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June 28, 2011

Via Email

Dorothy Burk, Ph.D., Chairperson, and Committee Members
Developmental and Reproductive Toxicant Identification Committee

Re: Designation of NTP-CERHR as an Authoritative Body

Dear Dr. Burk and Members of the DART IC:

I urge you to consider clarifying, refining or rescinding the designation of the NTP-CERHR as an "authoritative body" for purposes of Proposition 65.

There was a serious misunderstanding about the nature and rationale for this request when it was presented at your meeting on October 21, 2010, in the form of a petition by the American Chemistry Council (ACC). Since there was no opportunity for public comment on the petition, there was no opportunity to correct the misunderstanding. Please recall that I was a co-author of the petition. I am writing this letter to provide you with the background and basis for our request from a scientific (not a legal) perspective.

The misunderstanding was that ACC was arguing that NTP-CERHR does not have the requisite expertise to evaluate chemical substances for reproductive toxicity. That is not the issue, because NTP-CERHR clearly is qualified for such evaluations. The issue is whether the ***reports*** that NTP-CERHR issues indicate that NTP-CERHR has "formally identified" a chemical as "causing reproductive toxicity." The clarity of that designation in the NTP-CERHR Monographs is critical, because the law does not permit OEHHA to exercise its own scientific judgment when it reviews those reports. Instead, OEHHA's role is to determine whether ***NTP-CERHR*** "formally identified" the chemical as "causing reproductive toxicity" in the report.

When the Committee designated NTP-CERHR as an authoritative body in 2002, several members raised serious reservations that NTP-CERHR reports did not include clear "yes-or-no" determinations, and it was not clear from the reports whether NTP-CERHR had "formally identified" a chemical "as causing reproductive toxicity." Unfortunately, those concerns have proven to be well founded.

Bisphenol A is the most current and obvious example of why the designation of NTP-CERHR as an authoritative body needs to be reconsidered. As you will recall, this committee unanimously declined to list BPA as a developmental toxicant at your July 15, 2009 meeting. The Committee carefully considered the NTP-CERHR Monograph on BPA as part of that decision. Nevertheless, just six months later, without any new or different data, OEHHA announced it was considering granting a petition to list BPA as a developmental toxicant, based on ***your Committee's*** designation of NTP-CERHR as an authoritative body, citing the very same NTP-CERHR report that your committee had just considered.

Importantly, NTP-CERHR's interpretation of the BPA data was not materially different from that of your committee and simply identifies levels of concern. Relevant pages of the NTP Brief and the Expert Panel Report[1] show this. For instance, conclusions in the NTP Brief range from "some

[1] The NTP Monographs include two separate reports: the NTP Brief, which is written by the NTP staff, and the Expert Panel Report, written by the scientists whose names appear on the Expert Panel Report.

concern" to "negligible concern" for adverse effects "regarding the possibilities that human developmental or reproduction might be effected (sic) by exposure to bisphenol A." In fact, Dr. John Bucher, the Associate Director of the NTP, described the conclusions of the NTP Brief on BPA in an online audio statement solely in terms of the "level of concern," which is never greater than "some concern."[2] Figure 2B of the NTP Brief illustrates this, characterizing the "weight of the evidence" for different endpoