. At 300 mg/kg/day, maternal body weights, body weight gains, and feed consumption were also reduced. Reduced body weights of the male fetuses were also observed. At 100 mg/kg/day, there was no maternal or developmental toxicity observed. Therefore, in the presence of severe maternal toxicity from BPA exposure through pregnancy, there were increased pregnancy failures, increased pre- and postimplantation loss, and fetal developmental delay, but no embryo-fetal dysmorphogenesis at an oral dose of 1000 mg/kg/day.

The same (or better) evaluations of maternal, paternal, and offspring toxicity are made from GLP-compliant, regulatory guideline-compliant, one-, two- and three-generation reproductive toxicity studies of BPA in CD (SD) rats and CD-1 mice.

1. Three-generation reproductive toxicity study by Tyl et al. (2002b) of BPA in the diet of CD (SD) rats at 0, 0.015, 0.3, 4.5, 75, 750, or 7500 ppm (equivalent to 0, ~0.001, 0.02, 0.3, 5.0, 50.0, or 500.0 mg/kg/day), with 30 adult animals/sex/group. In the parental animals (F0, F1, F2) and F3 retained adults, there was demonstrable toxicity as follows:

Adult Toxicity

Body weights:

- There were reduced body weights and weight gains in both sexes of F0, F1, and F2 parents and retained F3 adults.
- There were reduced body weights during gestation and lactation for F0, F1, and F2 females at 7500 ppm and at 750 ppm for F0 and F2 females.
- There were reduced body weights during lactation for F1 females at 750 ppm.
- There were reduced body weights at terminal sacrifice for both males and females in all generations at 7500 ppm, for F1 females at 750 ppm, and for F2 and F2 males at 750 ppm.

Feed consumption: Variable

Clinical observations: None treatment related

Organ weights at necropsy: Absolute weights reduced at 7500 ppm: liver, kidneys, ovaries, adrenal glands, spleen, pituitary, and brain

Relative organ weights: Increased at 7500 ppm or unaffected

Histopathology:

- At 7500 ppm, slight to mild renal tubular degeneration and chronic hepatic inflammation in F0, F1, and F2 females
- Reproductive organ histopathology or function not affected

Reproduction and Offspring

- There were no effects on mating, fertility, gestational indices, ovarian primordial follicle counts, estrous cyclicity, precoital interval, gestational length, offspring sex ratio, postnatal survival, nipple/areolae retention in preweanling males, epididymal sperm number, motility or morphology, daily sperm production (DSP), or efficiency of DSP.

Offspring Toxicity

- Vaginal patency (VP; female) and preputial separation (PPS; male) were both delayed in F1, F2, and F3 offspring, associated with reduced body weights at 7500 ppm.
- Anogenital distance (AGD) on postnatal day (PND) 0 was unaffected for F2 and F3 males and F3 females. F2 female AGD increased at some doses but not at 7500 ppm (considered not biologically relevant).

Conclusions

- Adult systemic NOAEL: 75 ppm (5 mg/kg/day)
- Reproductive and postnatal NOAEL: 750 ppm (50 mg/kg/day)
- There were no treatment-related effects in the low-dose region (0.001 – 5 mg/kg/day) for any parameters and no evidence of non-monotonic dose-response curves across generations for either sex. "BPA should not be considered a selective reproductive toxicant based on the results of this study."

A very recent developmental neurotoxicity study of BPA in the diet of SD rats at 0, 0.15, 75, 750, and 2250 ppm, from GD 0 to PND 21 (Stump et al., 2010), reported systemic toxicity to dams and offspring, expressed as reduced body weights at 750 and 2250 ppm (NOAEL, 75 ppm), with no treatment-related effects on gestational lengths, parturition, litter sizes, acquisition of developmental landmarks, or on acquisition of puberty in either sex at any dose. There was also no evidence of any treatment-related neurobehavioral effects, of altered neuropathology, or of altered brain morphometry in offspring through PND 72. The NOAEL for developmental neurotoxicity was 2250 ppm, the highest dose tested. The authors concluded that there was no evidence that BPA is a developmental neurotoxicant in rats.

2. We also performed an abbreviated one-generation study (Tyl et al., 2002a, unpublished), designed to duplicate the species/strain (CD-1 mice), route (diet), and the top two dietary BPA concentrations (5,000 and 10,000 ppm) employed in the BPA RACB study (Reel et al., 1985), and to provide an enhanced evaluation of parental systemic and reproductive toxicity at the top two doses previously employed, to provide the context for the F1 offspring effects at the doses previously reported. CD-1 mice (F0 generation, 20/sex/group) were exposed to dietary BPA for two weeks prebreed, one-week mating (with the F0 males terminated after mating), and through gestation to parturition (PND 0 of the F1 offspring, with F0 females exposed to BPA for 5-6 weeks). F0 females and their F1 pups were necropsied on PND 0. At necropsy, F0 female body, liver, paired kidneys, paired ovaries, and uterine weights were reduced, and maternal livers and kidneys were fixed and evaluated histopathologically. Maternal blood was taken and serum evaluated for a full panel of BUN, creatinine, total protein, albumin, inorganic phosphate, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sodium, potassium, and chloride.

F0 parental systemic toxicity was present at both dietary BPA doses: increased absolute liver and kidney weights in both sexes (except for F0 male kidney weight at 10,000 ppm not statistically significantly different), increased relative liver and kidney weights at 10,000 ppm for both sexes, increased relative liver weights at 5000 ppm for both sexes, and increased relative kidney weights for F0 females at 5000 ppm. Maternal toxicity also included reduced body weights, reduced weight gains, reduced feed consumption and food efficiency during pregnancy, and significantly prolonged gestation at both doses (prolonged for ~10 hours at both doses; significance, if any, unknown). No effects were observed for precoital interval or ovarian or uterine absolute or relative weights. The F0 dams also exhibited histopathologic lesions in the liver (dose-related hepatocellular hypertrophy), kidneys (dose-related renal tubular epithelial degeneration, necrosis and regeneration), elevated BUN at 10,000 ppm, and reduced serum, sodium, potassium, and chloride at 5000 ppm, consistent with renal toxicity.

F1 offspring toxicity was observed only at 10,000 ppm, expressed as slightly (statistically significantly) reduced total and live pups/liver, with no significant effects on pre- or postimplantation *in utero* loss or on pup weights/litter (separate or combined) on PND 0 (day of birth).

These data confirmed the F1 litter size effects at 10,000 ppm observed in the RACB study for the first F1 litters. This study also demonstrated parental systemic toxicity (specifically to the liver and kidneys) at both doses; worse at 10,000 ppm. These data also support the interpretation of F1 litter size effects at 10,000 ppm in the RACB study and in this study as caused by the compromised status of the F1 dams after only 5-6 weeks of exposure in the present study, while the lesser maternal systemic toxicity observed at 5000 ppm did not cause litter size effects after the 5- to 6-week exposure regimen in this study. Note that F1 litter size effects were observed at 5000 ppm in the RACB study for only the fourth and fifth litters after a much longer parental exposure duration (>98 days, >14 weeks).

3. Two-generation reproductive toxicity study of dietary BPA in CD-1 (Swiss) mice by Tyl et al. (2008b) of BPA in the diet at 0, 0.018, 0.18, 30, 300, or 3500 ppm (equivalent to 0, 0.003, 0.03, 0.3, 5, 50, or 600 mg/kg/day), with 28 adults/sex/group, plus concurrent positive control group of dietary 17β-estradiol at 0.5 ppm (~ 0.080 mg/kg/day)

Adult Toxicity

- At 300 ppm: minimal centrilobular hepatic hypertrophy
- At 3500 ppm: reduced body weights, increased liver and kidney weights, minimal/mild centrilobular hepatocyte hypertrophy, and renal nephropathy in males
- There were no effects at any dose on adult mating, fertility or gestational indices, ovarian primordial follicle counts, estrous cyclicity, precoital intervals, sperm parameters (number,

motility, morphology), or reproductive organ weights or histopathology, including the testes and prostate. F1 absolute paired epididymal weights were reduced at 3500 ppm.

Offspring Toxicity

- At 3500 ppm, BPA reduced F1 and F2 weanling body weights, reduced weanling spleen and testes weights (with seminiferous tubule hypoplasia), slightly delayed PPS, and apparently increased the incidence of treatment-related undescended testes only in weanlings. This is considered a developmental delay in the normal process of testes descent, since all adult offspring had descended testes and normal reproductive structures and functions. It is likely that these transient effects were secondary to and caused by systemic toxicity. Gestational length was increased by 0.3 days in F1 and F2 generations. The toxicological significance, if any, is unknown. At low doses (0.018 to 30 ppm, 0.03 to 30 mg/kg/day), there were no effects and no evidence of non-monotonic dose response curves for any parameter.

Conclusions

- Adult systemic NOAEL: 30 ppm (~5 mg/kg/day)
- Reproductive and postnatal NOAEL: 300 ppm (~50 mg/kg/day)
- "Therefore, BPA is not considered a selective reproductive or developmental toxicant in mice."

Other researchers have also published robust studies where low BPA doses, in the absence of maternal toxicity, do not cause effects on the prostate in mice (Ashby et al., 1999), in reproductive organ development in mice (Cagen et al., 1999), on sexual development in rats (Tinwell et al., 2002), or on pubertal development in rats (Kwon et al., 2000). The strongly supported view that low oral BPA doses do not represent a risk has also been reflected in various national evaluatory and regulatory decisions.

IV. Additional Concerns and Aspects

There are two additional scientific concerns for studies used to evaluate the maternal and developmental toxicity of BPA. One is the profound difference in metabolism of BPA when administered orally (by gavage or dosed feed) versus parenterally. Non-oral routes of administration (e.g., subcutaneous or intravenous injection, intracisternal [brain] injections, subcutaneous implants, etc.) bypass the rapid and essentially complete first pass presystemic metabolic conjugation of BPA observed with oral exposures. Therefore, systemic concentrations of parent BPA are much higher, with higher and longer bioavailability, and the identities of the metabolites are different by these non-oral routes (Zalko et al., 2003). Confirmation of the lack of toxicity of orally administered BPA is reported in two

recent studies performed in a U.S. EPA NHEERL laboratory. In one of them, oral administration of BPA during gestation and lactation did not alter sexually dimorphic behavior, puberty, fertility, or anatomy in female rats, while ethinyl estradiol caused all of these effects (Ryan et al., 2010). In the other study, gestational and lactational oral exposure to BPA also did not affect androgen-dependent organ weights or epididymal sperm counts in male rats, while ethinyl estradiol caused all of these effects (Howdeshell et al., 2008). Since oral exposure is the relevant human route, use of non-oral routes in laboratory animals may inform hazard (the intrinsic capacity of the chemical to do harm) but not risk (effects by relevant routes, at relevant doses, during sensitive life stages).

A second scientific concern is the difference in metabolism from oral administration in humans versus rodents. It has been shown that in humans, oral administration of BPA results in essentially 100% metabolism of the parent to BPA glucuronide. In adults, BPA from oral exposure is not detected in the blood. BPA is glucuronidated in the intestinal walls and liver (prior to systemic exposure) into BPA glucuronide which is not estrogenic and rapidly excreted via the urine, with no bioaccumulation and a short elimination half-life of approximately 4-6 hours (Mathews et al., 2001; Volkel et al., 2005). This "first pass" effect (presystemic elimination) occurs from oral exposure but not from other routes of exposure (Pottenger et al., 2000). A secondary BPA metabolite, BPA sulfate, is formed at much lower concentrations and is also not estrogenic (Shimizu et al., 2002). Metabolism of BPA into non-estrogenic BPA glucuronide also occurs in rodent neonates (Domoradzki et al., 2003), in human neonates in hospital intensive care units, and in infants and children (Calafat et al., 2009). In rats, oral administration of BPA results in glucuronidation of BPA in the intestine and liver (less efficiently than in humans), but there is enterohepatic recirculation after hydrolysis of the conjugated BPA metabolites in the intestines and reabsorption of parent BPA. Therefore, parent BPA from oral dosing is transiently detected in rodent blood, and there is a longer half-life and higher bioavailability in rodents compared to humans. Consequently, since the weight of evidence indicates that BPA is not a selective reproductive or developmental toxicant in rodents, it is highly unlikely that BPA could be a reproductive or developmental toxicant in humans.

One important aspect of animal testing and human exposure to BPA is the presence of molecules with much higher affinity (versus BPA) for the estrogen receptor. Many components of the human and rodent diet, such as phytoestrogens (e.g., genistein found in soy), have similar or higher affinity than BPA for the estrogen receptors. Therefore, any bioavailable BPA with weak affinity for the estrogen receptor (4000- to 5000-fold less potent than endogenous estrogen) would compete with

endogenous estrogen (17β-estradiol) and/or dietary phytoestrogens (e.g., the soy phytohormones genistein, daidzein, glycitein), all with much greater affinity for the estrogen receptor than BPA. As a result, it is not biologically plausible that BPA could cause reproductive or developmental effects in humans, in particular endocrine-mediated effects.

A second important aspect is the inaccurate and unfounded assertions that the rat and mouse strains employed in the large, robust studies on BPA are not sensitive to estrogens. We have performed and published a three-generation reproductive toxicity study of dietary nonylphenol (Tyl et al., 2006) in CD (SD) rats with an E2 positive control group, and one-generation (Tyl et al., 2008a) and two-generation (Tyl et al., 2008c) reproductive toxicity studies of E2 in the diet of CD-1 mice. In these studies, E2 exposure caused the estrogenic effects anticipated at low dietary doses in both rats and mice. This is in stark contrast to the absence of BPA effects at low dietary doses. In fact, governmental laboratories have also reported no effects at low doses of BPA, but they did report effects from low-dose endogenous (E2) or synthetic (e.g., 17α-ethinyl estradiol; EE2) estrogens in rats (Howdeshell et al., 2008; Ryan et al., 2010).

V. Summary and Conclusions

Summary

1. The scientific evidence clearly indicates that BPA is not a selective developmental toxicant. Developmental toxicity occurs only at very high oral BPA doses in the presence of profound maternal toxicity. At lower doses with less , but still significant, maternal toxicity, there is no developmental toxicity.
2. BPA is not a developmental neurotoxicant, even in the presence of maternal toxicity.
3. The scientific evidence clearly indicates that BPA is not a selective reproductive toxicant. Reproductive and/or offspring effects from BPA, if they occur, occur only in the presence of substantial maternal toxicity. In the presence of less, but still significant, maternal toxicity, there is no reproductive or offspring toxicity.
4. Since intentional feed restriction, per se, results in maternal toxicity and subsequent embryo-fetal toxicity in rats and rabbits, it is likely that maternal toxicity is the critical determinant of embryo-fetal toxicity in the BPA studies as well.
5. Therefore, BPA does not satisfy the criteria for listing under Proposition 65.

Conclusions

This reviewer strongly believes, based on scientific data, that embryo-fetal offspring toxicity from exposure to high doses of BPA is caused by maternal toxicity.

The importance and central role of maternal toxicity in the causation and evaluation of embryo-fetal and postnatal offspring toxicity are explicitly acknowledged in all the national and international regulatory test guidelines for developmental toxicity. All of them specifically require demonstrable maternal toxicity at the top dose (see Section I for the list of findings encompassing maternal toxicity). The requirement for parental toxicity at the top dose is also present in all the national and international test guidelines for reproductive toxicity assessment. Reproductive or developmental effects that occur at high doses must be evaluated through the lens of maternal toxicity. These test guidelines include:

- FDA Segment II study (Goldenthal, 1966; FDA Redbook, 2000)
- FDA Segment III study (Goldenthal, 1966)
- FDA two-generation reproduction plus teratogenicity study
- EPA OPPTS developmental toxicity study (870.3700; 1998)
- EPA OPPTS reproduction and fertility effects (870.3800; 1998)
- OECD teratogenicity (TG 414; 1981, 2001a)
- OECD one-generation reproduction toxicity study (TG 415; 2001b)
- OECD two-generation reproduction toxicity study (TG 416; 2001c)
- ICH test guidelines (FDA, 1994, 1996)
- ICH test guideline, embryo-fetal development (like FDA Segment II) (ICH 4.1.3)
- ICH test guideline, two-study design in rodents (like FDA Segment III) (ICH 4.3; ICH 4.1.1 plus 4.1.2)

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Advanced Medical Technology Association

May 12, 2010

Ms. Cynthia Oshita
California Office of Environmental Health and Hazard Assessment
Sacramento, CA 95812

Dear Ms. Oshita:

I want to provide comments from the Advanced Medical Technology Association, AdvaMed, on OEHHA's Request for Relevant Information on the listing of Bisphenol-A by the Authoritative Bodies Mechanism.

AdvaMed member companies produce the medical devices, diagnostic products, and health information systems transforming health care through earlier disease detection, less invasive procedures, and more effective treatments. Our members produce nearly 90 percent of the healthcare technology purchased annually in the United States and more than 50 percent purchased around the world.

Medical device firms are committed to providing the safest, most effective devices to meet patients' health care needs. In many applications, BPA-derived polycarbonate plastic and epoxy resins have shown to be the optimal choice for meeting critical device performance characteristics, including shatter-resistance, optical clarity, heat resistance, dimensional stability, and electrical resistance.

Scientific debate continues to exist regarding the potential long-term health risks from exposures to BPA at low levels.1 Further toxicological study is needed to more clearly evaluate the potential concern in order to target the appropriate procedures and patient populations of concern. In January, the Food and Drug Administration indicated concern with BPA, called for reasonable steps to reduce infants' exposure, and is studying the chemical further, but has not called for restrictions on the it's use.

We would urge against actions that could limit BPA's availability for life-saving or life-enhancing medical devices or would undermine the public's confidence in the safety of medical devices. Consideration of the length and amount of exposure to affected populations is critical in light of the need to preserve patient access to needed therapies, particularly when there is a notable absence of demonstrably safer alternatives for medical applications.

Thank you for consideration of our concerns.

Sincerely,

Thomas E. Tremble
Vice President, State Government Relations

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1 U.S. Department of Health and Human Services, National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction, "NTP-CERHR Monograph on the Potential Human Reproductive and Development Effects of Bisphenol-A," NIH publication No. 08-5994 (September 2008)

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May 13, 2010

VIA ELECTRONIC-MAIL
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Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-19B
Sacramento, CA 95812-4010

Re: Request for Relevant Information on a Chemical Being Considered for Listing by the Authoritative Bodies Mechanism: Bisphenol-A

Dear Ms. Oshita:

We are submitting these comments on behalf of the Motion Picture Association of America (MPAA)[1] in response to OEHHA's request for information on potential listing of Bisphenol-A (BPA) as a Proposition 65 reproductive toxicant. A listing of BPA would have a significant adverse impact on the entertainment industry and would be extremely unlikely to result in any benefit to human health if applied to products produced by the industry.

The MPAA understands that some parties have raised concern that exposure to BPA, and its related products polycarbonate plastic and epoxy resins, could pose a potential risk of reproductive harm through the ingestion of food and beverages from BPA-containing baby bottles, food packaging or other food-related products. The MPAA also understands that there is considerable disagreement among experts in this country, as well as other countries that have considered the issue, and that many of these countries have decided not to regulate BPA or do so only with regard to items such as baby bottles. They also understand that in July of 2009, OEHHA considered listing BPA, and that the Proposition 65 Developmental and Reproductive Toxicant Identification Committee voted unanimously not to list BPA as a Proposition 65 reproductive toxicant. Obviously, this issue is both controversial and subject to different opinions. Since the MPAA lacks the expertise to comment on the underlying scientific studies, these comments will not do so.

[1] The Motion Picture Association of America, Inc. includes: The Walt Disney Company; Universal City Studios LLLP; Paramount Pictures Corporation; Sony Pictures Entertainment, Inc.; Twentieth Century Fox Film Corporation; and Warner Bros. Entertainment Inc.

However, the impacts of a potential listing of BPA are real and of great concern to the entertainment industry. Bisphenol-A is one of the most durable and versatile plastics available and provides numerous benefits to both manufacturers and consumers, including a high degree of durability, light weight, and heat and shatter resistance. More importantly, BPA is contained in DVDs and CDs produced by members of the MPAA as well as other entertainment-related merchandise.

The MPAA is concerned that the listing of BPA will trigger potential warning requirements for DVDs and CDs and subject the entertainment industry to a potential onslaught of litigation for which Proposition 65 is well known. The listing of a chemical under Proposition 65 imposes a significant burden on businesses that manufacture products containing Proposition 65 chemicals regardless of whether the actual product has any potential for harm. Your own website states that:

> If there is no safe harbor level for a chemical, businesses that knowingly expose individuals to that chemical would generally be required to provide a Proposition 65 warning, unless the business could show that risks of cancer or reproductive harm resulting from the exposure would be below levels specified in Proposition 65 and its accompanying regulations. Determining health risks is very complex, and we recommend that businesses consult a qualified professional if they believe an exposure to a listed chemical may not require a Proposition 65 warning.

The entertainment industry is like many other industries in California and elsewhere that use BPA for its useful properties. All such industries will be affected by a potential Proposition 65 listing even though their particular products are unlikely to cause harm. Should BPA be listed as a Proposition 65 chemical, of the potential compliance options available, reformulation does not appear to be an option for DVDs and CDs. The MPAA has been informed by replicators that no viable substitute for BPA exists at this time, or is likely to exist in the foreseeable future. Thus, the entertainment industry, like other affected industries, will have to make the choice to either label their products as potentially harmful or to conduct the necessary exposure analyses to demonstrate that their products do not present a risk of reproductive harm. Depending on the number of products involved, this testing could impose a very significant economic burden on the industry.

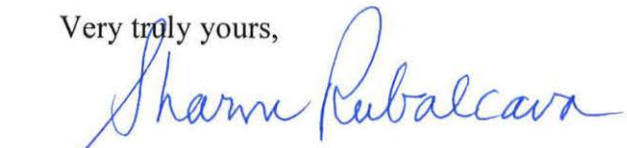
If it should become necessary to add a warning label on DVDs and CDs, this would pose both significant logistical challenges and added expense. These products are sold throughout the United States and are distributed in many different ways. Warning requirements unique to California would be burdensome to implement. DVDs and CDs are sold through retail locations in California, but they are also sold or distributed through

Amazon and Netflix, for example, where special rules for California could impose a greater burden than for retail sales.

In these difficult times for businesses, imposing such a costly burden cannot be justified. The MPAA urges OEHHA to carefully assess whether the science truly supports initiating the rulemaking process to list BPA. However, if OEHHA does reach the decision to initiate the listing process, the MPAA strongly urges you to consider every possible avenue available under Proposition 65 to avoid casting the net too broadly and to limit the application of that decision to just those uses of BPA that may present a risk of reproductive harm, or to concurrently adopt a Maximum Allowable Dose Level to minimize the impacts to affected industries and businesses.

If you need more information on the impacts to the entertainment industry, please contact Wendy Holt at (818) 565-0550 and for BPA-specific issues, contact me at (213) 576-1105.

Very truly yours,



Sharon Rubalcava
ALSTON & BIRD LLP

SFR:dtc

cc: Wendy Holt
Melissa Patack
Carol Lombardini

LEGAL01/13139411v1

May 13, 2010

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-19B
Sacramento, California 95812-4010

Dear Ms. Oshita:

Thank you for giving us the opportunity to provide comments to you regarding bisphenol A (BPA). As organizations that represent health affected communities, environmental health groups, public health organizations and workers, we are pleased that OEHHA is taking the necessary steps towards examining this chemical. We agree with OEHHA's initial assessment that BPA meets the criteria for listing as known to the State to cause reproductive toxicity under Proposition 65, based on findings of the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction.

We appreciate that you are receiving public comment to fully evaluate the science on this matter and agree that science should dictate this decision, rather than politics. However, with the politicization of science that has occurred on this issue, it is impossible to separate the scientific inquiry from the historical and political context.

As you know, scientists have known since at least the 1930s of BPA's ability to interfere with hormones. It was developed to be one of the first synthetic estrogens but shelved for pharmacological use in favor of the more potent DES (diethylstilbestrol). However, polymer scientists began to use BPA in consumer products as early as the 1950s. Today, BPA is one of the most pervasive chemicals in modern life with an annual national production exceeding two billion pounds and can be found in the bodies of 93% of Americans.

To date, over 200 studies have demonstrated the harm that comes from extremely low doses of BPA. All of these studies have been peer reviewed and demonstrate clear harm. Since the NTP's 2008 statement regarding BPA, additional research has come out that highlights the links between low-dose exposure to BPA and reproductive harm. A study published in 2010 showed that exposure of human placental cells to low doses of BPA may cause detrimental effects, leading *in vivo* to adverse pregnancy outcomes such as preeclampsia, intrauterine growth restriction, prematurity and pregnancy loss.[i] Animal studies conducted in 2009 suggested that BPA causes long-term adverse reproductive and carcinogenic effects if exposure occurs during critical periods of differentiation and neonatal exposure to BPA altered reproductive parameters and hypothalamicpituitary function in female rats.[ii,iii]

Due to this clear and compelling evidence, regulatory agencies in the United States are beginning to take action on the concerns surrounding BPA. In January 2010, the U.S. Food and Drug Administration (FDA) reversed its much-criticized position on BPA safety, stating its concern about the chemical's effects on fetuses, infants and children. FDA is now in agreement with a National Toxicology Program 2008 position that there is "some concern" regarding BPA. In March 2010, the United States Environmental Protection Agency announced that it will be working closely with other regulatory agencies on research to better assess and evaluate the potential health consequences of BPA exposures, including health concerns from non-food packaging exposures that fall outside of the FDA's reach but within EPA's regulatory authority. Finally, in January 2010, NIEHS announced plans to fund nearly 50 million dollars

of American Recovery and Reinvestment Act funds to produce data that will allow for a comprehensive assessment of BPA's possible human health effects.

Clearly there is growing scientific consensus that BPA is harmful. The Canadian Health Ministry recently listed it as a toxic substance, has banned its use in baby bottles and has announced its plans to regulate BPA in food and infant formula containers. Denmark has also banned the use of BPA in children's products. In addition, legislation to regulate BPA has been introduced in more than 29 states and localities. Five of those states have passed legislation regulating and banning BPA especially in relation to its uses in children's feeding devices and infant formula.

The case of BPA is reminiscent of the tobacco industry's campaign to deny the health hazards of smoking. For years, state agencies and scientific bodies were unsure about how to act on tobacco due to the "dueling science" that confronted decision makers. We now know that much of the science demonstrating no adverse effect from tobacco products was produced by the tobacco industry as a way to manufacture doubt in regulators' minds long enough to sell their product for a little while longer.

We are seeing the same scenario play out with BPA. Time and again, industry declares that they cannot replicate the findings of the independent scientists' studies and states that the chemical is safe. But further examination of their studies show serious flaws such as using rats that are predisposed to not be affected by synthetic estrogens or feeding the animals a diet that would mask the effects of BPA or even, as in the case of a recent study by Rebecca Tyl, downplaying the results of data clearly demonstrating an effect.

Too often, we give chemicals the same rights as people—demanding that we have absolute certainty of harm beyond all doubt, rather than relying on credible evidence of harm to take action. As a result, doubt is often manufactured through industry funded studies and inconsistencies in outcome from government funded studies are used as an excuse to not take action.

The job of the government is to protect public health. OEHHA's role in protecting public health is to determine if there is enough evidence to warrant informing the public of a risk to their health. The science is in and the evidence is clear. Public health, particularly the health of fetuses, infants and children is compromised by exposure to BPA. We urge OEHHA to use the evidence before it and not be swayed by industry tactics or their manufactured doubt and list BPA as a reproductive toxicant on the Proposition 65 list.

Sincerely,

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Breast Cancer Action

Sheila Davis
Executive Director
Silicon Valley Toxics Coalition

David W. Campbell
Secretary-Treasurer
United Steelworkers Local 675

Pam Palitz
Toxics Advocate and Staff Attorney
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Matt Prindiville
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Natural Resources Council of Maine

Tom Lent
Policy Director
Healthy Building Network

Jeanne Rizzo, R.N.
President and CEO
Breast Cancer Fund

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May 13, 2010

Via Email (coshita@oehha.ca.gov) and FedEx

Joan E. Denton, Ph.D., Director
c/o Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
1001 "I" Street
Sacramento, CA 95814

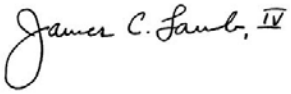
Re: Opposition to Petition for Listing of Bisphenol A Pursuant to Authoritative Bodies Mechanism of Safe Drinking Water and Toxic Enforcement Act of 1986

Dear Dr. Denton:

We were asked by the American Chemistry Council, based upon our knowledge about the potential reproductive and developmental toxicology of bisphenol A (BPA) and based on our experience with the National Toxicology Program and US EPA, to review the available data on BPA's potential developmental toxicity. We write this letter to voice our opposition to the petition by the Natural Resources Defense Council (NRDC) to list BPA as "known to the state to cause reproductive toxicity" under California's Proposition 65 (Prop 65) on the basis of concern for "high" dose developmental toxicity based on the report by NTP CERHR (National Toxicology Program Center for the Evaluation of Risks to Human Reproduction; 2008), under the Authoritative Bodies mechanism. The Authoritative Bodies mechanism of listing, however, does not absolve California from considering the sufficiency of the data in support of the proposed listing. We address in particular the issue of sufficiency of data, which the DART Committee of qualified experts has already voted is not sufficient for BPA to be listed. The statute requires that the determination of sufficiency take into account several factors, including "consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible." We believe that maternal (and adult) toxicity has not been

adequately considered in this petition, and that an association in humans between adverse reproductive effects and the toxic agent in question is not plausible. We conclude that BPA should not be listed by the State of California on the basis of "high dose" developmental toxicity.

Sincerely,



James C. Lamb, IV, Ph.D., DABT, Fellow ATS
Principal Scientist and Center Director
Center for Toxicology and Mechanistic Biology

Opposition to Petition for Listing of Bisphenol A Pursuant to Authoritative Bodies Mechanism of Safe Drinking Water and Toxic Enforcement Act of 1986

We were asked by the American Chemistry Council, based upon our knowledge about the potential reproductive and developmental toxicology of bisphenol A (BPA) and based on our experience with the National Toxicology Program and US EPA, to review the available data on BPA's potential developmental toxicity. We write this letter to voice our opposition to the petition by the Natural Resources Defense Council (NRDC) to list BPA as "known to the state to cause reproductive toxicity" under California's Proposition 65 (Prop 65) on the basis of concern for "high" dose developmental toxicity based on the report by NTP CERHR (National Toxicology Program Center for the Evaluation of Risks to Human Reproduction; 2008), under the Authoritative Bodies mechanism. The Authoritative Bodies mechanism of listing, however, does not absolve California from considering the sufficiency of the data in support of the proposed listing. We address in particular the issue of sufficiency of data, which the DART Committee of qualified experts has already voted is not sufficient for BPA to be listed. The statute requires that the determination of sufficiency take into account several factors, including "consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible." We believe that maternal (and adult) toxicity has not been adequately considered in this petition, and that an association in humans between adverse reproductive effects and the toxic agent in question is not plausible.

Listing of chemicals for reproductive and developmental toxicity is unique to California under Prop 65. Neither the US EPA nor the NTP CERHR, which are considered authoritative bodies by the State of California, create lists or categories of chemicals based on their types of non-cancer toxicity. The US EPA risk assessment process involves identifying the types of non-cancer toxicity produced by chemicals and derivation of reference doses (IRIS, US EPA, 2010) for the purpose of standard-setting in the context of the potential for human exposure. The process leading to the reference dose is a **hazard** evaluation process. The various risk assessment guidelines, including the developmental toxicity (US EPA, 1991) guidelines discuss the interpretation of data on specific types of toxicity or hazards, but do not propose labeling of chemicals based on their toxicity profile. The **risk** for toxicity of a chemical is based on the relationship between the reference dose and human exposure estimates. Thus, risk considers whether or not there is the potential for exposure at high enough levels to result in toxicity. Under Prop 65, chemicals are labeled for different types of toxicity based on their potential hazard rather than risk.

The NTP CERHR also does not label chemicals as such but rather provides "scientifically sound evaluations of the potential for adverse effects on reproduction or development resulting from human exposures to substances in the environment." It is not the purpose to generate lists of substances that might or might not be classified as reproductive or

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developmental toxicants, as required under California's Prop 65 (Prop 65). The Prop 65 determination cannot be made by simply extracting a sentence from the CERHR report. While the NTP CERHR is relied upon as an authoritative body by California, the underlying and different purposes of the CERHR and the California processes demands that California assess independently the sufficiency of the supporting data under its own standards, rather than relying upon a sentence taken out of context of the CERHR report. It is our understanding that this assessment in California has already been completed last year by the California Developmental and Reproductive Toxicant Identification Committee (DARTIC) whose members decided unanimously that BPA is not a developmental or reproductive toxicant.

The NTP CERHR conclusions about "weight of evidence" for effects of BPA at different dose levels (see Fig. 2b, NTP CERHR, 2008) do not take into account the maternal/adult toxicity at those levels. Specifically, in the case of the CERHR conclusion about "clear" developmental toxicity of BPA at "high" doses, the conclusion does not include the consideration that there was severe maternal/adult toxicity at these same doses, indicating the lack of specific or selective developmental toxicity for BPA, or that the dose levels at which those effects were seen are far in excess of any human exposures. In its overall conclusions, however, NTP-CERHR concluded that it has "*negligible concern* that exposure of pregnant women to BPA will result in fetal or neonatal mortality, birth defects, or reduced birth weight and growth in their offspring." This conclusion does take into account the unlikely potential for human exposures at such high dose levels.

The consideration of maternal toxicity is addressed in the US EPA developmental toxicity risk assessment guidelines (1991). The EPA guidelines discuss the various endpoints of maternal toxicity and state that "at doses that cause excessive maternal toxicity (that is, significantly greater than the minimal toxic level), information on developmental effects may be difficult to interpret and of limited value." The developmental effects reported in the major in vivo developmental toxicity studies on BPA are at high dose levels that cause more than minimal maternal toxicity and are far in excess of the levels at which human exposure may occur.

The NTP CERHR (2008) report was based upon the review and citation of 261 papers on toxicity and exposure to BPA. Many of the studies cited by NTP CERHR were judged as not relevant to the immediate question of the likelihood of BPA to cause developmental toxicity in humans. We have selected the most robust studies cited in that report to determine whether or not BPA can affect development in the absence of significant maternal toxicity. The two major in vivo developmental toxicity animal studies on BPA (Morrissey et al., 1987; Kim et al., 2001) and the four major reproductive toxicity studies (NTP, 1985; Tyl et al., 2002a; Tyl et al., 2002b, Tyl et al., 2008) cited in the CERHR (2008) report are reviewed here. Accompanying tables indicate those endpoints for which effects were seen, but do not detail all endpoints examined in each study. Based on this review, we have concluded that developmental effects were seen only at high dose levels that also caused severe maternal

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toxicity, are part of the pattern of general toxicity attributable to BPA at those doses, and are not specific or selective in terms of reproductive or developmental toxicity.

Developmental Toxicity Studies

Morrissey et al., 1987

In this study, time-mated CD rats were treated by gavage on gestation days (GD) 6-15 with doses of BPA at 0 (corn oil), 160, 320, or 640 mg/kg/day. Time-mated CD-1 mice were treated by gavage on GD 6-15 with doses of BPA at 0 (corn oil), 500, 750, 1000, or 1250 mg/kg/day. Rats were killed on GD20, mice on GD17, and fetuses were examined for external, visceral, and skeletal defects. The endpoints affected in this study are summarized in Table 1.

In the rat study, there were signs of significant maternal toxicity at all dose levels, including reduced maternal weight gain during treatment and gestation, as well as reduced weight gain corrected for gravid uterine weight (GUW). The latter effect, together with the fact that there were no effects on fetal body weight indicates that reduced weight gain during gestation was due to maternal toxicity. No fetal effects of any kind were seen in this study.

In mice, maternal toxicity occurred at all dose levels except controls, rising to death of 18% of animals at the highest dose. Liver weight relative to body weight was also increased at all doses, indicating maternal metabolic effects of BPA. The only fetal effects were an increase in resorptions and reduced body weight in survivors, both of which occurred only at the highest dose level, clearly a dose producing severe maternal toxicity.

Table 1. Endpoints Affected (Morrissey et al., 1987)

Group	Endpoint	Dose (mg/kg/day)				
Rats		0	160	320	640	
Maternal	Weight gain during gestation		↓12%	↓13%	↓14%	
	Weight gain corrected for GUW		↓28%	↓26%	↓34%	
	Weight gain during treatment		↓35%	↓53%	↓54%	
Fetal	None					

Table 1 (Continued). Endpoints Affected (Morrissey et al., 1987)

Group	Endpoint	Dose (mg/kg/day)				
Mice		0	500	750	1000	1250
Maternal	Maternal mortality		↑7%	↑4%	↑6%	↑18%
	Weight gain during gestation					↓32%
	Weight gain during treatment					↓43%
	Relative liver weight		↑9%	↑13%	↑17%	↑26%
Fetal	Resorptions					↑26%
	GUW					↓32%
	Fetal body weight					↓15%

Abbreviations: GUW=gravid uterine weight

Kim et al., 2001

This paper reported the effects of BPA dosing by gavage to Sprague-Dawley rats throughout gestation (GD 1-20) at doses of 0 (corn oil), 100, 300, or 1000 mg/kg. Dams were killed on GD 21, uterine contents examined, and fetuses evaluated for external, visceral and skeletal defects. The endpoints affected in this study are summarized in Table 2.

Maternal weight, weight gain, corrected weight gain and food consumption were all significantly reduced at 300 and 1000 mg/kg/day. Clinical signs were significantly increased at 300 and 1000 mg/kg/day, and included severe GI changes of the stomach, small intestine and large intestine, soft stool, diarrhea, urination and/or perineal soiling, piloerection, reddish tear, reduced locomotion, emaciation, sedation, etc. Pregnancy failure (mated animals that were not pregnant) was significantly increased only at 1000 mg/kg/day.

Fetal effects included a 5-fold increase in early resorptions, 10-fold increase in postimplantation loss, and a corresponding 36% reduction in live litter size. Fetal body weight was reduced in males at 300 and in both males and females at 1000 mg/kg/day. A related finding was a reduction at 1000 mg/kg/day in the number of ossification centers in bones developing around the time of examination.

Anogenital distance (AGD) was measured in this study and was significantly reduced in males at 300 or 1000 mg/kg/day. Females were not affected. When AGD in males was corrected by the cube root of body weight, there were no differences. The authors concluded that BPA was “not a selective reproductive or developmental toxicant in male [or female] fetuses even at a severe maternal toxic dose.”

Thus, fetal effects were seen only at doses in this study that produced severe maternal toxicity.

Table 2. Endpoints Affected (Kim et al., 2001)

Group	Endpoint	Dose (mg/kg/day)			
		0	100	300	1000
Maternal	Weight[A]			↓13%	↓19%
	Weight gain			↓35%	↓52%
	Weight gain corrected for GUW			↓14%	↓15%
	Food consumption[B]			↓24%	↓57%
	Clinical signs[D]			↑	↑
	Pregnancy failure			10%[C]	30%
Fetal	Early resorptions				↑ 5-fold
	Postimplantation loss				↑10-fold
	Litter size				↓36%
	Body weight			↓ 14% (males)	↓20/21% (males/ females)
	Ossification centers				↓8-37%[E]

[A]Weight reduced GD 7 and later at 1000 mg/kg/day, GD 14 and later for 300 mg/kg/day. Percent reductions shown for GD 21.
[B]Significant reduction at GD 4 only.
[C]Not significant; 2/20 females.
[D]See text.
[E]Depending on the bones considered, e.g., 16% reduction in ossification of 1st and 2nd phalanges in forelimbs, 37% reduction in hindlimbs; 8% reduction in ossification of metacarpals or metatarsals; 13% reduction in ossification of sternebrae.

Reproductive Toxicity Studies

Four multi-generation studies have been conducted on BPA, three in mice (Reel et al., 1985; Tyl et al., 2002a; Tyl et al., 2008) and one in rats (Tyl et al., 2002b). Although these studies involved continuous exposure over two or more generations, rather than prenatal-only exposure, they provide support for the conclusion that developmental effects occur only at maternally toxic levels and that BPA is not specific or selective for developmental toxicity.

Reel et al., 1985

This study used the NTP Reproductive and Fertility Assessment by Continuous Breeding protocol which involved 4 tasks and are described below. The endpoints affected in this study are summarized in Table 3.

- Task 1 was the dose-finding phase involving male and female CD-1 mice treated for 14 days with 5 doses of BPA ranging from 0.31-5.0% in feed. BPA at 2.5 or 5.0%

caused severe clinical signs of toxicity and three-fourths of the animals in the 5.0% group died. The data from Task 1 were used to set the dose levels for Task 2.

- Task 2 was the continuous breeding (cohabitation) phase and involved exposing males and females of CD-1 mice for 1 week, then mating pairs for 13 weeks to 0, 0.25, 0.5 or 1.0% BPA, and a during a 3 week separation period for delivery of the last litter. Although not reported specifically, it appears from the tables in the report that F0 body weights were reduced at 0.5% and 1.0% by the end of the cohabitation period. Postpartum maternal weight was significantly reduced in the 1.0% dams. The ability of F0 mating pairs to produce a single litter was not affected, but the cumulative days to produce a litter was increased at 1.0% and the mean number of litters /pair and the number of live pups/litter was reduced at both 0.5% and 1.0%.

- Task 3 involved a cross-over mating of control and high dose (1.0% BPA) males and females. Three combinations of breeding pairs were included: control females x control males, control females x 1.0% males, and 1.0% females x control males. The number of live pups/litter was reduced in the control female x 1.0% male group. In the 1.0% female x control male group, the number of pups and number of live pups was significantly less than in the control x control group or the control female x 1.0% male group. There was an increase in F1 pup mortality before weaning at 1.0% BPA.

  When control and 1.0% F0 animals were killed after Task 3, body weights of females in the 1.0% group were significantly reduced and both males and females showed increased absolute and relative liver and kidney weights and histopathological changes in liver (males: centrilobular hepatocytomegaly, multifocal necrosis and multinucleated giant hepatocytes; females: multifocal necrosis, multinucleated giant hepatocytes) and kidney (both sexes: tubular cell nuclear variability and amplification of normally-occurring tubular and interstitial lesions; females: large microcalculi in the cortical tubules, tubular regeneration and/or dilated tubules containing proteinacious or slightly pigmented tubular casts). In addition, seminal vesicle weight was reduced in males, as was sperm motility.

- Task 4 involved an evaluation of the F1 offspring, as adults. Selected males and females were raised to 74 $\pm$ 10 days of age, then a male and female from different litters but within treatment groups were paired for 7 days. After the 7-day cohabitation period, pairs were separated and females allowed to deliver their litters. F2 pups were counted, sexed and weighed, then discarded. F1 males and females were killed and evaluated three weeks after the 7 day cohabitation period.

  There were no effects on mating, the production of F2 litters, litter size, or pup weight. However, liver and kidney weights were significantly increased at all dose levels, and liver and kidney histopathology was seen in both sexes at all doses,

> except for liver histopathology at 0.25% in females. In addition, seminal vesicle and right epididymal weights were reduced in males at all dose levels. Sperm counts were reduced at all dose levels up to 18% in the 1.0% BPA group, but were not significantly different from controls and did not affect reproductive function.

The complexity of this study design and the limitations in terms of incomplete evaluation of adult toxicity at all dose levels, particularly in the F0 generation, makes interpretation of these data somewhat difficult. However, it is clear that there was severe toxicity in F0 adults at 1.0% BPA (the only dose group evaluated) after the cross-over mating in Task 3, and that F1 animals exhibited significant toxicity at all 3 dose levels. Effects on litter size, number of live pups and survival were seen at 0.5% and 1.0% in the F0 mating pairs (Task 2) and are likely part of the general pattern of BPA toxicity at these exposure levels.

Table 3. Endpoints affected by BPA exposure (Reel et al., 1985)

Group	Endpoint	Dose (%)			
		0	0.25 (437.5 mg/kg/d)	0.5 (875 (mg/kg/d)	1.0 (1750 mg/kg/d)
F0 (Task 2)	Postpartum dam weights				↓ 8-9%
	Cumulative days to litter				↑ 10%
	Mean # Litters/pair			↓ 5%	↓ 9%
	# Live pups/litter			↓ 20%	↓ 48%
BPA-M x C-F (Task 3)	# pups				↓ 25 %
BPA-F x C-M (Task 3)	# live pups				↓ 51%
F0 M (end of Task 3 – only controls and 1.0% evaluated)	Liver weight Liver histopathology Kidney weight Kidney histopathology Seminal vesicle weight (adj) [A] Sperm motility				↑ 29% ↑ ↑ 16% ↑ ↓ 19% ↓ 39%
F0 F (end of Task 3 – only controls and 1.0% evaluated)	Body weight Liver weight (adj) [A] Liver histopathology Kidney weight (adj) Kidney histopathology				↓ 4% ↓ 27% ↑ ↓ 10% ↑
F1 pups	Mortality before weaning				↑ (stat sign)
F1 M (end of Task 4)	Liver weight (adj) [A] Liver histopathology Kidney weight (adj)[A] Kidney histopathology Right epididymal weight Seminal vesicle weight Sperm counts		↑ 7% ↑ ↑ 16% ↑ ↓ 7% ↓ 11%	↑ 7% ↑ ↑ 20% ↑ ↓ 16% ↓ 10% (NS)	↑ 9% ↑ ↑ 20% ↑ ↓ 18% ↓ 28% ↓ 18% (NS)
F1 F (end of Task 4)	Liver weight (adj) [A] Liver histopathology Kidney weight (adj) [A] Kidney histopathology		↑ 6% ↑ 13% ↑	↑ 13% ↑ ↑ 15% ↑	↑ 20% ↑ ↑ 13% ↑
F2	No effects				

Abbreviations: C-M=control males, C-F=control females, F=females, M=males

[A] Adjusted for body weight

Tyl et al., 2002a

This abbreviated one-generation study was conducted in CD-1 mice exposed to 0, 5000 (0.5%) or 10,000 (1.0%) ppm in the diet beginning 2 weeks before mating, 1 week during mating, and throughout gestation. The purpose of this study was to duplicate the basic design components of the Reel et al. (1985) study using a more standard one-generation design and to include a more enhanced evaluation of parental toxicity. Males were necropsied after mating and females and their litters were necropsied after parturition (PND 0).

Toxicity to the F0 males and females was evident at both BPA exposure levels with increases in liver and kidney weights (See Table 4). In addition, F0 maternal animals had reduced body weight, weight gain, food consumption and food efficiency, as well as a slight prolongation of gestation length (10 hours in both exposure groups). At necropsy, F0 females were found to have significant liver and kidney histopathology, and changes in clinical chemistries at both doses. Reductions in pup numbers and live litter size were evident only at the higher dose level.

Data from this study support the conclusion that litter effects occurred only in the presence of severe maternal toxicity. In the Reel et al. (1985) study, there were also litter effects at 0.5%, but the exposure period in that study was much longer (>98 days versus only 5-6 weeks in this study).

Table 4. Endpoints Affected (Tyl et al., 2002a)

Group	Endpoint	Dose (ppm)		
		0	5000 (0.5%) (F 968 PB, 841 G; M 760 PB mg/kg/d)	10,000 (1.0%) (F 1932 PB, 1661 G; M 1518 PB (mg/kg/d)[A]
F0	Absolute & relative liver weight Absolute & relative kidney weight		↑ ↑ (relative weight – F only)	↑ ↑ (absolute weight - F only)
Pregnant F	Weight		↓	↓
	Weight gain		↓	↓
	Food consumption Food Efficiency		↓ ↓	↓ ↓
	Prolonged gestation		↑	↑
F0 F (M not evaluated)	Liver pathology Kidney pathology		Hepatocellular hypertrophy Tubular epithelial degeneration, necrosis, regeneration	Hepatocellular hypertrophy Tubular epithelial degeneration, necrosis, regeneration
	Clinical chemistries		↓ Na, K, Cl	↑ BUN
F1	Total pups/litter			↓
	Live pups/litter			↓

Abbreviations: PB = pre-breed, G = gestation, M = male, F = female

Tyl et al., 2008

This two-generation study in CD-1 mice evaluated the effects of BPA dietary administration at levels of 0, 0.018, 0.18, 1.8, 30, 300, and 3500 ppm (0.003 – 600 mg/kg/day). Animals were exposed for 8 weeks, then mated over a period of 14 days. Pregnant females were individually housed and allowed to deliver. After weaning, pups were selected to raise and mate for production of an F2 generation. Exposure continued for 8 weeks prior to breeding of the F1 animals. F2 pups were examined and necropsied at PND 21. The endpoints affected in this study are summarized in Table 5.

Adult systemic toxicity in the F0 animals included centrilobular hepatocyte hypertrophy at 300 and 3500 ppm, renal nephropathy in males only at 3500 ppm, and reduced body weight, increased kidney and liver weight at 3500 ppm. Gestation length was slightly but significantly delayed (0.3 days) in both the F0 and F1 maternal animals. Effects on reproduction and offspring were seen only at 3500 ppm and included reduced weanling body weight, spleen and testis weight, delayed preputial separation and undescended

testes in weanlings. The effects on reproductive organs did not result in adverse effects on adult reproductive structures or functions, so were considered a developmental delay.

Table 5. Endpoints Affected (Tyl et al., 2008)

Group	Endpoint	Dose – ppm (mg/kg/day)						
		0	0.018 (0.003)	0.18 (0.03)	1.8 (0.3)	30 (5)	300 (50)	3500 (600)
F0	Weight							↓
	Kidney, liver weights							↑
	Centrilobular hepatocyte hypertrophy						↑	↑
	Renal nephropathy – males only							↑
F0, F1	Gestation length							↑ (0.3 days)
F1, F2	Weanling body weight							↓
	Weanling spleen, testis weight							↓
	Preputial separation							Delayed
	Undescended testes - weanling							↑

Conclusions regarding BPA developmental toxicity in mice:

From the four studies conducted in CD-1 mice, it appears that adult toxicity occurred at doses as low as 500 mg/kg/day after prenatal exposure (Morrissey et al., 1985) or 50 mg/kg/day in a two-generation reproduction protocol (Tyl et al., 2008). Developmental toxicity in mice occurred only at doses that also produced severe maternal and adult toxicity (1250 mg/kg/day in the prenatal exposure study, and 600 mg/kg/day in the two-generation study).

Tyl et al., 2002b

A three-generation study was conducted in CD Sprague-Dawley rats administered BPA at dietary concentrations of 0, 0.015, 0.3, 4.5, 75, 750, or 7500 ppm (0.001 – 500 mg/kg/day). In this study, the pre-breeding exposure period was 10 weeks for the F0, F1 and F2 generations. F3 offspring were maintained until adulthood. The endpoints affected in this study are summarized in Table 6.

Adult systemic toxicity included reduced body weight and weight gain, reduced absolute and increased relative weanling and adult organ weights (liver, kidneys, adrenals, spleen, pituitary, and brain) at 750 and 7500 ppm. Females showed slight/mild renal and hepatic pathology at 7500 ppm. Relative ovarian weights were reduced in F0, F1, and F2 females, as were the number of implants, number of pups, and number of live pups/litter on PND 0 and PND 4. On PND 7, 14 and 21, the weight of F1, F2, and F3 pups/litter was reduced. In male offspring, epididymal sperm concentration was reduced in F1s and daily sperm production was reduced in F3s at 7500 ppm.

Table 6. Endpoints Affected (Tyl et al., 2002b)

Group	Endpoint	Dose – ppm (mg/kg/day)						
		0	0.015 (0.001)	0.3 (0.02)	4.5 (0.3)	75 (5)	750 (50)	7500 (500)
F0, F1, F2, F3	Weight, weight gain						↓	↓
	Absolute liver, kidney, adrenal, spleen, pituitary, brain weights						↓	↓
	Relative organ weights						↑	↑ (or unaffected)
F0, F1, F2 F	Slight/mild renal & hepatic pathology							↑
	Relative ovarian weight							↓
F1 M	Epididymal sperm concentration							↓
F3 M	Daily sperm production							↓
F1, F2, F3 offspring	# implants, # pups, live pups/litter PND0 & PND 4							↓
F1, F2, F3 pups	Weight/litter on PND 7, 14, 21							↓
F1, F3 F	Vaginal patency (adj)[A]							↓
F1, F2, F3 M	Preputial separation (adj) [A]						↓ (F1)	↓ (F2, F3)

Abbreviations: M = male, F = female
[A] Adjusted for body weight

Conclusions regarding BPA developmental toxicity in rats:

The rat studies reviewed indicated that maternal/adult toxicity occurred at doses as low as 160 mg/kg/day in the prenatal developmental toxicity study (Morrissey et al., 1987) or 50 mg/kg/day in a three-generation protocol (Tyl et al., 2002b). There were no developmental effects reported in the prenatal developmental toxicity study. In the three-generation study, developmental effects occurred at 500 mg/kg/day, except for delays in preputial separation in the F1 males, which were reduced at 50 mg/kg/day.

Overall Conclusions

The NRDC petition requests the addition of BPA to California's list of Prop 65 chemicals "known to the state to cause reproductive toxicity." The petition is based upon the NTP CERHR report on BPA that was published in 2008. Certain statements have been cited from that report in an attempt to support the petition, though they rely entirely upon effects from excessively high exposures that also caused severe maternal toxicity. The reliance on the CERHR document and on the NTP CERHR as an authoritative body overlooks the requirement to consider the sufficiency of the data. Having reviewed the data underlying the CERHR report, we conclude that BPA should not be listed by the State of California on the basis of "high dose" developmental toxicity. Listing on this basis would raise questions about a number of chemicals that show developmental effects only in the presence of maternal/adult toxicity, and ignores the importance of both general toxicity and the plausibility of such high exposures in humans in drawing conclusions about concern.

We have reviewed the critical studies cited by the NTP CERHR report and have summarized the key findings above. In every case, effects on offspring seen were at dose levels that also produced maternal/adult systemic toxicity greater than what would be considered minimal toxicity. In addition, the levels of exposure at which the maternal/adult toxicity and reproductive and developmental toxicity occurred are far above those exposure levels that might plausibly occur in humans. We believe that the developmental effects reported as a result of BPA exposure are part of the pattern of general toxicity caused by BPA and are not specific or selective for developmental toxicity.

We do not believe the data provide sufficient evidence of developmental toxicity, even at high doses of BPA, due to the degree of maternal/adult toxicity at the same dose levels. Therefore, it is inappropriate to list BPA under Prop 65 as a developmental toxicant in any case, and particularly on the basis of "high dose" effects because the effects seen are part of a general pattern of overall toxicity.

Ex™

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Authors

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Dr. Carole A. Kimmel is a Senior Managing Scientist in Exponent's Health Sciences Center for Toxicology and Mechanistic Biology. She has 40 years experience in reproductive and developmental toxicology, children's environmental health, and risk assessment, and is an internationally recognized expert in these areas. She led the National Toxicology Program's Reproductive and Developmental Toxicology Program from 1980 to 1984, and was the project officer for the contract with Research Triangle Institute under which the developmental toxicity study on bisphenol A was conducted. From 1984 to 2004, she was a Senior Scientist in the National Center for Environmental Assessment, US EPA, where she worked on advances in risk assessment approaches and development of risk assessment guidelines for non-cancer health effects, particularly reproductive and developmental toxicity and neurotoxicity risk assessment. Her leadership in developing the U.S. EPA *Guidelines for Developmental Toxicity Risk Assessment* is particularly relevant to the issues in this review.

Dr. Kimmel was on the organizing panel that led to the creation of the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (CERHR), and served as a Board member for several years. She has also served on expert panels for the National Academy of Sciences/National Research Council to evaluate health and safety issues related to environmental contaminants. Dr. Kimmel is Past President of the Teratology Society, the Neurobehavioral Teratology Society, and the Reproductive and Developmental Toxicology Specialty Section of the Society of Toxicology. She has published 175 research manuscripts, reviews and book chapters, and edited several books and proceedings.

James C. Lamb, Ph.D., DABT, Fellow ATS

Dr. James C. Lamb is a Principal Scientist and the Director of Exponent's Health Sciences Center for Toxicology and Mechanistic Biology. He has over 30 years experience in toxicology, risk assessment, and scientific and regulatory policy. Dr. Lamb was the Head of the Fertility and Reproduction Group at the National Toxicology Program (NTP), where he led the NTP project on the Fertility Assessment by Continuous Breeding which included the study of bisphenol A.

Dr. Lamb was also on the organizing panel that led to the creation of the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (CERHR). Dr. Lamb served on several National Academy of Sciences committees on risk assessment, endocrine disruption, and toxicology. He served as President of the American Board of Toxicology, is on the Board of the Academy of Toxicological Sciences and has served in many leadership positions in the Society of Toxicology. He has been an Associate Editor of the

journal *Environmental Health Perspectives*. He has published over a hundred peer-reviewed publications and numerous abstracts and book chapters.

Acknowledgement of Funding: These comments reflect solely the opinions of the authors. The review of the literature and preparation of these comments were supported financially by the American Chemistry Council.

CALIFORNIA SOCIETY OF PEDIATRIC DENTISTRY

May 11, 2010

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
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Re: Office of Environmental Health Hazard Assessment request for public comments concerning whether Bisphenol A (BPA) meets the authoritative bodies listing criteria set forth in the Proposition 65 regulations in Title 27, California Code of Regulations, Section 25306.

Dear Ms. Oshita:

The California Society of Pediatric Dentistry, the professional organization representing California's nearly 600 pediatric dental practitioners, educators and researchers, appreciates the opportunity to provide comment on the proposed consideration of listing of bisphenol-A under the posting requirements of Proposition 65 in conjunction with the placement of dental sealants.

A review of the pertinent literature provides ample evidence that bisphenol-A is not an ingredient in the materials used as dental sealants to prevent enamel demineralization by bacterial plaque formation in the pits and fissures of posterior teeth. What intraoral exposure to BPA that occurs in the sealant process is a byproduct of the degradation of other components of sealant materials, which fall below the *no observable effects level* (NOEL). In fact, the estimated one time exposure (upon sealant placement) to BPA is approximately 5.5 micrograms[1], which is two to five times lower than the estimated daily exposure from foods and environmental sources[2].

As an additional consideration, irrigation of the placed and cured sealant, now a recommended best practice, further reduces levels of any uncured resin and byproducts on the chewing surface.

Of equal weight is the importance of dental sealants in the prevention of dental caries (tooth decay), especially in high-risk populations. According to the 2006 *California Smile Survey*[3], an oral health assessment of over 20,000 California kindergarten and first grade children, approximately two-thirds, or 6.3 million, experience tooth decay by the time they reach third grade. Placement of dental sealants can dramatically reduce this number. Reduction of caries incidence in children and adolescents after placement of resin-based sealants ranges from 86

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percent at one year to 78.6 percent at two years and 58.6 percent at four years[4,5]. Reapplication of sealants as indicated by periodic observation can produce even better oral health outcomes.

We believe the posting of a Proposition 65 warning in association with the placement of dental sealants is unnecessary. The products used by dental professionals in sealant placement do not contain BPA and the brief exposure to BPA as a byproduct of degradation is a singular (acute) event that poses no known or demonstrated threat to health. The posting of such a notice, however, could lead to public confusion about sealant safety and subsequent decreasing utilization of sealants in schools, public health settings, and private offices. This would have a devastating effect on public health, especially among those children and adolescents most at risk for the effects of dental disease.

David Rothman, DDS
President
California Society of Pediatric Dentistry

Paul Reggiardo, DDS
Public Policy Advocate
California Society of Pediatric Dentistry

c: Dr. Ray Stewart, Executive Director, California Society of Pediatric Dentistry
Officers and Directors, California Society of Pediatric Dentistry

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1 Joskow R, Boyd Barr D, Barr JR, Calafat AM, Needham LL, Rubin C. Exposure to bisphenol A from bis-glycidyl dimethacrylate-based dental sealants. J Am Dent Assoc. 2006;137:353-62.

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The California Society of Pediatric Dentistry is the professional membership organization representing California's nearly 600 pediatric dental providers, educators and researchers. Our members provide primary and specialty care to infants, children, adolescents and patients with special medical and developmental needs. The mission of the California Society of Pediatric Dentistry is to serve its members and the public by advocating for the optimal oral health of infants, children, and adolescents.

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May 13, 2010

Via E-mail

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Re: Consideration of BPA Listing under Proposition 65

Dear Ms. Oshita:

The North American Metal Packaging Alliance, Inc. (NAMPA)[1] is pleased to submit these comments in response to the Office of Environmental Health Hazard Assessment's (OEHHA) consideration of a petition from the Natural Resources Defense Council (NRDC) to list bisphenol A (BPA) as a reproductive toxicant under the Safe Drinking Water and Toxic Enforcement Act of 1986 (also known as Proposition 65 or Prop 65). As discussed below, NAMPA strongly disagrees with NRDC's July 15, 2009, petition, which asserts that the authoritative bodies listing mechanism under Prop 65 should be triggered by the report on BPA by the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR).[2]

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1 NAMPA's membership includes companies and associations representing various sectors along the supply chain for the food and beverage packaging industry. NAMPA and its members support sound science and trust the scientific review process that has protected our food supply for decades.

2 National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. NIH Publication No. 08-5994 (Sept. 2008) (NTP Report).

The North American Metal Packaging Alliance, Inc. is an organization whose objectives are to support risk-based regulations in North America; influence regulation in other geographies, provide customers with needed information regarding well-founded technologies, and advocate risk-based decision-making in technology decisions.

NTP Report Already Thoroughly Reviewed under Prop 65

NAMPA notes that the report on BPA by NTP-CERHR was part of a focused and thorough review by the Developmental and Reproductive Toxicant Identification Committee (DARTIC) during its consideration of BPA in July 2009. At that time, the DARTIC carefully considered all the issues highlighted in the NTP Report and unanimously agreed BPA did not meet the Prop 65 criteria.

Furthermore, there are new data available that address the specific reproductive concern raised in the NTP Report. For the NTP finding of "some concern," the report stated the studies in laboratory animals provided only limited evidence for adverse effects on development and that more research is needed. Several new, scientifically robust studies showing no adverse effects have been published since the NTP Report was finalized, including a U.S. Environmental Protection Agency (EPA) study specifically designed to address the reproductive concerns raised by NTP. The EPA study provides compelling new scientific evidence that exposure to BPA at extremely low doses has no effect on female development and fertility in test animals. This study is very important to OEHHA's consideration of the NRDC petition because it provides scientifically valid data that were not considered by NTP and clearly settles those concerns, providing comprehensive answers to questions raised by NTP.

Finally, NTP itself has noted that its report "is not a quantitative risk assessment nor is it intended to supersede risk assessments conducted by regulatory agencies." Given this statement, any attempt to rely on the NTP Report for Prop 65 listing purposes would be inconsistent with NTP's own advice and thus entirely inappropriate.

Finding in NTP Report Is Not Relevant or Plausible for Humans

The California Code of Regulations clearly state that if the authoritative body listing is used based on experimental animal data, the data must show "that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible."[3]

The NRDC petition references the high dose study review included in the NTP Report, which states:

> These "high" dose effects of bisphenol A are not considered scientifically controversial and provide clear evidence of adverse effects on development in laboratory animals. However, the

[3] Cal. Code Regs. tit. 27, § 25306(g)(2).

> administered dose levels associated with delayed puberty (≥ 50 mg/kg bw/day), growth reductions (≥ 300 mg/kg bw/day), or survival (≥ 500 mg/kg bw/day) are far in excess of the highest estimated daily intake of bisphenol A in children (< 0.0147 mg/kg bw/day), adults (< 0.0015 mg/kg bw/day), or workers (0.100 mg/kg bw/day).[4]

The NTP Report also notes that the majority of human exposure to BPA occurs through food and beverages. Based on a Canadian sampling of beverage cans, the average amount of BPA found in beverages was 0.57 µg/l.[5] With this in mind, NAMPA notes that to achieve the lowest dose level reference above that elicited adverse effects (≥ 50 mg/kg bw/day), a person would need to consume over 14 million cans of food or beverage per day, every day over a lifetime.[6] Clearly, such consumption levels are not physically or biologically possible. Even incorporating a 100-fold safety factor, persons will still have to ingest 14,000 cans of food or beverage per day.

Additional Government Reviews of BPA

Since the unanimous decision by DARTIC in July 2009, the following government reviews or decisions have been issued:

- On January 15, 2010, the U.S. Food and Drug Administration (FDA) issued its interim update on BPA. In its announcement, FDA clearly stated that BPA has not been proven to be harmful to children or adults in any of its current uses.

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4 NTP Report at 7.

5 Survey of Bisphenol A in Canned Drink Products. Health Canada Bureau of Chemical Safety (Mar. 2009).

6 Based on the following calculation:

The Health Canada beverage analysis of 72 samples yielded an average of 0.57 µg/l per can. Assuming the average can is 12 ounces, or 355 ml, which equals 0.355 liters, the intake of an entire can containing 0.57 µg/l would be 0.355 liters X 0.57 µg/l, or 0.2024 µg. Applying the dose referenced in the NPT report (50 mg/kg bw/day) to an average human (60 kg), the human equivalent intake would be 3,000 mg/day.

(3000 mg /day)(0.2024 µg/can)(1000 µg/mg) = **14,822,134 cans in a day**

- On October 2, 2009, the German Federal Institute for Risk Assessment (BfR) -- the German equivalent of the U.S. FDA -- reiterated its conclusions that BPA does not pose a health risk to people. In an updated Frequently Asked Questions (FAQ) document posted to its website, BfR responded to several questions about the safety of BPA in plastic baby bottles, stating that "[f]ollowing careful examination of all studies, in particular the studies in the low dose range of bisphenol A, BfR comes to the conclusion in its scientific assessment that the normal use of polycarbonate bottles does not lead to a health risk from bisphenol A for infants and small children."

- In February 2010, the European Commission's Institute for Health and Consumer Protection issued a complete risk assessment report on BPA and included a new 2008 addendum to the substance's original 2003 report. In this latest update, European Union officials concluded that for consumers exposed to BPA, "there is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied already." The Commission stated that there are no risks from physico-chemical properties arising from the use of BPA, and as a result there is no need for further information and/or testing and for risk reduction measures beyond those that are being applied already.

Unintended Human Health Hazard Consequences

NAMPA urges OEHHA to evaluate the potential health hazards that might arise as unintended consequences of listing BPA as a Prop 65 reproductive toxicant and is no longer available for certain applications.

BPA is an essential component in the epoxy resin coatings used in metal food packaging. Epoxy coatings enable the high temperature sterilization of food products when initially packaged. Epoxy coatings are resistant to the wide range of chemistries found in food and beverage products; this chemical resistance virtually eliminates any interactions between the metal package and the food contents. This is critical in maintaining the sterility of the food product. The coating protects the food product from interacting with the metal package and prevents perforation defects from forming in the container that would allow bacteria and microorganisms to enter.

The use of epoxy coatings in metal packaging is the most effective way to protect the food product. The initial high temperature sterilization, coupled with the continued product protection enabled by the epoxy-based coatings, eliminates the dangers of food poisoning from microbial contaminants. According to FDA records, there has not been an incidence of food-borne illness resulting from a failure of metal packaging in more than 30 years. The same cannot

be said for fresh, refrigerated, or frozen foods, all of which have been involved in the highly publicized tragic food poisoning cases that have occurred the last few years.

According to a March 2010 report from the Produce Safety Project, an initiative of the Pew Charitable Trusts and Georgetown University,[7] food-borne illnesses cost the United States $152 billion annually in health care and other losses. Each year, 76 million people become sick through food contamination, hundreds of thousands are hospitalized, and approximately 5,000 people die. We cannot dismiss the essential role of epoxy resin coatings in protecting against these very real, costly, and tragic results. By reducing the potential for the serious and often deadly effects from food-borne illnesses, epoxy coated metal packaging protects human health.

California citizens that receive assistance from food pantries as well as the Women, Infant, and Children (WIC) program rely significantly on the availability of metal packaged products. In 2009, more than 60% of all infants born in California were dependent upon WIC for nutritional support. WIC is an FDA supported program, with FDA issuing requirements and regulations for items provided. How will California's program -- which is the largest WIC program in the United States -- be impacted if it does not line up with the federal program? FDA has already clearly indicated that no changes should be made in food packaging or consumption, whether by industry or consumers, that could jeopardize either food safety or reduce access to and intake of food needed to provide good nutrition, particularly for infants.

With regard to other food assistance programs, according to an April 2009 policy paper from the California Association of Food Banks, five million Californians report that they are unable to afford the food they need. These include working parents and senior citizens. And the need is increasing. A June 2009 Los Angeles Regional Foodbank Policy Brief indicates the current distribution rate for food pantries has increased 31% compared to last year, and by 24% over the last six months. Even those who may not typically use food assistance programs could find themselves relying on metal packaged products in situations such as power outages, an earthquake, or other natural disasters.

Despite reports to the contrary, the simple fact is there is no readily available, suitable alternative to BPA-based can coatings that meets the essential safety and performance requirements for the broadest spectrum of foods now packaged in metal containers. There are some alternatives currently being used, but only for certain niche markets. They are not applicable for the wide range of food and beverages currently on the market. In an effort to

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[7] Richard Scharff. Health Related Costs From Foodborne Illness in the United States. Produce Food Safety Product at Georgetown University (Mar. 3, 2010).

address marketplace concerns, the industry has and continues to research alternatives to BPA. But before any alternatives that might be under development today can be commercialized, they must undergo thorough, multi-year testing programs to ensure that food safety is not compromised. Assuming a new approach is found to be viable, modifications in production lines for the resin producers, the coating manufacturers, the package manufacturers, and fillers will need to be made. Furthermore, any alternative will require ongoing safety, environmental, and quality evaluations as required by law. At this time, there is no drop-in replacement available.

Conclusion

As previously noted, the listing of BPA and the conclusion in the NTP Report were carefully and thoroughly considered by the DARTIC. That Committee determined that BPA did not meet the listing criteria and voted unanimously not to include BPA on Proposition 65.

If OEHHA proceeds with listing BPA as a reproductive toxicant and consequently requires warning labels on metal packages, it will, in fact and reality, be encouraging its citizens to move away from a proven method for ensuring food safety and will put their health at risk. NAMPA strongly urges OEHHA not to proceed with any initiative to list BPA under Prop 65.

* * * * *

Thank you for consideration of our input. We look forward to OEHHA's decision on this very important matter.

Sincerely,

John Rost

John M. Rost, Ph.D.
Chair, NAMPA

GT GreenbergTraurig

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May 12, 2010

VIA E-MAIL

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Re: Comments of the California Dental Association and the CDA Foundation on the Proposed Listing of Bisphenol-A Under Proposition 65

Dear Dr. Denton:

This response to OEHHA's March 23, 2010, request for comments on the proposed listing of Bisphenol-A (BPA) is submitted on behalf of the California Dental Association and the CDA Foundation (collectively, "CDA"). CDA appreciates this opportunity to comment on the proposal.

CDA supports dental health professionals in their practices and service to the public through innovation in education, advocacy and related programs. CDA is the recognized leader for excellence in member services and advocacy promoting oral health and the profession of dentistry.

As a champion of oral health, CDA supports the use of sealants and other products to prevent and treat dental caries. Dental sealants are no longer made with BPA, and do not cause exposures that would require a warning. It is rare for dental sealants to cause any exposure to BPA. In the few brands that elevate BPA saliva levels, the exposures last for less than an hour.

Nevertheless, the listing of BPA is likely to lead dentists and other oral health professionals to use warnings to avoid baseless litigation. Such warnings would discourage Californians, and especially pregnant women, from obtaining proper dental care. Moreover, the proliferation of warnings would undermine the legislative purposes of Proposition 65.

The National Toxicology Program document upon which the proposed listing is based does not formally identify BPA as causing reproductive toxicity within the meaning of Proposition 65 or of Title 27, California Code of Regulations, § 25306. NTP did not

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determine that there was sufficient evidence of reproductive toxicity in experimental animals to conclude that BPA is a reproductive toxicant.. As the DART-IC recently determined, BPA is not known to cause reproductive toxicity. BPA should not be listed under Proposition 65.

Moreover, as the Court of Appeal for the Second District made clear in *Nicolle-Wagner v. Deukmejian* (1991) 230 Cal.App.3d 652, 661, OEHHA is authorized to take regulatory action that promotes the purposes of Proposition 65 by protecting businesses and the public from proliferating and unnecessary warnings that "dilute to the point of meaninglessness" those required by Proposition 65. Since the DART-IC recently determined that BPA is not clearly shown to cause reproductive toxicity within the meaning of Proposition 65, the proposed listing would not promote accurate information or consumer safety. The public health is better served if OEHHA exercises discretion by refraining from listing.

Sealants and Composites Have Important Public Health Benefits.

According to the U.S. Centers for Disease Control and Prevention, dental caries remains the most common chronic disease of children aged 5 to 17 years and is 5 times more common than asthma.[1] Untreated cavities can cause pain, dysfunction, absence from school, and poor appearance—problems that can greatly affect a child's quality of life. The 2006 California Smile Survey[2] showed that dental disease disproportionately affects the poor, ethnic minorities and the uninsured. This is consistent with data from the National Health and Nutrition Examination Survey (NHANES), which demonstrated that caries in permanent teeth was not distributed evenly among children and adolescents; among five to 17 year olds, 80% of caries occurred in just 25% of the population.[3]

Dental sealants play an essential role in prevention of caries, especially in high-risk groups. Sealants have been extensively studied and are recognized as one of the most effective methods for preventing tooth decay thereby decreasing the need for restorations. Reduction of caries incidence after placement of resin-based sealants ranges from 86% at one year to 79% at two years and 60% at four years. There is consistent evidence from private dental insurance and Medicaid databases that sealants on first and second

[1] Centers for Disease Control and Prevention and the American Dental Association (2006). Fluoridation: nature's way to prevent tooth decay. Available at www.cdc.gov/Fluoridation/pdf/natures_way.pdf
[2] Dental Health Foundation, California Department of Health Services Office of Oral Health et al. (2006). Mommy, it hurts to chew: the California smile survey, an oral health assessment of California's kindergarten and 3rd grade children. Available at www.healthysmilesoc.org/Documents/ CaliforniaSmileSurvey.pdf
[3] Vargas, C.M. et al (1998). Sociodemographic distribution of pediatric dental caries: NHANES III, 1988–1994. *Journal of the American Dental Association* 129:1229-1238. See also Kaste, L.S et al. (1996) Coronal caries in the primary and permanent dentition of children and adolescents 1-17 years of age: United States, 1988–1991. *Journal of Dental Research* 75:631-641.

permanent molars in children and adolescents is associated with reductions in the subsequent provision of restorative services.

Sealants and Composites Cause No Proposition 65 Exposure.

Contrary to the statement in OEHHA's notice, BPA is not an ingredient in dental sealants. The use in dental sealants of bis-DMA, which may degrade to release BPA after placement, is now rare. The estimated short-term exposure to a child from application of dental sealants that did release BPA was approximately one-ten-thousandth of the NOEL of 50 mg/kg. There is no detectable trace of BPA in saliva, blood or urine after 24 hours of sealant placement, and in most cases, none after 1 hour.

Listing BPA Would Undermine the Public Health.

Since there is no Proposition 65 exposure, no Proposition 65 warning is required. However, safe-harbor levels and exposures are the defendant's burden of proof, and meeting that burden requires expensive litigation through trial. This makes the settlement value of cases high, drawing actions against defendants who are not legally required to warn. To avoid costly civil litigation, many dentists will choose to provide warnings.

Warnings will promote misinformation about sealants, and may reduce sealant use. Reductions in sealant use would undermine state and federal goals for improving oral health.

In 2009, the Developmental and Reproductive Toxicant Identification Committee carefully reviewed the evidence on BPA and determined that it is *not* clearly shown to cause reproductive toxicity. Therefore, the addition of BPA to the Proposition 65 list cannot promote accurate information or any other public good.

BPA Is Not a Known Reproductive Toxicant.

Under Section 25306, the National Toxicology Program is an authoritative body "solely as to final reports of the National Toxicology Program's Center for Evaluation of Risks to Human Reproduction." Listing would be permitted under that section only if the NTP-CERHR report "concludes that the chemical causes … reproductive toxicity."

But the NTP-CERHR does not so conclude. Rather, the NTP reported "some concern" that BPA "possibly" may "affect human development or reproduction," (see Abstract at vii). Therefore, the addition of BPA to the Proposition 65 list is not legally required. Thus there is no justification for causing the public health problems that would result from the proposed listing.

For all these reasons, CDA believes the public good is best served by and urges OEHHA to determine that BPA is not known to cause reproductive toxicity within the meaning of Proposition 65, and to exercise its discretion to promote the purposes of Proposition 65 by refraining from the proposed listing.

Yours truly,

Lisa L. Halko

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May 13, 2010

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Re: Request for Public Hearing Re Bisphenol-A

Dear Ms. Oshita:

The Grocery Manufacturers Association ("GMA") – whose members produce, process, and prepare foods consumed by virtually all Californians – is pleased to provide these comments on the Request for Relevant Information on a Chemical Being Considered for Listing by the Authoritative Bodies Mechanism: Bisphenol-A (the "Request"), published by the Office of Environmental Health Hazard Assessment ("OEHHA") on February 12, 2010.

The use of Bisphenol-A ("BPA") in epoxy resin coatings has for over 30 years helped improve the safety and quality of food and beverages by protecting the integrity and performance of cans and metal closures for glass jars. The unique properties of these coatings assure that fruits, vegetables, fish, and other foods can be canned and stored safely over long periods of time, providing a relatively low-cost source of nutrients to consumers and delivering an important health benefit to Californians.

Many consumers face economic and logistical obstacles limiting their access to fresh fruits, vegetables, and proteins. Product packaging employing BPA allows them to obtain the benefits of those foods. Moreover, because epoxy resins keep foods safe for extended periods of time, canned foods are critical to emergency preparedness; they also are essential for persons who are elderly or otherwise unable to do frequent food shopping. Although research continues on alternative materials that would serve the same function as BPA, at present there are no commercially viable substitutes that will work for all food uses. Any decision that has the consequence of discouraging consumers from buying canned foods whose liners contain very low levels of BPA could, therefore, have a material adverse impact on consumer well-being.

For all these reasons and others described below, the prospect of adding BPA to the Proposition 65 list raises numerous public health issues of great importance to food manufacturers, retailers, and consumers. It is essential, therefore, that OEHHA have as robust a record as possible for any decision that may profoundly impact public health from changes in consumers' purchasing and food consumption decisions, and we had requested a short additional time period to respond to OEHHA's Request. We reiterate our request for an additional 30 days to comment on this subject.

Given the benefits delivered every day by protective linings in food packaging, it is critical that OEHHA use the resources available to it to be sure that its decision is (1) scientifically supported and (2) consistent with the language, purpose, and intent of the statute and its implementing regulations. Based on the extensive record currently before OEHHA, it is clear that a decision to list BPA administratively – through the authoritative bodies mechanism – does not pass either test.

I. DISCUSSION

OEHHA is poised to take an unprecedented step in interpreting and applying Proposition 65. Specifically, OEHHA proposes to allow its staff to overrule a determination by the Developmental and Reproductive Toxicant Identification Committee ("DART IC") that BPA is not "known to the state" to cause reproductive toxicity.

The DART IC's unanimous vote not to list BPA rested on a full body of scientific evidence from a number of different sources, including the 2008 monograph prepared by the National Toxicology Program ("NTP"). The DART IC expressly requested that OEHHA bring the chemical back for further review by the DART IC should new information come to light.

Instead, OEHHA now proposes to list BPA under the authoritative body criterion of subdivision (b) of section 25249.8 of Proposition 65, based on a narrow slice of the scientific record considered by the DART IC. Such an application of subdivision (b) is flatly inconsistent with the language, structure, and intent of the statute; it also exceeds OEHHA's authority to implement the statute.

If there were new evidence supporting listing, OEHHA should have referred BPA back to the DART IC for further consideration. Where, as here, the more recent scientific evidence supports the DART IC's unanimous decision *not to list*, OEHHA should simply put BPA back into the pool of candidate chemicals in accordance with its Prioritization Procedures.

A. OEHHA May Not Use the Authoritative Bodies Criterion to Overrule the State's Qualified Experts.

When Proposition 65 was presented on the November 1986 ballot, voters were told that the new statute would include only those chemicals "known — not merely suspected, but known — to cause cancer and birth defects," and that Proposition 65 would require the application of more rigorous science than any other toxics law.[1] To ensure this high degree of scientific integrity, Proposition 65 requires the Governor to appoint a panel of scientific experts and, "only after full consultation" with that panel, to update the list.[2]

Section 25249.8, subdivision (b), provides that "[a] chemical is known to the state to cause cancer or reproductive toxicity within the meaning of this chapter 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 or reproductive toxicity, or
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> if a body considered to be authoritative by such experts has formally identified it as causing cancer or reproductive toxicity, or
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> if an agency of the state or federal government has formally required it to be labeled or identified as causing cancer or reproductive toxicity."

Cal. Health & Saf. Code § 25249.8(b).

In OEHHA's Request announcing its consideration of listing BPA under the authoritative body criterion, and again at the April 20, 2010 public forum, OEHHA argued that the criteria set forth in section 25249.8 of Proposition 65 for adding chemicals to the list are "co-equal" and independent of one another, and that no single criterion takes precedence over another.[3] However, as explained below, this view is inconsistent with the context and purpose of

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[1] California Secretary of State, Restrictions on Toxic Discharges into Drinking Water; Requirement of Notice of Persons' Exposure to Toxics. Initiative Statute (1986) ("Ballot Pamphlet"), at p. 55.

[2] Cal. Health & Saf. Code § 25249.8, subd. (d); Ballot Pamphlet at p. 54.

[3] OEHHA, Request for Relevant Information on a Chemical Being Considered for Listing by the Authoritative Bodies Mechanism: Bisphenol-A (Feb. 12, 1010), available at http://www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/requests_info/callinBPA021210.html, visited May 3, 2010.

section 25249.8 and its implementing regulations, and is not consistent with OEHHA's actual practices.[4]

1. The state's qualified experts criterion is the "primary approach to listing."

Regulations implementing the authoritative body criterion were promulgated in 1990.[5] The final statement of reasons explaining the regulations makes clear that it was not intended to replace, let alone *contradict*, work already done by the science panels. Indeed, the state's qualified experts criterion under subdivision (b) of section 25249.8 was intended to serve as the "*primary approach to listing*."[6]

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[4] For example, OEHHA has prioritized the listing criteria according to its view of how much process is required prior to listing under various listing criteria. In 2006, for example, OEHHA publicly articulated a new legal theory (the validity of this theory has been challenged and is the subject of a lawsuit currently pending in the Court of Appeals) that an incorporation provision used to create the initial version of the Proposition 65 list in 1987 creates an ongoing current mandate for OEHHA staff to list chemicals identified by reference to California Labor Code section 6382, subdivisions (b)(1) and (d), automatically and with no opportunity for the SAB or the public to present contrary scientific evidence or for the SAB or OEHHA staff to consider such evidence. *See, e.g.*, OEHHA, Request for Comments on Chemicals Proposed for Listing by the Labor Code Mechanism (June 12, 2009), at p. 2, available at http://www.oehha.ca.gov/prop65/docs_admin/pdf/LCDART061209.pdf (visited May 3, 2010). Thus, on August 7, 2009, OEHHA listed 20 such chemicals at once. OEHHA, Chemicals Listed Effective August 7, 2009 As Known to the State of California to Cause Cancer Or Reproductive Toxicity, available at http://www.oehha.ca.gov/prop65/docs_admin/LClist080709.html. Many of these chemicals were listed because they had been identified by NTP and would therefore be subject to additional process (including scientific challenges by the public or a member of the SAB) under OEHHA's own regulations had they been proposed for listing under the authoritative body criterion. *See* Cal. Code Regs., tit. 27 § 25306(h), (i). Chemicals listed pursuant to the "state's qualified expert" criterion under subdivision (b) of section 25249.8 are subject to the most process – including public meetings of the Committees, consideration of written comments, and quorum voting. Cal. Code Regs., tit. 27 § 25302(d)-(f). As a practical matter, OEHHA has used all three rationales to consider various NTP chemicals, without any explanation for how it chooses one over the other.

[5] These regulations were promulgated by the Health & Welfare Agency, which was the lead agency for implementing Proposition 65 until 1991, when OEHHA assumed the role. (*People ex rel. Lungren v. Super. Ct.* (1996) 14 Cal.4th 294, 309-310; *Baxter Healthcare Corp. v. Denton* (2004) 120 Cal.App.4th 333, 346, fn. 2.) For simplicity, all references to the lead agency (without regard to dates) are to OEHHA.

[6] Final Statement of Reasons for Rule 25306 (formerly 12306) (hereinafter "25306 FSOR"), at 8 (emphasis added). The Court of Appeal for the Second Appellate District recently echoed this view of the purpose and intent of section 25249.8, subdivision (b). *Exxon Mobil Corp. v. Office of Environmental Health Hazard Assessment*, 169 Cal. App. 4th 1264, 1282 (2009).

Regulations implementing the qualified expert criterion established a Scientific Advisory Board ("SAB") consisting of two committees, the DART IC and the Carcinogen Identification Committee ("CIC"). Cal. Code Regs., tit. 27 § 25302(a). The SAB committees conduct a thorough review of the scientific evidence and determine "whether a chemical has been clearly shown, based upon scientifically valid testing according to generally accepted principles, to cause cancer or reproductive toxicity." Cal. Health & Saf. Code § 25249.8 (subd. b); Cal. Code Regs., tit. 27 § 25305(a)(1), (b)(1).

The SAB committees are required to receive and consider written materials and oral comments from interested members of the public. Once all such comments are considered, the committee has three choices on how to proceed:

> The Committee may render an opinion that the chemical has been clearly shown to cause cancer or reproductive toxicity, may fail to reach such a conclusion, or may defer the decision to a later meeting.[7]

Where the committee decides to defer, it is required to present an action plan and set a timetable for completion and reconsideration at a future meeting.[8] Otherwise, the chemical will not be added to the list.

2. The authoritative body criterion was not intended to bypass a decision already made by the DART IC.

Unlike the qualified experts criterion, the purpose of the authoritative body provision of section 25249.8, subdivision (b), was to conserve the panel's limited resources: "The apparent purpose of the authoritative bodies provision is to establish a streamlined process for the Panel." *Exxon*, 169 Cal. App. 4th at 1282 (citing 25306 SFOR, at 8). This approach "takes full advantage of the resources available through the Agency, *and conserves the energies of the Panel as the Act apparently intended.*" 25306 FSOR at 8 (emphasis added).

Further evidence of the primacy of the SAB is found in the regulations implementing the authoritative body criterion. Under both the statute and its implementing regulations, the

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[7] OEHHA, *Procedure for Prioritizing Candidate Chemicals for Consideration under Proposition 65 by the "State's Qualified Experts" Reproductive and Cancer Hazard Assessment Section Office of Environmental Health Hazard Assessment California Environmental Protection Agency*, at p. 13 (May 1997), available at http://oehha.ca.gov/prop65/pdf/priodoc.pdf, visited May 3, 2010 ("Prioritization Procedure").

[8] *Id.*

SAB retains control over which bodies are considered authoritative. Cal. Health & Saf. Code § 25249.8, (subd. b); Cal. Code Regs., tit. 27 §§ 25305(a)(2), (b)(2); 25306 (b).

Thus, the regulations also reserve to the SAB the right to set conditions on designations. 25306 FSOR at p. 27 ("If the Panel has discretion in designating authoritative bodies, it may condition its designation."). This was deemed necessary to guard against "uncontrolled" listings based on stale or invalid science:

> The science of hazard identification is not static. Studies relied upon today may, in the light of new data, be unreliable tomorrow. The identification of chemicals under the Act was intended by the voters to be based on scientific testing. It would make little sense to have chemicals listed under the Act where the data relied upon by an authoritative body is outdated and clearly contradicted by newer data. . . . [T]he regulatory implications of listing under the Act require a consideration of new data.

25306 FSOR at p. 20; see also *id.* at 22, 26-28. Therefore, at the recommendation of the SAB, the regulations establish procedures intended to ensure against the "uncontrolled listing" of chemicals that do not satisfy the statutory criteria. (25306 FSOR at 22, 26-28.)

Among these controls is a reservation of the SAB's authority to review of a chemical being considered for listing under the authoritative body criterion:

> Within 30 days following the publication of the notice, interested parties, including any member of the appropriate Committee, shall submit to the lead agency their written objections to the addition of the chemical to the list of chemicals known to the state to cause cancer or reproductive toxicity, along with any supporting documentation.

Cal. Code Regs., tit. 27 § 25306(i). Thus, where the public or a member of the DART IC comes forward with scientific evidence demonstrating that there is no "substantial evidence" that a chemical causes reproductive toxicity, it must be referred to the DART IC for further consideration:

> Objections shall be made on the basis that there is no substantial evidence that the criteria identified in subsection (e) or in subsection (g) have been satisfied. The lead agency shall review such objections. If the lead agency finds that there is no substantial evidence that the criteria identified in subsection (e)

> or in subsection (g) have been satisfied, *the lead agency shall refer the chemical to the appropriate Committee* to determine whether, in the Committee's opinion, the chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer or reproductive toxicity.

Cal. Code Regs., tit. 27 § 25306(i) (emphasis added). Section 25306(g) of the regulations for authoritative bodies listing requires that the body in question has formally identified a chemical as "causing reproductive toxicity" based on one or both of the following criteria:

> (1) Studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity, or
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> (2) Studies in experimental animals indicate that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible.[9]

In addition, OEHHA cannot list a chemical as a reproductive toxicant pursuant to the authoritative body criterion where "scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria of subsection (g), paragraph (1) or subsection (g), paragraph (2)." Cal. Code Regs., tit. 27 § 25306(h).

These controls serve the resource conservation purpose of the listing criteria set forth in section 25249.8, subdivision (b), by limiting the SAB's review to only those chemicals that would not pass muster if reviewed by the DART IC or the CIC under its own regulations.

The administrative record is replete with scientific evidence demonstrating that the considerable body of scientific research on BPA – including, but not limited to, the studies cited in the NTP Monograph – provide "no substantial evidence" that the chemical is "known to cause" reproductive or developmental toxicity. Comments and testimony submitted by GMA, the American Chemistry Council, and many others have already set forth this

[9] Cal. Code Regs., tit. 27 § 25306(g).

evidence. If anything, the information emerging after the DART IC's decision not to list BPA offers stronger support for that decision.[10] A decision to list BPA would flatly contradict this record.

B. Listing BPA Will Disrupt the Important Public Health Benefits that Canned Foods Deliver to Californians Every Day.

For all of the reasons above, interpreting the law to allow an administrative decision by OEHHA staff – which by its very nature is made without scientific input – to override the science-based decision of the experts on the DART IC is inconsistent with the language, purpose, and structure of the statute and its implementing regulations. Listing BPA also represents an indefensible public policy and health policy choice, placing such action even farther out of line with the intent of the California voters in adopting Proposition 65.

1. Cans made with epoxy resin liners provide frontline protection against food-borne illnesses.

Epoxy resins made with BPA have been used for over 30 years to improve the safety and quality of food and beverages by providing protective coatings for cans and the metal closures for glass jars. The use of these materials in can lining applications is necessary to protect public health. Without them, interactions between the metal and the can contents over time eventually leads to corrosion and contamination of the food by dissolved metals, and to formation of container defects that allow entry into the product of microorganisms that cause spoilage or illness.

Protective can linings slow down the rate of these interactions to such an extent that modern canned foods, even high acid foods like fruits and vegetables, can be counted on to retain their nutrition, quality, and consumer acceptability for years under a wide range of environmental and handling conditions. Epoxy resins promote safety because they stand up well to the temperatures necessary to sterilize foods and protect against microbes:

> Microbes are killed by heat. If food is heated to an internal temperature above 160°F, or 78°C, for even a few seconds this [is] sufficient to kill parasites, viruses or bacteria, except for the Clostridium bacteria, which produce a heat-resistant form called a spore. *Clostridium* spores are killed only at temperatures above boiling. This is why canned foods must be

[10] *See, e.g.*, Richard M. Sharpe, *Is It Time to End Concerns over the Estrogenic Effects of Bisphenol A?, Toxicological Sciences* 114, no. 1, at pp. 1-4 (2010) (hereinafter, "Sharpe") (analyzing studies conducted on BPA after the NTP Monograph and concluding that further concerns about reproductive toxicity are unwarranted).

> cooked to a high temperature under pressure as part of the canning process.[11]

As OEHHA heard at the April 20, 2010 forum, FDA records reveal no incidence of food-borne illness resulting from a failure of metal packaging *in over three decades.*[12] The use of BPA has been an indispensible component of that remarkable record.

For these reasons, and because they will not break and do not require additional water for preparation, canned foods are a staple component of emergency preparedness. They figure prominently on lists of items universally recommended by government and private response organizations for inclusion in emergency kits.[13] For these uses, fresh or frozen foods are not, and cannot be, substituted.

2. Canned foods are an important source of affordable, high-quality nutrition for all Californians.

Fresh meats, fruits, and vegetables are not readily available at all times of year. Even when fresh foods are available, their optimal nutritional content wanes quickly – often within days.[14] For some Californians living in economically depressed urban and rural areas, access to fresh foods is limited.[15] Transportation difficulties may prevent frequent trips to grocery

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[11] Center for Disease Control, Food Borne Illness: Frequently Asked Questions, at 8, available at http://www.cdc.gov/ncidod/dbmd/diseaseinfo/foodborneinfections_g.htm#howmanycases, visited May 6, 2010. For example, as the result of high-temperature sterilization techniques, botulism in canned foods "has disappeared in this country.")

[12] Testimony of Kathleen M. Roberts on behalf of the North American Metal Packaging Alliance, Inc., April 20, 2010.

[13] *See, e.g.,* Federal Emergency Management Agency, United States Department of Homeland Security, *Food and Water in an Emergency*, at pp. 2-3 (Aug. 2004), available at http://www.fema.gov/pdf/library/f&web.pdf (visited March 7, 2010); Los Angeles Fire Department, Emergency Preparedness (2008 Edition), available online at http://www.ci.la.ca.us/lafd/eqbook.pdf, at pp. 17 (list of foods for emergency kits); American Red Cross, *Talking About Disaster: Guide for Standard Messages: Stocking and Storing Food and Water Safely*, available online at http://www.redcross.org/images/pdfs/code/Storing_Food%20_and%20_Water_Safely.pdf (visited May 7, 2010), at pp. 1, 2; *see also*, San Francisco Chronicle, *Make Your Own Preparedness Kit*, available at http://www.sfgate.com/cgi-bin/article.cgi?f=/earthquakes/archive/ready.dtl (visited May 7, 2010).

[14] Joy C Rickman, Diane M Barrett and Christine M Bruhn, *Nutritional Comparison of Fresh, Frozen And Canned Fruits And Vegetables. Part 1. Vitamins C and B And Phenolic Compounds*, 87:6 J. Sci. Food & Agriculture, pp. 930-944 (April 30, 2007) (hereinafter, *Rickman*).

[15] *See, e.g., Access to Healthy Foods in Low-Income Neighborhoods: Opportunities for Public Policy*, Ruud Report, Rudd Center For Food Policy & Obesity, Yale University (Fall 2009), available

stores, which are often located far away, making reliance on fresh foods impractical.[16] And the fact that fresh fruits and vegetables generally cost more than "fast food" alternatives has been a source of substantial media attention and public health concern. Canned fruits and vegetables, and meals made from them, generally provide a practical, accessible, and affordable alternative.[17]

Moreover, canned foods retain comparable levels of nutrients over a longer period of time than fresh or frozen foods.[18] Thus, they can be purchased in bulk and remain available (i.e., safe, nutritious, and flavorful) for longer periods, thereby stretching their value to consumers.

It is no surprise, therefore, that consumers and institutions that cater to them – schools, hospitals, nursing homes, and others – have long depended on this reliable and affordable source of nutrition for a significant part of their diets.[19] According to consumption data collected between 1999 and 2008 by the United States Department of Agriculture ("USDA"), on average, canned goods make up approximately 27% of total fish and shellfish, 24% of vegetables, and 15% of fruits consumed nationwide.[20]

Guidelines published in 2005 by the U.S. Departments of Health and Human Services and Agriculture suggest that males and females increase their overall fruit and vegetable

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at
http://www.yaleruddcenter.org/resources/upload/docs/what/reports/RuddReportAccesstoHealthyFoods2008.pdf.

[16] Mark Vallianatos, Amanda Shaffer, Robert Gottlieb, *Transportation and Food: The Importance of Access, A Policy Brief of the Center for Food and Justice*, Urban and Environmental Policy Institute, at pp. 2-3 (October 2002).

[17] *See e.g.*, GMA, *Current WIC Authorized Fruit and Vegetable Formats by State* (summarizing an analysis of costs for fresh and frozen foods authorized for use under the WIC Program).

[18] *Rickman*, at p. 942; *see also*, Juliann Schaeffer, Canned Foods Make a Comeback, Today's Dietitian, Vol. 11 No. 3, p. 44 (March 2009), available at http://www.todaysdietitian.com/newarchives/td_030909p44.shtml.

[19] U.S. Department of Agriculture, Fact Sheet: *Meeting the Challenge of Rising Food Costs for Healthier School Meals*, available at http://www.fns.usda.gov/TN/Resources/DGfactsheet_challenge.pdf (recommending increased use of canned fruits and vegetables in school lunch programs as an affordable, nutritious alternative to more expensive fresh fruits and meats).

[20] Drawn from data available from the USDA Economic Research Service, *Food Availability (Per Capita) Data System*, available at www.ers.usda.gov/Data/FoodConsumption (visited May 6, 2010).

consumption to nine servings per day as part of a 2000-calorie diet.[21] The Guidelines explicitly recommend the use of canned fruits and vegetables to meet these goals.[22] The Centers for Disease Control and Prevention also includes canned fruits and vegetables in its "Five-A-Day" program, designed to encourage the consumption of fruits and vegetables.[23]

Canned foods are also an important part of programs aimed at providing nutritious meals to Californians in need of assistance. The California Women, Infants, and Children ("WIC") Program, for example, provides "WIC checks" with which approved foods may be purchased from grocery stores around the state.[24] Canned fruits, vegetables, fish, and infant formula are all included on the WIC list of approved foods.[25] Canned foods also figure prominently in food donations most sought by organizations that provide supplementary nutrition to economically pressed Californians.[26]

3. There is no proven alternative to BPA that will work for all products.

At the April 20, 2010 forum, a commenter appearing on behalf the Natural Resource Defense Counsel ("NRDC"), whose petition triggered this proposal by OEHHA, argued that alternatives to BPA are available. As evidence, the commenter pointed to a single food manufacturer's announcement that it intends to introduce BPA-free cans for a single product.

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[21] U.S. Department of Health and Human Services, U.S. Department of Agriculture, *Dietary Guidelines for Americans*, at 24 (2005), available at www.healthierus.gov/dietaryguidelines.

[22] *Rickman*, at 932.

[23] *Id.*

[24] *Id.* Canned fruits packed in water or juice are included, but those packed in syrup are not. Regular or low-sodium canned vegetables are allowed, but those packaged with added sugars, fats, or oils are excluded. A brochure describing foods included in the WIC program is available at http://www.cdph.ca.gov/programs/wicworks/WIC%20Foods/WICAuthorizedFoodListShoppingGuide-4-2010.pdf.

[25] *Id.*

[26] *See, e.g.*, "Most Wanted" Foods for the Food Bank of Contra Costa and Solano, available at http://www.foodbankccs.org/docs-pdfs/mostwantedfoodflyer-color.pdf; Top Foods Needed by the Marin Food Bank, available at http://www.marinfoodbank.org/topItems.html; San Francisco Food Bank, Food Dropoff Locations By Neighborhood, available at http://www.sffoodbank.org/give_food/dropoff_locations.html ("Our most-needed foods include rice and pasta, canned fruits and vegetables, tuna or other canned meats, soups and stews, peanut butter, and cereal. ***Please, do not deposit glass containers in our food-drive barrels.***")

Even assuming that this company's single-product goal is realized, the fact is that there is no across-the-board replacement for BPA in can linings at this time. Despite substantial ongoing industry efforts, a substance that offers the exceptional combination of toughness, adhesion, formability, chemical resistance, and affordability that has made BPA the industry standard since the 1970s, has not yet been found. Those research efforts continue with the goal and expectation of identifying a substitute.

Moreover, each food product formulation has its own set of demands. Technology that works for tomatoes may not work for canned peaches or canned tuna. Acidic and thermally processed foods present particular challenges. Once a BPA replacement candidate is identified, its performance must be ascertained over the entire shelf life of the food product and its safety, and regulatory approval and compliance with other applicable regulations must be assured before it can be commercially used. Retooling of can manufacturing and food processing equipment may be necessary. While a search for alternatives is underway, a universal conversion to non-BPA linings that will work for all canned foods is at least several years away.[27]

4. Listing BPA will discourage consumers from eating fruits, vegetables, and other canned foods and will reduce the availability of safe, affordable nutrition provided by these foods.

As OEHHA's Chief Deputy Director Allan Hirsch reminded the audience at the April 20, 2010 forum, Proposition 65 does not ban the use of a listed chemical in consumer products. However, as discussed below, listing BPA will subject foods packaged with even trace amounts of the chemical to expensive and burdensome litigation over Proposition 65's warning requirement, despite the fact that they pose no real risk to consumers. Because there is no reliable alternative available for BPA, these effects will be felt by companies that make and sell all foods on the canned food aisle of every supermarket. This result is contrary to a fundamental purpose of the statute.

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[27] Even companies that have switched to alternative technologies have discovered that eliminating low levels of BPA from packaged foods is difficult. *See* Lindsey Layton, *Alternatives to BPA Containers Not Easy for U.S. Foodmakers to Find*, Washington Post, Tuesday February 23, 2010, available at http://www.washingtonpost.com/wp-dyn/content/article/2010/02/22/AR2010022204830.html?referrer=emailarticle. For this reason, even the twelve-month statutory "grace period" for warnings about newly listed chemicals will not prevent these effects. Cal. Health & Saf. Code § 25249.10(b).

5. The scientific record is clear: any BPA present in canned foods poses no risk to consumers.

OEHHA is relying on high-dose animal studies cited in the September 2008 NTP Monograph as the basis concluding that NTP has formally identified BPA as a developmental toxicant:

> In 2008, the NTP-CERHR published a report on BPA (NTP-CERHR, 2008). This report concludes *that the chemical causes developmental toxicity at high levels of exposure*, and appears to satisfy the formal identification and sufficiency of evidence criteria in the Proposition 65 regulations[28]

OEHHA has received ample evidence from its own qualified experts on the DART IC and numerous commenters about why these studies do not provide a proper scientific basis for identifying BPA as a chemical "known to cause reproductive toxicity" under Proposition 65.[29] GMA agrees with the DART IC and other commenters on this point, and will not repeat these arguments here.

Separately, taking the NTP Monograph at face value, it makes clear that the adverse effects observed in the studies on which its conclusions were based occurred only at doses that are completely irrelevant to human exposure – doses thousands, or even hundreds of thousands of times above the worst case estimates of combined exposures to BPA from *all dietary sources*:

> The "high" dose effects of bisphenol A that represent clear evidence for adverse effects on development, i.e., reduced survival . . . , reduced birth weight and growth of offspring early in life . . . , and delayed puberty in female rats and male rats and mice . . . , ***are observed at dose levels that are more than 3,500- times higher than "worst case" daily intakes*** of bisphenol A in infants and children less than 6 years of

[28] OEHHA, *Request for Relevant Information on a Chemical Being Considered For Listing by the Authoritative Bodies Mechanism: Bisphenol-A* (Feb. 12, 2010), available at http://www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/requests_info/callinBPA021210.html (visited May 8. 2010) (emphasis added).

[29] *See* Transcript from July 15, 2009 Meeting of the State of California Office of Environmental Health Hazard Assessment Proposition 65 Developmental and Reproductive Toxicant Identification Committee (hereinafter "DART IC Tr."); May 13, 2010 comment letter submitted by Stan Landfair of McKenna & Aldridge LLP on behalf of the American Chemical Council.

> age . . . . ***The differences in exposures are much greater, more than 160,000- times different, when the high oral dose level is compared to estimated daily intakes for children ages 6 – 11 and adult women*** . . . .[30]

The most recent – and most definitive – work on the subject also describes the only levels found to produce any discernable reproductive effects in animals to be thousands of times below the worst-case human exposure scenario:

> The results from Ryan et al. (2009) are unequivocal and robust and are based on a valid and rational scientific foundation. They tell us that, in vivo in female rats, bisphenol A is an extremely weak estrogen—so weak that even at levels of exposure 4000-fold higher than the maximum exposure of humans in the general population there are no discernible adverse effects.[31]

These data, published in the leading toxicology journal, Toxicological Sciences, appeared after the NTP Monograph was published, raising further doubts about the legality and appropriateness of relying on the Monograph to make a decision about listing that is blinkered to the scientific and public health policy issues raised by such listing.

Whatever one's views of the merits of the NTP Monograph as far it goes, there is no remaining doubt that BPA levels reported in canned foods are safe, individually and collectively. As is well known, however, that does not immunize businesses that produce, sell, or serve foods containing a detectable amount of BPA from being sued under Proposition 65 if BPA is added to the list.

6. The fact that canned foods are safe will not prevent Proposition 65 lawsuits if BPA is listed.

Despite the mythology to the contrary, Proposition 65, by its plain language, prohibits a business from exposing an individual to a detectable amount of a Proposition 65 reproductive toxicant without first providing a warning that the product it makes, sells, or serves contains

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[30] National Toxicology Program, Center or the Evaluation of Risks to Human Reproduction, *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A* ("Monograph"), at 36 (emphasis added).

[31] *Sharpe*, at 1 (discussing Bryce C. Ryan, Andrew K. Hotchkiss, Kevin M. Crofton, and L. Earl Gray Jr., *In Utero and Lactational Exposure to Bisphenol A, in Contrast to Ethinyl Estradiol, Does Not Alter Sexually Dimorphic Behavior, Puberty, Fertility, and Anatomy of Female LE Rats*, *Toxicological Sciences* 114, no. 1 (2010): 133–48).

a chemical known to cause birth defects or other developmental or reproductive harm. Period. If it does not do so, it can be sued (and, given the vehemence with which organizations that regularly bring Proposition 65 enforcement actions have advocated this listing, there is little doubt there will be such lawsuits).

Proposition 65 enforcement actions, whether private or public, can be and have been brought not only against the manufacturers of the food packaging, but also against the food processors and their retailer or restaurant customers. Once sued – assuming that they have the financial resources to do so and that their downstream customers provide them the flexibility to defend the case – those companies may assert various affirmative defenses that are fact- and expert-intensive, take many years to litigate, and represent a substantial and unrecoverable expense to the defendants.[32]

From data considered in the NTP Monograph and that more recently published, it is plain that businesses whose products contain trace levels of BPA will be able to demonstrate that they satisfy the affirmative defense. But it is equally true that they and their customers can be sued under Proposition 65, forcing them to incur the burden and expense of discovery and to endure the adverse publicity which may accompany such lawsuits. The situation will be made worse if OEHHA lists BPA without a "safe harbor" MADL, rendering it impossible for companies whose products cause only a miniscule exposure to make a threshold showing and that could deter protracted litigation.[33]

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[32] Two of the recent acrylamide cases – *People v. Frito-Lay, Inc., et al.,* (Los Angeles Superior Court Case No. BC338956) and the related case of *Center for Education and Research on Toxics v. McDonald's Corp., et al.,* (Case No. BC 280980) – are illustrative. Eight separate experts offered evidence on subjects related to toxicology, risk assessment, and epidemiology to establish the proper warning threshold for acrylamide. Another six experts testified about acrylamide concentrations, test methodologies, consumption levels, and statistical analysis to determine the "average intake" by the "average consumer" of the french fries and potato chips at issue in that case. The trial court in that case found that factual disputes on each of these issues prevented resolution of the case on summary judgment. The Attorney General's case was filed in 2005 and was not fully resolved until 2008. The *CERT* case was filed in 2002 and resolved in 2007. Unlike plaintiffs, who can recover fees incurred in successfully prosecuting an enforcement action, Cal. Code Civil Proc. § 1021, companies cannot recover the cost of successfully defending such claims.

[33] A MADL would also make it easier for the California Attorney General to evaluate certificates of merit accompanying 60-day notices and determine whether to pursue enforcement or to intervene, as has happened on a few occasions, to dissuade a private plaintiff from pursuing meritless claims. *See, e.g.*, March 3, 2008 letter from then-Supervising Deputy Attorney General Edward G. Weil to JL Sean Slattery, David Lavine, and Larelei Paras, available at http://ag.ca.gov/prop65/pdfs/Lipstick_Letter-a.pdf (concluding that threatened claims against cosmetic companies lacked merit because the products did not exceed the safe harbor MADL for lead).

Thus, companies that have no means of eliminating BPA epoxy resins – and there currently is no commercially available substitute for most uses – face powerful pressure to put warnings on their products, *even where such a warning is not legally required, as the Court of Appeal has recognized*:

> Even though [the company] could demonstrate that its products do not pose a significant risk of causing cancer in humans, it had to provide a stigmatizing warning to the contrary – which could dissuade the public from using its products – or risk having to defend itself against being slapped with an injunction and costly civil penalties.

See Baxter Heathcare Corp. v. Denton, 120 Cal. App. 4th 333, 344 (2004). The result will be pointless litigation, widespread food warnings, and/or decisions to discontinue the production and sale of certain products in California. Any combination of these effects could reduce the availability of safe, nutritious, and useful food products to California consumers with *no* commensurate benefit.

The effect of such widespread defensive warnings on foods that are actually safe for consumers is contrary to the purpose and intent of Proposition 65. *Nicolle-Wagner v. Deukmejian*, 230 Cal. App. 3d 652, 660-661 (1991). In *Nicolle-Wagner*, the Court of Appeal upheld the regulation exempting chemicals that are "naturally occurring" in foods from the scope of the statute. *Id.*[34] The Court reasoned that grocers and other businesses, which bear the burden of proof under section 25249.10(c), would feel compelled to provide warnings to avoid litigation, even on foods that have been eaten safely "for thousands of years." *Id.*

> The Agency's final statement of reasons for section 12501 includes the observation that the "[a]bsence of such an exemption could unnecessarily reduce the availability of certain foods or could lead to unnecessary warnings, which could distract the public from other important warnings on consumer products." Since one of the principal purposes of the

[34] This reasoning is present elsewhere in Proposition 65's regulations as well. The so-called "cooking exception" to the default 10-5 no significant risk level for carcinogens in foods was also adopted in part to avoid indiscriminate defensive warnings on food products. Final Statement of Reasons for Cal. Code Regs., tit. 27 § 25703(b), at p. 5 ("Businesses may have considerable difficulty determining in any particular case whether cooking has resulted in the concentrations of listed chemicals which meet the 10-5 standard. Thus, businesses may feel compelled to provide a warning to protect them from liability in the event the level of risk does exceed 10-5. The confusion which would result if all purveyors of cooked or heat-processed foods provide a warning with their product, to avoid any potential liability, could be enormous.").

> statutes in question is to provide "clear and reasonable warning" of exposure to carcinogens and reproductive toxins, such warnings would be diluted to the point of meaninglessness if they were to be found on most or all food products.

Id. at 660-61. Stigmatizing canned foods by forcing them to carry warnings that they contain a chemical "known to the State to cause reproductive toxicity" will almost certainly lead to the same type of counterproductive overwarning described by the Court of Appeal in *Nicolle-Wagner*.[35]

C. OEHHA has Authority to Consider—And Avoid—the Adverse Consequences of Listing BPA.

At the April 20, 2010 forum, OEHHA heard from numerous commenters concerning the public health benefits delivered by epoxy resins formulated from BPA for use in food packaging and the negative effects that would occur as the result of requiring Proposition 65 warnings.[36] OEHHA's Senior Council acknowledged these comments, and asked for legal authority for the proposition that OEHHA can consider these facts in its decision whether to list BPA. As discussed below, OEHHA not only has legal authority for considering the consequences of its interpretation, it must do so to avoid acting in contravention of the voters' intent in adopting Proposition 65.

1. OEHHA has ample legal authority to consider the consequences of its actions in implementing Proposition 65.

OEHHA has cast its consideration of BPA as a ministerial application of the authoritative body criterion, over which it has little discretion. But what OEHHA has proposed is, in fact, a legal interpretation of how the three criteria for listing found in subsection (b) of section 25249.8 work together to achieve the goals of the statute. As such, the ordinary rules of statutory and regulatory construction apply. *Schmidt v. Found. Health,* 35 Cal. App. 4th 1702, 1710-11 (1995).

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[35] *See also, Dowhal v. SmithKline Beecham Consumer Health Care* (2004) 32 Cal. 4th 910, 933. In *Dowhal*, the California Supreme Court also refused to interpret the statute in such a way that would avoid federal preemption and require birth defect warnings for nicotine in smoking cessation products that might scare women away from products that could help them stop smoking. *Id.* ("The mere existence of the risk, however, is not necessarily enough to justify a warning; the risk of harm may be so remote that it is outweighed by the greater risk that a warning will scare consumers into foregoing use of a product that in most cases will be to their benefit.")

[36] Testimony of Patrick Leathers, on behalf of the Canned Food Institute; testimony of Kathleen Roberts on behalf of the North American Metal Packaging Alliance.

Administrative agencies, like courts, are to utilize common sense and to consider the policy implications and likely consequences when they implement their enabling statutes. *People v. Sup. Ct. ex rel Maury*, 145 Cal. App. 4th 473, (2006) ("[S]tatutes must be construed in a reasonable and common sense manner consistent with their apparent purpose and the legislative intent underlying them – one practical, rather than technical, and one promoting a wise policy rather than mischief or absurdity."); *City of Costa Mesa v. McKenzie*, 30 Cal. App. 3d 763, 770 (1973) ("[In] construing a statute the courts may consider the consequences that might flow from a particular interpretation. They will construe the statute with a view to promoting rather than to defeating its general purposes and the policy behind it.")

Such considerations – where necessary to fulfill the purpose of a law – may even trump the literal language of a statute or regulation. *Times Mirror Co. v. Super. Ct. of Sacramento County*, 53 Cal. 3d 1325, 1335, n.7 ("Moreover, while ambiguity is generally thought to be a condition precedent to interpretation, this is not always the case. 'The literal meaning of the words of a statute may be disregarded to avoid absurd results or to give effect to manifest purposes that, in light of the statute's legislative history, appear from its provisions considered as a whole.'"); *Silver v. Brown* (1966) 63 Cal.2d 841, 845; accord *Friends of Mammoth v. Board of Supervisors* (1972) 8 Cal.3d 247, 259 ("Once a particular legislative intent has been ascertained, it must be given effect 'even though it may not be consistent with the strict letter of the statute.'"); *County of Sacramento v. Hickman* (1967) 66 Cal.2d 841, 849, fn. 6.

OEHHA's apparent belief that it has no discretion over what evidence it may consider in deciding how to proceed with regard to BPA is therefore misplaced. Nothing in the authoritative body criterion of subdivision (b) of section 25249.8 or its implementing regulations requires OEHHA to ignore the consequences of its listing decisions.[37] Specifically, there is no question that OEHHA is authorized to structure and/or time its actions and decisions with regard to BPA in a way that minimizes these consequences.

2. At a minimum, OEHHA must not list BPA without having first adopted a final safe harbor MADL.

As discussed above and in comments submitted by other interested parties, there are numerous legal and scientific reasons that OEHHA must not list BPA pursuant to the authoritative body criterion. Whatever its decision regarding listing, *at a minimum*, OEHHA must not add BPA to the list without the simultaneous adoption of a final "safe harbor"

[37] In apparent recognition of the principle described here, OEHHA's Senior Counsel stated at the public forum that if OEHHA decided not to proceed with listing BPA under authoritative body criterion, OEHHA would not bother to refer the chemical to the DART IC for further consideration as provided in section 25306(i) of the authoritative body regulations because, as a practical matter, OEHHA already knows that the DART IC would not vote to list BPA.

warning threshold based "on evidence and standards of comparable scientific validity" to the high-dose studies "which form the scientific basis" for the listing of the chemical. Cal. Code Regs., tit. 27 § 25801(a). This is the only way to assure that warnings reflect the affirmative defenses/warning thresholds adopted by the voters rather than serving simply and solely as a guard against litigation. It would also diminish overwarning by bringing the application of the warning requirement into alignment with the actual risks found in evidence from the Monograph on which OEHHA relies.[38]

The adoption of a final MADL must occur simultaneously with listing BPA if it is to avoid the consequences set forth above. While chemicals added to the list do not become subject to its warning requirement for twelve months, Cal. Health & Saf. Code § 25249.10(b), the *effect* of adding a chemical to the list is immediate. Among other things, retailers will begin considering whether to continue to carry the relevant products, in light of the associated risks that they will be sued; government and quasi-governmental organizations, many of which have statutory or policy prohibitions on serving foods that pose a reproductive risk or are so labeled, may choose or be forced to consider alternative products; and so forth. The presence of a safe harbor threshold may reduce or eliminate such consequences. Given the abundance of recent data on the risk – or, rather, absence of risk – posed to human beings by BPA, the adoption of a safe harbor should be straightforward.

II. CONCLUSION

The use of BPA in the manufacture of food packaging has provided concrete health benefits to consumers for over 30 years. The combination of toughness, flexibility, and reliability of the epoxy resins made with BPA render it an important component of delivering safe, affordable, available, reliable nutrition to all Californians. Whether through warnings that prevent litigation but unnecessarily scare consumers, disappearance of certain products from the market, or the switch to less effective alternatives, listing BPA stands to render these important benefits unavailable.

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[38] That the low-dose studies about which NTP expressed concern are not of "comparable scientific validity" to the studies now cited by OEHHA as the basis for listing has been firmly established by studies published later than the Monograph. *See, e.g.*, Bryce C. Ryan, Andrew K. Hotchkiss, Kevin M. Crofton, and L. Earl Gray Jr., *In Utero and Lactational Exposure to Bisphenol A, in Contrast to Ethinyl Estradiol, Does Not Alter Sexually Dimorphic Behavior, Puberty, Fertility, and Anatomy of Female LE Rats*, *Toxicological Sciences* 114, no. 1 (2010): 133–48.; Sharpe, at 1–4 ("Ryan et al. (2009) and other similarly detailed studies in rodents more or less close the door on the possibility that bisphenol A is an environmental chemical to be concerned about because of its ER-mediated estrogenic activity.").

After more than ten years of controversy, it is clear that the scientific evidence does not support a conclusion that BPA causes developmental toxicity or other reproductive harm in humans:

> For more than a decade, there has been a heated controversy over whether or not the environmental chemical, bisphenol A, exerts adverse estrogenic effects in animal studies, and by extrapolation, in humans. In the present issue of Toxicological Sciences, Ryan et al. (2009) publish a detailed study that throws cold water on this controversy by showing complete absence of effect of a range of bisphenol A exposures perinatally on reproductive development, function, and behavior in female rats.[39]

Based on this record, it is time for OEHHA to close the books on BPA and to turn its attention and limited administrative resources to other issues:

> Fundamental, repetitive work on bisphenol A has sucked in tens, probably hundreds, of millions of dollars from government bodies and industry which, at a time when research money is thin on the ground, looks increasingly like an investment with a nil return.[40]

Should scientific evidence emerge in the future in support of a determination that BPA is a reproductive toxicant, OEHHA must, as it promised, return the chemical to the DART IC for further consideration. Until that time, the chemical should be returned to the pool of candidate chemicals. In the interim, the agency must ***not*** short-circuit the structure and intent of the statute by allowing a staff decision based on only part of the scientific record overrule the Committee's determination that BPA cannot be defined as a chemical "known to cause reproductive toxicity."

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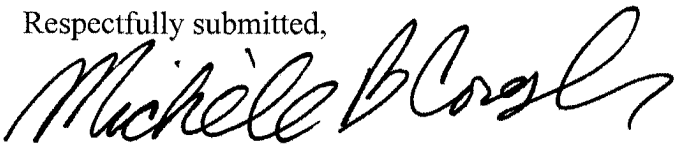
[39] Sharpe, at 1.

[40] *Id.* at 3.

Should OEHHA decide to proceed in spite of the litany of contrary legal, scientific, and procedural reasons not to, it must delay listing until it has adopted a final safe harbor MADL in order to avoid the overwarning and loss of safe, affordable, nutritious foods that canned foods represent.

Respectfully submitted,



Michèle B. Corash

cc: Dr. Joan Denton (jdenton@oehha.ca.gov)
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May 13, 2010

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Dear Ms. Oshita:

The Environmental Working Group (EWG) and the Natural Resources Defense Council (NRDC) strongly encourage OEHHA to list the chemical Bisphenol A (BPA) as a reproductive and developmental toxicant under Proposition 65, via the "authoritative bodies" mechanism (22 CCR § 12306). There is a robust body of science that supports the listing of BPA as a chemical that may pose risks to human reproduction and development.

As NRDC's petition demonstrated and as OEHHA recognized in proposing listing, BPA meets the requirements for listing under the authoritative bodies listing mechanism[1] as it has been formally identified by an authoritative body recognized by the State of California under Proposition 65 as causing reproductive toxicity (NRDC 2008).

Consistent with the rules guiding the Authoritative Bodies listing mechanism[2], BPA was the subject of a report published by the National Toxicology Program report in September 2008, which concluded that the chemical causes reproductive toxicity. NTP states there is "clear evidence of adverse developmental effects at 'high' doses of Bisphenol A in the form of fetal death, decreased litter size, or decreased number of live pups per litter in rats (≥ 500 mg/kg bw/day) and mice (≥ 875 mg/kg bw/day) reduced growth in rats (≥ 300 mg/kg bw/day) and mice (≥ 600 mg/kg bw/day), and delayed puberty in male mice (600 mg/kg bw/day), male rats (≥ 50 mg/kg bw/day) and female rats (≥ 50 mg/kg bw/day)."

[1] 27 Cal. Code Regs. § 25306(c).
[2] 27 Cal. Code Regs. § 25306(d)(1).

Moreover NTP also concluded, "These high dose effects of bisphenol A are not considered scientifically controversial and provide clear evidence of adverse effects on development in laboratory animals" (NTP 2008).

The two listing mechanisms are completely independent

Despite the chemical industry's argument to the contrary, the State Development and Reproductive Toxicity Identification Committee's (DART IC) determination not to list BPA in July 2009 has no bearing on listing under the Authoritative Bodies listing mechanism. As OEHHA has consistently asserted, the various listing mechanisms are independent of each other.[3] Accordingly, listing must proceed under any mechanism for which the listing requirements are met. BPA satisfies the requirements for listing under the authoritative body mechanism and thus must be listed, irrespective of the DART Committee's findings under a different listing mechanism.

In evaluating chemicals for listing as a reproductive toxin, the DART Committee is required to "[r]ender an opinion . . . as to whether specific chemicals have been clearly shown, through scientifically valid testing according to generally accepted principles, to cause reproductive toxicity." 27 Cal. Code Regs. § 25305(b)(1). The DART Committee thus determines, whether, in its opinion, a chemical has been "clearly shown" to cause reproductive toxicity.

On the other hand, the authoritative bodies mechanism *requires* listing by OEHHA if the chemical has "been formally identified by an authoritative body as causing . . . reproductive toxicity." *Id.* § 25306(c). A chemical is "formally identified" by an authoritative body when the "*lead agency*," i.e. OEHHA, determines that the chemical has been included on a list of chemicals causing reproductive toxicity issued by the authoritative body or is the subject of a report concluding that chemical causes reproductive toxicity or has otherwise been identified as causing reproductive toxicity by the authoritative body in a final document. *Id.* § 25306(d)(1). The Proposition 65 regulations define how a chemical is identified "as causing reproductive toxicity" for purposes of the authoritative bodies listing mechanism. A chemical "causes" reproductive toxicity if:

> *Studies in experimental animals indicate that there are sufficient data*, taking into account, the adequacy of the experimental design and other parameters such as, but not limited to, route of administration,

[3] Memorandum from Colleen Murphy, OEHHA Chief Counsel, to Members of the Carcinogen Identification Committee and DART Committee (July 20, 1998), at http://oehha.ca.gov/prop65/public_meetings/cicdart2.html; OEHHA, Request for Relevant Information on a Chemical Being Considered for Listing by the Authoritative Bodies Mechanism: Bisphenol-A, February 12, 2010, at http://oehha.ca.gov/prop65/CRNR_notices/admin_listing/requests_info/callinBPA021210.html; *see* OEHHA, Mechanisms for Listing and Delisting Chemicals Under Proposition 65, May 15, 2007, at http://www.oehha.ca.gov/prop65/policy_procedure/listde051007.html.

> frequency and duration of exposure, number of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, *indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biological plausible.*

27 Cal. Code Regs. § 25306(g)(2) (emphasis added).

Whether or not a chemical has or has not been previously considered by the DART Committee is irrelevant to whether the chemical meets the independent listing requirement of having been formally identified by an authoritative body as causing reproductive and developmental harm pursuant to Section 25306. The only time that DART becomes involved in the authoritative bodies listing process is if OEHHA determines that a chemical *does not* meet the requirements of Section 25306, in which case OEHHA procedure requires that the chemical be referred to the DART committee for evaluation. 27 Cal. Code Regs. § 25306(i). If the chemical *does* meet the Section 25306 requirements, DART has no role.

BPA easily meets the listing requirements via the authoritative bodies mechanism

This chemical easily meets the Proposition 65 standard for listing under the authoritative bodies mechanism based on the *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A* ("NTP Monograph") published by an authoritative body, the Center for the Evaluation of Risks to Human Reproduction of the National Toxicology Program of the U.S. Department of Health and Human Services. 27 Cal. Code Regs. § 25306(l)(3). First, contrary to American Chemistry Council's ("ACC") implication, *see* ACC Comments at 19-20, 22, the fact that the NTP Monograph did not directly state in the "Conclusions" section that BPA is a reproductive toxicant in humans or the precise categorization of the form of the monograph is immaterial. *See Exxon Mobil v. OEHHA,* 169 Cal. App. 4th 1264, 1281-82 (2009) ("We do not agree . . . that the authoritative body's report is the only permissible evidence that the authoritative body made the regulatory findings. . . . So long as OEHHA can conclude, on the basis of the entire record before it, that the authoritative body made the regulation 25306(g) findings, it may list a chemical pursuant to the authoritative body provision of the statute.").

Second, there is more than sufficient basis in the NTP Monograph for OEHHA to conclude that NTP-CERHR formally identified BPA as "causing reproductive toxicity." OEHHA's regulations make clear that animal studies showing that it is "biologically plausible" for BPA to cause harmful effects in humans are sufficient to establish that BPA "causes" reproductive toxicity. *See also Exxon Mobil*, 169 Cal. App. 4th at 1288 ("Nothing in the regulation thus precludes OEHHA from concluding that there is substantial evidence of biological plausibility based solely on animal studies—to the contrary, the regulation appears to contemplate extrapolation from animal studies to humans.").

That criterion is easily met for BPA. The finding that animal studies show "clear evidence of development effects at high doses" indicates that it is "biologically plausible" for BPA to have adverse effects in humans, in light of the generally accepted toxicological assumption that a chemical that causes developmental harm in experimental animals will cause similar harm in humans. *See id.* at 1288-89 (citing EPA guidance and referring to the record in the case). The NTP monograph relies on the high-dose studies as evidence supporting the conclusion that BPA can "possibly" affect "human development and reproduction," thus explicitly recognizing the biological plausibility of adverse effects in humans from BPA. NTP Monograph, NTP Brief on Bisphenol A at 6-7, NIH Publication No. 08-5994 (September 2008). The NTP monograph also relies on animal studies, including both high- and low-dose studies, to reach an explicit "conclusion" regarding the "possibility that human development or reproduction might be effected by exposure to bisphenol A"— stating that there is "some concern for adverse effects" vis a vis "development toxicity for fetuses, infants & children (effects on the brain, behavior and prostate gland)." *Id.* at 7-8, 38. The NTP Monograph relies on a variety of evidence, including evidence of adverse developmental effects in animal studies involving levels of exposure comparable to human exposures:

> In addition to effects on survival and growth seen at high dose levels of bisphenol A, a variety of effects related to neural and behavior alterations, potentially precancerous lesions in the prostate and mammary glands, altered prostate gland and urinary tract development, and early onset of puberty in females have been reported in laboratory rodents exposed during development to much lower doses of bisphenol A (≥ 0.0024 mg/kg bw/day) that are more similar to human exposures.

Id. at 7. Thus, the NTP Monograph states that "the possibility that bisphenol A may alter human development cannot be dismissed." *Id.*

These statements meet the requirements for listing BPA under Section 25306. The record amply supports OEHHA's proposed conclusion that the NTP-CERHR has formally identified BPA as causing reproductive toxicity for the purposes of Section 25306 and the authoritative bodies mechanism.

OEHHA has listed chemicals with similar toxicity profiles using this mechanism.

As of 2001, OEHHA has used the Authoritative Bodies mechanism to identify roughly half of all listed Prop 65 chemicals (Denton 2001). The National Toxicology Program (NTP), specifically its Center for the Evaluation of Risks to Human Reproduction (CERHR), is recognized as an authoritative body for the listing of reproductive toxins under Proposition 65. 27 Cal. Code Regs. § 25306(l)(3). CERHR determinations have been used as triggers to seven list chemicals, including five phthalates (diisodecyl phthalate - DIDP in 2007, Di(2-ethylhexyl)phthalate (DEHP) in 2003, Butyl benzyl phthalate (BBP) in 2005, Di-*n*-hexyl phthalate (DnHP) in 2005, and dibutyl phthalate - DBP in 2005) and 1-bromopropane in 2003 and 2-Bromopropane (2-BP) in 2005. Appendix 1 compares the determinations reached by the NTP CERHR for each of these

chemicals in terms of exposure, effects on reproduction, level of concern, weight of evidence and overall conclusions. BPA is also listed in this table for comparison to demonstrate that the determinations reached on BPA are clearly consistent with those reached on other chemicals listed on Prop 65 by the authoritative bodies mechanism recognizing the NTP CERHR analyses.

Other entities designate BPA as a reproductive and developmental toxicant

The NTP determination is in line with other governments and regulatory agencies. The European Chemicals Bureau (ECB) has classified Bisphenol A as a Category 3 reproductive toxicant; that is a substance which causes concern for human fertility based on sufficient evidence of reproductive toxicity in experimental animals (ECB 2003). The Canadian government has listed BPA as a "Toxic Substance" adding it to its "Schedule 1" list, which allows agencies to develop risk management tools under the Canadian Environmental Protection Act (Canada 2009).

More recently the U.S. Environmental Protection Agency determined that BPA is a chemical of concern, publishing an Action Plan to assess and avert exposure to the chemical. In its justification EPA stated: "Because BPA is a reproductive, developmental, and systemic toxicant in animal studies and is weakly estrogenic, there are questions about its potential impact particularly on children's health and the environment" (EPA 2010). Like other Agencies EPA found strong evidence of high-dose toxicity. "There is general agreement that BPA is a reproductive and developmental toxicant at doses in animal studies of > 50 mg/kg-bw/day [delayed puberty] > 235 mg/kg-bw/day [reduced growth or bodyweight and testicular damage]; and > 500 mg/kg-bw/day [fertility, estrous cycling and survival]. Systemic effects were observed at doses above 5 mg/kg-bw/day" (EPA 2010).

Recent findings from an American Chemistry Council-sponsored BPA study confirmed body weight reductions at 50 and 130 mg/kg-d (for gestation and lactation) (Stump 2010).

BPA exhibits "low dose" toxicity

In addition to the clear evidence of reproductive and developmental damage at higher doses, there is also extensive evidence suggesting toxicity at much lower exposure levels. NTP acknowledged the strength of this evidence and raised concern about the safety of current exposures to the developing fetus, neonate, and small child, which occur at lower doses. NTP determined there is "*some concern* for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to Bisphenol A" (NTP 2008).

In the United States, both OEHHA and the NTP identify studies showing loss of sexually dimorphic behavior as the strongest and most consistent findings of developmental toxicity. NTP highlighted 7 high quality studies administering low doses of BPA orally. OEHHA adds that the effects noted in sex-differentiated behavioral studies are

particularly well designed and performed, consistent with known impacts of estrogenic chemicals, and focused on gestational exposures, which are relevant to the State's focus on post-natal exposures (OEHHA 2009).

In recent comments to the FDA, John Bucher, the Associate Director for the National Toxicology Program, stated that the "collected results" of low-dose studies demonstrate adverse findings to human health and urged FDA to drop its claim of No Adverse Effects at levels 5 mg/kg-day. He predicted that studies using oral dose levels of 10 ug/kg-d will be considered as the lowest doses that cause harm (Bucher 2009).

Since the NTP CERHR report was published, there have been additional studies published which support the conclusions of the report that there is "some concern" for the impacts of low dose exposure to BPA on brain and behavior. Studies of non-human primates and now humans have found alterations in brain development and behavior that support the previously described rodent data linking neurodevelopmental harm to BPA exposure.

In non-human primate studies BPA was found to alter estradiol-induced synaptogenesis in pre-frontal cortex and hippocampus of non-human primates (Leranth 2008). This study examined the impacts of daily exposure to the current reference dose, on estradiol-induced synapse formation in the hippocampus and prefrontal cortex of a nonhuman primate model. BPA was found to completely abolish the synaptogenic response to estradiol. Because remodeling of synapses may play a critical role in cognition and mood, the ability of BPA to interfere with synapse formation has profound implications. This study is the first to demonstrate an adverse effect of BPA on the brain in a nonhuman primate model.

In a second study of non-human primates, BPA was found to alter sexually dimorphic behavior. Infant male monkeys exposed to BPA at low doses behaved more like infant females (Nakagami 2009). This study is in agreement with rodent models which have demonstrated alterations in sexually dimorphic behavior after BPA exposure.

Now, a study in toddlers has found that girls whose mothers were exposed to higher levels of BPA during pregnancy were more aggressive and hyperactive at age 2 than other girls who were exposed to lower levels of BPA (Braun 2009).

Animal models and now primate studies have demonstrated exposure to BPA during vulnerable periods of development interferes with development of the brain and dopaminergic signaling which could impact behavior and learning.

Human exposure to BPA is widespread

Finally, it is important to note that the listing of BPA under Proposition 65 via the authoritative bodies mechanism has some urgency due to the mounting evidence of nearly universal exposure to BPA within the general population. A recent review summarized BPA detections in more than 80 published biomonitoring studies. These

include the detection of toxicologically-active, unconjugated BPA in most studies analyzing human blood samples (Vandenberg 2010). In December 2009, EWG released the first U.S. results detecting BPA in umbilical cord blood samples. EWG found BPA in 9 or 10 samples analyzed, with a geometric mean of 2.8 ng/g in serum, and a maximum value of 8.6 ng/g (EWG 2009). BPA is widely detected in urine samples for more than 95% of the general population. In addition the chemical is found in amniotic fluid, follicular fluid, breast milk, and urine samples from newborn babies in Neonatal Intensive Care units (Vandenberg 2010, Calafat 2009).

Conclusion

In conclusion, the high-dose evidence of BPA toxicity, and formal identification by NTP-CERHR as a reproductive toxicant offers sufficient evidence for listing BPA under Proposition 65. Actions by the European Chemicals Bureau and Canadian government support these determinations. In addition to the high-dose evidence, OEHHA should carefully consider the results of low-dose toxicity studies, as experts suggests that BPA may be toxicologically active as levels that overlap current exposures for newborns, children and adults.

Thank you for considering these comments.

Sincerely,

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References:

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Appendix 1. Chemicals listed on Prop 65 through the authoritative body mechanism as evaluated by NTP CERHR							
Chemical	**On Prop 65 List?**	**Are People Exposed?**	**Can it Affect Human Development or Reproduction?**	**Are Current Exposures Cause for Concern?**	**Weight of Evidence in Humans**	**Weight of Evidence in Laboratory Animals**	**NTP Conclusions about possible adverse effects to human development or reproduction might be adversely affected**
Di-(2-ethylhexyl) Phthalate (DEHP)	Yes	Yes	Probably	Yes	Developmental and Reproductive Toxicity → Insufficient evidence for a conclusion	Developmental and Reproductive Toxicity → Clear evidence of adverse effects	Critically ill male infant → Serious concern for adverse effects
							Male infants younger than one year → Concern for adverse effect
							Male offspring of women undergoing certain medical treatments during pregnancy → Concern for adverse effects
							Male offspring exposed during pregnancy → Some concern for adverse effects
							Male children older than one year → Some concern for adverse effects
							Reproduction in adults →Minimal concern for adverse effects

Chemical	On Prop 65 List?	Are People Exposed?	Can it Affect Human Development or Reproduction?	Are Current Exposures Cause for Concern?	Weight of Evidence in Humans	Weight of Evidence in Laboratory Animals	NTP Conclusions about possible adverse effects to human development or reproduction might be adversely affected
Butyl Benzyl Phthalate	Yes	Yes	Probably	Probably not	NA	Developmental Toxicity → Clear evidence of adverse effects	Developmental effects → Minimal concern for adverse effects
					NA	Reproductive Toxicity (Males) → Some evidence of adverse effects	Reproductive effects (adult males) → Negligible concern for adverse effects
					NA	Reproductive Toxicity (Females) →Limited evidence of adverse effects	Reproductive effects (adult females) → Insufficient hazard and/or exposure data
Di-n-Butyl Phthalate (DBP)	Yes	Yes	Probably	Possibly	NA	Developmental and Reproductive Toxicity → Clear evidence of adverse effects	Developmental effects at high exposures → Some concern for adverse effects
							Developmental effects → Minimal concern for adverse effects
							Reproductive effects in adults → Negligible concern for adverse effects

Chemical	On Prop 65 List?	Are People Exposed?	Can it Affect Human Development or Reproduction?	Are Current Exposures Cause for Concern?	Weight of Evidence in Humans	Weight of Evidence in Laboratory Animals	NTP Conclusions about possible adverse effects to human development or reproduction might be adversely affected
Di-isodecyl phthalate (DIDP)	Yes	Yes	Possibly	Probably not	NA	Developmental Toxicity → Clear evidence of adverse effects	Developmental effects → Minimal concern for adverse effects
						Reproductive Toxicity → Some evidence of no adverse effects	Reproductive effects → Negligible concern for adverse effects
					NA	Reproductive Toxicity → Limited evidence of no adverse effects	
Di-n-Hexyl Phthalate (DnHP)	Yes	Yes	Possibly	Unknown	NA	Developmental Toxicity → Limited evidence of adverse effects	Development and Reproduction → Insufficient hazard and/or exposure data
					NA	Reproductive Toxicity → Clear evidence of adverse effects	
					NA	Reproductive toxicity → Some evidence of no adverse effects	

Chemical	On Prop 65 List?	Are People Exposed?	Can it Affect Human Development or Reproduction?	Are Current Exposures Cause for Concern?	Weight of Evidence in Humans	Weight of Evidence in Laboratory Animals	NTP Conclusions about possible adverse effects to human development or reproduction might be adversely affected
1-Bromopropane	Yes	Yes	Possibly	Possibly	NA	Developmental and reproductive toxicity → Clear evidence of adverse effects	Developmental and reproductive effects (Exposure at 18 to 381 ppm) → Serious concern for adverse effects
							Developmental and reproductive effects (Exposure at 0.04 to 0.63 ppm) → Minimal concern for adverse effects
2-Bromopropane	Yes	Yes	Probably	Possibly	NA	Reproductive Toxicity → Clear evidence of adverse effects	Reproductive Toxicity (Upper end of Occ. Exp) → Some concern for adverse effects
						Developmental toxicity →Limited evidence of adverse effects	Reproductive Toxicity (Lower end of Occ. Exp) → Minimal concern for adverse effects
							Developmental Toxicity → Insufficient hazard and/or exposure data

Chemical	On Prop 65 List?	Are People Exposed?	Can it Affect Human Development or Reproduction?	Are Current Exposures Cause for Concern?	Weight of Evidence in Humans	Weight of Evidence in Laboratory Animals	NTP Conclusions about possible adverse effects to human development or reproduction might be adversely affected
Bisphenol A (BPA)	No – but meets the criteria for listing	Yes	Possibly	Possibly	Developmental and reproductive toxicity → Insufficient evidence for a conclusion	"High" dose developmental toxicity → Clear evidence of adverse effects	Developmental toxicity for fetuses, infants & children (effects on the brain, behavior and prostate gland) → Some concern for adverse effects
						Reproductive toxicity → Some evidence of adverse effects	Developmental toxicity for fetuses, infants & children (effects on mammary gland & early puberty in females) → Minimal concern for adverse effects
						"Low" dose developmental toxicity → Limited evidence of adverse effects	Reproductive toxicity in workers → Minimal concern for adverse effects
							Reproductive toxicity in adult men and women → Negligible concern for adverse effects
							Fetal or neonatal mortality, birth defects, or reduced birth weight and growth → Negligible concern for adverse effects

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August 10, 2011

VIA U.S. MAIL AND EMAIL

George Alexeeff, Ph.D.
Acting Director
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Hazard Assessment
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Sacramento, California 95812

RE: SUPPLEMENTAL RESPONSE TO REQUEST FOR RELEVANT INFORMATION ON BISPHENOL A

Dear Dr. Alexeeff:

On behalf of our client the Polycarbonate/BPA Global Group of the American Chemistry Council ("ACC"), we are submitting this supplemental response to OEHHA's February 12, 2010 Request for Relevant Information on bisphenol A ("BPA"). This supplemental response should be considered together with ACC's detailed written submittals dated May 13, 2010 and September 15, 2009.

In the February 2010 Request for Relevant Information, OEHHA incorrectly stated that the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction ("NTP-CERHR") had "concluded" that there is clear evidence of adverse developmental effects in laboratory animals at 'high' levels of exposure. In both the Request for Relevant Information and in public meetings since that Request was issued, OEHHA has made it clear that this purported "conclusion" is based on "Figure 2b" of the NTP-CERHR "Brief" which is a component of the 2008 Monograph on BPA.

In both prior submittals, ACC presented multiple reasons why BPA should not be considered for listing, and does not meet the criteria for listing as a developmental or reproductive toxicant under Proposition 65's "authoritative bodies mechanism" based upon the conclusions stated in the September 2008 "Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A" published by the NTP-CERHR. Prominent among those

reasons, although by no means the only reason, was that NTP-CERHR Monographs evaluate risk in a way that is inconsistent with the hazard-based requirement for listing under Proposition 65. It is well established that Proposition 65 is purely a hazard-based system that does not take exposure or risk into account in listing decisions. From its beginning, though, NTP-CERHR's purpose was to reach qualitative risk-based conclusions that consider both hazard and exposure information and are expressed in the form of "levels of concern." These are very different approaches and the NTP-CERHR approach is incompatible with the strict Proposition 65 requirement to base listing decisions only on hazard considerations.[1]

The distinction between NTP-CERHR's risk-based approach and the hazard-based approach under Proposition 65 was expressed clearly by NTP's leaders in a recent announcement of the formation of the new NTP Office of Health Assessment and Translation:

> *"To our knowledge, CERHR was the only resource of its kind, producing evaluations that considered toxicity findings in the context of current human exposures to derive* ***"level-of-concern" conclusions****. This qualitative integration step is what distinguished CERHR documents from more traditional hazard evaluations prepared by other agencies."*[2]

The NTP-CERHR level-of-concern conclusions are expressed on a standardized five-level scale that ranges from "negligible" to "high concern." Following this approach, the NTP-CERHR Monograph on BPA reached seven level-of-concern conclusions that qualitatively characterize different combinations of exposure and reproductive or developmental toxicity end points. Notably, the most severe conclusion reached by NTP-CERHR was "some concern" for certain developmental effects, which is the midpoint on the level-of-concern scale. In addition to being a risk-based conclusion, which is inherently not suitable for Proposition 65 purposes, the equivocal nature of the conclusion does not satisfy Proposition 65's "clearly shown" standard.

As ACC has argued at length in both its prior submittals, it is invalid and unsupportable for OEHHA to ignore the actual – and equivocal – **conclusions** of the NTP-CERHR Monograph while relying upon Figure 2b, which is described in the Monograph itself not as NTP's "conclusions" but rather, as a summary of the "weight of evidence" in certain laboratory animal studies.[3] We will not restate ACC's prior arguments here but, in this supplemental submission,

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[1] As also discussed in our prior submittals, the Proposition 65 hazard considerations are restricted only to developmental effects that result from pre-natal exposure. In contrast, NTP-CERHR has no such restriction and their risk-based conclusions are based on all relevant studies with pre-natal exposure, post-natal exposure or both.

[2] See http://ehp03.niehs.nih.gov/article/fetchArticle.action?articleURI=info%3Adoi%2F10.1289%2Fehp.1103645 (emphasis added)

[3] Figure 2b, at p. 8 in the NTP Brief is captioned "The **weight of evidence** that bisphenol A causes adverse developmental or reproductive effects in **laboratory animals**." (Emphasis added.) By contrast, Figure 3 on that

(footnote continued on next page)

we do want to draw OEHHA's attention to certain facts involved in NTP-CERHR's own peer-review process. In this process, NTP's "Board of Scientific Counselors" ("BSC") examines the qualitative risk-based level-of-concern conclusions in the draft Brief and then votes to accept, reject or modify these conclusions.[4] Significantly, the BSC does not vote either on the entire draft Brief or on any other specific part of the draft Brief, nor does it otherwise endorse any specific parts of the draft Brief beyond the level-of-concern conclusions. This process confirms that NTP-CERHR's **conclusions** are unambiguously the level-of-concern conclusions that are voted on by the BSC.

The draft NTP Brief on BPA was released for public comment on April 15, 2008 (Minutes, June 11 – 12, 2008, at 5). On June 11, 2008, NTP's BSC met in Research Triangle Park, North Carolina to review the draft NTP Brief on BPA. NTP's charge to the BSC and additional *ad hoc* reviewers was:

> To determine whether the scientific information cited in the draft NTP Brief on BPA is technically correct, clearly stated, and supports the NTP's **conclusions** regarding the potential for BPA to cause adverse reproductive and developmental effects in exposed humans (Minutes at 19; Peer Review Comments and NTP Response at 2) (emphasis added).

The June 11, 2008 BSC review of the draft NTP Brief on BPA began with an overview of the CERHR process and of the draft Brief itself, followed by general comments from the BSC and oral public comments. Next, Dr. Kristina Thayer of NIEHS presented the detailed scientific evidence supporting the NTP's (draft) **conclusion** on each of the topic areas covered in the draft Brief (Minutes at 5). Dr. Thayer's presentation included among other things a Figure summarizing the "weight of the evidence that BPA causes adverse developmental or reproductive effects in laboratory animals" that is essentially identical to Figure 2b in the final NTP Monograph. Dr. Thayer described the reasons for NTP's decision on assigning a weight of evidence for each endpoint. Following each section of her presentation, the *ad hoc* and BSC members discussed the topic of that section. Upon completion of the discussion of all topics, the BSC voted on the proposed **conclusions** of the draft Brief (Minutes at 16). See "Actions on the draft NTP Brief by the NTP Board of Scientific Counselors"; see also "Bisphenol A Peer Review Comments and NTP Response."

(footnote continued from previous page)

same page is captioned "NTP **conclusions** regarding the **possibilities** that **human** development or reproduction **might** be effected [sic] by exposure to bisphenol A." (Emphasis added). As noted above, Figure 3 states "levels of concern" and the highest level of concern indicated for bisphenol A is "some concern."

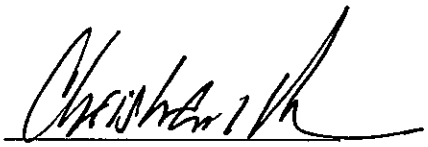
[4] All the documents referred to in the following discussion can be found on NTP's website at this link: http://ntp.niehs.nih.gov/?objectid=720164F2-BDB7-CEBA-F5C6A2E21851F0C4.

A review of the cited documents clearly demonstrates what ACC has consistently asserted: the **conclusions** of the NTP Brief are its "levels of concern" for each endpoint, the most serious of which was "some concern." The scientific evidence relevant to each endpoint and decision on level of concern was considered by the BSC as they decided how to vote on each **conclusion**, but the evidence itself was not considered a "conclusion" and was not the subject of any votes. This specifically includes the predecessor version of Figure 2b in the final NTP Brief – it was presented, it was considered, but it was not an NTP "conclusion" requiring a vote and it was not the subject of a vote, in contrast to NTP's actual level-of-concern **conclusions**.

In view of this additional documentary evidence that Figure 2b clearly was not considered a **conclusion** by NTP-CERHR itself – the authoritative body – or by the NTP BSC, which reviewed the draft NTP-CERHR Brief, we respectfully submit that OEHHA should reconsider its previously stated position on this point and agree that NTP-CERHR did not **conclude** that BPA is a developmental toxicant and thus, that the NTP-CERHR Brief does not "formally identify" BPA as a developmental toxicant.

Respectfully submitted,

Stanley W. Landfair



Christian Volz

SWL/CV/gmp

cc: Steven G. Hentges, Ph.D.
F. J. Murray, Ph.D.

SF:27483740.4

May 13, 2010

Via U.S. Mail and Email

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
Post Office Box 4010, MS-19B
Sacramento, CA 95812-4010

Re: Response to Request for Relevant Information on Bisphenol A

Dear Ms. Oshita,

Please find attached written comments from the Polycarbonate/BPA Global Group of the American Chemistry Council in response to the OEHHA Request for Information of February 12, 2010 (Request for Relevant Information on a Chemical Being Considered for Listing by the Authoritative Bodies Mechanism: Bisphenol-A). The Polycarbonate/BPA Global Group consists of the leading global manufacturers of bisphenol A and polycarbonate plastic, which for many years have supported and conducted scientific research to understand whether bisphenol A has the potential to cause health or environmental effects and to support scientifically sound public policy.

As indicated by the signatures at the end of the attachment, the comments were prepared jointly with Stanley Landfair and Christian Volz (McKenna Long & Aldridge), Dr. F. Jay Murray (Murray & Associates), and Dr. Arthur Lawyer (Technology Sciences Group Inc.).

Please do not hesitate to contact me if I can be of further assistance to clarify any of the information provided or if additional information is needed. I can be reached at (703) 741-5588 or by e-mail at steve_hentges@americanchemistry.com.

Regards,

Steven G. Hentges, Ph.D.
Executive Director
Polycarbonate/BPA Global Group

AMERICAN CHEMISTRY COUNCIL

POLYCARBONATE / BPA GLOBAL GROUP

RESPONSE TO
REQUEST FOR RELEVANT INFORMATION
ON A
CHEMICAL BEING CONSIDERED FOR LISTING
BY THE AUTHORITATIVE BODIES MECHANISM:
BISPHENOL A

F. Jay Murray, Ph.D., D.A.B.T.
MURRAY & ASSOCIATES

Arthur L. Lawyer, Ph.D.
TECHNOLOGY SCIENCES GROUP INC.

Christian Volz
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MAY 13, 2010

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I. INTRODUCTION

The American Chemistry Council and its Polycarbonate/BPA Global Group ("ACC") and the undersigned counsel and consultants to ACC hereby submit this Response to OEHHA's February 12, 2010 Request for Relevant Information on a Chemical Being Considered for Listing by the Authoritative Bodies Mechanism: Bisphenol A (hereinafter referred to as the "Request"). The Request follows a petition by the Natural Resources Defense Council ("NRDC"), filed just moments after the Developmental and Reproductive Toxicant Identification Committee ("DART IC") voted unanimously that Bisphenol A ("BPA") should not be listed under Proposition 65,[1] demanding that BPA be listed under the Authoritative Bodies Mechanism on the theory that the NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A ("NTP-CERHR Monograph" or "Monograph") "concludes" that BPA causes reproductive toxicity.[2] Our September 15, 2009 response to that petition and our June 30, 2009 submission to the DART IC are incorporated as part of this Response, and appear as Attachments 1 and 2.[3]

II. BACKGROUND

Any consideration of BPA under the Authoritative Bodies Mechanism must take into account the unanimous decision of the DART-IC ***not*** to list BPA. Indeed, even the Request points that out. The Request omits, however, that seven members of the DART IC evaluated the same NTP-CERHR Monograph that OEHHA now identifies as a basis for listing, including all of the scientific testing data and studies discussed therein. After careful consideration of this information, the DART IC deliberated in open forum for nearly an hour, and voted as follows:

QUESTIONS TO DART IC	NO	YES
Has BPA been clearly shown to cause developmental toxicity?	7	0
Has BPA been clearly shown to cause reproductive toxicity (female)?	7	0
Has BPA been clearly shown to cause reproductive toxicity (male)?	7	0

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[1] Proposition 65 is the popular name for California's Safe Drinking Water & Toxic Enforcement Act of 1986, Cal. Health & Safety Code § 25249.5 *et seq.*

[2] NTP-CERHR is the acronym for the Center for the Evaluation of Risks to Human Reproduction, operated by the National Toxicology Program under the auspices of the U. S. Department of Health and Human Services.

[3] On April 9, 2010, we submitted two requests to OEHHA pursuant to the Public Records Act ("PRA") for OEHHA documents that we believe are pertinent to the Request and to this Response. As of May 13, 2010, the date this Response is being filed, we have received no documents or any formal response to our PRA requests, and no explanation except for a statement from OEHHA's PRA coordinator that responsive documents are "confidential." We respectfully reserve the right to supplement this Response on the basis of documents responsive to our PRA requests, when they are provided.

In other words, seven members of the DART IC, who serve as the statutorily appointed "State's Qualified Experts," concluded ***unanimously*** that BPA should ***not*** be listed.

The information considered by the DART IC in reaching this conclusion included a comprehensive Hazard Identification Document ("HID"), prepared by OEHHA in May 2009 to "address the reproductive toxicity of [BPA]," and to "provide information on whether this compound should be identified as known to cause reproductive toxicity under Proposition 65."[4] The HID acknowledged the Monograph and the fact that NTP-CERHR was an "authoritative body" for purposes of Proposition 65. OEHHA pointed out that the Monograph included studies that identified "clear evidence of 'high' dose developmental toxicity of BPA ***in laboratory animals***," acknowledged that the agency staff had reviewed those studies, incorporated the Monograph as part of the HID and then referred the matter to the State's Qualified Experts, explaining that "the most efficient, timely and appropriate mechanism for consideration of BPA for listing under Proposition 65 was to bring it forward for consideration by the DART IC."[5]

At the July 15 public meeting, OEHHA identified and summarized all of the relevant data, including the data in the NTP-CERHR Monograph and all of the data that OEHHA now identifies as the potential basis for listing. At no place in its HID or at any time during this presentation did OEHHA or any member of its staff indicate or offer any opinion that the NTP-CERHR Monograph, the NTP Brief on BPA (2008) ("NTP Brief"), or the NTP Expert Panel Report concluded that BPA is a reproductive toxicant within the meaning of Proposition 65.[6,7] It defies both legislative intent and logic to assert that the exact same evidence that the State's Qualified Experts rejected now be treated as the basis for listing BPA under the Authoritative Bodies Mechanism.

III. SUMMARY

Any proposal to designate BPA as a "chemical known to cause . . . reproductive toxicity"[8] would be unlawful under Section 25249.8(b) of the Act and Section 25306 of the implementing regulations, because:

- the NTP-CERHR Monograph that OEHHA identifies as the basis for an authoritative bodies listing does not "formally identify" BPA as a developmental toxicant, as required under Section 25306(d);
- the determination by the State's Qualified Experts that the information in and the data underlying the Monograph do not support listing BPA cannot

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[4] OEHHA (2009) Evidence on the Developmental And Reproductive Toxicity of Bisphenol A, Draft, at 8.

[5] OEHHA (2009) Evidence on the Developmental And Reproductive Toxicity of Bisphenol A, Draft, at 8. (emphasis added).

[6] OEHHA (2009) Evidence on the Developmental And Reproductive Toxicity of Bisphenol A, Draft, at 8.

[7] Transcript, July 15, 2009 Meeting of Developmental and Reproductive Toxicant Identification Committee, pp. 1-259.

[8] Cal. Health & Safety Code § 25249.8(a).

be superseded or overruled by a second review of the same information and data by OEHHA under the Authoritative Bodies Mechanism under Section 25306; and

- the scientific data to which OEHHA now points as the basis for listing under the Authoritative Bodies Mechanism, if they were reviewable and reviewed on the merits, are not "sufficient" to indicate an "association between adverse reproductive toxic effects in humans and [BPA]," as Section 25306(g)(2) would require.

For these and other reasons stated below, any decision to designate BPA as a chemical "known to cause . . . reproductive toxicity" within the meaning of Proposition 65 would be arbitrary and capricious and an abuse of discretion.

BPA has not been "formally identified" as "causing reproductive toxicity. It is clear from the text of the Monograph that the document does not "formally identify" BPA as a developmental toxicant. The Monograph is a "report" for purposes of Section 25306(b). As a "report," neither the Monograph nor its summarizing component, the "NTP Brief," expresses a "conclusion" that BPA causes developmental toxicity, as OEHHA indicates in the Request.

According to the Request, "OEHHA is relying on the NTP-CERHR's ***conclusions*** in the report that ***BPA causes reproductive toxicity***." The only explanation is the following: "The NTP-CERHR report ***concluded*** that there is clear evidence of adverse developmental effects ***in laboratory animals*** at 'high' levels of exposure. Developmental effects include fetal death and reduced litter size in rats and mice exposed prenatally."[9]

It is obvious from the face of the NTP Brief, however, that this was not NTP's "conclusion" regarding the potential of BPA to cause reproductive toxicity in humans, which Section 25306(d) would require, but only its evaluation of some of the data ("high" dose tests in laboratory animals) that NTP considered. The NTP Brief plainly expresses a contrary "conclusion" as to whether these animal data are "sufficient" to predict adverse developmental effects in humans.

This is patently clear from the standardized format and terminology that NTP uses to frame the conclusions in its NTP Briefs. A review of every one of the NTP-CERHR Monographs on chemicals that NTP has evaluated for reproductive toxicity reveals below a glaring contrast between the cases where an NTP Brief actually concluded that a chemical agent, in NTP's words, "may adversely affect human development," as opposed to the conclusion that NTP declined to reach with respect to BPA. The NTP Briefs are drafted in a consistent, standardized format. Each NTP Brief expresses the NTP conclusion in a paragraph that (a) uses terms that clearly denominate "conclusions" as "conclusions;" (b) recites that NTP employs a "weight-of-the-evidence" approach in evaluating all of the data to reach a conclusion; (c) summarizes in a sentence or clause the value of the human and animal data; and then (d) pronounces a judgment whether the scientific evidence is "sufficient" to conclude that the

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[9] Request at 1 (emphasis added).

chemical under evaluation may (or does not) "adversely effect human development and/or reproduction."

In the NTP Brief on Di-isononyl phthalate ("DINP"), for example, NTP expressed its conclusion as follows:

> Scientific decisions concerning health risks are generally based on what is known as the ***"weight of the-evidence."*** In this case, recognizing the absence of human data, some evidence of developmental effects, and limited evidence of no reproductive effects in animals, the ***NTP judges the scientific evidence sufficient to conclude that DINP might adversely affect development of the human fetus if the levels of exposure are sufficiently high.***

NTP Brief on DINP (2003) at p. 2 (emphasis added).

In the NTP Brief on BPA, by contrast, NTP stated the following:

> Recognizing the lack of data on the effects of bisphenol A in humans and despite the limitations in the evidence for "low" dose effects in laboratory animals discussed in more detail below, ***the possibility that bisphenol A may alter human development cannot be dismissed.***

NTP Brief on BPA (2008) at p. 7 (emphasis added).

We demonstrate herein that the contrasts between the "conclusion" that NTP reached with respect to DINP and the conclusion that NTP failed to reach with respect to BPA, and their outcomes for purposes of Proposition 65: (1) in the case of BPA, NTP did not state that it "concluded" that the evidence was sufficient to show that humans would be affected, and (2) the "conclusion" that NTP did reach – that "the possibility that bisphenol A may alter human development cannot be dismissed – is not a "conclusion" that BPA does cause adverse developmental effects in humans.

Thus, the NTP-CERHR Monograph does not "formally identify" BPA as a developmental toxicant for purposes of Section 25249.8(b), which establishes the Authoritative Bodies Mechanism. Because the Monograph is a "report" within the meaning of Section 25306(d), the question is whether it "concludes" that BPA causes developmental toxicity.

For the reasons above, it obviously does not. OEHHA has confused an ***evaluation of some of the evidence that NTP-CERHR considered***, which applies only to laboratory animals, for a ***conclusion regarding the sufficiency of those data to predict adverse effects in humans***, which OEHHA now would interpret to include a judgment for purposes of Section 25306(g) that those data are "sufficient" to show an association between effects shown in humans and exposure to BPA. As the NTP Brief notes, NTP-CERHR did not reach such a conclusion, but instead acknowledged only that the "possibility" that BPA may alter human development "cannot be dismissed" – and made even that equivocal statement based *not* on the "high" dose data upon which OEHHA now relies, but rather on the "low" dose studies that OEHHA now ignores.

Because BPA is not "formally identified" in the NTP-CERHR Monograph as causing reproductive toxicity, it is beyond OEHHA's authority to examine the data itself to reach a different conclusion. Section 25306(d) of the implementing regulations assigns OEHHA the duty to review documents such as "lists" and "reports" issued by the various "authoritative bodies," in order to "determine which chemicals have been formally identified by an authoritative body as causing cancer or reproductive toxicity." If such a determination is made, OEHHA then is required to review the scientific evidence on which the authoritative body's "formal identification" was made, in order to ensure that the data satisfy the toxicological criteria set forth at Section 25306(g).

This is OEHHA's long-held position, memorialized by the Court of Appeal in *Exxon Mobil v. OEHHA*: "[T]he authoritative body provision is triggered if a body considered authoritative under the statute identifies a chemical in a report, list, or other document as a developmental toxicant. . . . [O]nce the chemical is 'formally identified' by an authoritative body as a developmental toxicant, OEHHA reviews the scientific record before the authoritative body to determine whether there is substantial evidence to support a listing."[10]

The purpose of this review, to be conducted only if, and then after, OEHHA finds that a chemical has been "formally identified," is to prevent "the unrestrained listing of chemicals" by agencies whose criteria might be ***less stringent*** than those imposed by Proposition 65.[11] Thus, the Section 25306 criteria were established with input from the State's Qualified Experts, in order to "ensure that the standards applied by an authoritative body are the same as or substantially similar to those used by the Panel to evaluate chemicals."[12]

Thus, neither Section 25249.8 of the Act nor Section 25306 of the Regulations are a mandate for OEHHA to review data citied in authoritative body documents to make listing decisions on the Agency's own behalf. Where a chemical was not "formally identified" by the authoritative body, the Agency has no further responsibility or authority. Therefore, to proceed further would be contrary to Section 25249.8(b) of the Act, and contrary to Sections 25306(d) and (g) of the implementing regulations.

The Authoritative Bodies Mechanism does not allow OEHHA to effectively overrule the State's Qualified Experts in evaluating the exact same data. Section 25249.8(b) of the Act and Section 25306(g) of the regulations do not allow the Authoritative Bodies Mechanism to be used as vehicle to overrule or supersede a decision by the State's Qualified Experts. Although the Request asserts that these mechanisms are "separate and distinct," the statue and regulations indicate the State's Qualified Experts Mechanism is the

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[10] *Exxon Mobil Corporation v. Office of Environmental Health Hazard Assessment*, 169 Cal.App.4th 1264, 1278 (2009) (hereinafter, "*Exxon Mobil v. OEHHA"*).

[11] "Final Statement of Reasons," dated March 29, 1990, accompanying the adoption of Section 12306 of Title 22 of the California Code of Regulations, Division 2, the precursor to Section 25306 at 2.

[12] Final Statement of Reasons at 15.

"primary approach to listing"[13] and that the toxicological criteria that OEHHA is required to apply in executing its purely ministerial duties under the Authoritative Bodies Mechanism are substantially the same criteria that the DART IC applies in evaluating data under the State's Qualified Expert Mechanism. The Final Statement of Reasons for Section 25306 further makes clear that the purpose of the Authoritative Bodies Mechanism, and the delegation of ministerial duties under that mechanism to the OEHHA staff, was merely to conserve the resources of the State's Qualified Experts "to focus [their] attention on chemicals which have not previously been evaluated."[14] For OEHHA to ignore the unanimous views of the State's Qualified Experts and to supersede their conclusions with a contrary interpretation of the very same data would be arbitrary and capricious in itself, and would exceed the agency's statutory authority.[15]

Even if OEHHA were authorized to evaluate the data in the NTP CERHR Monograph anew, the studies cited by NTP-CERHR do not satisfy the "sufficient data" requirement of Section 25306(g)(2). As a preliminary matter, it is unclear from the Request that OEHHA has applied the correct standard under Section 25306(g)(2) in stating its conclusion that the data appear to satisfy the requirements for listing.

The Request recites that the NTP-CERHR Monograph "appears to satisfy the sufficiency criteria in the Proposition 65 regulations," but says nothing more to explain than "[t]he NTP-CERHR report concludes that there is clear evidence of adverse developmental effects in laboratory animals at "high" levels of exposure. Developmental effects include fetal growth and reduced litter size in rats and mice exposed prenatally." It is obvious that such a "conclusion," if it were a conclusion (and even if were correct) would not equate to a finding to satisfy the definitional standard in Section 26305(g)(2). "Evidence of adverse developmental effects in laboratory animals" is only the starting point, not the finish line.

The pertinent question under Section 26305(g)(2) is whether evidence of such adverse effects in laboratory animals is "***sufficient,***" taking into account many specified and unspecified factors, to find that an "***association***" between those effects observed in animals and the same effects due to exposure to BPA "***in humans***" is "***biologically plausible***." The failure to apply the correct standard is cause in itself to bring the listing process to a close.

Examination of the criteria that the DART IC and OEHHA are required to apply reinforces that conclusion. Following the DART IC "Criteria for Recommending Chemicals for Listing as 'Known to the State to Cause Reproductive Toxicity" (hereinafter, "DART IC Criteria") the Experts reviewed the same studies to which OEHHA now points, and employed a ***"weight-of-the-evidence***" approach to determine whether those studies constitute "***sufficient***

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[13] Final Statement of Reasons at 8. *See also Exxon Mobil v. OEHHA*, 169 Cal.App.4th at 1282 (referring to State's Qualified Expert Mechanism as "primary approach" to listing).

[14] Final Statement of Reasons at 8.

[15] For reasons explained herein, we believe the Proposition 65 implementing regulations do not extend this authority to OEHHA. To the extent OEHHA would interpret the regulations otherwise, the regulations are contrary to the meaning and intent of the Act, and are invalid. *See Exxon Mobil v. OEHHA*, 169 Cal.App.4th at 1279 at n. 11.

evidence in experimental animals, such that ***extrapolation to humans is appropriate,***" taking into account factors such as "study design," "relevan[ce] to expected human exposures," and "***consideration of maternal toxicity."***[16]

Section 25306(g)(2), the operative provision for OEHHA's analysis, basically restates the DART IC Criteria, in nearly the same words. Section 25306(g)(2) would require the agency to determine whether there are ***"[s]ufficient data***, taking into account the adequacy of the experimental design and other parameters such as . . . route of administration, frequency and duration of exposure . . . choice of dosage levels, and ***consideration of maternal toxicity***, indicating that ***an association between adverse reproductive effects in humans*** and the toxic agent in question is ***biologically plausible***." (emphasis added).

As OEHHA is aware, the DART IC considered the issue of maternal toxicity extensively and conclusively. There is no valid reason for OEHHA to disagree with the DART IC on this issue. Moreover, OEHHA has no statutory power to reach a different conclusion under the circumstances presented. Even if OEHHA's staff or management personally disagree, they should defer to the findings of the State's Qualified Experts on this issue. It is simply untenable for the secondary decision maker, whose role was crafted by statute and regulation to carry out the views of the State's Qualified Experts as the primary decisionmaker, to arrogate unto itself the role to make its own decision, which is plainly arbitrary and capricious, and completely outside the statute. That would be the height of arbitrariness, particularly here, where the issue of "of maternal toxicity" was thoroughly "considered."

The agency should recall that the spokesperson for the petitioner NRDC, Dr. Solomon, raised this issue at the DART IC meeting on July 15, 2009. Expert opinion was presented in person by the principal author of three of the eight studies that NTP-CERHR and the DART IC considered. Following these presentations, the State's Qualified Experts addressed, debated and resolved the issue on the public record. The essence of that resolution is summarized in the following colloquy by two of the DART IC members:

> **Committee Member Roberts,** addressing developmental toxicity:
>
> We referred to high dose studies. ***The high dose studies have clear evidence of developmental toxicity. They do occur in the presence of maternal toxicity. And the issue isn't whether or not developmental toxicity occurs. It's whether or not there is sufficient maternal toxicity to potentially be causing the other***.
>
> * * *
>
> **Committee Member Keen**, following Dr. Roberts:
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> My reading of the binders was remarkably similar to what you read . . . As I look at the literature, ***I see very little evidence that there is an increased risk, absence***

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[16] DART IC, Criteria for Recommending Chemicals for Listing as "Known to the State to Cause Reproductive Toxicity" (1993), (referred to herein as "DART IC Criteria"), at 4, attached hereto as Attachment 3.

of maternal toxicity [sic.; Dr. Keen said "absent maternal toxicity" or "in the absence of maternal toxicity"], of fetal or neonatal mortality.[17]

The unanimous vote of the State's Qualified Experts following this exchange reflects the conclusion of the DART IC that the animal studies showing adverse developmental effects at high doses, *i.e.*, the same data to which OEHHA now points as the basis for designating BPA "as causing reproductive toxicity" within the meaning of Section 25306(g)(2), did not demonstrate that BPA should be listed. The State's Qualified Experts found, applying the appropriate statutory and DART IC Criteria, that the animal data were not "sufficient" to make "extrapolation to humans . . . appropriate," taking into account factors such as "relevan[ce] to expected human exposures," and "***consideration of maternal toxicity.***"[18]

As to the toxicological data, there are only eight studies to consider, referred to herein as "NTP References 36 – 43," as they are identified in the bibliography to the NTP Brief. They consist of three developmental toxicity studies (NTP References 36, 38 and 43), and five reproductive toxicity studies, all in the mouse and rat (NTP References 37, 39, 40, 41, 42, and 43). Applying the pertinent criteria under Proposition 65 and Section 25306(g)(2) (*i.e.,* "taking into account adequacy of the experimental design and other parameters, such as but not limited to, route of administration, frequency and duration of exposure"), analysis requires that five of the eight studies be excluded or significantly discounted, because they included effects potentially caused in whole or in part by post-natal exposure, which is not pertinent to the designation of a chemical as a developmental toxicant for purposes of Proposition 65. One study had no pre-natal exposure whatsoever; by definition, that study could not possibly demonstrate developmental toxicity, as Proposition 65 treats that effect. Four other studies had both pre-natal and post-natal exposure, and the effects in these studies could be due to exposure that occurs outside of gestation (*i.e.*, not pre-natal exposure). Furthermore, both male and female parents were exposed to BPA prior to mating in all four of these studies, raising the possibility that the "developmental" effects, such as a decrease in litter size, may be due to male or female reproductive toxicity, not to developmental toxicity as meant by Proposition 65. In fact, one of these studies specifically looked at male reproductive toxicity through a semen evaluation and a cross-mating study; substantial evidence of male reproductive toxicity (including a decrease in litter size when only the male parent was exposed to BPA and a decrease in sperm quality) was seen at doses that produced systemic toxicity. Just three studies had only pre-natal exposure, and none of these studies showed adverse developmental effects in the absence of severe maternal toxicity (a factor addressed below).

OEHHA would agree that "developmental toxicity" is limited for purposes of Proposition 65 to developmental effects caused by pre-natal exposure alone. NTP's use of that term and the similar term "adverse developmental effects," by contrast, embraces a much broader range of effects, including effects attributable to post-natal exposure. Thus, where the NTP Brief indicates that there is "clear evidence of adverse developmental effects"[19] in animals, the term "adverse

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[17] Transcript of July 15, 2009 DART IC Meeting, at pp. 236-238.

[18] DART IC Criteria, at 4.

[19] NTP Brief at 7.

developmental effects" does not have the same meaning as it does for purposes of Proposition 65. Therefore, the proposal to list BPA on the basis of effects that do not represent developmental toxicity for purposes of Proposition 65 would exceed the mandate under Section 25249.8 of the act, as well as Section 25306(g)(2) of the implementing regulations, and expand the boundaries of Proposition 65 well beyond its well-recognized limits.

Looking to other factors identified under Section 25306(g)(2), "consideration of maternal toxicity" leads to the conclusion that the adverse developmental effects observed at high doses in laboratory animals are likely due to maternal toxicity – not to fetal exposure to BPA. It is a widely accepted principle of developmental toxicology that all virtually all substances are capable of causing developmental toxicity in laboratory animals, if they are administered at doses high enough to cause maternal toxicity. Even common substances, such as table salt, can cause developmental toxicity in animals, (including even birth defects) at doses high enough to injure the mother. Indeed, we present data which show that the spectrum of developmental effects observed in animals given high doses of table salt was far more serious than the developmental effects observed after administration of maternally toxic doses of BPA. The purpose of developmental toxicity testing is not to confirm that every chemical agent is capable of causing developmental effects in animals. Rather, it is to identify substances that pose true developmental hazards to humans — such as ***selective*** developmental toxicants, *i.e.,* substances that cause developmental effects in the absence of maternal toxicity, or developmental toxicants to which humans are likely to be exposed at maternally toxic dose levels (*e.g.,* alcohol or anti-neoplastic drugs). BPA fits neither category.

In two of the eight studies, maternal toxicity was not monitored (or "considered," in the words of Section 25306(g)(2)) at all. (In fact, one of these studies did not use a single pregnant animal (since only young males were exposed to BPA, and then only post-natally). Thus, neither of these studies could possibly constitute "sufficient evidence" of developmental toxicity.

In all six studies where maternal toxicity was evaluated, developmental effects were observed only in the presence of serious maternal toxicity, and the magnitude of the maternal toxicity was sufficient to account for the developmental effects. This universal observation – the presence of significant maternal toxicity in the presence of developmental effects in all of the studies identified in the NTP Brief that "considered" maternal toxicity – is so overwhelming that it dictates the outcome of any analysis under Section 25306(g)(2). And yet, a proper analysis is actually even more restrictive. As noted above, adverse effects attributable to post-natal exposures are not relevant to a determination of developmental toxicity for purposes of Proposition 65, and Section 25306(g)(2) identifies other factors that must be considered as well.

An additional factor identified under Section 25306(g)(2), relating to the "choice of species," is pharmacokinetics. Pharmacokinetic differences between rodents and humans make it "biologically implausible" that BPA would cause developmental effects in humans. While rats and mice are the most commonly used species for developmental and reproductive toxicity studies, it is important to recognize that many scientific organizations and regulatory agencies,

including NTP-CERHR, the European Food Safety Institute,[20] and the United States Food and Drug Administration,[21] have described major species differences in the way the BPA is processed in and eliminated from the bodies of rodents versus humans. Indeed, the NTP-CERHR Expert Report devoted 24 pages to the pharmacokinetics of BPA. To summarize, when BPA is administered orally to humans, the chemical is bio-transformed quickly to BPA-glucuronide, and the kidneys excrete the substance rapidly from the body in the urine. Consequently, blood concentrations of BPA in humans are estimated to be very low under even the heaviest conditions of human exposure. Rodents, by contrast, excrete BPA-glucuronide through the liver into the bile duct where BPA is cleaved from BPA-glucuronide and readily reabsorbed back into the bloodstream, and thus excreted from the body more slowly. Because of these pharmacokinetic differences, even if humans received the same high doses that were given to rodents in the developmental and reproductive toxicity studies, developmental effects would not be expected in humans because relatively little BPA would be found in the blood of humans compared to rodents. In other words, an association between the adverse developmental effects seen in animals and the same effects in humans due to exposure to BPA is not "biologically plausible," based on pharmacokinetic differences alone.

Given these findings, and the additional observation that the level of exposure in the laboratory animals was several ***thousand*** times higher than calculated exposures in the relevant human population, the ***conclusions*** in the NTP Brief (indicating a "***negligible concern*** **that exposure to pregnant women to bisphenol A will result in fetal or neonatal mortality, birth defects or reduced birth weight and growth in their offspring"** (emphasis in original)) demonstrate that NTP did not find that an association between exposure to BPA and developmental toxicity in humans is biologically plausible. To the contrary, NTP found (implicitly if not explicitly) that the animal data do not satisfy the criteria that OEHHA would be required to apply under Section 23506(g)(2).

Further reasons that BPA should not be listed. In addition to the three grounds above, we demonstrate in Section IV of this Response (1) that the studies cited in NTP-CERHR Monograph as "clear evidence of adverse effects" for "'high' dose developmental toxicity" "in laboratory animals" would not satisfy the "weight-of-the-evidence" test if the agency considered only the data that are relevant for purposes of Proposition 65; (2) that, if OEHHA were to reach a conclusion that the studies above satisfy the "sufficient data" above, the agency would be substituting its judgment for that of the authoritative body (and the DART-IC) contrary to Section 25306(g); and that scientifically valid data not considered by NTP, which OEHHA should consider under Section 25306(f), demonstrate convincingly that that the only data that gave NTP-CERHR cause for "some concern" that BPA may cause adverse effects in humans now have been discounted, so there is no basis remaining to consider that BPA is a "known reproductive toxin" for purposes of Proposition 65.

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[20] European Food Safety Institute, 2008. Scientific opinion of the panel on food additives, flavourings, processing aids and materials in contact with food on a request from the commission on toxicokinetics of bisphenol A. The EFSA Journal (2008) 759, 1-10.

[21] FDA (August 14, 2008) Draft Assessment of Bisphenol A for Use in Food Contact Applications.

IV. REASONS WHY BISPHENOL A SHOULD NOT BE LISTED

We present below the reasons that Proposition 65 and its implementing regulations do not allow OEHHA to overrule the unanimous vote of the DART IC and to list BPA instead under the Authoritative Bodies Mechanism. Turning to the scientific merits of the matter, we also present the reasons why the statements in the NTP Brief and underlying data presented in the NTP-CERHR Monograph do not support a conclusion that BPA is a developmental toxicant within the meaning of Proposition 65.

A. *BPA Has Not Been "Formally Identified" as "Causing Reproductive Toxicity"*

In order for BPA to be listed as a reproductive toxicant under the "Authoritative Bodies Mechanism," the chemical must be "formally identified" by a "body considered to be authoritative" as "causing reproductive toxicity."[22] NTP-CERHR is designated as an "authoritative body" for this purpose at the present time,[23] and will remain an "authoritative body" unless that status is revoked or rescinded.[24] Nevertheless, BPA was not "formally identified" in the NTP-CERHR Monograph as "causing reproductive toxicity," as those terms are defined in the Proposition 65 implementing regulations.

1. *The NTP-CERHR Monograph Is a "Report" Within the Meaning of Section 25306(d)*

Section 25306(d)(1), quoted below, establishes three ways in which a chemical may be "formally identified:"

> For purposes of this section, a chemical is ***'formally identified'*** by an authoritative body when [OEHHA] determines that . . . the chemical . . .[1] ***has been included on a list*** of chemicals causing . . . reproductive toxicity; or [2] ***is the subject of a report*** which is published by the authoritative body and ***which concludes that the chemical causes . . . reproductive toxicity;*** or [3] ***has otherwise been identified as causing . . . reproductive toxicity*** by the authoritative body in a document that indicates that such identification is a final action . . . .[25,26]

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22 Cal. Heath & Safety Code § 25249.8(b).

23 Cal. Code Regs., *tit*. 27, § 25306(l)(3).

24 Cal. Code Regs., tit 27, § 25306(i).

25 Cal. Code Regs., *tit*. 27, § 25306(D)(1) (emphasis added).

26 The same regulation goes on, at subsection (2), to establish various alternative criteria by which a "list, report, or document" referred to in subsection (1) may be published or adopted for purposes of the regulation. See Cal. Code Regs., tit. 27, § 25306(D)(2). Publication or adoption is not at issue here.

The Request states that "[i]n 2008, the NTP-CERHR published a ***report*** on BPA [which] ***concludes*** that the chemical causes developmental toxicity at high levels of exposure. . . ." *Id.* at 2 (emphasis added). Thus, it appears that OEHHA has decided that the NTP CERHR Monograph is a "***report*** . . . which ***concludes***" that BPA causes developmental toxicity, and not that BPA has somehow been "otherwise identified as causing . . . reproductive toxicity in a document . . . ."

2. *The NTP-CERHR Monograph Does Not Conclude That BPA Causes Reproductive Toxicity*

As noted above, the Request states that "NTP-CERHR published a report on BPA [that] concludes that the chemical causes developmental toxicity at high levels of exposure. . . ."

> OEHHA is relying on the NTP-CERHR's ***conclusions*** in the ***report*** that BPA causes reproductive toxicity. The NTP-CERHR Monograph concludes that there is clear evidence of adverse developmental effects in laboratory animals at 'high' levels of exposure. Developmental effects include fetal death and reduced litter size in rats and mice exposed prenatally.[27]

We disagree that NTP expressed any such conclusion. The isolated statements in the NTP Brief that OEHHA identifies, which refer only to some of the data that the NTP and the NTP-CERHR Expert Panel reviewed, cannot accurately be called NTP's "conclusions" about the chemical, on which a listing may be based.

It is obvious from reviewing and comparing all NTP-CERHR's monographs regarding chemicals that the statements to which OEHHA refers do not represent a conclusion by NTP-CERHR that BPA is a developmental toxicant in humans. NTP-CERHR's website discloses that to date, NTP-CERHR has issued final monographs on nineteen chemicals, including BPA.[28] Each monograph consists of an expert panel report, public comments on the expert panel report, and the "NTP Brief" in which NTP summarizes its findings and conclusions regarding the chemical in question.

Every NTP Brief follows the same, consistent format. Each NTP Brief consists of four sections, addressing in the same order the following questions: (1) "What is [the chemical in question]?"; (2) "Are people exposed to the chemical?"; (3) "Can the chemical affect human reproduction or development?"; and (4) "Are current exposures to the chemical high enough to cause concern?" In this format, section (1) provides basic information about the chemistry of the product or chemical at issue, its economic uses, and its presence in products and/or the

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[27] Request at 1, paraphrasing the NTP Brief at 7.

[28] The chemicals are: acrylamide, BPA, 1-bromopropane, 2-bromopropane, fluoxetine, ethylene glycol, propylene glycol, hydroxyurea, methanol, butyl benzyl phthalate, di-n-butyl phthalate ("DBP"), di(2-ethylhexyl) phthalate ("DEHP"), diiosodecyl phthalate ("DIDP"), diisononyl phthalate ("DINP"), di-n-hexyl phthalate ("DNHP"), di-n-octyl phthalate, amphetamines, methylphenidate, and styrene. In addition, a "soy formula" monograph is in draft form, and genestein (a compound related to soy formula) has an expert report but no monograph. Copies of the NTP Briefs for these chemicals appear in a separate binder submitted with this Response.

environment. Sections (2) and (4) are closely related, and provide NTP-CERHR's conclusions regarding the estimated risks to humans from exposures to the chemical. Section (3) provides NTP-CERHR's conclusions regarding hazard identification, *i.e.*, whether available human and animal data are sufficient to conclude that the chemical in question is a reproductive or developmental toxicant in humans. NTP-CERHR's conclusions in Section (3) alone can potentially be the basis for an "authoritative bodies" listing of a chemical under Proposition 65; and in fact, OEHHA's Request for BPA refers to certain statements and figures in Section (3) of the NTP-CERHR Brief on BPA as OEHHA's proposed basis for finding that NTP has "concluded" that BPA is a developmental toxicant in humans.

While OEHHA is correct in looking to Section (3) of the NTP Brief on BPA for NTP-CERHR's conclusions, OEHHA is mistaken in suggesting that NTP "concluded" that BPA causes developmental toxicity in humans. The nineteen NTP-CERHR monographs demonstrate clearly that when NTP has reviewed the human and animal data on a chemical and reached a conclusion concerning its human reproductive or developmental toxicity, NTP consistently expresses its conclusions in Section (3) by using the key words "conclude" and "conclusion." Indeed, NTP consistently uses almost the exact same wording in expressing its conclusions, with only slight and insignificant variations. For example, in the NTP Brief for DINP, in answering the question "Can DINP affect human development or reproduction?", NTP stated:

> Possibly. . . .
>
> * * * * *
>
> Scientific decisions concerning health risks are generally based on what is known as the ***"weight of the evidence."*** In this case, recognizing the absence of human data, some evidence of developmental effects, and limited evidence of no reproductive effects in animals, ***the NTP judges the scientific evidence sufficient to conclude*** that DINP might adversely affect development of the human fetus if the levels of exposure are sufficiently high.[29]

In the NTP Brief on hydroxyurea, in answering the question "Can hydroxyurea affect human development or reproduction?", NTP stated:

> Probably…
>
> * * * *
>
> Scientific decisions concerning health risks are generally based on what is known as the ***"weight of evidence."*** In this case, the NTP recognizes the lack of sufficient data on the effects of hydroxyurea in humans and the clear evidence of adverse effects in laboratory animals and ***judges the scientific evidence sufficient***

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[29] NTP Brief on DINP (2003), at p. 2 (emphasis added).

> ***to conclude*** that hydroxyurea may adversely affect human development and reproduction if exposures are sufficiently high (see Figure 3).[30]

In the NTP Brief on methanol, in answering the question "Can methanol affect human development or reproduction?", NTP stated:

> Possibly…[T]he NTP believes it is reasonable and prudent to ***conclude*** that the results reported in laboratory animals indicate a potential for adverse effects in humans.
>
> Scientific decisions concerning health risks are generally based on what is known as ***"weight of evidence"*** approach. In this case, recognizing the lack of human data and the clear evidence of laboratory animal effects (Figure 2), the NTP ***judges the scientific evidence sufficient to conclude*** that methanol may adversely affect human development if exposures are sufficiently high.[31]

In the NTP Brief on 1-bromopropane, in answering the question "Can 1-BP affect human development or reproduction?", NTP stated:

> Possibly…
>
> Scientific decisions concerning health risks are generally based on what is known as a ***"weight of evidence"*** approach. Recognizing the lack of data on 1-BP toxicity in humans, the NTP ***judges the scientific evidence of effects in laboratory animals sufficient to conclude*** that 1-BP may adversely affect human development if exposures are sufficiently high.[32]

We could go on. In addition to the NTP Briefs quoted from above, the conclusion paragraphs in the NTP Briefs for the following chemicals read almost identically to the ones above: acrylamide (at p. 3), 2-bromopropane (at p. 1), amphetamine (at p. 2), DEHP (at p. 3), DBP (at p. 2), DIDP (at p. 1), and ethylene glycol (at p. 2). In ***every case*** NTP refers to the ***"weight-of-the-evidence"*** principle and provides a clear statement that "***NTP judges the scientific evidence sufficient to conclude*** that [the chemical] may adversely affect human" development or reproduction. We emphasize for the record that we do not endorse the accuracy of NTP's conclusions regarding these chemicals and, moreover, that an NTP conclusion that a chemical "might" or "may" cause reproductive or developmental toxicity does not appear to satisfy Proposition 65's "known to the state to cause" standard. Nevertheless, the point for present purposes follows: ***this is how NTP states its conclusion that a chemical causes adverse***

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30 NTP Brief on hydroxyurea (2008), at pp. 2-3 (emphasis added).

31 NTP Brief on methanol (2003), at p. 2 (emphasis added).

32 NTP Brief on 1-bromopropane (2003), at p. 2 (emphasis added)

reproductive or developmental effects in humans, if and when NTP judges the data sufficient to reach a conclusion.[33]

Section (3) of the NTP Brief for BPA presents a clear departure from the systematic, indeed formulaic, articulation of conclusions in all other NTP Briefs. Consistent with all the other Briefs, NTP asks the question, "Can Bisphenol A affect human development or reproduction?" Also consistent with its practice in several Briefs, NTP answers that question: "Possibly." Also consistent with other Briefs, NTP then briefly discusses the human and animal data on BPA.

The consistency ends there, however. Rather than pronouncing judgment regarding the sufficiency of the evidence and expressing a conclusion whether BPA can cause developmental or reproductive effects in humans, NTP stops short. Instead, in the critical place in the NTP Brief where NTP always states its "conclusions," based on the "weight of the evidence" and its judgment concerning the "sufficiency of the data," as illustrated by the passages from NTP Briefs above, the NTP Brief for BPA states only the following:

> Recognizing the lack of data on the effects of bisphenol A in humans and despite the limitations in the evidence for "low" dose effects in laboratory animals discussed in more detail, below, ***the possibility that bisphenol A may alter human development cannot be dismissed*** (see Figure 3).[34]

Several crucial points can be drawn from this paragraph. First, and most important, NTP makes ***no reference to the "weight-of-the-evidence"*** principle and ***does not state NTP's "judgment"*** that the scientific evidence is ***"sufficient to conclude"*** that BPA causes reproductive or developmental toxicity in humans. Considering that in virtually every other NTP Brief, NTP ***does*** explicitly state its ***judgment***, based on the ***weight of evidence***, whether the available evidence is "sufficient" to reach a ***conclusion***, NTP's avoidance of that language in BPA's case

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[33] NTP-CERHR followed the same pattern and used essentially the same language in five other Briefs in which NTP "concluded" that the available data did ***not*** suggest that the chemical in question was a developmental or reproductive toxin: (1) DNHP, "NTP judges the scientific evidence insufficient to reach a conclusion . . . ."; (2) di-n-octyl phthalate, "NTP judges the scientific evidence to indicate DNOP is not likely to affect human reproductive systems. The data are insufficient to make a judgment on possible developmental effects."; (3) Methylphenidate, "the panel judged the data largely insufficient to support clear conclusions . . . "; (4) Styrene, "NTP judges the total scientific evidence sufficient to conclude that it is unlikely that styrene [causes DART effects in exposed humans]"; and (5) Propylene glycol, "NTP judges the scientific evidence sufficient to conclude that PG probably does not adversely affect human development or reproduction."

Finally, in two Briefs NTP used slightly different language that still unambiguously communicated NTP's conclusions. In the NTP Brief on butyl benzyl phthalate, NTP stated "NTP judges the scientific evidence sufficient to support the levels of concern for effects on development and reproduction expressed below . . . ." In the case of fluoxetine, the NTP Brief stated in Section (3) that fluoxetine "probably" affects human development and reproduction, and cited to human studies showing developmental toxicity and impaired male and female sexual function, as well as animal studies supporting those human studies. It appears that the evidence on fluoxetine was so strong that NTP did not think it necessary to refer, as usual, to "weight-of-the-evidence."

[34] NTP Brief on BPA (2008), at p. 7 (emphasis added).

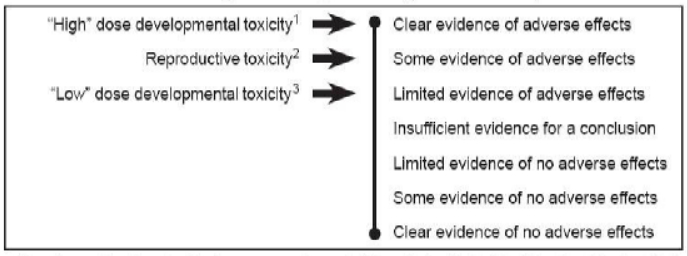
must be understood to mean that NTP ***did not reach a conclusion*** whether BPA does or does not cause developmental toxicity in humans**.**

Second, even if one were to ignore NTP's conspicuous avoidance of the terms that it constantly uses to express a conclusion and focus on the substance of what NTP says "as if" it were a "conclusion," all NTP says is that "the possibility that bisphenol A may alter human development cannot be dismissed." That statement is consistent with the interpretation stated above: NTP was unable to conclude whether BPA does or does not cause developmental toxicity in humans. Conversely, NTP's opinion that "the possibility cannot be dismissed" falls well short of a ***conclusion*** by NTP that BPA ***does*** cause developmental toxicity in humans, and cannot be the basis for a Proposition 65 listing.

Third, it is noteworthy that NTP's highly equivocal statement that the "possibility" of adverse developmental effects "cannot be dismissed" was based ***not*** on the "high-dose" studies to which OEHHA now points as the basis for listing, but rather exclusively on the controversial "low-dose studies" on BPA that OEHHA now disregards. NTP specifically referred to those studies showing adverse effects in laboratory animals on the same page, and just two paragraphs prior to its above-quoted opinion, or "conclusion," about possible adverse effects in humans, so NTP's failure to reference those "high-dose" data in addition to the low dose studies must be considered intentional. Specifically, it must be interpreted to mean that NTP considered those "high-dose" studies to be of so little relevance to potential adverse effects ***in humans*** that those studies were not even supportive of NTP's opinion that adverse effects in humans are a "possibility" that "cannot be dismissed." NTP does not explain why it deemed those high-dose effects in animals not to be evidence of potential adverse effects in humans, but one obvious explanation would be the reason stated by the DART IC—the effects seen in animals were secondary to maternal toxicity.

We understand that OEHHA's tentative determination in the Request that the NTP-CERHR Brief "concluded" that BPA "causes developmental toxicity" in humans is based on Figure 2b, reproduced below, and on certain isolated references in the text of the NTP Brief that are summarized in Figure 2b. We note, however, that Figure 2b does not purport to state or summarize NTP's "conclusions" but instead summarizes the "weight of the evidence that bisphenol A causes adverse developmental or reproductive effects in laboratory animals." As noted above, in the section of the NTP Brief in which NTP always states its "conclusions" about a chemical agent's potential adverse developmental or reproductive effects in humans, NTP conspicuously did not state that the weight-of-the-evidence is sufficient to conclude that BPA causes developmental toxicity in humans, and conspicuously did not even refer to the "high dose developmental effects" studies referenced in Figure 2b in support of its highly equivocal statement that adverse developmental effects in humans are a "possibility."

Figure 2b. The weight of evidence that bisphenol A causes adverse developmental or reproductive effects in laboratory animals



[1]Based on reduced survival in fetuses or newborns (≥500 mg/kg bw/day) *(36–40)*, reduced fetal or birth weight or growth of offspring early in life (≥300 mg/kg bw/day) *(36, 37, 41)*, and delayed puberty in female rats (≥50 mg/kg bw/day) and male rats and mice (≥50 mg/kg bw/day) *(37, 41–43)*.

[2]Based on possible decreased fertility in mice (≥875 mg/kg bw/day) *(40)*; altered estrous cycling in female rats (≥600 mg/kg bw/day) *(110)*, and cellular effects on the testis of male rats (235 mg/kg bw/day) *(111)*.

[3]Based a variety of effects related to neural and behavior alterations (≥10 µg/kg bw/day) *(44–50)*, lesions in the prostate (10 µg/kg bw/day) *(51)* and mammary glands (0.0025–1 mg/kg bw/day) *(52, 53)*; altered prostate gland and urinary tract development (10 µg/kg bw/day) *(54)*, and early onset of puberty (2.4 and 200 µg/kg bw/day) *(48, 55)*.

As the title of Figure 2b reflects, the figure itself and the statements within it and referenced by it do not purport to be NTP's "conclusions" about BPA based on NTP's weighing of all the human and animal data; rather, they are just observations about some of the animal data that NTP-CERHR considered. NTP's actual "conclusion" about BPA has been quoted and discussed above. It is illogical and improper to conflate the observations in Figure 2b about some of the data with an NTP "conclusion" about the ultimate weight of those data on the question to be answered — whether the studies are sufficient evidence to conclude that BPA causes developmental effects in humans.

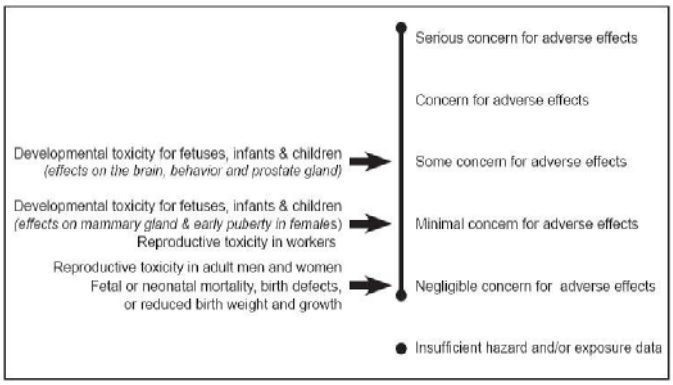
In this regard, it is important to note that every NTP Brief, like the NTP Brief on BPA, contains a "Figure 2b," and that the Figure 2b for BPA is unique among all NTP Briefs for all of the chemicals that NTP has examined. This is the only Figure 2b that has more than one arrow to depict the weight of the evidence for developmental effects in laboratory animals. The first arrow, labeled "high dose developmental toxicity," points to "clear evidence of adverse effects," and the footnote clarifies that those effects are reduced survival in fetuses and newborns, reduced fetal or birth weight or growth early in life, and delayed puberty in female rats and male and female mice. This arrow, and this statement referring to "clear evidence of adverse effects" at "high doses," is what OEHHA mischaracterizes as a "conclusion" by NTP that BPA causes developmental effects in humans. The second arrow, labeled "low dose developmental toxicity," points to "limited evidence of adverse effects," and the footnote clarifies that those effects are neural and behavioral alterations, lesions in the prostate and mammary glands, altered prostate and urinary tract development, and early onset of puberty. OEHHA's Request does not refer to this arrow and it is clear that OEHHA is not proposing to list BPA on the basis of those effects and NTP's assessment of the evidence for them.

The use of two arrows here reinforces the fact that the arrows and the words in the table, consistent with its title, are intended only to summarize the "weight of the evidence that bisphenol A causes adverse developmental or reproductive effects ***in laboratory animals***," and not to convey a "conclusion" about potential adverse developmental in humans, as noted above. This point is underscored by a review of NTP's conclusions about potential risks to humans, summarized in Figure 3, below. Comparison of the "conclusions" in Figure 3 with the statements

in Figure 2b further demonstrates that OEHHA is confusing the two, with a tortured, illogical result.

Figure 3, reproduced below, consistently with Figure 2b, includes more than one arrow to depict the potential for adverse effects in humans.

Figure 3. NTP conclusions regarding the possibilities that human development or reproduction might be effected by exposure to bisphenol A



Each arrow corresponds to different types of reproductive or developmental effects, and the placement of the arrows from top to bottom corresponds to NTP's hierarchical "levels of concern," with "Serious" appearing at the top of the table and lower levels below. The top-most arrow for BPA, which points to "***some*** concern for adverse effects" (the highest level of concern expressed by NTP for BPA), corresponds to "developmental toxicity for fetuses, infants and children (effects on the brain, behavior and prostate gland)." Clearly, those effects are not the effects associated with "high dose developmental toxicity" in Figure 2b. The middle arrow points to "minimal concern for adverse effects," and corresponds to "developmental toxicity for fetuses, infants and children (effects on mammary gland and early puberty in females)." Clearly, those effects also are not the effects associated with "high dose developmental toxicity" in Figure 2b, either. Finally, the third arrow, which corresponds to "Reproductive toxicity in adult men and women, fetal or neonatal mortality, birth defects, or reduced birth weight and growth," points to "Negligible concern for adverse effects." It is these effects – fetal or neonatal mortality, reduced birth weight and growth – that are associated with "high dose developmental toxicity" in Figure 2b.

Given the interrelationship of these tables in the NTP Brief, it makes no sense for OEHHA to equate the five words from Table 2b – "clear evidence of adverse effects" – which obviously characterize only the weight of the evidence that BPA causes developmental effects at high doses in certain animal studies, as a "conclusion" on the part of NTP regarding the potential for an association between those effects in animals and similar effects in humans. Indeed, Figure 3 is proof that this is not the intended meaning: there, the NTP Brief indicates that NTP has only "negligible concern" (the lowest possible level) concerning the possibility of these effects ***in humans,*** and expresses a greater level of concern for other adverse effects in humans for which there was only "limited evidence" in laboratory animals.

The comments (indeed, the ***conclusions***) of the DART IC on this point are instructive: the DART IC members ***agreed*** with NTP's observation that there is "clear evidence of adverse

effects" at high doses in certain laboratory animal studies, but concluded that maternal toxicity accounted for those effects, and thus, that the studies are not evidence of potential adverse effects in humans. DART IC Member Roberts summarized this point perfectly at the hearing in July 2009, in discussing the very same animal studies referenced in Figure 26:

> We referred to high dose studies. ***The high dose studies have clear evidence of developmental toxicity. They do occur in the presence of maternal toxicity. And the issue isn't whether or not developmental toxicity occurs. It's whether or not there is sufficient maternal toxicity to potentially be causing the other***.
>
> And when you have situations where the animals are either losing weight or gaining very little weight or they're described as emaciated, that to me can be a cause of something like an increase in resorptions pre-natally. Surprisingly, ***even when there were some fairly strong forms of maternal toxicity, it did not cause malformations. So it doesn't seem that that particular endpoint out of the four is of concern.***
>
> ***When there is maternal toxicity, it does have a decrease in fetal body weight. It has an increase in pre-natal loss. Those are both endpoints that are more commonly associated with severe maternal toxicity than others.***
>
> And a decrease in ossification does not – as long as it is a decrease in ossification, and not a structural change, it tends to go along with decrease in fetal body weight. Tr. at 236 – 237 (emphasis added).

These conclusions by the State's Qualified Experts, along with NTP's pointed and conspicuous refusal to state a "conclusion" that the weight of the evidence is sufficient to identify BPA as a developmental toxicant in humans (referring instead to only a "possibility that . . . cannot be dismissed . . . .") conclusively refute the proposition that the isolated characterization of the "high dose findings" in Table 2b was intended by NTP-CERHR to "formally identify" BPA as "causing . . . reproductive toxicity" within the meaning of the Act. By the regulatory standard applicable here, set forth in Section 25306(d)(1), it cannot be said that the NTP-CERHR Monograph "concludes that [BPA] causes reproductive toxicity."

B. *Because BPA Is Not "Formally Identified" in the NTP-CERHR Monograph as Causing Reproductive Toxicity, It Is Beyond the Authority of OEHHA to Re-examine the Data to Reach a Different Conclusion*

OEHHA is exceeding its authority in issuing the Request, and in proposing to list BPA under the Authoritative Bodies Mechanism. Under the Act, a chemical is to be listed as a reproductive toxicant under this "mechanism" if "a body considered to be authoritative by [the State's Qualified Experts] has formally identified it as causing . . . reproductive toxicity."[35]

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[35] Cal. Health & Safety Code, § 25249.8(b).

Because the Act does not indicate expressly who should make this determination, OEHHA, as the "lead agency," was assigned by regulation the responsibility to "determine which chemicals have been formally identified by an authoritative body."[36] If an authoritative body does "formally identify" a chemical as a reproductive toxicant, then OEHHA has a further responsibility to determine whether the underlying data constitute "sufficient evidence" for support that identification, by the standards set forth in Section 25306(g)(2).[37]

But the converse is not true. Where an authoritative body declines to "formally identify" a chemical as a reproductive toxicant, nothing in the Act or the implementing regulations gives OEHHA the authority, much less responsibility, to examine the underlying data to see if the agency would reach a different conclusion.

If this is not clear from the face of the regulations themselves, it is abundantly clear from the Statement of Reasons, which indicates that the Authoritative Bodies Mechanism was intended primarily "to establish a streamlined process for the [Scientific Advisory] Panel."[38] The Statement of Reasons explains that the State's Qualified Experts Mechanism, referred to as the "***primary approach to listing***," is a "time-consuming process."[39] Therefore, the Authoritative Bodies Mechanism was designed as a "streamlined" process, and duties were delegated to OEHHA, rather than to the Panel, simply to conserve the Panel's resources.

Nevertheless, as recounted above, the Scientific Advisory Panel expressed significant concerns that the Authoritative Bodies Mechanism would result in "unrestrained listings" if adequate controls and criteria were not put in place. The regulations that were drafted to address that concern created essentially a two step-process. First, OEHHA is required to "determine which chemicals have been formally identified by an authoritative body as causing cancer or reproductive toxicity."[40] Then, if a determination is made that a chemical has been "formally identified," OEHHA must also determine whether there is "sufficient evidence" to support that formal identification.

This is clear from the structure of the regulations, which address the phrases "formally identified" and "as causing reproductive toxicity" separately, in Sections 25306(d) and 25306(g), respectively. With respect to Section 25306(d), the Final Statement of Reasons explains:

> [Section] 25306(d) defines the circumstances under which a chemical is "formally identified" within the meaning of section 25249.8. The lead agency must make a determination that specified requirements of identification and formality have been satisfied.

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36 Cal. Code Regs., *tit.* 27, § 25306(c).

37 *Exxon Mobil v. OEHHA,* 169 Cal.App.4th at 1282.

38 Final Statement of Reasons at 8.

39 Final Statement of Reasons at 8 (emphasis added).

40 Cal. Code Regs., *tit.* 27, § 25306(c).

> [Section] 25306(d)(1) requires some kind of written identification. Specifically, the chemical must (1) be included on a list of chemicals causing cancer or reproductive toxicity, or (2) the subject of a report which is published by the authoritative body concluding that the chemical causes cancer or reproductive toxicity, or (3) be otherwise identified as causing cancer or reproductive toxicity by the authoritative body in a document which indicates that such identification is a final action. List and reports are methods of identification commonly used by governmental and non-governmental entities alike to identify chemical hazards.

The purpose and meaning of Section 25306(g) are explained by portions of the Statement of Reasons that address Section 25306(e) as well as Section 25306(g), because those provisions are virtually identical, and are different only insofar as one addresses cancer and the other addresses reproductive toxicity. Addressing Section 25306(e), the Final Statement of Reasons explains:

> [Section] 25306(e) provides that, for purposes of section [25306, the phrase "as causing cancer" means that either of two scientific criteria have been satisfied. Generally, the authoritative body may rely on either studies in humans or studies in animals . . . .
>
> As originally proposed, subsection (e) (then subsection (d)) provided:
>
> "Except as provided in subdivisions (e), (h), or (i), the lead agency shall determine that a chemical is formally identified by an authoritative body as causing cancer when either of the following criteria has been satisfied: . . . [passage regarding proposed-and-rejected changes omitted for brevity] . . . To avoid . . . confusion, subsection (e) was amended . . . to resemble subsection (d), and simply provide, "For purposes of this section, 'as causing cancer' means that either of the following criteria has been satisfied: . . ." ***This made clear that subsections (d) and (e) implement different terms. Subsection (d) implements the terms "formally identified," and subsection (e) implements the terms "as causing cancer."***[41]

By substitution, everything said above about subsection (e) (addressing cancer) also applies to its parallel provision, subsection (g) (addressing reproductive toxicity). Thus, it is clear that in determining whether a chemical has been "formally identified as causing reproductive toxicity," Section 25306(d) addresses the criteria for determining when a chemical has been "formally identified" as a reproductive toxicant, and Subsection 25306(g) addresses separately the criteria for determining whether there are "sufficient evidence" to support that "formal identification." The formal identification comes first; the examination of the supporting evidence comes second.

That is the only reading of these regulations that is consistent with their purpose. Given that the reason for the criteria in Section 25306(g) was to prevent "unrestrained listings," what

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[41] Final Statement of Reasons at pp. 15–16 (emphasis added).

purpose would be served by examining the data underlying an authoritative body's decision ***not*** to formally identify a chemical as a carcinogen or reproductive toxicant? Similarly, and to better illustrate the point, recall that Section 25306 applies to "lists" of chemicals that identify carcinogens and reproductive toxins as well as "reports" that "conclude" that chemicals present those hazards. If a chemical did not appear on an authoritative body's "list" of such hazardous chemicals, would OEHHA proceed to examine the data that were the basis of the decision not to list it? Of course not. Then why, when an "authoritative body" like the NTP-CERHR ***declines*** to conclude in a report that a chemical causes reproductive toxicity, should OEHHA proceed to evaluate the data underlying the authoritative body's "conclusion"? The answer: it should not.

If OEHHA has any doubt concerning these requirements and the relationship between the "formal identification" that must occur under Section 25306(d) as a condition precedent to OEHHA's authority to examine the record for data that would satisfy Section 25306(g), we urge the Agency to reconsider in light of OEHHA's position and the ruling of the Court of Appeal in *Exxon Mobil v. OEHHA*. In that case, Exxon Mobil contended that the listing of DIDP was unlawful, among other reasons, because OEHHA "abused its discretion by concluding, on the scientific record before NTP, that there was substantial evidence that the criteria identified in [Section] 25306(g) had been satisfied."[42] While the case presented many issues not pertinent here, the core analysis is dispositive.

The case turned on two critical issues: (1) whether the NTP Brief "formally identified" DIDP as a developmental toxicant for purposes of Section 25306(d) and if so, (2), whether OEHHA reasonably concluded that the data were "sufficient" evidence to support that formal identification, taking into account the factors prescribed by Section 25306(g). In so framing the case, the court responded to Exxon Mobil's contention that the NTP Brief on DIDP could not serve as the basis for listing under the Authoritative Bodies Mechanism – and hence the matter should have been referred to the DART IC – because the NTP Brief on its face did not include findings to address of the factors identified in Section 25306(g). OEHHA's response is so pertinent here that we quote the Court's recitation of it in full.

> ***[T]he authoritative body provision is triggered if a body considered authoritative under the statute identifies a chemical in a report, list, or other document as a developmental toxicant***. The authoritative body's report must satisfy the "formality" requirements of the statute – that is, it must accurately identify the chemical, have been reviewed by an advisory committee in a public meeting, have been made subject to public review and comment, and have been adopted as a final report by the authoritative body – but it need not include the detailed findings set out in [Section] 25306(g). Instead, ***once the chemical is "formally identified" by an authoritative body as a developmental toxicant, OEHHA reviews the scientific record before the authoritative body to determine whether there is substantial evidence to support a listing.*** If it concludes on the basis of its review that the [Section] 25306 criteria are satisfied – *i.e.,* that the experimental animal

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[42] *Exxon Mobil v. OEHHA*, 169 Cal.App.4th at 1287. The ultimate and determinant issue in this case was whether OEHHA was permitted to go beyond the NTP Brief to the underlying scientific record to make these findings. This issue is not presented here.

> data considered by the authoritative body are sufficient to support a conclusion that an association between adverse reproductive effects in humans and the toxic agent is biologically plausible – then it lists the chemical.[43]

In this framework, and citing the passage of the NTP Brief quoted above, the court thus ruled:

> "***The NTP Brief unambiguously identified DIDP as a developmental toxicant.*** [Emphasis added here.] It stated: 'Scientific decisions concerning health risks are generally based on what is known as 'weight-of-the-evidence.'
>
> In this case, . . . ***NTP judges the scientific evidence sufficient to conclude that DIDP is a developmental toxicant and could adversely affect human development*** if the levels of exposure were sufficiently high.' [Emphasis as it appears in court opinion.]
>
> ***Based on this statement***, [emphasis added here] there can be little doubt that ***NTP made the determination pivotal to the authoritative body scheme***: That ***DIDP is a developmental toxicant in humans*** [emphasis added here]."[44]

Thus, Section 25249.8(b) of the Act, Sections 25306(d) and 25306(g) of the implementing regulations, the Final Statement of Reasons, OEHHA's own statement of these requirements before the Court of Appeal and the Court's ruling all demonstrate that "formal identification" of a chemical as a reproductive or developmental toxicant ***in humans*** must be made ***by the authoritative body*** before the Authoritative Bodies Mechanism can be "triggered." It is equally clear that such formal identification for BPA was not made by NTP. The contrast between the "unambiguous" statements that persuaded the Court of Appeal that DIDP was formally identified, versus the patently ambiguous and equivocal observations articulated in the NTP Brief for BPA could hardly be more stark, and demonstrates clearly that BPA was not formally identified as a developmental toxicant in the NTP-CERHR Monograph. In the absence of a "formal identification," there is no basis for an authoritative bodies listing.

C. *The Authoritative Bodies Mechanism Does Not Allow OEHHA to Effectively Overrule the State's Qualified Experts in Evaluating the Same Data*

A proposal to list BPA under the Authoritative Bodies Mechanism on the basis of isolated statements in the 2008 NTP-CERHR Monograph after the DART IC's unanimous July 15, 2009 decision rejecting that very report as a basis to list BPA necessarily presupposes that an authoritative body listing validly can be based on: (1) the very same report and underlying data that the State's Qualified Experts considered and rejected as a basis for listing the chemical, and (2) a scientific/legal standard less stringent than the standard that the Experts applied when they

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43 *Exxon Mobil v. OEHHA*, 169 Cal.App.4th at 1278-79 (emphasis added).

44 *Exxon Mobil v. OEHHA,* 169 Cal.App.4th at 1285 (reformatted for emphasis and clarity).

determined that BPA should not be listed. That presupposition is contradicted by Sections 25306(e), (g) and (i) of the Proposition 65 implementing regulations,[45] which require an authoritative body listing to be based on scientific evidence that satisfies the standards of the State's Qualified Experts, and which collectively demonstrate a clear intention to prevent the listing of a chemical on the basis of a report that, although issued by an authoritative body, has "formally identified [the chemical] as causing cancer or reproductive harm" based on standards less stringent than the State's experts themselves would require.

1. *Section 25306(g) Was Promulgated to Ensure That Decisions Made by OEHHA in Implementing the Authoritative Bodies Mechanism Would Be Consistent with Those Made by the State's Qualified Experts*

The regulatory history of Section 25306, which implements the Authoritative Bodies Mechanism authorized by Section 25249.8(b) of the Act, makes it very clear that the mechanism is not intended to allow or result in the listing of chemicals that do not satisfy the Proposition 65 listing criteria, as the State's Qualified Experts apply them. The Final Statement of Reasons[46] shows that the State's Qualified Experts,[47] who are the persons authorized by Section 25249.8(b) of the Act to designate – or ***not*** to designate – bodies as "authoritative" and hence empowered to formally identify chemicals as causing cancer or reproductive toxicity, were very concerned to ensure that any listings by such authoritative bodies would satisfy Proposition 65's stringent criteria**.**

The Scientific Advisory Panel was concerned that the Authoritative Bodies Mechanism could result in unjustified or "unrestrained" listing of chemicals that do ***not*** satisfy the Proposition 65 criteria, and was unwilling to designate any body as authoritative unless and until regulatory safeguards were implemented to prevent such unjustified listings. This concern was the genesis of the development of Section 25306 (then Section 12306), as explained in the passage from the Final Statement of Reasons below.

> "PROCEDURAL BACKGROUND
>
> "The concept of this regulation was conceived following the Panel's meeting of October 1987. In that meeting, ***the Panel expressed strong reservations about designating any body as authoritative due to its concern that the designation would result in the unrestrained listing of chemicals. Consequently, the Agency determined that it would be necessary to implement and make specific the provisions of the Act relating [to] authoritative bodies*** to enable the Panel to take advantage of this listing mechanism. Subsequently, the Agency commenced

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45 Cal. Code Regs., *tit*. 27, § 25306(e), (g), (i).

46 Final Statement of Reasons, *supra*.

47 At that time, the "Scientific Advisory Panel" ("Panel"), the precursor to the CIC and DART IC.

drafting this regulatory proposal. Copies of early proposals were circulated to interested persons and the Panel.

"On April 14, 1989, following a command from the Sacramento Superior Court, the Panel considered the question whether the United States Environmental Protection Agency (EPA) is an "authoritative body" within the meaning of the Act and concluded that EPA is authoritative, but ***conditioned the designation upon application of certain controls to the listing of chemicals pursuant to that designation, and asked the Agency to draft rules embodying these controls***. The terms of the condition were similar to the controls in the draft regulatory proposal. Subsequently, on July 17, 1989, the Agency proposed section 12306 [recently renumbered as Section 25306] for adoption."[48]

Section 25306 defines in its subsections the criteria that authoritative body listings must satisfy. For both carcinogens and reproductive toxicants, the Statement of Reasons explains that authoritative body listings are to be based on scientific evidence that satisfies the ***Scientific Panel's own criteria.***

Section 25306(e) sets forth the criteria that must be met for data to support an authoritative body listing for carcinogens. The Statement of Reasons recites:

"SUBSECTION (E)

"Subsection (e) provides that, for purposes of section 12306 [now section 25306], the phrase "as causing cancer" means that either of two scientific criteria have been satisfied. Generally, the authoritative body may rely on either studies in humans or studies in animals. ***These criteria are consistent with the criteria the Panel presently uses in evaluating chemicals for listing.*** The Panel utilizes the EPA's Classification System for Categorizing Weight of Evidence for Carcinogens From Human and Animal Studies [51 Fed. Reg. 33999 (Sept. 24, 1986)]. The same, or substantially similar criteria have been adopted by many regulatory agencies and scientific organizations involved in hazard identification. ***The use of these criteria will ensure that the standards applied by an authoritative body are the same as or substantially similar to those used by the Panel to evaluate chemicals."***[49]

Section 25306(g) defines the scientific criteria that must be met for data to support an authoritative body listing for a reproductive toxicant.[50] As was the case with carcinogens, the Final Statement of Reasons explicitly indicates that any authoritative body listing of a reproductive toxicant must be based on scientific evidence that satisfies ***the Scientific Panel's own criteria*:**

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[48] Final Statement of Reasons at 2 (emphasis added).

[49] Final Statement of Reasons at 15 (emphasis added).

[50] The language of subsection (g) that was adopted in 1990 (as Section 12306(g)) is exactly the same as the current language of § 25306(g).

"SUBSECTION (G)

"Subsection (g) provides that, for purposes of section 12306 [now section 25306], the phrase "as causing reproductive toxicity" means that either of two scientific criteria have been satisfied. Generally, the authoritative body may rely on either studies in humans or studies in animals.

"Paragraph (g)(1) describes the criteria for determining that a chemical causes reproductive toxicity where the authoritative body relied on studies in humans. As with carcinogens discussed above, the proposed regulation requires that sufficient evidence exist from such studies, in that studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity.

"Paragraph (g)(2) describes the criteria for determining that a chemical causes reproductive toxicity where the authoritative body relied on studies in animals for its identification of a chemical as a reproductive toxicant. ***Again, the proposed regulation requires that sufficient evidence exist from such studies. "Sufficient evidence" is defined to mean that there is sufficient data, which take into account the adequacy of the experimental design and other specified parameters,*** indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible. ***This is consistent with the criteria utilized by the Panel when it evaluates reproductive hazards."***[51]).

Finally, Section 25306(i) establishes the procedure that OEHHA must follow in proposing an authoritative body listing. The references in subsection (i) to the scientific criteria of subsections (e) and (g) clearly signify that any authoritative body listing must be based on scientific evidence that satisfies the Proposition 65 listing criteria, as the State's Qualified Experts would apply them. The Statement of Reasons confirms that subsection (i) was intended as a fail-safe mechanism to ensure that in the rare instance in which an authoritative body might "formally identify" a chemical as a carcinogen or reproductive toxicant on the basis of evidence that does ***not*** satisfy the Proposition 65 criteria, the chemical will be referred to the State's experts for review prior to listing ***so that such unjustified listing will be prevented:***

"SUBSECTION (I)

"Subsection (i) sets forth a procedure to be followed by the lead agency prior to the listing of chemicals on the ground that they are formally identified by authoritative bodies as causing cancer or reproductive toxicity. At least 60 days prior to causing the chemical to be added to the list of chemicals known to the state to cause cancer or reproductive toxicity, the lead agency must publish a notice identifying the authoritative body and the chemical, stating its intention to cause the chemical to be added to the list. ***Interested parties will have 30 days within which to object to the proposed listing on the ground that there is no***

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[51] Final Statement of Reasons at 21 – 22 (emphasis added).

substantial evidence that the scientific criteria set forth in subsection (e) and (g) have been satisfied. Such objections must be in writing and be accompanied by supporting documentation.

* * * *

Subsection (i) arises out of concerns that chemicals formally identified by authoritative bodies might be listed even though the criteria utilized by the Panel had not been satisfied.[52]

These provisions of Section 25306, as explained by the foregoing excerpts from the Final Statement of Reasons, conclusively establish that authoritative body listings legally may ***not*** be based on scientific evidence less stringent than the evidence that the State's Qualified Experts – here, the DART IC – apply in their own review of chemicals for potential listing. To the contrary, the Authoritative Bodies Mechanism was implemented with considerable safeguards and requirements to ensure that authoritative body listings would satisfy the ***same*** criteria.[53]

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[52] Final Statement of Reasons at 24 (emphasis added).

[53] There is no authority to support a contrary conclusion. In particular, the July 20, 1998 memorandum authored by a former Chief Counsel to the Agency (hereinafter, "Counsel's Memo") and attached as Attachment 5, is not authority, and does not support a contrary view.

The Counsel's Memo addresses, among other questions, "What effect, if any, does a determination by the CIC or DART Committee to not identify a chemical for listing under Proposition 65 have on the authority of the lead agency to list a chemical as causing cancer or reproductive toxicity on the basis of an authoritative body formal identification?" The author concludes that "each of the three listing mechanisms is independent of the other methods and has its own authority. Accordingly, a determination by the CIC or DART Committee to not identify a chemical for listing under the 'State's qualified expert' mechanism is no bar or limitation on the authority of authoritative body to formally identify a chemical as causing cancer or reproductive toxicity. Again, the Statute (Section 25249.8(b)) is framed in the disjunctive – 'or.' If a chemical meets one of the three listing methods, it may be added to the list."

In response, we note that the Counsel's Memo is not a statute, regulation, rule or other authority, but only an opinion of the former Chief Counsel, by which the Agency is not bound, and which can and should be corrected as a misstatement of the law, if it would be mistaken as authority to allow the Petition to be granted. First, the author cites no authority other than her observation that the three listing mechanisms identified in Section 25249.8(a) of the statute are "independent," because they are connected by the word "or." Second, while it is obviously true that the various "mechanisms" are independent, that is no reason to conclude that the mechanisms are intended to support different results, or that the separate clauses of Section 25249.8(b) that establish separate listing "mechanisms" should be read to establish different listing ***criteria***. Third, the Statement of Reasons, which includes the Agency's official interpretation of the Act and implementing regulations, provides expressly to the contrary. As noted above and in the Statement of Reasons, Section 25249.8(b) of the statute vests in the State's Qualified Experts the exclusive authority to determine what bodies are "considered to be authoritative" and thus, implicitly, to establish criteria for their designation as "authoritative." Given that the clause in Section 25249.8(b) that provides for authoritative bodies – which reads in its entirety as follows: "or if a body considered to be authoritative by such experts has formally identified [a chemical] as causing cancer or reproductive toxicity" – includes ***no*** listing criteria, the Agency at the Scientific Advisory Panel's request promulgated Section 25306, which does include listing criteria, for the express purpose of ensuring that the any bodies that the Panel deemed to be authoritative would be bodies that applied criteria that are ***"consistent with the criteria used by the Panel."***

(footnote continued on next page)

2. *The Section 25306(g) Criteria Thus Are Essentially the Same as the Criteria Employed by the DART IC*

It is important here to examine the criteria by which the DART IC makes its determinations whether a chemical should be listed, because they identify the same factors that OEHHA is supposed to evaluate when it reviews documents published by authoritative bodies to determine whether chemicals that have been "formally identified" as reproductive toxicants. Those criteria, formally known as "Criteria for Recommending Chemicals for Listing As 'Known to the State to Cause Reproductive Toxicity," are referred to herein simply as the DART IC Criteria.[54]

The DART IC Criteria give the Committee "maximum flexibility" to evaluate ***"all pertinent scientific information***," taking a ***"'weight of the evidence' approach."***[55] Like Section 25306(g), the DART IC Criteria require listing where there is ***"sufficient evidence in humans***" to show a "***causal relationship***" between "exposure to the chemical and the developmental or reproductive effect.".[56] Regarding animal studies, and in further similarity to Section 25306(g), they require listing where there is "[***s]ufficient evidence*** in experimental animals (mammals), ***such that extrapolation to humans is appropriate*** , . . . based on the adequacy of the . . . ***experimental design***, [where the] exposure, in terms of route of administration, is relevant to expected human exposures," and taking into account ***"[c]onsideration of maternal … toxicity***."[57]

Regarding maternal toxicity, the DART IC Criteria go on to explain that the ***"high dose level [in animal studies] should elicit maternal toxicity in developmental studies***, and systemic toxicity in female and male reproductive studies, and that ***the low dose should elicit*** no observable adverse effect for adult and offspring."[58] Under the heading "Consideration of maternal toxicity," they indicate that "[d]ifferentiating between (a) the effects of a toxic agent on the conceptus or reproduction and (b) the effects on the conceptus or reproduction that are

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Fourth, putting the above legal premises aside, the ultimate conclusion expressed in the Counsel's Memo – that a ruling by the CIC or DART IC that a chemical does not qualify for listing under Proposition 65 is "no bar or limitation on the authoritative body to formally identify a chemical as causing cancer or reproductive toxicity" – does not address the situation here. We are not faced with the question whether the decision of a Scientific Advisory Panel (here, the DART IC) has any effect on the authoritative body to go about its business, as the Counsel's Memo addresses. Indeed, we would agree with the conclusion that an authoritative body has every right to consider a chemical for whatever purposes its statutory mission may require, and to accept or reject the findings of the DART IC. The different question that we must answer here is whether the Agency may ignore the conclusion of a Scientific Advisory Panel (again, the DART IC) that a report issued by an authoritative body (here, the NTP-CERHR) does not establish that a chemical meets the § 25306(g)(2) criteria for listing under Proposition 65. For the reasons discussed in the text of these comments above, the Agency may not ignore that opinion. The Counsel's Memo does not say otherwise.

54 DART IC Criteria (Nov. 1993), attached hereto as Attachment 3.

55 DART IC Criteria at 1 (emphasis added).

56 DART IC Criteria at 3 (emphasis added).

57 DART IC Criteria at 4 (emphasis added).

58 DART IC Criteria at 4 (emphasis added).

secondary to the maternal or systemic toxicity effects is sometimes difficult and may require special attention, on a case by case basis."[59]

3. *The DART IC Decision Not to List BPA Is Consistent With The DART IC Criteria (and Section 25306(g))*

At the hearing, on the record, the DART IC discussed the animal studies on which OEHHA now relies and stated explicitly that those studies do ***not*** satisfy the DART IC Criteria – and why. The scientific evidence in the HID, reviewed by the DART IC at and prior to the public meeting, included all the scientific evidence reviewed by NTP-CERHR, and in addition, included NTP-CERHR's own discussion of the data. The transcript of the July 15, 2009 public hearing shows that the DART IC reached its decision not to list BPA based on two general conclusions regarding the scientific evidence on BPA:

> (1) the conventional, well-conducted studies described in the NTP-CERHR Monograph as showing "clear evidence of developmental effects at high doses" showed maternal toxicity at the same and lower doses, making the evidence of developmental effects unpersuasive; and
>
> (2) the very large number of "unconventional" studies purporting to show effects at low doses did not qualify as "scientifically valid testing according to generally accepted principles."

The significance of maternal toxicity in the well-conducted conventional studies – the studies cited in the NTP CERHR Monograph as showing "clear evidence of developmental effects at high levels of exposure" – was addressed explicitly, first in oral presentations by Dr. Solomon (for NRDC) and then by Dr. Tyl and Dr. Murray (for ACC) at the July 15 hearing, and then by the DART IC members themselves in their discussion of the scientific evidence prior to their unanimous votes not to list BPA. The issue was introduced by Dr. Solomon, who argued that the principal studies cited in the NTP CERHR Monograph showed "clear evidence of adverse effects with high doses . . . ."[60]

> **Dr. Solomon:**
>
> ***[T]he conclusion was that they're not simply secondary to maternal toxicity*** . . . [M]ost of the ones we're talking about are the Research Triangle Institute studies by Tyl, *et al.*, the study abstracts when you just read those and the conclusions seem to indicate that the developmental effects are only in the setting of maternal toxicity, might not represent true developmental toxicity.
>
> And then when you actually go through and you look at the data in the reports, it's actually quite clear that there are effects in the setting of minimal, if any, maternal

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59 DART IC Criteria at 4-5.

60 Transcript of July 15, 2009 DART IC Meeting ("Transcript"), p. 51 (emphasis added).

toxicity in most of those studies. ***And that's what the CERHR panel based their conclusion of clear evidence of adverse effects on.***[61]

As a matter of context, we must point out that there is no basis in the NTP Brief to support Dr. Solomon's assertion that NTP-CERHR reached the conclusion that Dr. Solomon asserted about the role of maternal toxicity in the studies in question. As to the data themselves, Dr. Tyl, the principal author of three of the crucial studies, described her studies in detail. Tr. at 112 – 129. Dr. Tyl directly addressed and refuted Dr. Solomon's assertion that the developmental effects in certain studies at high dose levels were "not simply secondary to maternal toxicity" and that they occurred "in the setting of minimal, if any, maternal toxicity." Addressing the multi-generation rat study (Tyl, *et al*., 2002b)[62], Dr. Tyl stated:

Dr. Tyl:

[W]e only saw . . . reproductive and developmental effects of BPA at a dose that was clearly systemically toxic and at a dose that was lower than that and still toxic, we still didn't see anything.

We concluded that BPA was not considered a selective reproductive or developmental toxicant in rats. Okay, because ***you didn't see the reproductive or developmental effects, unless you also saw maternal toxicity***.

And even at lower maternal toxicity, you didn't see the effects.[63]

Dr. Tyl went on to explain that there were similar findings in a comparable two-generation study on mice, describing in detail the design, and the results:

Dr. Tyl:

We got adult systemic toxicity at the top two doses, sound vaguely familiar. Hepatic histopathology at 50. And at 600 milligrams per kilogram per day, we got reduced body weights. We got increased liver and kidney weights. And we saw the same kind of histopathological problems in the liver and the kidneys.

"The developmental effects at 600 milligrams per kilogram per day, included delayed testis descent, which you normally see in the last week of lactation. It ultimately happened, but it happened slightly later. Transient hypoplastic testes, because we looked at weanling animals histopathologically, and slightly delayed acquisition of puberty in offspring males okay, considered not driven by estrogenic activity, but ***likely secondary to systemic tox***.

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61 Transcript, p. 52 (emphasis added).

62 The dates for the Tyl studies (e.g., 2002b) are as they appear in the NTP Brief.

63 Transcript, p. 118 (emphasis added).

> We saw no effects on adult reproductive functions, including andrology or structures, included testes, epididymides, prostate, ovaries, mammary glands, uterus/cervix. And we looked at those in the weanlings and the adults for the F0 adults, the F1 weanlings, the F1 adults and then the F2 weanlings. There were no low dose effects again at .5 to .003 milligrams per kilogram per day. No evidence for non-monotonic dose response curves for any parameter at any dose in any generation. Responses to the E2 positive control, confirmed the sensitivity of the CD-1 mouse to estrogens and confirmed the findings that we had presented for the one-gen and the two-gen[] study, because ***we only saw effects in the presence of systemic tox, and only at the highest dose. And the second to highest dose also has systemic tox and no reproductive or developmental effects.*** We considered ***BPA was not a selective reproductive or developmental toxicant in mice either***.[64]
>
> * * * * *
>
> [S]o BPA is not a selective developmental reproductive toxicant in rats or mice. ***The reproductive and developmental effects seen at high BPA-dietary doses are only observed in the presence of systemic tox. So they are considered secondary to the systemic toxicity observed.***
>
> ***[T]here was no evidence of effects at low BPA doses and no non-monotonic dose response curves in any parameter in either species in rats or in mice at any dose level***.
>
> [T]he interesting thing is the insensitive rat and the sensitive mouse have exactly the same systemic and reproductive NOELs, which I think is fascinating.
>
> [T]he final comment is the BPA reproductive and developmental effects observed at these high doses are not consistent with estrogenic activity. We know what the normal estrogenic activity should be, because we did the one- and two-generation E2 studies to make sure we could document those. And the effects we saw at high doses are not those associated with an estrogen." Tr. at 126 – 127 (emphasis added).

Dr. Murray followed Dr. Tyl, further contradicted Dr. Solomon's claims about CERHR's "conclusions," and concurred with Dr. Tyl's conclusions. Tr. at 131 – 132. Dr. Murray also addressed the large number of "unconventional" studies listed in the HID. He noted that CERHR had described many of these studies as "inadequate or of limited utility," Tr. at 133, and went on to draw attention to a long list of shortcomings in terms of study design, route of administration, inadequate numbers of test animals, etc. Tr. at 133 – 136. Dr. Murray concluded that the weight of the scientific evidence clearly did not support listing BPA. Tr. at 138 – 139.

Significantly, the transcript leaves no doubt that the DART IC members were focused closely on maternal toxicity, consistently following the DART IC Criteria. The record is quite

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[64] Transcript, pp. 124-125 (emphasis added).

clear that the DART IC concluded that the adverse developmental effects observed in the studies at "high dose levels" (the very studies to which OEHHA points now) occurred only in the presence of significant maternal toxicity, and that the numerous unconventional studies listed in the HID were too inconsistent and of insufficient quality to satisfy the Proposition 65 criteria for listing.

> **Committee Member Roberts,** addressing developmental toxicity:
>
> We referred to high dose studies. ***The high dose studies have clear evidence of developmental toxicity. They do occur in the presence of maternal toxicity. And the issue isn't whether or not developmental toxicity occurs. It's whether or not there is sufficient maternal toxicity to potentially be causing the other***.
>
> And when you have situations where the animals are either losing weight or gaining very little weight or they're described as emaciated, that to me can be a cause of something like an increase in resorptions prenatally. Surprisingly, ***even when there were some fairly strong forms of maternal toxicity, it did not cause malformations. So it doesn't seem that that particular endpoint out of the four is of concern.***
>
> ***When there is maternal toxicity, it does have a decrease in fetal body weight. It has an increase in prenatal loss. Those are both endpoints that are more commonly associated with severe maternal toxicity than others.***
>
> And a decrease in ossification does not – as long as it is a decrease in ossification, and not a structural change, it tends to go along with decrease in fetal body weight.[65]
>
> * * *
>
> **Committee Member Keen**, following Dr. Roberts:
>
> My reading of the binders was remarkably similar to what you read . . . As I look at the literature, ***I see very little evidence that there is an increased risk, absence of maternal toxicity [sic.; Dr. Keen said "absent maternal toxicity" or "in the absence of maternal toxicity"],*** of fetal or neonatal mortality. I don't see any clear trends for malformations or specific birth effects. No clear evidence of reduced birth weight or growth.
>
> In the occasional paper, and there's over 70, which I went back and read each of the individual papers, you'll find a sporadic report of something. But where I get a little concerned or actually quite concerned is the lack of consistency as you go across the reports.[66]

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[65] Transcript, pp. 236-237 (emphasis added).

[66] Transcript, pp. 238-239 (emphasis added).

The DART IC was equally clear that the balance of the data, including the so-called "'low' dose studies," did not support a finding that BPA is a developmental of reproductive toxicant in humans.

> **Committee Member Keen:**
>
> [A]s I read the literature now, it's confusing, and it doesn't, by any criteria, meet my definition of clear. So I'll stop at that point.[67]
>
> **Chairperson Burk, following Dr. Keen:**
>
> But again, most of the studies are not our generally accepted sort of things, due to the numbers, as you mentioned, and the, you know, single dose and all those kind of things.[68]
>
> **Committee Member Keen:**
>
> ***But I think it's also worth noting those as when they did signal some out as being, what they thought I guess were, the more robust studies, I see females no effect, males no effect***.[69]
>
> **Committee Member Roberts**, following Dr. Keen:
>
> I'm looking at the NTP brief on page 20. And on the left-hand column, it says, ***Overall the current literature cannot yet be fully interpreted for biological or experimental consistency or for relevance to human health,***" which implies that they think that something may come of this in the future, but they are not there yet."[70]

Thus, the record could not be any more clear. The question of whether the "clear evidence of developmental effects at high doses" in certain studies was, or was not, secondary to maternal toxicity was presented squarely to the DART IC for its decision, and the Committee clearly decided that it was. It is also clear that the DART IC, NTP-CERHR and other expert agencies determined that the numerous "unconventional" were not convincing because they were not conducted according to generally accepted principles.

We recognize that OEHHA has authority, if not a responsibility, to review the NTP-CERHR Monograph to determine whether it "formally identifies" BPA as causing reproductive toxicity, *see* Cal. Code Regs., *tit.* 27, § 25306(d), and if so, whether the data that NTP-CERHR relied on are "sufficient," *see* Cal. Code Regs., *tit*. 27, § 25306(g), to support that identification. Thus, if the DART IC had not reviewed the data already, and if the NTP-CERHR Monograph

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67 Transcript, p. 243.

68 Transcript, p. 243.

69 Transcript, p. 248 (emphasis added).

70 Transcript, p. 248 (emphasis added).

had "formally identified" BPA as a developmental toxicant pursuant to § 25306(d) (which it did not in this case), OEHHA would be justified in reviewing the data summarized in the NTP-CERHR Monograph to determine whether those data were "sufficient" to support listing under Proposition 65. But this is clearly not the case, and OEHHA cannot ignore the fact that the DART IC did review all those data and reached a conclusion exactly the opposite of what OEHHA now proposes. To elaborate, the DART IC reviewed all the available scientific evidence, including not only the studies reviewed by NTP-CERHR but also the conclusions and observations expressed in the NTP Brief, and reached the unanimous conclusion that BPA has ***not*** been "clearly shown through scientifically valid testing according to generally accepted principles to cause . . . reproductive toxicity." Moreover, the DART IC was quite clear in explaining how and why the evidence on BPA fails to satisfy the DART IC Criteria, which are essentially a more detailed statement (or "more fully articulated statement") of the same criteria set forth in Section 25306(g).

Under these circumstances, the DART IC's decision is conclusive. If OEHHA were to determine now that those animal data ***do*** satisfy the requirements of Section 25306(g), it is clear that the agency would be applying a standard different than the DART IC itself applies and substituting its judgment for that of the DART IC, which would be a clear violation of Section 25306 as a whole. For these reasons, OEHHA should acknowledge and respect the conclusions of the DART IC as the State's Qualified Experts, and recognize that as a matter of both fact and law, the Committee has already decided that "there is no substantial evidence that the criteria of [Section 25306(g)] have been satisfied."

D. *Even if OEHHA Were to Evaluate the Data in the NTP CERHR Monograph Anew, the Studies Cited by NTP-CERHR Clearly Do Not Satisfy the "Sufficient Data" Requirement of Section 25306(g)(2)*

For the reasons recited above, it should not be necessary to reach this issue. Because the NTP-CERHR Monograph does not "formally identify" BPA as a reproductive toxicant, it is beyond OEHHA's authority to review the data discussed in the Monograph independently, and substitute its judgment for that of the authoritative body. And because the DART IC explicitly considered the data and determined that BPA has not been shown to cause developmental toxicity (or reproductive toxicity), the only way that OEHHA could determine now that the animal data summarized above *do* satisfy the requirements of Section 25306(g) would be to substitute its judgment for that of the DART IC and to apply a different and less stringent standard than DART IC applies, in clear violation of Section 25306.

Nevertheless, if OEHHA were to re-examine the data, the agency would have to conclude that the studies cited in the NTP-CERHR Monograph as showing "clear evidence of developmental effects at high doses" are not "sufficient" to indicate that "an association between adverse reproductive effects in humans and the toxic agent is biologically plausible" as required under Section 25306(g)(2). Any contrary decision would not be justifiable by scientific

standards, and would be so lacking in evidentiary support as to render the decision arbitrary and capricious and therefore an abuse of discretion by legal standards.[71]

1. *Section 25306(g)(2) Requires Consideration of Many Factors to Determine Whether an Association Between Adverse Effects Observed in Animals and BPA Is Biologically Plausible in Humans*

The starting point for this analysis is Section 25306(g)(2) itself, which provides as follows:

> (g) for purposes of this section, "***as causing reproductive toxicity" means*** that either of the following criteria have been satisfied:
>
> (1) studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity, or
>
> (2) ***studies in experimental animals*** indicate that there are ***sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to***, ***route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels and consideration of maternal toxicity***, ***indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible***.[72]

Turning next to the Request, under the heading "Formal Identification and sufficiency of evidence," OEHHA recites that the NTP-CERHR Monograph expressed "conclusions" that there is "clear evidence of adverse developmental effects in laboratory animals" (including "fetal death and reduced litters size in rats") at 'high' levels of exposure," and that "based on the NTP CERHR report and ***the references cited in the report,*** the evidence appears sufficient for listing by the authoritative bodies mechanism."[73]

Even taking the recitation in the Request at face value – *i.e.*, assuming for the sake of argument that the NTP Brief did "conclude" that there is "clear evidence of adverse developmental effects in laboratory animals at 'high' levels of exposure" – that in itself would not be sufficient cause for listing BPA. Under Proposition 65, the critical question remains whether – assuming such effects in animals – an association between those adverse effects observed in animals and the same effects in humans due to exposure to BPA is "biologically

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[71] *Exxon Mobil v. OEHHA*, 169 Cal.App.4th at 1277.

[72] Cal. Code Regs., *tit.* 27, § 25306(g) (emphasis added; reformatted for clarity).

[73] OEHHA, *Request for Relevant Information on a Chemical Being Considered for Listing buy the Authoritative Bodies Mechanism: Bisphenol A [2/12/10]* at 1 (emphasis added).

plausible." In order to reach that conclusion, OEHHA must evaluate the "references cited in the report" against (at a minimum) the factors recited above in the text of Section 25306(g)(2).[74]

The "references cited in the report" are the same eight animal studies identified above and referenced in the footnote of Figure 2b of the NTP Brief on BPA. For purposes of Proposition 65, five of those studies are not relevant in evaluating BPA as a developmental toxicant, because they involved post-natal as well as pre-natal exposure (one involved only post-natal exposure) and it is not possible to distinguish adequately between the effects observed in those studies that are attributable to pre-natal or post-natal exposure. Removing from consideration those studies that are not relevant, the remaining three studies would not support NTP's observation of the "weight of the evidence." Furthermore, to the extent that any of the four "partially post-natal" studies are relevant, the adverse effects observed in the studies continue to be secondary to maternal toxicity.

a. *Pre-Natal v. Post-Natal Exposure*

It is well-recognized that developmental effects attributable to post-natal exposure are not within the purview of Proposition 65. This principle, established from the outset in the implementation of Proposition 65, was explained and confirmed at a public meeting of the DART IC on December 4. 1996. At that meeting, OEHHA's then-Chief Counsel William Soo Hoo confirmed on the record the long-standing principle that "postnatal exposures [are] not encompassed by Proposition 65." This position, Mr. Soo Hoo explained, was first enunciated by Dr. Steven Book, the "former and original Director for OEHHA," who also served as the Science Advisor to the Secretary of the California Health and Welfare Agency (the first "lead agency" responsible for the administration of Proposition 65), as well as Mr. Peter Baldridge, Mr. Soo Hoo's predecessor as Chief Counsel. Mr. Soo Hoo further explained that this principle is "reflected in the DART Committee's . . . guidelines . . . [and] affirm that ***developmental toxicity is to be considered by the DART Committee only with regard to pre-natal exposures.***"[75] Because this standard is imposed as a matter of statutory interpretation, and for all of the other reasons discussed in the Statement of Reasons regarding the designation of authoritative bodies, the same constraint applies to OEHHA in examining the NTP-CERHR Monograph. Judged against this standard, the eight studies cited in the NTP-CERHR Monograph do not constitute "sufficient data," within the meaning of Section 25306(g)(2), to support a finding that BPA causes adverse developmental effects for purposes of Proposition 65.

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[74] We understand from discussions with OEHHA personnel following the issuance of the Request, and from the holding in *Exxon Mobil v. OEHHA*, that the agency applies the US EPA Guidelines for Developmental Toxicity Risk Assessment ("US EPA Guidelines" or "Guidelines") in its application of Section 25306(g). While certain aspects of those Guidelines ***may*** be appropriate in the implementation of Proposition 65, their wholesale adoption in listing decisions clearly is not appropriate. As the full name of the Guidelines indicates, they were developed for purposes of risk assessment, of which hazard identification is just one part. The confusion of these two concepts and their underlying purposes may tend toward confusion in listing decisions. As discussed above, the criteria under Section 25306(g) are intended to be applied consistently with, not different from, the DART IC Criteria.

[75] Statement and testimony of Mr. William Soo Hoo, OEHHA General Counsel, delivered at the December 4, 1996 meeting of the DART IC, pp. 13-14 (emphasis added). Mr. Soo Hoo's statement appears at Attachment 6 to this response. Relevant pages from the transcript of the December 4, 1996 Committee meeting appear at Attachment 7.

In this regard, the references to "adverse developmental effects" in the NTP Brief are themselves unclear for purposes of Proposition 65: the fact that the NTP Brief speaks of "adverse developmental effects" cannot be taken to mean that NTP observed effects that would fall in the category of "developmental toxicity" for purposes of Proposition 65. To explain, there is nothing either in the Expert Report or the NTP Brief to indicate that the term "developmental effects" is restricted to effects from pre-natal exposure. Rather, the studies to which the NTP Brief cites as showing "adverse developmental effects" include many studies where exposure occurred post-natally. In other words, NTP uses terms such as "developmental toxicity" and "adverse developmental effects" to include effects caused by pre-natal ***or*** post-natal exposure, and thus embraces effects that would not cause a chemical to be designated as a developmental toxicant for purposes of Proposition 65. Thus, where the NTP Brief indicates that the eight "cited references" show "clear evidence of adverse developmental effects," NTP is including studies that are not "sufficient," within the meaning of Section 25306(g) to support a conclusion that the chemical is a developmental toxicant for purposes of Proposition 65.[76]

To demonstrate this, the references in the NTP Brief to "adverse developmental effects" are reproduced below. At pages 6 and 7, NTP Brief, raises the question "Can bisphenol A affect human development or reproduction?" The summary response indicates, by its scope, that NTP included effects attributable to post-natal exposure (during the lactation period) in answering that question.

> **CAN BISPHENOL A AFFECT HUMAN DEVELOPMENT OR REPRODUCTION?**
>
> Possibly. Although there is no direct evidence that bisphenol A adversely affects reproduction or development, studies with laboratory rodents show that exposure to high dose levels of bisphenol A during pregnancy ***and/or lactation*** can reduce survival, birth weight, and growth of offspring early in life, and delay onset of puberty in males and females. [Emphasis added.] These effects were seen at the same dose levels that also produced some weight loss in pregnant animals ("dams"). These "high" dose effects of bisphenol A are not considered scientifically controversial and provide ***clear evidence of adverse effects on development in laboratory animals.*** However, the administered dose levels associated with delayed puberty (≥ 50 mg/kg bw/day), growth reductions (≥ 300 mg/kg bw/day), or survival (≥ 500 mg/kg bw/day) are far in excess of the highest estimated daily intake of bisphenol A in children (<0.0147 mg/kg bw/day), adults (<0.0015 mg/kg bw/day), or workers (0.100 mg/kg bw/day).[77] [Emphasis added.]

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[76] Reliance on the US EPA Guidelines similarly may result in the inappropriate consideration of certain adverse effects as "developmental effects." Like NTP-CERHR, US EPA uses the term "developmental toxicity" more broadly than Proposition 65 allows, thus placing the Guidelines in fundamental conflict with Proposition 65. *See, e.g.,* US EPA Guidelines at p. 3 (defining "developmental toxicology" as the "study of adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation").

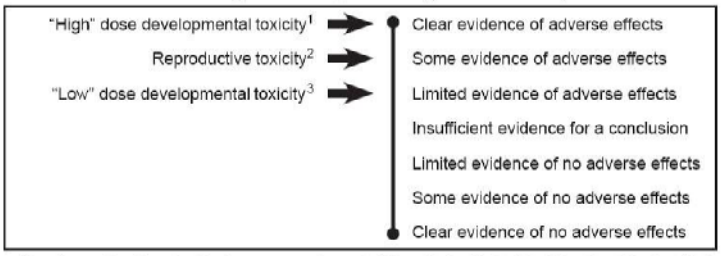
[77] NTP Brief at 6-7.

Elsewhere on page 7, the following appears:

> **SUPPORTING EVIDENCE**
>
> The NTP finds that there is ***clear evidence of adverse developmental effects*** at "high" doses of bisphenol A in the form of fetal death, decreased litter size, or decreased number of live pups per litter in rats (≥ 500 mg/kg bw/day) (36, 37) and mice (≥ 875 mg/kg bw/day) (38,40), reduced growth in rats (≥ 300 mg/kg bw/day) (36,37) and mice (≥ 600 mg/kg bw/day) (38, 39, 41), and delayed puberty in male mice (600 mg/kg bw/day) (41), male rats (≥50 mg/kg bw/day) (37, 42) and female rats (≥ 50 mg/kg bw/day) (37, 43).[78]

Figure 2b (discussed previously and reproduced again below), shows that NTP's response was based in part on NTP References 37, 39, 40, 41 and 42.

Figure 2b. *The weight of evidence that bisphenol A causes adverse developmental or reproductive effects in laboratory animals*



[1]Based on reduced survival in fetuses or newborns (≥500 mg/kg bw/day) *(36–40)*, reduced fetal or birth weight or growth of offspring early in life (≥300 mg/kg bw/day) *(36, 37, 41)*, and delayed puberty in female rats (≥50 mg/kg bw/day) and male rats and mice (≥50 mg/kg bw/day) *(37, 41–43)*.

[2]Based on possible decreased fertility in mice (≥875 mg/kg bw/day) *(40)*; altered estrous cycling in female rats (≥600 mg/kg bw/day) *(110)*, and cellular effects on the testis of male rats (235 mg/kg bw/day) *(111)*.

[3]Based a variety of effects related to neural and behavior alterations (≥10 µg/kg bw/day) *(44–50)*, lesions in the prostate (10 µg/kg bw/day) *(51)* and mammary glands (0.0025–1 mg/kg bw/day) *(52, 53)*; altered prostate gland and urinary tract development (10 µg/kg bw/day) *(54)*, and early onset of puberty (2.4 and 200 µg/kg bw/day) *(48, 55)*.

The table below demonstrates that all five of those studies (NTP References 37, 39, 40, 41, and 42) were reproductive toxicity studies, which by their nature included post-natal exposure. In fact, one of the five reproductive toxicity studies (NTP Reference 42), was conducted on the basis of post-natal exposure only, and thus should not be considered at all. Only three of the eight studies (NTP References 36, 38, and 43) were conducted using pre-natal exposures only.

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78 NTP Brief at 7.

TABLE 1 PERIOD(S) OF EXPOSURE AMONG THE STUDIES CITED IN THE NTP BRIEF			
NTP REFERENCE NO. (AUTHOR & DATE)	TYPE OF STUDY	REPORTED EFFECT(S)	PRE- OR POST- NATAL EXPOSURE
36 (Kim *et al.,* 2001)	Developmental toxicity (rat)	Decrease in litter size; decrease in fetal body weight	Pre-natal exposure only
37 (Tyl *et al*., 2002b)	Reproductive toxicity, 3-generation (rat)	Decrease in litter size; decrease in pup body weight; delayed puberty (male and female)	Pre- and post-natal exposure
38 (Morrissey *et al*., 1987)	Developmental toxicity (mouse)	Increase in resorptions and litter size; decrease in fetal body weight	Pre-natal exposure only
39 (Tyl *et al.,* 2002a)	Reproductive toxicity 1-generation (mouse)	Decrease in litter size; decrease in pup body weight	Pre- and post-natal exposure
40 (NTP, 1985)	Reproductive toxicity, continuous breeding (mouse)	Decrease in litter size	Pre- and post-natal exposure
41 (Tyl *et al*., 2008b)	Reproductive toxicity, 2-generation (mouse)	Decrease in pup body weight; delayed puberty (male)	Pre- and post-natal exposure
42 (Tan *et al*., 2003)	Reproductive toxicity (rat)	Delayed puberty (male)	Post-natal exposure only
43 (Tinwell *et al.,* 2002)	Developmental toxicity (rat)	Delayed puberty (female)	Pre-natal exposure only

The distinction between effects caused by pre-natal exposure and effects caused by post-natal exposure is vitally important in designating a chemical as a developmental toxicant, as reflected in the presentation by Mr. Soo Hoo to the DART IC, discussed above. As noted earlier, an adverse developmental effect does not come within the purview of Proposition 65 unless it is attributable to pre-natal exposure.

For purposes of Proposition 65, developmental toxicity studies with "pre-natal exposure only" (*i.e.,* with no post-natal exposure) are of the highest utility in evaluating a chemical for developmental toxicity, because the reviewer can eliminate the possibility that an adverse effect resulted from post-natal exposure. Similarly, a study based on "post-natal exposure only" (*i.e.*, with no pre-natal exposure) has no utility at all for purposes of Proposition 65, because such a study cannot demonstrate that an effect is the result of pre-natal exposure. The utility of a study that includes both pre-natal and post-natal exposure depends on whether it is possible to differentiate an effect that resulted from pre-natal or post-natal exposure, or both. Importantly, most of the effects observed in the eight studies may be attributed to exposures other than pre-natal exposure, which means that these effects are not relevant to Proposition 65.

Among the four reproductive toxicity studies, which had both pre-natal and post-natal exposure, the effects in these studies could be due to exposure that occurs outside of gestation (*i.e.*, not pre-natal exposure). Further, both male and female parents were exposed to BPA prior to mating in all four of these studies, raising the possibility that the "developmental" effects, such as a decrease in litter size, may be due to male or female reproductive toxicity, not to developmental toxicity as meant by Proposition 65. In fact, one of these studies specifically looked at male reproductive toxicity through a semen evaluation and a cross-mating study; substantial evidence of male reproductive toxicity (including a decrease in litter size when only the male parent was exposed to BPA and a decrease in sperm quality), was seen at doses that produced systemic toxicity.

As noted in the Summary above, "developmental toxicity" is limited for purposes of Proposition 65 to developmental effects caused by pre-natal exposure alone. The use of that term in the NTP-CERHR Monograph, and specifically in the NTP Brief, embraces a much broader range of effects, including effects attributable to post-natal exposure. Thus, where the NTP Brief indicates that there is "clear evidence of adverse developmental effects"[79] in animals, the term "adverse developmental effects" does not have the same meaning as it does for purposes of Proposition 65. Similarly, when the NTP Brief indicates "clear evidence of adverse effects" in laboratory animals for "high dose developmental toxicity,"[80] that determination was made based on the weight-of-the-evidence from eight studies that included effects that would not be considered developmental effects for purposes of Proposition 65. Therefore, the proposal to list BPA on the basis of effects that do not represent developmental toxicity for purposes of Proposition 65 would exceed the mandate under Section 25249.8 of the act, as well as Section 25306(g)(2) of the implementing regulations, and expand the boundaries of Proposition 65 well beyond its recognized limits.

Furthermore, all five of the reproductive toxicity studies cited in the NTP Brief exposed both parents – male and female. There is evidence that at least part of the "developmental" effects observed were due to paternal exposure to BPA, not maternal exposure. In a cross-mating study conducted by NTP (NTP, 1985) employing the same animals used in the continuous-breeding reproduction and fertility study, a 26% decrease in the number of live pups per litter

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[79] NTP Brief at 7.

[80] NTP Brief at 8, Figure 2b.

was observed when BPA-exposed males (high dose) were cross-mated with control (unexposed) females.

With this background in mind, we examine each of the NTP References summarized above, beginning with the five reproductive toxicity studies.

NTP Reference 37 (Tyl *et al.,* 2002b), a 3-generation reproductive toxicity study, reported a decrease in litter size on post-natal day 0 or "PND" 0, suggesting that pre-natal exposure, rather than post-natal exposure, caused this effect. However, the possibility exists that the decrease in litter size at birth was not due to pre-natal exposure. First, the decrease in litter size may have been due to male or female reproductive toxicity from exposure prior to pregnancy, since both the male and female parents were exposed to BPA throughout the mating period and for a minimum period of 10 weeks prior to mating. Second, the decreased litter size may have been due to post-natal exposure to BPA. Pups may have been exposed post-natally to BPA through mothers' milk prior to any observations on PND 0. Pups begin to nurse shortly after delivery, and pups may be up to 24 hours old before the birth of a litter is discovered (PND 0). Mothers may cannibalize pups during the interval prior to the discovery of the birth of a litter, resulting in an observed decrease in litter size on PND 0. Third, it is possible that a decrease in litter size on PND 0 is due to a direct effect on the mother, and not due to pre-natal exposure of the offspring at all. For example, if the mother is not lactating properly, a decrease in litter size on PND 0 may have been the result mother failing to feed their pups or mothers killing their pups shortly after birth. An underweight dam might cannibalize live pups after birth due to hunger and general stress. In summary, the decrease in litter size on post-natal day 0 in this study may have been due to pre-mating exposure, pre-natal exposure, post-natal exposure or a combination of the three. It is not possible to conclude that the decrease in litter size on PND 0 in Reference 37 is due to pre-natal exposure to BPA.

NTP Reference 39 (Tyl *et al*., 2002a), an abbreviated one-generation reproduction study in mice, also reported a decrease in litter size on PND 0, as well as a decrease in pup body weight on PND 0. For all the reasons articulated in the previous paragraph, it is not possible to conclude definitively that the decrease in litter size on PND 0 in Reference 39 is due to pre-natal exposure to BPA. Similarly, a decrease in pup weight on PND 0 may be due to pre-natal and/or post-natal exposure to BPA.

NTP Reference 40 (NTP, 1985), includes a continuous-breeding reproduction and fertility study in mice. Male and female mice were given 0, 437.5, 875, and 1750 mg/kg bw/day of BPA through dietary administration. At the two higher dose levels, exposure to BPA produced a decrease in the number of litters per mated pair of mice (an apparent effect on fertility) and a decrease in the number of live pups per litter. Males and females were exposed continuously throughout the experiment (including 7 days of pre-mating and 98 days of mating), which incorporated multiple matings and pregnancies. The mice were exposed prior to mating, during mating, during pregnancy, and during the lactation period until the pups were sacrificed. It cannot be concluded with certainty that the decrease in litter size was due to prenatal exposure in this study. For example, the decrease in litter size may have been a male or female reproductive effect that was caused by exposure to BPA prior to pregnancy. In fact, there is direct evidence that the effect may be mediated, at least in part, through the father. As noted previously, a cross-mating study was conducted by the same investigators using the same animals used for the

continuous-breeding study of BPA. When BPA-exposed males (high dose) were cross-mated with control females, there was a decrease of 26% in the number of live pups per litter, even though the males were not exposed to BPA in the diet during the cohabitation period due to the cross-mating study design. In addition, a decrease in semen quality, as manifest by a significant decrease in sperm motility, as also observed in the high dose male mice; semen quality was not evaluated at other dose levels. These results suggest that the decrease in the number of live pups per litter is male-mediated – at least in part. This has implications for all of the other reproductive toxicity studies of BPA because both males and females were exposed to BPA.

When BPA-exposed females (high dose) were cross-mated with control males, a 51% decrease in the number of live pups per litter was observed. This demonstrates that exposure to BPA among the females also plays a significant role. But, it is not clear whether the effect among the offspring of exposed BPA-exposed females is due to exposure prior to pregnancy, during gestation, or post-natally.

As noted regarding the previous studies, it also is possible that the decrease in litter size was due to postnatal exposure of the pups. Finally, the decrease in litter size may have been due to an effect on the mother's ability to maintain her pups shortly after birth.

NTP Reference 41 (Tyl *et al.,* 2008b), a 2-generation reproductive toxicity study in mice, reported a significant decrease in pup weight. Both male and female parents were exposed to BPA prior to mating. This effect was first observed on PND 7. Because this effect was not observed before PND 7 and exposures occurred pre-mating, during gestation, and post-natally, there is no way of knowing whether this effect was caused by pre-natal exposure. The decrease in pup weight may have been due to pre-mating exposure, pre-natal exposure, or post-natal exposure, or to a combination of these exposures to BPA, rather than to pre-natal exposure alone.

NTP Reference 42 (Tan *et al.,* 2003) reported delayed puberty in males as measured by the day of preputial separation. This study was based entirely on post-natal exposure, and thus would not support any conclusions regarding developmental toxicity for purposes of Proposition 65. In fact, exposure did not begin until PND 23. Therefore, the effect that was reported could not possibly have been due to pre-natal exposure to BPA.

Thus, in summary, only three of the eight studies to which OEHHA cites (NTP References 36, 38 and 43) are relevant, because these are the only studies cited upon by NTP in which an effect may be attributed with requisite certainty to pre-natal exposure to BPA. Yet, in two of these studies, maternal toxicity was excessive or severe, indicating that the developmental effects were uninterpretable or secondary to maternal toxicity. In the third study, the investigators did not evaluate maternal toxicity at all. Because maternal toxicity presents a separate reason that the data are not "sufficient," we address that issue separately below.

b. *Consideration of Maternal Toxicity*

Even if one were to ignore the issue of pre-natal vs. post-natal exposure and treat all eight studies as relevant, consideration of maternal toxicity indicates that these studies do not constitute sufficient evidence of developmental toxicity under 25306(g). Like the issue of pre-natal v. post-natal exposure, maternal toxicity is an extremely important factor in evaluating whether a study

that shows adverse developmental effects is of any value in determining whether those effects are biologically plausible in humans. Virtually all chemicals have the potential to cause developmental toxicity when they are given at sufficiently high doses to kill or damage the health of the mother.[81]

For example, in a classical developmental toxicity study, a high (but not maternally lethal) dose of table salt (sodium chloride) was shown to cause an increase in resorptions, a decrease in fetal body weight, and fetal malformations in mice (Nishimura and Miyamoto, 1969). In fact, the spectrum of developmental effects observed in mice that were administered high doses of table salt was far more serious than the developmental effects observed after administration of maternally toxic doses of BPA. In this study, pregnant mice were given 0, 1900 or 2500 mg/kg bw/day of table salt on gestation day 10 or 11. These doses approached the maternally lethal dose of table salt, which has an LD50 (the acute dose required to kill 50% of the animals) of 4000 mg/kg bw/day in mice. When table salt was administered subcutaneously to pregnant mice on a single day of gestation, table salt caused an increase in fetal malformations (*e.g.,* cleft palate, missing digits, extra digits, club foot, shortness of forelimb) and up to 48% fetal death or resorptions at doses of 1900 and 2500 mg/kg bw/day. These dose levels of table salt are only slightly higher than the oral dose levels of BPA that were associated with less severe developmental effects and greater maternal toxicity. While there is "clear evidence of adverse effects" for high dose developmental toxicity in laboratory animals exposed to table salt, table salt is not considered to be a human hazard for developmental toxicity, taking into consideration the nearly lethal doses of table salt required to produce developmental toxicity.

Thus, the critical objective in a developmental toxicity study is to determine whether the test substance is a ***selective*** developmental toxicant in humans, *i.e*, to determine whether exposure to the substance is likely to cause adverse effects to the fetus at doses that are not expected to cause so much harm to the mother that the adverse effects to the mother in turn cause adverse effects to the fetus. This also is the purpose, if not a re-statement of, the "sufficient evidence" standard, and the reason why it requires "consideration of maternal toxicity."[82]

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[81] If OEHHA is inclined to apply the US EPA Guidelines, it must consider maternal toxicity, as Section 25306(g)(2) requires. Like the regulation, and like the DART IC Criteria, the Guidelines recognize the impact of maternal toxicity on reproductive and developmental health, and caution that "often it is difficult to distinguish between effects mediated through the parents versus direct interaction with developmental processes. For example, developmental toxicity may be influenced by the effect of toxic agents on the maternal system when exposure occurs during pregnancy or lactation." US EPA Guidelines at p. 4. The Guidelines similarly counsel that "individual endpoints of maternal and developmental toxicity are evaluated in developmental toxicity studies. In order to interpret the data fully, an integrated evaluation must be performed considering all maternal and developmental endpoints." *Id*. at 18.

[82] To the extent that OEHHA is considering the US EPA Guidelines, the following is appropriate to the consideration of the factor identified in Section 25306(g) as "experimental design," counseling that a well-designed study should include doses that will produce "some" maternal toxicity in order to stress the test animals, but that the level of toxicity should not be "excessive" if the results are to be considered valid. "The high dose is selected to produce some minimal maternal or adult toxicity (*i.e.*, a level that at least produces marginal but significantly reduced body weight, reduced weight gain or specific organ toxicity, and the most produces no more than 10% mortality). At doses that cause excessive maternal toxicity (that is, significantly greater than the minimal toxic level) information on developmental effects may be difficult to interpret and of limited value." US EPA Guidelines at 6.
(footnote continued on next page)

The developmental effects reported in the BPA studies cited by the NTP are to be expected, given the degree of maternal toxicity reported by the investigators (with the obvious exception of the study that did not evaluate maternal toxicity). In fact, many of the investigators themselves concluded that the developmental effects observed in these studies were secondary to maternal toxicity. Thus, after consideration of maternal toxicity, these studies do not provide sufficient data to support a conclusion that would, in the words of Section 25306(g) "indicat[e] that an association between adverse [developmental] effects ***in humans*** and [BPA] is biologically plausible" (emphasis added).

(1) *Maternal Toxicity in the Three Developmental Toxicity Studies*

As noted above, only three of the eight studies relied upon by NTP, References 36, 38, and 43, produced effects that can be definitively attributed to pre-natal exposure to BPA. These are the only studies that should be relevant to the issue of whether the data that NTP relied upon present sufficient evidence of developmental toxicity. None of these studies demonstrated developmental effects in the absence of maternal toxicity. In fact, one of these studies (NTP Reference 43) did not even monitor or measure maternal toxicity, precluding any evaluation of the role of maternal toxicity in this study. The other two studies (NTP References 36 and 38) did measure maternal toxicity, and both of these studies demonstrated that the degree of maternal toxicity observed is more than sufficient to account for developmental effects.

Table 2, below, summarizes the evidence of maternal toxicity observed in the three developmental toxicity studies, and compares the Lowest Observed Adverse Effect Level ("LOAEL") for maternal and developmental effects.

TABLE 2
EVIDENCE OF MATERNAL TOXICITY IN THE THREE DEVELOPMENTAL TOXICITY STUDIES WITH PRE-NATAL ONLY EXPOSURE CITED IN THE NTP BRIEF

NTP REFERENCE NO. (AUTHOR & DATE)	REPORTED DEVELOPMENTAL EFFECT(S)	REPORTED MATERNAL EFFECT(S) AT LOAEL FOR DEVELOPMENTAL EFFECTS	MATERNAL LOAEL/ DEVELOPMENTAL LOAEL
36 (Kim *et al.,* 2001)	Decrease in litter size; decrease in fetal body weight	Abnormal clinical signs (severe diarrhea and urination throughout the study, decreased in locomotor activity, emaciation, sedation, piloerection, dull fur, reddish tear, perineal soiling; expansion and/or congestion of the stomach and	300 mg/kg bw/day 1000 mg/kg/ bw/day

In observing this Guideline, OEHHA should take note that this guidance is directed at study design, and counsels investigators to design their studies using dose levels that produce adult mortality rates no higher than 10%. The Guideline should not be interpreted as a directive to evaluators to treat adult mortality rates of lower than 10% as insignificant, or to decline to acknowledge maternal toxicity as the cause of adverse developmental effects unless adult mortality exceeds 10%.

TABLE 2 EVIDENCE OF MATERNAL TOXICITY IN THE THREE DEVELOPMENTAL TOXICITY STUDIES WITH PRE-NATAL ONLY EXPOSURE CITED IN THE NTP BRIEF			
NTP REFERENCE NO. (AUTHOR & DATE)	REPORTED DEVELOPMENTAL EFFECT(S)	REPORTED MATERNAL EFFECT(S) AT LOAEL FOR DEVELOPMENTAL EFFECTS	MATERNAL LOAEL/ DEVELOPMENTAL LOAEL
		intestines); decrease in body weight (15% decrease in corrected body weight) and body weight gain (52% decrease); decrease in food consumption; inc. pregnancy failure. In a preliminary study, a dose of 1200 mg/kg bw/day caused maternal death.	
38 (Morrissey *et al*., 1987)	Increase in resorptions and litter size; decrease in fetal body weight	Maternal death (18% death rate); decrease in weight gain; increase relative liver weight, clinical signs, including arched back, lethargy, piloerection, rough coat, vaginal bleeding, vocalization, alopecia, weight loss, and wheezing	500 mg/kg bw/day 1250 mg/kg bw/day
43 (Tinwell *et al.,* 2002)	Delayed female puberty (vaginal patency) in one of two strains of rats; no effect on estrous cycle in either strain.	Not measured	Not Available

A more detailed analysis of each study confirms this.

NTP Reference 36, Kim *et al*., (2001), reported serious maternal toxicity at the high dose (1000 mg/kg bw/day), which is the only dose that produced developmental toxicity (*i.e*., decreased litter size). According to the summary in the NTP Expert Panel Report, the "[s]tudy authors concluded that exposure of rats to a maternally toxic dose of bisphenol A during the entire gestation period resulted in pregnancy failure, post-implantation loss, reduced fetal body weight, and retarded fetal ossification but no dysmorphogenesis."[83] The Expert Panel apparently agreed. Commenting on the strengths and weaknesses of the study, the Expert Panel wrote: This report presents a fairly standard embryo-fetal developmental toxicity study. One strength is that

[83] NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A ["NTP-CERHR Expert Panel Report"] (2008) Birth Defects Research (Part B) 83:157-395, at 238.

the doses utilized incorporated both a no-effect dose and a high maternally toxic dose, reveal fetal effects only at the high-dose that showed marked maternal toxicity."[84]

Looking to the data themselves, the clinical observations of toxicity reported among the pregnant rats at this dose were substantial and included: severe diarrhea and urination throughout the study, decreased locomotor activity, emaciation, sedation, piloerection, dull fur, reddish tear, perineal soiling, expansion and/or congestion of the stomach and intestines. Other signs of maternal toxicity included decreased body weight (15% decrease in corrected body weight), decreased body weight gain (52% decrease), decreased food consumption, and an increase in pregnancy failure. Importantly, in a range-finding study by the same investigators, a slightly higher dose (1200 mg/kg bw/day) caused maternal death. The degree of maternal toxicity observed in this study is more than enough to explain the decrease in litter size observed at the high dose in this study. In fact, given the degree of maternal toxicity observed at a nearly lethal dose, it is surprising that more evidence of developmental toxicity was not seen. No developmental effects were observed at the middle dose (300 mg/kg/day), a dose which still produced maternal toxicity, albeit less than was observed at the high dose.

NTP Reference 38, Morrissey *et al*., (1987), reported an increase in fetal resorptions in a developmental study of BPA in the mouse. According to the NTP-CERHR Expert Panel, "One or 2 of 29-34 dams died in each of the 3 lowest doses [500, 750, and 1000 mg/kg bw/day] and 6 of 33 dams [18%] died in the 1250 mg/kg bw/day group." Clinical signs reported in mice treated with BPA included arched back, lethargy, piloerection, rough coat, vaginal bleeding, vocalization, alopecia, weight loss, and wheezing. Statistically significant increases in relative liver weight were observed at all doses. An increase in resorptions and a decrease in fetal body weight was observed at the high dose, 1250 mg/kg bw/day. No signs of developmental toxicity were observed at doses below 1250 mg/kg bw/day. The study authors concluded that BPA is not teratogenic in mice at doses that result in maternal toxicity.[85]

As the NTP-CERHR Expert Panel noted, administration of the high dose (1250 mg/kg bw/day), which was the only dose that produced increased fetal resorptions, produced maternal death among 18% of the pregnant mice. A maternal death rate above 10% is not only enough to explain an increase in fetal resorptions, it is also considered to be an unacceptably high level of maternal toxicity to interpret the results of a developmental toxicity study Regulatory agencies generally require that the high dose level in a developmental toxicity study be sufficiently high to cause some maternal toxicity. If the dose is too high, however, it can cause excessive maternal toxicity, which makes it extremely difficult, if not impossible, to interpret the results of the study.

Thus, the US EPA Guidelines for Developmental Toxicity Risk Assessment (1991) state: "The high dose is selected to produce some minimal maternal toxicity or adult toxicity (*i.e.,* a level that at least produces marginal but significantly reduced body weight, reduced weight gain, or specific organ toxicity, and at most produces no more than 10% mortality). At doses that cause excessive maternal toxicity (that is, significantly greater than the minimal toxic level) information on developmental effects may be difficult to interpret and of limited value."

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[84] NTP-CERHR Expert Panel Report at 238.

[85] NTP-CERHR Expert Panel Report at 237.

Therefore, according to the US EPA criteria, the effect observed at the high dose in NTP Reference 38 is of virtually no value for human hazard identification, because the only dose that produced developmental toxicity caused excessive maternal toxicity, such that any developmental effects are "difficult to interpret and of limited value." Indeed, the increased incidence of resorptions per litter is attributed to seven litters at the high dose that were completely resorbed. BPA had ***no*** significant effect on the number of live fetuses per litter for those litters that were not completely resorbed. It is not surprising that a dose that killed 18% of the pregnant females was so maternally toxic that seven of the surviving dams resorbed their entire litter. Virtually any substance that is given at such a high dose to pregnant rats that it kills 18% of the mothers would be expected to cause an increase in resorptions. As noted by US EPA, such a result is of limited value for human hazard identification.

Finally, NTP Reference 43, Tinwell *et al*., (2002), a developmental toxicity study in the rat, made no attempt to monitor for maternal toxicity. This was not a conventional developmental toxicity study. The US EPA Guidelines for Developmental Toxicity Risk Assessment (1991) contain at page 10 a description of the minimal amount of information considered useful for evaluating maternal toxicity; this study did not monitor any of these minimal endpoints. Because no observations of maternal toxicity were made at all, it is not possible to (1) take maternal toxicity into consideration, and (2) conclude that any adverse effects observed in this study were due to the direct action of BPA on the embryo or fetus (and not due to maternal toxicity).

In summary, consideration of maternal toxicity among the three studies with pre-natal only exposure indicates that there is insufficient evidence to satisfy the listing requirement of Section 25306(g). In two studies, there was excessive or serious maternal toxicity at the only dose that produced developmental effects. The developmental effects are easily explained by the degree of maternal toxicity because, in both studies, a lower dose also produced maternal toxicity, but no evidence of developmental toxicity. These studies thus indicate that developmental toxicity is secondary to maternal toxicity. In the third study, the authors did not even look for maternal toxicity.

(2) *Maternal Toxicity in the Five Studies Considered Relevant by OEHHA*

It is our understanding that OEHHA considers five of the eight studies relied upon by NTP, NTP References 36-40, to be relevant, because these are the studies that reported a decrease in litter size or an increase in resorptions. As discussed above, three of these studies are not relevant; the reported effect cannot be attributed to pre-natal exposure with certainty, because exposure to BPA occurred both pre-natally and post-natally. Nevertheless, assuming for the sake of argument that all five of these studies demonstrate developmental effects due to pre-natal exposure (which they do not), it is instructive to examine the evidence of maternal toxicity observed in these five studies, as summarized in Table 3.

In all five studies, developmental effects were observed only in the presence of significant maternal toxicity. In fact, the LOAEL for maternal toxicity was less than the LOAEL for developmental toxicity in all five studies. The degree of maternal toxicity observed was more

than enough to account for the developmental effects reported in these studies. In all cases, the developmental effects were secondary to maternal toxicity.

The evidence of maternal toxicity in NTP References 36 and 38 is summarized above. The evidence of maternal toxicity in the remaining three studies, NTP References 37, 39 and 40, is discussed below.

NTP Reference 37 (Tyl *et al*., 2002b) is a state-of-the-art, three-generation reproductive toxicity study in rats. The Expert Panel Report summarizes: "The study authors identified an offspring and reproductive NOAEL of 750 ppm (~50 mg/kg bw/day). A systemic NOAEL for adult rats was identified at 75 ppm (~5 mg/kg bw/day) by the study authors; therefore, bisphenol A was not considered a selective developmental toxicant."[86]

In more detail, BPA was administered to male and female rats in the diet at levels to provide doses of 0, 0.001, 0.02, 0.3, 5, 50, and 500 mg/kg bw/day. Developmental effects were observed at the high dose only (500 mg/kg bw/day); these effects included decreased litter size, decreased pup body weight, and delayed puberty. Therefore, the LOAEL for developmental toxicity was 500 mg/kg bw/day. At this dose, substantial maternal toxicity was observed. Signs of maternal toxicity at 500 mg/kg bw/day included decreased maternal body weight (approximately 30% decrease) and body weight gain. No consistent effect on food consumption was reported. The investigators also reported a decrease in absolute and increase in relative organ weights (liver, kidneys, adrenals, spleen, pituitary, brain). Mild histological changes in female kidneys and livers were observed at the high dose.

The degree of maternal toxicity reported at the high dose in NTP Reference 37 was more than sufficient to account for the observations of developmental effects. Less pronounced maternal toxicity was evident at the next lower dose, 50 mg/kg bw/day, but no developmental effects were seen at this dose level. As such, the LOAEL for maternal toxicity was less than the LOAEL for developmental effects. The results of this study show that the developmental effects are secondary to maternal toxicity.

NTP Reference 39 (Tyl *et al.,* 2002a) is an abbreviated one-generation reproductive toxicity study in mice. BPA was administered in the diet in amounts to provide doses of 0, 870, and 1716 mg/kg bw/day. Developmental effects were reported at the high dose only. According to NTP, the developmental effects that were observed included a decrease in litter size and a decrease in pup body weight. At the only dose that produced developmental effects, BPA caused significant maternal toxicity, including a decrease in body weight gain, an increase in absolute liver and kidney weight, an increase in the incidence and severity of hepatocyte hypertrophy and an increase in kidney lesions (renal tubular epithelial necrosis degeneration, and regeneration). Thus, the only dose associated with developmental effects in this study caused significant maternal toxicity. The lower dose (870 mg/kg bw/day) also caused some maternal toxicity, but no developmental effects were reported at this dose. The degree of maternal toxicity observed at the high dose is sufficient to have caused the developmental effects reported in this study.

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[86] NTP-CERHR Expert Panel Report at 249.

NTP Reference 40 (NTP, 1985) is a continuous-breeding reproduction and fertility study in mice. Male and female mice were given 0, 437.5, 875, and 1750 mg/kg bw/day of BPA through dietary administration. Mice were exposed continuously throughout the experiment (7 days of pre-mating and 98 days of mating), which included multiple matings and pregnancies. The mice were exposed prior to mating, during mating, during pregnancy, and during the lactation period until the pups were sacrificed. At the two higher dose levels, exposure to BPA produced a decrease in the number of litters per mated pair of mice, a decrease in the number of live pups per litter, and an increase in live pup weight. Measurements of adult systemic toxicity were limited. The investigators reported a significant decrease in postpartum body weights at the high dose, "indicating generalized maternal toxicity." According to the investigators, "Since F0 maternal postpartum weights tended to decrease at doses of 0.5% [875 mg/kg bw/day], and were significantly less than controls in the 1.0% BPA group, the observed toxicity to the conceptus may be all or in part due to generalized maternal toxicity." Organ weights and histopathology were evaluated only in the control and high dose groups. Liver weight was significantly increased in the high dose dams. Histopathological evaluation revealed "significant hepatic and renal toxicity." The authors concluded: "It is possible, therefore, that some or all of the adverse effects on reproductive performance observed in the present study may be secondary to the generalized toxicity of BPA."

TABLE 3
EVIDENCE OF MATERNAL TOXICITY IN THE FIVE DEVELOPMENTAL OR REPRODUCTIVE TOXICITY STUDIES CONSIDERED RELEVANT BY OEHHA

NTP REFERENCE NO. (AUTHOR & DATE)	REPORTED DEVELOPMENTAL EFFECT(S)	REPORTED MATERNAL EFFECT(S) AT LOAEL FOR DEVELOPMENTAL EFFECTS	MATERNAL LOAEL/ DEVELOPMENTAL LOAEL,
36 (Kim *et al.,* 2001)	Decrease in litter size; decrease in fetal body weight	Abnormal clinical signs (severe diarrhea and urination throughout the study, decrease in locomotor activity, emaciation, sedation, piloerection, dull fur, reddish tear, perineal soiling; expansion and/or congestion of the stomach and intestines); decrease in body weight(15% decrease in corrected body weight) and body weight gain (52% decrease); decrease in food consumption; increase in pregnancy failure; maternal death at dose of 1200 mg/kg bw/day in preliminary study	300 mg/kg bw/day 1000 mg/kg bw/day
37 (Tyl *et al.,* 2002b)	Decrease in litter size; decrease in pup body weight; delayed puberty (male and female)	Decrease in body weight (~ 30%) and body weight gain; decrease in absolute and increase I relative organ weight (liver, kidneys, adrenals, spleen, pituitary, brain); mild histologic changes in female kidney and liver	50 mg/kg bw/day 500 mg/kg bw/day

TABLE 3 EVIDENCE OF MATERNAL TOXICITY IN THE FIVE DEVELOPMENTAL OR REPRODUCTIVE TOXICITY STUDIES CONSIDERED RELEVANT BY OEHHA			
NTP REFERENCE NO. (AUTHOR & DATE)	REPORTED DEVELOPMENTAL EFFECT(S)	REPORTED MATERNAL EFFECT(S) AT LOAEL FOR DEVELOPMENTAL EFFECTS	MATERNAL LOAEL/ DEVELOPMENTAL LOAEL,
38 (Morrissey *et al*., 1987)	Increase in resorptions and litter size; decrease in fetal body weight	Maternal death (18% death rate); decrease in weight gain; increase relative liver weight, clinical signs, including arched back, lethargy, piloerection, rough coat, vaginal bleeding, vocalization, alopecia, weight loss, and wheezing	500 mg/kg bw/day 1250 mg/kg bw/day
39 (Tyl *et al.*, 2002a)	Decrease in litter size; decrease in pup body weight	Decrease in body weight gain; increase in absolute and relative liver and kidney weight, incidence and severity of hepatocyte hypertrophy and kidney lesions (renal tubular epithelial necrosis, degeneration, and regeneration)	870 mg/kg bw/day 1716 mg/kg bw/day
40 (NTP, 1985)	Decrease in litter size	Decrease in food consumption (13% decrease); increase in relative liver and kidney weight and significant hepatic and renal toxicity at high dose; not measured at 437 or 875 mg/kg bw/day	437 mg/kg bw/day 875 mg/kg bw/day

(3) *Maternal Toxicity in All Eight Studies Evaluated by NTP*

Even if one were to consider all eight studies of BPA relied upon by NTP, it is apparent that the amount of evidence of developmental toxicity does not satisfy the requirements of Section 25306(g) after consideration of maternal toxicity. Setting aside the issue that most of these studies do not provide evidence of developmental toxicity, as that term is defined by Proposition 65, it is helpful to examine the relationship between doses required to produce developmental effects and those that cause maternal toxicity. Two studies did not evaluate maternal toxicity; in one case, the investigators simply did not monitor for maternal toxicity, and in the other there was no pre-natal exposure so no mothers were exposed to BPA. Among the six studies that evaluated maternal toxicity, all showed that developmental effects were always associated with significant or even excessive maternal toxicity, and all show types of developmental effects (e.g., reduced weight, not malformations) consistent with maternal toxicity. Of note, in all cases, the dose required to produce maternal toxicity was always lower than the dose required to produce developmental toxicity. In every case, the degree of maternal toxicity observed was more than sufficient to explain the developmental effects.

In the previous two sections, we described all of these studies but two (NTP References 41 and 42). In this section, the two remaining studies are summarized with respect to the relationship between developmental effects and maternal toxicity. Table 4 provides a summary of the evidence of maternal toxicity in all eight studies relied upon by NTP.

NTP Reference 41 (Tyl, *et al.,* 2008b) is a state-of-the-art, two-generation reproductive toxicity study of BPA in mice. The Expert Panel Report summarizes: "The study authors identified bisphenol A NOELs of 30 ppm (~ 5 mg/kg bw/day) for systemic effects and 300 ppm (50 mg/kg bw/day) for developmental toxicity."[87] This study was conducted subsequent to the abbreviated one-generation reproductive toxicity study of BPA in mice (Tyl *et al.,* 2002a), by the same investigators. BPA was administered to mice in the diet at dose levels of 0, 0.003, 0.03, 0.3, 5, 50 and 600 mg/kg bw/day. Some developmental effects were reported at the high dose (600 mg/kg bw/day); these effects included a decrease in pup weight on PND 7-21 among F1 pups (but not among F2 pups) and a slight delay in male puberty that the authors did not consider to be biologically significant. At 600 mg/kg bw/day, maternal toxicity included an increase in absolute and/or relative liver and kidney weights, as well as histopathological changes in the liver. The investigators concluded that the delay in puberty was secondary to systemic toxicity: "It is likely that these transient effects were secondary to (or caused by) systemic toxicity." At the second highest dose, 50 mg/kg bw/day, some maternal toxicity was observed, but no developmental effects were reported. Thus, the results of NTP Reference 41 are consistent with the other studies. Developmental effects were observed only at a dose that produced significant maternal toxicity. In fact, the authors attributed the developmental effects to maternal toxicity.

NTP Reference 42 (Tan *et al.*, 2003) is a reproductive toxicity that evaluated the effect of post-natal exposure to BPA on the timing of the onset of puberty. There was no pre-natal or maternal exposure to BPA in this study. Obviously, there was no observation of maternal toxicity in this study since the study design did not include exposing pregnant rats. This study, by definition, cannot be evidence of adverse developmental effects for purposes of Proposition 65.

TABLE 4
EVIDENCE OF MATERNAL TOXICITY IN THE EIGHT DEVELOPMENTAL OR REPRODUCTIVE TOXICITY STUDIES CITED IN THE NTP BRIEF

STUDY (NTP REFERENCE & AUTHOR)	REPORTED DEVELOPMENTAL EFFECT(S)	REPORTED MATERNAL EFFECT(S) AT LOAEL FOR DEVELOPMENTAL EFFECTS	MATERNAL LOAEL/ DEVELOPMENTAL LOAEL
36 (Kim *et al.,* 2001)	Decrease in litter size; decrease in fetal body weight	Abnormal clinical signs (severe diarrhea and urination throughout the study, decrease in locomotor activity, emaciation, sedation, piloerection, dull	300 mg/kg bw/day 1000 mg/kg bw/day

[87] NTP-CERHR Expert Panel Report at 302.

TABLE 4 EVIDENCE OF MATERNAL TOXICITY IN THE EIGHT DEVELOPMENTAL OR REPRODUCTIVE TOXICITY STUDIES CITED IN THE NTP BRIEF			
STUDY (NTP REFERENCE & AUTHOR)	REPORTED DEVELOPMENTAL EFFECT(S)	REPORTED MATERNAL EFFECT(S) AT LOAEL FOR DEVELOPMENTAL EFFECTS	MATERNAL LOAEL/ DEVELOPMENTAL LOAEL
		fur, reddish tear, perineal soiling; expansion and/or congestion of the stomach and intestines); decrease in body weight (15% decrease in corrected body wt.) and body weight gain (52% decrease); decrease in food consumption; increase in pregnancy failure. In a preliminary study, a dose of 1200 mg/kg bw/day caused maternal death.	
37 (Tyl *et al*., 2002b)	Decrease in litter size; decrease in pup body weight; delayed puberty (male and female)	Decrease in body weight (~ 30%) and body weight gain; decrease in absolute and increase relative organ weight (liver, kidneys, adrenals, spleen, pituitary, brain); mild histologic changes in female kidney and liver	50 mg/kg bw/day 500 mg/kg bw/day
38 (Morrissey *et al*., 1987)	Increase in resorptions and litter size; decrease in fetal body weight	Maternal death (18% death rate); decrease in weight gain; increase relative liver weight, clinical signs, including arched back, lethargy, piloerection, rough coat, vaginal bleeding, vocalization, alopecia, weight loss, and wheezing	500 mg/kg bw/day 1250 mg/kg bw/day
39 (Tyl *et al*., 2002a)	Decrease in litter size; decrease in pup body weight	Decrease in body weight gain; increase in absolute and relative liver and kidney weight; increase in incidence and severity of hepatocyte hypertrophy and increase in kidney lesions (renal tubular epithelial necrosis, degeneration, and regeneration)	870 mg/kg bw/day 1716 mg/kg bw/day
40 (NTP, 1985)	Decrease in litter size	Decrease in food consumption (13% decrease); increase in relative liver and kidney weight and significant hepatic and renal toxicity at high dose; not measured at 437 or 875 mg/kg bw/day	437 mg/kg bw/day 875 mg/kg bw/day
41 (Tyl *et al.,* 2008b)	Decrease in pup body weight; delayed	Increase in absolute and/or relative liver and kidney weight;	50 mg/kg bw/day 600 mg/kg bw/day

TABLE 4 EVIDENCE OF MATERNAL TOXICITY IN THE EIGHT DEVELOPMENTAL OR REPRODUCTIVE TOXICITY STUDIES CITED IN THE NTP BRIEF			
STUDY (NTP REFERENCE & AUTHOR)	REPORTED DEVELOPMENTAL EFFECT(S)	REPORTED MATERNAL EFFECT(S) AT LOAEL FOR DEVELOPMENTAL EFFECTS	MATERNAL LOAEL/ DEVELOPMENTAL LOAEL
	puberty	histopathological change in liver (centrilobular hepatocyte hypertrophy of minimal severity)	
42 (Tan *et al*., 2003)	Delayed puberty	Not measured (no pre-natal exposure)	Not Available
43 (Tinwell *et al.,* 2002)	Delayed female puberty (vaginal patency) in one of two strains of rats; no effect on estrous cycle in either strain.	Not measured	Not Available

2. *The Animal Data Do Not Show That an Association Between the Effects Observed in Animals and Adverse Developmental Effects in Humans Is Biologically Plausible*

Even in their totality, the eight studies relied upon by the NTP do not show that an association between exposure to BPA and the observed effects in humans is biologically plausible. Again, Section 25306(g)(2) sets the standard and, in full, requires a determination that there are "***sufficient data***" from animal studies, taking into account such factors as "***route of administration,***" "***frequency and duration of exposure***," "***choice of dosage levels,***" "***consideration of maternal toxicity***," ***and others***, to indicate "an association between adverse reproductive effects in humans and the toxic agent in question" that is "biologically plausible."

The full articulation of this standard, taken directly from Section 25306(g)(2), raises two objections to any proposal to list BPA. Either is cause for OEHHA to halt the listing process.

First, it appears the Request is premised on a finding that does not meet the correct regulatory standard. At page one, under the heading "Background on listing via the authoritative bodies mechanism," the Request correctly recites that "[a] chemical must be listed under the Proposition 65 regulations when OEHHA determines that two conditions are met: . . . 1. The evidence considered by the authoritative body meets the sufficiency criteria contained in [Section] 25306(g)." The only information offered in the Request to indicate that the "sufficiency criteria" are satisfied, however, is the following statement at page two: "The NTP-CERHR report concludes that there is clear evidence of adverse developmental effects in

laboratory animal at "high" levels of exposure. Developmental effects include fetal death and reduced litter size in rats and mice exposed prenatally."

As noted above, the definitional standard under Section 25306(g) requires a showing of "biological plausibility" in an association between exposure to BPA and adverse developmental effects in humans. The observation that "there is clear evidence of adverse developmental effects in laboratory animals" is merely an indication that ***one*** of the factors enumerated under Section 25306(g) has been recognized. Without more, however, it is not a statement that the correct regulatory standard is being followed, much less satisfied. Clear evidence of developmental toxicity in animals in the absence of a biologically plausible threat of a developmental hazard to humans is not sufficient. Unless the agency is prepared to establish that Section 25306(g) is satisfied, *i.e.,* that an association between those effects and exposure to BPA in humans is "biologically plausible," then the listing process should be halted.

Second, the correct regulatory standard cannot be met. Assuming that the Request merely mis-states the Section 25306(g) standard, and OEHHA believes that all of the factors identified therein have been addressed, the animal data do not demonstrate that an association between exposure to BPA and developmental effects ***in humans*** is biologically plausible. Thus, the all-important end-point under Section 25306(g), referred to herein simply as a "biologically plausible association," has not been reached.

There are at least four reasons why a biologically plausible association has not been established. First, as discussed previously, the animal studies demonstrate that maternal toxicity in animals is consistently observed at dose levels lower than those required to produce developmental toxicity. Second, also discussed above, maternal toxicity is sufficient to cause the developmental effects observed at high doses in developmental toxicity studies of BPA in mice and rats. Third, it is clear that humans are not exposed at levels even remotely close to maternally toxic levels of BPA. Fourth, pharmacokinetic differences between rodents and humans are substantial, and even if humans were exposed to the same high doses of BPA used in the laboratory animal studies, developmental effects would not be expected in humans due to differences in pharmacokinetic handling.

As the articulation of these four reasons indicates, the issue of dose is extremely important, not only in its own right, but also in the consideration of maternal toxicity and pharmacokinetics. According to the NTP Brief, the doses that produced "high" dose developmental effects in rodents were over ***3500 times higher*** than "worst-case" doses in infants and children and ***160,000 times higher*** than estimated daily intakes in children ages 6 - 11 and adult women.[88] In other words, the dose that was required to induce adverse developmental

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[88] NTP Brief at p. 36 (The "high" dose effects of bisphenol A that represent clear evidence for adverse effects on development, *i.e.,* reduced survival (≥ 500 mg/kg bw/day) (36 – 40), reduced birth weight and growth of offspring early in life (≥ 300 mg/kg bw/day) (36 – 39, 41), and delayed puberty in female rats and male rats and mice (≥ 50 mg/kg bw/day) (37, 41 – 43), are observed at dose levels that are ***more than 3,500- times higher than "worst case" daily intakes of bisphenol A in infants and children*** less than 6 years of age (≥ 50 mg/kg bw/day versus 0.008 – 0.0147 mg/kg bw/day). The differences in exposures are much greater, more than 160,000- times different, when the high oral dose level is compared to estimated daily intakes for children ages 6 – 11 and adult women (as an indicator

(footnote continued on next page)

effects in rats and mice was over 3500 times more the exposure of the subset of the human population with the highest exposure relative to body weight.

It is clear from the NTP-CERHR Monograph, and extremely important for purposes of any proposal to list BPA under the authoritative bodies mechanism, that NTP took this into account when it declined to conclude that BPA is a reproductive toxicant. This is clear because, as noted previously, NTP concluded that it has only "negligible concern" that BPA might produce the same adverse developmental effects in humans that were seen in laboratory animals. (In fact, NTP took into account both the choice of dose levels and maternal toxicity. Indeed, the NTP's reasoning was practically identical to that of the DART IC when it considered maternal toxicity and other relevant factors made by the DART IC at the July 15, 2009 public meeting on BPA, as noted earlier.)

It is important that NTP took this into account because OEHHA is prohibited from "substituting its judgment" for that of the authoritative body. *See* Section IV.F, below. As discussed at length in Section IV.A. above, NTP-CERHR did not formally identify BPA as a reproductive toxicant within the meaning of Proposition 65, and did not conclude that BPA causes developmental toxicity for purposes of the Act. With that issue resolved, it is not OEHHA's role to examine the data independently to see if the agency would reach a different conclusion.

Even if it were to do so, however, OEHHA should not reach a different conclusion. Section 25306(g)(2) expressly recognizes the importance of "dose-response" in identifying reproductive and developmental toxicants. Indeed, the US EPA Guidelines, on which OEHHA is known at times to rely, also take dose-response relationships into account, indicating that hazard identification (in this case, the identification of chemical agents that produce adverse developmental effects) should be conducted in conjunction with an evaluation of dose-response relationships. In relevant part, the US EPA Guidelines state: "[h]azard identification for developmental toxicity is usually done in conjunction with an evaluation of dose-response relationships, since the determination of a hazard is often dependent on whether a dose-response relationship is present. One advantage of this approach is that it reflects ***hazard*** within the context of ***dose***, ***route*** and ***duration*** and ***timing*** of exposure, all of which are important in comparing the toxicity information available to potential human exposure scenarios."[89]

Again, if NTP had concluded there that an association between exposure to BPA and developmental effects in humans were biologically plausible, NTP would never have concluded that there is "negligible concern" for developmental effects in humans from BPA. By the same reasoning, it would make no sense for the State of California to designate BPA as a "chemical that causes birth defects or other reproductive harm" on the basis of the conclusions expressed in the NTP Brief, when NTP so plainly concluded that the chemical poses no more than a "negligible concern for adverse effects" for "[r]eproductive toxicity in adult men and women[,] [f]etal or neonatal mortality, birth defects, or reduced birth weight and growth."

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of exposure for pregnant women) at the 95th percentile of 0.311 and 0.271 μg/kg bw/day, respectively (35). (Emphasis added.)

[89] US EPA Guidelines for Developmental Toxicity Risk Assessment, at ix.

Finally, there are differences in the pharmacokinetics of BPA between rodents and humans that make it biologically implausible that BPA causes developmental effects in humans. The NTP-CERHR Expert Panel Report (Chapin *et al.,* 2008) reviewed in detail the many pharmacokinetic studies of BPA in rodents and humans, and the differences between rodents and humans in how the body handles BPA. In fact, the NTP-CERHR Expert Panel Report devoted a full 24 pages to the review of the pharmacokinetic data. Similarly, the European Food Safety Authority (2006, 2008) noted toxicokinetic data showing "major species differences" in the way that BPA is handled in the bodies of rodents and humans, including "major differences in disposition of BPA-glucuronide due to different pathways of elimination from the liver in rodents and primates."

When administered orally to humans and other primates, BPA "is rapidly transformed to BPA-glucuronide during first pass metabolism in the gut wall and the liver." Accordingly, "[d]ue to this rapid biotransformation and excretion and plasma protein binding in humans, peak BPA-concentrations after dietary exposures to BPA available for receptor binding are predicted to be very low even in worst case exposure scenarios." By contrast, BPA-glucuronide formed in rats "is excreted from the liver into the gut in the bile" where it "is then cleaved into BPA and glucuronic acid and BPA is reabsorbed as such into the bloodstream," resulting in "slow elimination of BPA in rodents." As to mice, the EFSA Panel observed that "oxidation products of BPA have been identified after low-dose administration, suggesting possible formation of metabolites with higher oestrogenic potency," but noted "major species differences between the mouse and the human, both in the physiology of gestation and in their toxicodynamic sensitivity to oestrogens, the mouse being particularly sensitive to weak oestrogens such as BPA." BPA, which is regarded as the active toxicological moiety, is conjugated rapidly with glucuronide in humans in the GI tract of humans, even before it can be absorbed into the body. Glucuronidation effectively "deactivates" BPA by converting it into a different substance, which has no estrogenic activity and is rapidly eliminated from the body.

The differences in the pharmacokinetics of BPA in rodents and humans are directly relevant to the issue of biological plausibility. Even if humans received the same high level of exposure to BPA as the rodents received in the high-dose studies of BPA where developmental effects were reported in rodents, developmental effects would not be expected in humans due to pharmacokinetic differences in the disposition of BPA between rodents and humans. In other words, developmental effects in humans from BPA are not biologically plausible based on pharmacokinetic differences alone.

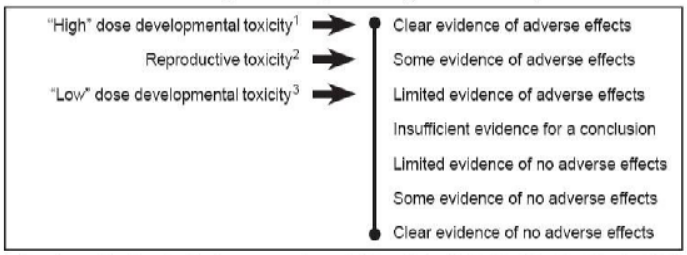
In summary, after taking into account the pharmacokinetic differences between rodents and humans, as well as consideration of maternal toxicity, dose-response relationships and other factors, an association between adverse reproductive effects in humans and BPA is biologically implausible and highly unlikely.

E. *The Studies That Are Relevant for Purposes of Proposition 65 Would Not Satisfy the "Weight of the Evidence" Test*

In evaluating the "high" dose data, NTP followed the well-known "weight of the evidence" approach. This is implicit throughout the NTP Brief and explicit in Figure 2b,

reproduced again below, with its heading "The ***weight of evidence*** that bisphenol A causes adverse developmental or reproductive effects in laboratory animals," and the top-most arrow, which points to the words "Clear evidence of adverse effects." (Emphasis added.)

Figure 2b. The weight of evidence that bisphenol A causes adverse developmental or reproductive effects in laboratory animals



[1]Based on reduced survival in fetuses or newborns (≥500 mg/kg bw/day) *(36–40)*, reduced fetal or birth weight or growth of offspring early in life (≥300 mg/kg bw/day) *(36, 37, 41)*, and delayed puberty in female rats (≥50 mg/kg bw/day) and male rats and mice (≥50 mg/kg bw/day) *(37, 41–43)*.

[2]Based on possible decreased fertility in mice (≥875 mg/kg bw/day) *(40)*; altered estrous cycling in female rats (≥600 mg/kg bw/day) *(110)*, and cellular effects on the testis of male rats (235 mg/kg bw/day) *(111)*.

[3]Based a variety of effects related to neural and behavior alterations (≥10 µg/kg bw/day) *(44–50)*, lesions in the prostate (10 µg/kg bw/day) *(51)* and mammary glands (0.0025–1 mg/kg bw/day) *(52, 53)*; altered prostate gland and urinary tract development (10 µg/kg bw/day) *(54)*, and early onset of puberty (2.4 and 200 µg/kg bw/day) *(48, 55)*.

Again, it is noteworthy that the studies cited to support this designation are the eight studies discussed above, NTP References 36 – 43. As a general matter, the "weight-of-the-evidence" approach is taken when no single study and no single modality of studies (*e.g.*, human, animal, *in vitro, etc.*) is conclusive in itself to demonstrate a causal relationship. Under this approach, the "weight of the evidence" is the eight studies which, in their totality, which show "clear evidence of adverse developmental effects" at "high" doses in laboratory animals.

For the reasons discussed above, however, not all of these eight studies can be considered to support a conclusion that exposure to BPA causes "developmental" effects within the meaning of Proposition 65. As discussed above, only three studies (NTP Reference 36, 38 and 43) demonstrate adverse effects as a result of pre-natal exposure alone (and the relevance of even these three studies is questionable, when maternal toxicity is considered). The remaining studies should be removed from consideration.

It is not possible to determine from the NTP CERHR Monograph whether NTP would have considered that there is "clear evidence" of high dose developmental toxicity (in laboratory animals) if NTP had removed from consideration those studies that are irrelevant for purposes of Proposition 65. It is clear that three studies, none of which reported developmental toxicity in the absence of significant maternal toxicity, present less weight than eight.

Hypothetically, a single study might constitute "clear evidence." But that obviously is not the case here. NTP did not state that ***each*** of the eight studies, or that any one of the eight, provided "clear evidence." Nor did NTP state that any given subset of the eight studies was sufficient to constitute "clear evidence." To the contrary, NTP explicitly cited all eight studies collectively as the "weight" of the evidence. And, despite the obvious opportunity, NTP did not state that it would have been satisfied with less. In this context, the fact that one study (NTP Reference 42) was based exclusively on post-natal exposure, and thus clearly is not relevant under Proposition 65, is extremely important: removal of that one study from consideration quite

logically might have caused NTP to have reached a different result. Removal of all studies that included post-natal exposure likely would have tipped balance in the other direction. Further, one cannot deduce what NTP would have concluded if it had limited its evaluation to the studies with developmental toxicity, as defined by Proposition 65.

F. *In Reaching a Conclusion That the Studies Above Satisfy the "Sufficient Data" Requirement of Section 25306(g), OEHHA Would Substitute Its Judgment for That of the Authoritative Body*

For all of the reasons above, it is clear that NTP did not "conclude" that BPA is a developmental toxicant. Rather, OEHHA has interpreted these studies itself, concluded on its own that BPA is a developmental toxicant, and has determined that these studies would be "sufficient" to support such a conclusion for purposes of Section 25306(g).

This distinction is extremely important: by interpreting the data to reach its own conclusions (which NTP did not reach), OEHHA would substitute its judgment for that of the authoritative body, NTP-CERHR. The authoritative body regulations clearly do not allow this. To the contrary, in promulgating those regulations, OEHHA's predecessor agency recited no less than four times in the Final Statement of Reasons that "[i]t is not the intention of the Agency to substitute its scientific judgment for that of the authoritative body."[90]

G. *Scientifically Valid Data Not Considered by NTP Further Demonstrate That BPA Does Not Cause Adverse Developmental Effects in Humans*

Even if the statements referred to in the Request could be interpreted validly as an NTP "conclusion" that BPA "causes . . . reproductive toxicity" within the meaning of Section 25306(d) (and we maintain that they cannot), the analysis would not end there. Rather, it would proceed to Section 25306(h), which requires OEHHA to "find that a chemical does not satisfy the definition of 'as causing reproductive toxicity' if scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria of [Section 25306(g)(2).]" That analysis is appropriate here, because significant data have been developed since the publication of the NTP-CERHR Monograph (that NTP obviously did not consider) that go to the heart of NTP's expression of "some concern for adverse [developmental] effects," which, as noted above, was based not on the "high dose" studies but on the numerous and controversial "low dose" studies.

An article published in Toxicological Sciences in October 2009, entitled *In Utero and Lactional Exposure to Bisphenol A, In Contrast to Ethinyl Estradiol, Does Not Alter Sexually Dimorphic Behavior, Puberty, Fertility, and Anatomy of Female LE Rats,* reported on a recent

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[90] Final Statement of Reasons at 16, 18, 19, 22.

study conducted by scientists from the United States Environmental Protection Agency (another "authoritative body" for purposes of Proposition 65), among others.[91]

The abstract of the article appears verbatim below:

> "Many concerns have been raised about the potential effects of BPA. ***The National Toxicology Program rated the potential effects of low doses of BPA on behavior and central nervous system (CNS) as an area of "Some concern,"*** whereas most of the effects were rated as of "negligible" or "minimal" concern. However, the number of robust studies in this area was limited. ***The current study was designed to determine if maternal exposure to relatively low oral doses of EE2 or BPA in utero and during lactation would alter the expression of well-characterized sexually dimorphic behavior of alter the age of puberty or reproductive function in the Female Long-Evans rat offspring.*** Pregnant rats were gavaged with vehicle, EE2 (0.05-50 µg/kg/day), or BPA (2,20 and 200 µg/kg/day) from day 7 of gestation to post-natal day (PND) 18, and the female offspring were studied. EE2 (50 µg/kg/day) increases anogenital distance and reduced pup body weight at PND2, accelerated the age at vaginal opening, reduced F1 fertility and F2 litter sizes, and induced malformations of the external genitalia (5 µg/kg/day). F1 females exposed to EE2 also displayed a reduced (male-like) saccharin preference (5 µg/kg/day) and absence of lordosis behavior (15 µg/kg/day), indications of defeminization of the CNS. ***BPA had no effect on any of the aforementioned measures***. . . ."[92]

These new data have reduced greatly the concerns in the toxicological community regarding potential estrogenic effects of BPA. Indeed, another article in Toxicological Sciences appropriately raises in its title the following question: *"Is it Time to End Concerns over the Estrogenic Effects of Bisphenol A?"* The author, Richard M. Sharpe, from the Medical Research Council Human Reproductive Science Unit, Center for Reproductive Biology, The Queen's Medical Research Institute, and one of the world's preeminent experts in reproductive toxicology, writes as follows:

> "For more than a decade, there has been a heated controversy whether or not the environmental chemical bisphenol A exerts adverse estrogenic effects in animal studies, ***and by extrapolation, in humans***. . . . Ryan, *et al*. (2009) publish a detailed study that throws cold water on this controversy by showing complete absence of effect of a range of bisphenol A exposures perinatally on reproductive development, function and behavior in female rats."[93]

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[91] Ryan, B.C., Hotchkiss, A.K., Crofton, K.M., and Gray,Jr., E.L (2009). In Utero and Lactional Exposure to Bisphenol A, In Contrast to Ethinyl Estradiol, Does Not Alter Sexually DiMorphic Behavior, Puberty, Fertility, and Anatomy of Female LE Rats. *Toxicol. Sci.* 114(1), 133-148 (2010).

[92] Ryan, *et. al.,* at 133.

[93] Sharpe RM. 2010. Is it time to end concerns over the estrogenic effects of Bisphenol A. Toxicol Sci. 114:1-4, at 1.

The author continues:

> "The results from Ryan, *et al*., (2009) are unequivocal and robust and are based on a valid and rational scientific foundation.[94] . . ."

The author concludes:

> "Therefore, based on the results of Ryan, *et al.,* (2009) and other similarly detailed studies that examined effects of bisphenol A on different end points (Ema *et al*, 2001; Howdeshall *et al*., 2008; Tinwell *et al*., 2002; Tyl *et al.,* 2002), ***the only scientifically logical conclusion is that bisphenol A, at doses considerably in excess of human exposure levels, does not reliably affect parameters of development and function in male or female rats/mice that are estrogen sensitive***."[95]

The importance of Ryan, *et al*., (2009) in the debate as to whether BPA causes adverse estrogenic effects is obvious, for the reasons Sharpe explains. For those same reasons, they are vital to the concerns expressed in the NTP Brief, and specifically the statement that "NTP has ***some concern*** for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to bisphenol A."[96] Ryan *et al.,* (2009) and Sharpe address directly the data that gave NTP reasons to have "some concern for adverse effects," and explain convincingly why those data now have far less importance, in light of the Ryan *et al.,* (2009) findings. In other words, Ryan *et al.,* (2009) and Sharpe demonstrate that the hypothesis that was supported by the data that gave NTP cause for "some concern" has been disproved. Thus, those studies would no longer support an expression by NTP of "some concern" or a "conclusion" that the possibility of adverse effects in humans "cannot be dismissed."

In addition, new information has been published recently regarding the potential for BPA to cause neurodevelopmental toxicity. Stump *et al*. (2010) reported the results of an important new developmental neurotoxicity study of BPA in rats, to which BPA was administered in the diet at concentrations of 0, 0.15, 1.5, 75, 750, and 2250 ppm from gestation day 0 through lactation day 21. Significantly, there was no evidence of that BPA is a developmental neurotoxicant in rats in this large, state-of-the-art developmental neurotoxicity study. This study is important because there were no neurological or neurobehavioral effects at either high or low doses. Consequently, this study did not confirm, and tends to disprove, allegations that low doses of BPA cause neurodevelopmental effects.

The relevance of Ryan *et al.* (2009) and Stump *et al.* (2010) in responding to OEHHA's Request is this: if OEHHA were to restrict itself to determining whether the NTP-CERHR Monograph, in the words of Section 25306(d)(1), "concludes that [BPA] causes . . . reproductive toxicity," then the NTP conclusion that shows its highest level of concern for developmental effects ("some concern," in the NTP lexicon) would no longer stand. Rather, the highest "level

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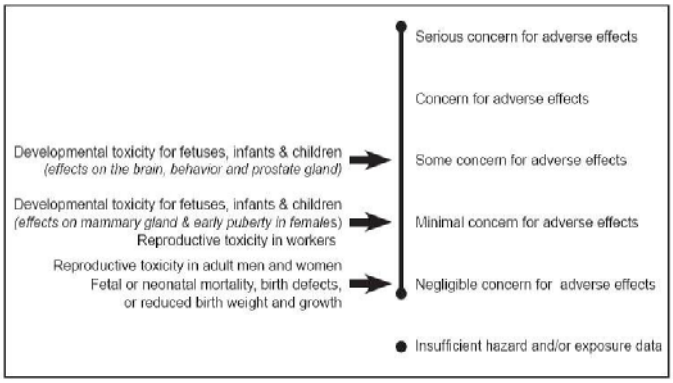
94 Sharpe RM, at 1.

95 Sharpe RM, at 2 (emphasis added).

96 NTP Brief at 8, Fig. 3 (emphasis added).

of concern" that NTP would express regarding the "possibilities that human development or reproduction might be effected by exposure to bisphenol A," as depicted in the above-mentioned Figure 3, reproduced below, would be a "minimal concern," for developmental toxicity for fetuses, infants and children," derived from the "low-dose" data that OEHHA does not address in the Request, or a "negligible concern" for "[r]eproductive toxicity in adult men and women," [f]etal or neonatal mortality, birth defects, or reduced birth weight and growth," derived from the data that OEHHA does address in the Request.

Figure 3. NTP conclusions regarding the possibilities that human development or reproduction might be effected by exposure to bisphenol A



Neither of these "conclusions" would warrant listing under the Authoritative Bodies Mechanism. In this regard, the following cases are instructive.

In *AFL-CIO v. Deukmejian*, the Health & Welfare Agency (OEHHA's predecessor agency) defended its judgment that certain "animal carcinogens" (chemicals for which there was data to show evidence of carcinogenicity in animals, but not humans) should not be placed on the "initial list" of chemicals "known to cause cancer or reproductive toxicity" pursuant to Section 25249.8(a) of the Act, which provided that "[s]uch list shall include at a minimum those substances identified by reference in Labor Code Section 6382(b)(1) and those substance identified additionally by Labor Code Section 6382(d)." The controversy centered on whether the list was required to include chemicals that came within the "scope" of the Hazard Communication Standard, because they were designated by the International Agency for Research on Cancer ("IARC") as "Group 2B" ("probable" or "possible" human carcinogens under IARC's carcinogenicity classification system). Defending its decision, the OEHHA's predecessor argued:

> "a literal construction of Section [25249.8(a) would] lead to absurd results, requiring the listing of substances not known to cause cancer [because the Hazard Communication Standard] referred to in Labor Code Section 6382 includes thousands of substances that are not carcinogens or reproductive toxins. A literal construction of the statute, [the State argued], would require the initial list to include these substances . . . ."

The Court of Appeal responded:

> "It is true that 'any substance within the scope of the federal [Hazard Communication Standard]' includes chemicals other than known carcinogens. Section [25249.8(a)] and the Act itself, however, are concerned only with those substances that authoritative bodies have concluded are known to cause cancer or reproductive toxicity. ***Thus, the initial list, and subsequent lists published thereafter, need not include all substances listed under [the federal Hazard Communication Standard] but only known carcinogens and reproductive toxins*** listed there."[97]

More recently, in *Styrene Information and Research Center v. OEHHA,* the Superior Court for Sacramento issued an order enjoining OEHHA from listing the chemicals styrene and vinyl acetate monomer under the Labor Code Listing Mechanism. OEHHA proposed to list the styrene because a monograph published by IARC classified the chemical in Group 2B and, as such was "within the scope of the federal Hazard Communication Standard." Nevertheless, classification in Group 2B meant only that that styrene is "possibly carcinogenic to humans," within the IARC classification system.

In moving for judgment on the pleadings and a permanent injunction to prohibit the listing of styrene, the plaintiff Styrene Information and Research Center argued that chemicals may not be listed under Proposition 65 unless they are "known to cause" cancer or reproductive toxicity, and that in order for a chemical to be "known to cause cancer," there must be "sufficient evidence" of carcinogenicity.[98] The fact that IARC classified styrene in Group 2B did not, in itself, establish "sufficient evidence" of carcinogenicity for purposes of Proposition 65. To the contrary, SIRC pointed out that "recent studies 'show no causal link' between styrene exposure and human cancer. New mechanistic evidence and animal exposure studies show that the 'limited evidence' of carcinogenicity in mice does not apply to human beings."[99]

These arguments run parallel to the facts here. As to styrene, OEHHA argued that the chemical must be listed under the Labor Code Mechanism because it had been "classified" as a potential carcinogen when IARC placed the chemical in its Group 2B. As to BPA, OEHHA similarly indicates that the chemical must be listed under the Authoritative Bodies Mechanism because it has been "formally identified" as a reproductive toxin, when NTP concluded only that "the possibility that bisphenol A may alter human development cannot be dismissed," and recent studies (*i.e.*, Ryan *et al.* (2009)) show that the basis of that concern now can be discounted.

The Sacramento Court resolved the matter as follows: citing the same passage from *Deukmejian*, the Court noted that "only those chemicals that are known, and not merely

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97 *AFL-CIO v. Deukmejian* (1989) 212 Cal.App.3d 425 ["Deukmejian"] at 437, 438 (emphasis added).

98 *See Deukmejian* at 434, n. 3 (stating that although the IARC does not use the term "known carcinogen" for the purpose of interpreting the IARC monographs, "sufficient evidence" of carcinogenicity is the equivalent of "known" carcinogenicity).

99 *Styrene Information and Research Center v. OEHHA (2009)*, Minute Order Granting Preliminary Injunction at 3.

suspected, of causing cancer or reproductive toxicity must be on the list. The IARC Group 1 substances, made up of chemicals for which there is sufficient evidence of carcinogenicity to humans, clearly are subject to the Act. Beyond that, the question is not whether a chemical is "probably' carcinogenic to humans, but where it is in fact a known carcinogen or reproductive toxin."

Deukmejian, recently interpreted and applied to enjoin the listing of styrene, thus instructs that the ultimate test for listing any substance is whether it is "known to cause cancer or reproductive toxicity." To the extent that OEHHA's implementing regulations would provide for a different result, whether based on "classifications" or "formal identifications," they are inconsistent with the statute. To the extent that Sections 25306(d) or Section 25306(g) would allow for the listing of BPA, when NTP has concluded only that the "possibility that the chemical causes adverse developmental effects cannot be dismissed," the listing would be arbitrary, capricious, and contrary to law.

V. CONCLUSION

On July 15, 2009, the DART IC concluded that BPA has not been "clearly shown to cause developmental toxicity," and thus should not be listed pursuant to Section 25249.8(b) of the Act. Any proposal to list the chemical now under the Authoritative Bodies Mechanism on the basis of the NTP-CERHR Monograph is unlawful under Section 25259.8(b) and Section 25306 of the implementing regulations, because the Monograph does not "formally identify" BPA as a developmental toxin, and neither the Act nor the regulations authorize OEHHA to overrule the DART IC or list the chemical on the basis of its own evaluation of the same data that the DART IC already considered. If OEHHA were to continue nevertheless to consider BPA for listing, the chemical should not be listed, because the data identified in the Request as the basis for listing are not "sufficient" within the meaning of Section 25306(g)(2). Moreover, OEHHA would be required under Section 25306(h) to acknowledge the existence of new data not available to NTP-CERHR at the time it published the Monograph, which mitigate the concerns that NTP expressed regarding both estrogenic and neurodevelopmental effects. Although these data do not relate directly to the studies identified in the Request, it appears they would reduce NTP-CERHR's "level of concern" that BPA is a reproductive or developmental toxicant from "some concern" to only a "negligible" concern.

For all of these reasons, OEHHA should conclude that it is inappropriate and unlawful to list BPA as a chemical "known to the state to cause . . . reproductive toxicity" under Section 25249.8(a) of the Act. We respectfully request that OEHHA issue a public notice consistent with this conclusion and cease any further activity to list the chemical under the Authoritative Bodies Mechanism on the basis of the NTP-CERHR Monograph.

Respectfully submitted,

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SF:27424311.7

September 1, 2011

VIA U.S. MAIL AND EMAIL

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Re: SUPPLEMENTAL RESPONSE TO REQUEST FOR RELEVANT INFORMATION ON BISPHENOL A

Dear Dr. Alexeeff:

On behalf of the Polycarbonate/BPA Global Group of the American Chemistry Council ("ACC"), I am submitting this supplemental response to OEHHA's February 12, 2010 Request for Relevant Information on bisphenol A ("BPA"). This supplemental response addresses a series of related in-depth studies that have been published in recent months, with the most recent study published in August 2011. These recent studies, along with other scientific literature previously identified by ACC, show that BPA does not satisfy the definition of causing reproductive toxicity and thus cannot be listed under the authoritative bodies mechanism. This supplemental response should be considered with ACC's prior written submittals dated September 15, 2009, May 13, 2010, and August 10, 2011.

Since the publication of the NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of BPA ("NTP-CERHR Monograph") in September 2008, BPA has continued to be a popular subject for additional research. As stated by NTP, "*the scientific literature on the toxic effects of bisphenol A in laboratory animals is extensive and expanding*."[1] ACC's May 13, 2010 submittal detailed significant data that had been developed after the publication of the NTP-CERHR Monograph. This supplemental response provides additional important studies that have been published more recently.

[1] NTP Brief on Bisphenol A, part of the NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of BPA, September 2008, page 16 (available at http://ntp.niehs.nih.gov/ntp/ohat/bisphenol/bisphenol.pdf).

All of the studies highlighted in this supplemental response and our May 13, 2010 submittal are relevant to OEHHA's decision whether to designate BPA as a reproductive toxicant under the "authoritative bodies" mechanism pursuant 25306, subsection (h). This section of the implementing regulations provides: "[t]he lead agency shall find that a chemical does not satisfy the definition of 'as causing reproductive toxicity' if scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria of subsection (g), paragraph (1) or subsection (g), paragraph (2)."

Both the NTP-CERHR expert panel, in its final report on BPA,[2] and NTP itself, in its Brief on BPA,[3] acknowledged the need for additional research to better understand the potential for BPA to cause adverse health effects. The expert panel itemized a list of Critical Data Needs at the end of its report and NTP interspersed a series of data gaps and research needs throughout its Brief. In addition, after consideration of the NTP-CERHR Monograph, FDA also acknowledged the need for additional research, stating that in cooperation with NTP, "FDA's National Center for Toxicological Research is carrying out in-depth studies to answer key questions and clarify uncertainties about the risks of BPA."[4]

Many of the studies designed by NTP and FDA to address identified research needs are now being completed and published in the peer-reviewed scientific literature. Without question these studies are relevant to the conclusions of the NTP-CERHR Monograph and, thus, of substantial importance to OEHHA's decision whether to designate BPA as a reproductive toxicants based on the NTP-CERHR Monograph.

One of the key areas for additional research relates to the NTP-CERHR conclusion that it had "some concern" for potential effects on the brain and behavior from current human exposures in fetuses, infants and children. As stated by the NTP-CERHR expert panel, "*A concerted effort is needed to better understand the effects of gestational and lactational exposure to bisphenol A on maternal behavior and offspring brain structure and behavior*."[5] The NTP fully agreed with this recommendation, stating "*The NTP also concurs with the CERHR Expert Panel on Bisphenol A*

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[2] NTP-CERHR Report on the Reproductive and Developmental Toxicity of Bisphenol A, November 26, 2007 (available at http://ntp.niehs.nih.gov/ntp/ohat/bisphenol/BPAFinalEPVF112607.pdf).

[3] NTP Brief on Bisphenol A, September 2008.

[4] See http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm064437.htm.

[5] NTP-CERHR Report on the Reproductive and Developmental Toxicity of Bisphenol A, November 26, 2007, page 383.

that additional research is needed to more fully assess the functional, long-term impacts of exposures to bisphenol A on the developing brain and behavior. Overall, the current literature cannot yet be fully interpreted for biological or experimental consistency or for relevance to human health."[6] The inability to interpret the literature existing at that time was the primary basis for the "some concern" conclusion, which essentially was a signal for additional research.

Most recently, researchers at FDA's National Center for Toxicological Research have published initial results from their study on the potential for developmental exposure to BPA to cause effects on the brain and behavior.[7] Although effects were observed for ethinyl estradiol, a known potent estrogen used as a reference compound, no effects were found for BPA. As concluded by the authors, "*These results add to the literature indicating developmental BPA treatment at these doses has no effects on gestational or lactational body weight, offspring anogenital distance, preweaning behaviors or hormone levels and whole and regional brain weights measured at weaning*."

These new results, combined with the results of the Ryan et al. (2010)[8] and Stump et al. (2010)[9] studies that were highlighted in our May 13, 2010 submittal, substantially address the NTP-CERHR Monograph conclusion of "some concern" for effects on the brain and behavior. Had all of these results been available to the NTP-CERHR expert panel and to NTP when their reports were being generated, it is quite likely that the "some concern" conclusion would have been downgraded to a lower level.

This downgrade is made more likely and reinforced by the new findings, summarized below, on the metabolism of BPA.

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[6] NTP Brief on Bisphenol A, September 2008, page 20.

[7] Ferguson, S. A., Law, C. D., and Abshire, J. S. 2011. Developmental treatment with bisphenol A or ethinyl estradiol causes few alterations on early preweaning measures. Toxicological Sciences. In Press. Available at http://dx.doi.org/10.1093/toxsci/kfr201.

[8] Ryan, B. C., Hotchkiss, A. K., Crofton, K. M., and Gray Jr., L. E. 2010. In utero and lactational exposure to bisphenol A, in contrast to ethinyl estradiol, does not alter sexually dimorphic behavior, puberty, fertility and anatomy of female LE rats. Toxicological Sciences. 114(1):133-148. Available at http://dx.doi.org/10.1093/toxsci/kfp266).

[9] Stump, D. G., Beck, M. J., Radovsky, A., Garman, R. H., Freshwater, L. L., Sheets, L. P., Marty, M. S., Waechter, J. M., Dimond, S. S., Van Miller, J. P., Shiotsuka, R. N., Beyer, D., Chappelle, A. H., and Hentges, S. G. 2010. Developmental neurotoxicity study of dietary bisphenol A in Sprague-Dawley rats. Toxicological Sciences. 115(1):167-182. Available at http://dx.doi.org/10.1093/toxsci/kfq025.

As stated by NTP in its Brief on BPA, "*Understanding the degree to which bisphenol A is metabolized is very important in determining whether bisphenol A poses a potential risk to human reproduction and development. While free bisphenol A and its major metabolites (bisphenol A-glucuronide and bisphenol A-sulfate) can all be measured in humans, only free bisphenol A is considered to be biologically active*."[10] The importance of this comment cannot be overstated. All of the concern level conclusions expressed in the NTP-CERHR Monograph are dependent on understanding how BPA is processed in the human body. If BPA is effectively metabolized and eliminated from the human body, in particular relative to the laboratory animals used for toxicity testing, the potential for adverse human health effects decreases substantially. Understanding the metabolism of BPA is critical to understanding the biological plausibility of adverse human health effects.

Because of the importance of this question, both NTP and the NTP-CERHR expert panel highlighted significant research needs. The expert panel stated "*Additional data are needed to clarify bisphenol A exposures and internal dosimetry in the general population, newborns, and occupationally-exposed individuals… These data would provide insight into the roles of metabolism and exposure route on internal dose*."[5] Likewise, NTP stated "*Additional research is needed to understand the metabolism of bisphenol A in both laboratory animals and humans*" and "*Thus, the understanding of bisphenol A metabolism during development in the rat is still incomplete. In addition, it is difficult to translate the rat findings to humans…*"[11]

To address these important research needs, FDA has now completed and published a series of four in-depth studies that examine the metabolism and pharmacokinetics of BPA in both rodents and primates.[12,13,14,15] While these studies will not be reviewed here in detail, they

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[10] NTP Brief on Bisphenol A, September 2008, page 6.

[11] NTP Brief on Bisphenol A, September 2008, page 13.

[12] 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. Available at http://dx.doi.org/10.1016/j.taap.2010.06.008.

[13] 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. Available at http://dx.doi.org/10.1016/j.toxlet.2010.09.022.

[14] 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. In Press. Available at http://dx.doi.org/10.1016/j.taap.2011.07.009,

collectively demonstrate that BPA is efficiently metabolized to biologically inactive metabolites, which are then quickly eliminated from the body. Notably, a study in rats demonstrated that the developing fetus also has the ability to metabolize BPA, although very little BPA reaches the fetus due to the efficient metabolism of BPA by the mother. Also, the ability of neonatal monkeys only a few days after birth to metabolize BPA is essentially equivalent to that of adult monkeys. As a result of efficient metabolism, estrogenic effects from BPA are unlikely due to the very low levels of un-metabolized BPA in the body after oral exposure.

Although both rodents and primates have the ability to metabolize and eliminate BPA from the body, there are important differences between them. For example, primates clear BPA from the body faster than rodents and, in contrast to rodents, the ability of primates to metabolize BPA is not dependent on age. Because of these differences, the FDA authors concluded "*These observations imply that any toxicological effect observed in rats from early postnatal exposures to BPA could over-predict those possible in primates of the same age, based on significantly higher internal exposures and overall immaturity at birth*."[15] This conclusion is of particular importance for consideration of BPA for listing as a reproductive toxicant under Proposition 65 since essentially all of the relevant toxicity data is from studies on rodents. Due to differences in developmental timing between rodents and primates, an early postnatal exposure in a rodent might be equivalent to a late prenatal exposure in a primate.

As a prelude to the metabolism/pharmacokinetic studies, FDA developed a sensitive analytical method for measurement of BPA (both parent and conjugated forms) in biological specimens.[16] Although the method development itself is not directly relevant to the potential toxicity of BPA, in the course of developing the method FDA gained considerable experience with the confounding issue of laboratory contamination during sample analysis. This is an important issue since a number of small-scale studies have reported the presence of un-metabolized BPA in human blood, which would appear to conflict with extensive data demonstrating that BPA is efficiently metabolized. Based on direct experience with laboratory contamination, the FDA authors commented on the apparent discrepancy by stating "*The*

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[15] 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. Available at http://dx.doi.org/10.1016/j.taap.2010.07.009.

[16] Twaddle, N. C., Churchwell, M. I., Vanlandingham, M., and Doerge, D. R. 2010. Quantification of deuterated bisphenol A in serum, tissues, and excreta from adult Sprague-Dawley rats using liquid chromatography with tandem mass spectrometry. Rapid Communications in Mass Spectrometry. 24(20):3011-3020. Available at http://dx.doi.org/10.1002/rcm.4733.

simplest explanation for this discordance is sample contamination leading to false positive determinations of aglycone BPA in human blood, which otherwise would contain levels undetectable by any current analytical methodology."

This issue was more directly addressed in a human volunteer study conducted by the Pacific Northwest National Laboratory with participation from the FDA and CDC laboratories.[17] In this study, a group of 20 volunteers were provided with a diet enriched in canned foods, which resulted in an atypically high intake of BPA. Blood and urine samples were collected at frequent intervals throughout the clinical study and analyzed for un-metabolized BPA (blood) and metabolized BPA (blood and urine). Consistent with previous human and animal studies, including those detailed above, this study confirms that BPA is efficiently metabolized and rapidly excreted in urine. Illustrating the efficiency of human metabolism, no un-metabolized BPA was detected in the blood of any participant at any time point in the study, even with a very sensitive analytical method and atypically high exposure levels. Only the biologically inactive metabolite of BPA was transiently found at low levels before it was eliminated from the body. Based on their results, the authors note that reported high levels of un-metabolized BPA in blood are unlikely to be valid, and that sample contamination has likely been the cause of high levels of BPA reported in small-scale studies.

As noted above, the results of this study, along with the recent studies in rodents and primates, strongly indicate that, because of the efficient way that BPA is processed in the body, it is very unlikely that BPA could cause human health effects. In particular, these studies indicate that the biological plausibility of human health effects has not been clearly shown. To the contrary, these and other studies indicate that human health effects are biologically implausible.

Notably, the findings from the initial FDA studies have already been incorporated into an updated assessment from the Japanese National Institute of Advanced Industrial Science and Technology (July 2011), which confirmed that BPA is not a human health hazard. Based substantially on the FDA findings, this assessment also reduced the "uncertainty factor" for BPA, which indicates that the science supporting the safety of BPA is stronger and with less uncertainty.

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[17] 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. Available at http://dx.doi.org/10.1093/toxsci/kfr160.

It is clear from all the foregoing recent studies, along with the prior available scientific literature, that there is not a basis upon which OEHHA can conclude that BPA is a reproductive toxicant under the criteria of section 25306, subsection (g). Accordingly, we respectfully submit that OEHHA should find, under section 25306, subsection (h), that BPA does not satisfy the definition of "as causing reproductive toxicity" and should not be listed under the authoritative body mechanism.

Please do not hesitate to contact me if I can be of further assistance to clarify any comments or if additional information is needed. I can be reached at (202) 249-6624 or by e-mail at steve_hentges@americanchemistry.com.

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Washington, DC 20002

cc: Cynthia Oshita (OEHHA)
Stanley W. Landfair (McKenna Long & Aldridge)
F. Jay Murray, Ph.D.

2400 West Lloyd Expressway Evansville, IN 47721-0001 812-429-5000

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
Sacramento, California 95812-4010

Dear Ms. Oshita:

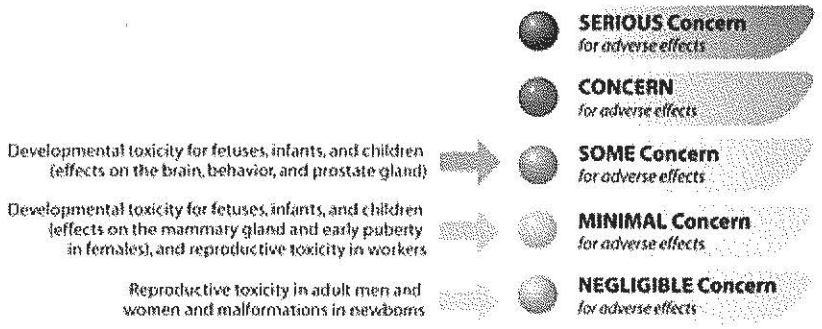
On behalf of Mead Johnson Nutrition, I write to urge you not to list bisphenol A (BPA) as a "*chemical known to the state to cause reproductive toxicity*" under Proposition 65 by the authoritative bodies mechanism.

Bisphenol A does not meet the criteria to be added to the list under Proposition 65 through this mechanism because the authoritative body cited in the petition has not determined that BPA is hazardous to health. According to section 25249.8(b) of the Act, and 27 Cal. Code Reg. § 25306, this requirement must be met before a chemical is listed.

Perhaps of greatest importance is the fact that the NTP's peer-reviewed analysis of BPA found no serious concern about its effects on human reproduction or development in adults or children. Rather, it was the NTP's opinion that there are insufficient data from studies in humans to reach a conclusion on reproductive or developmental hazards presented by current exposures to bisphenol A and more research is needed to better understand its implications for human health.

Using its five-level scale of concern, the NTP used the term 'some concern' to characterize possible effects of BPA on fetuses. The definition of 'some concern' means that further studies are recommended to better understand any implications to human health. It does not mean that the NTP deemed BPA harmful or its use should be restricted.

NTP conclusions regarding the possibilities that human development or reproduction might be adversely affected by exposure to bisphenol A. The NTP uses a five-level scale of concern:



As recently as January 15, 2010, the FDA reaffirmed the safety of BPA. Joshua Sharfstein, FDA's principal deputy commissioner said in a news conference, "if we thought [BPA] was unsafe, we would be taking strong regulatory action." Our confidence in the safety of BPA is further reinforced by expert opinions of numerous recognized scientific and regulatory bodies confirming the safety of its use. These include:

- U.S. Food and Drug Administration
- Health Canada
- European Food Safety Authority
- Japanese National Institute for Advance Industrial Science and Technology
- Food Safety Australia New Zealand
- German Federal Institute for Risk Assessment
- Japanese Ministry of Environment

The FDA is currently conducting its most extensive review of BPA to date and is expected to be complete a safety assessment within the next 15 to 21 months. In addition, the National Institutes of Health has devoted $30 million to study the safety of BPA. If the FDA or other competent regulatory authorities conclude that BPA is a health risk to our consumers we will move quickly to address these risks. The health and safety of infants and children are our top priorities.

We respect the commitment of the State of California to protect the health and well-being of its youngest citizens and ask that you continue to abide by the requirements of the California Code of Regulations and not list BPA under Proposition 65 by the authoritative bodies mechanism taking into consideration the above arguments.

Sincerely,

Hugh N. Tucker, Ph.D.
Distinguished Research Fellow
Global Research and Development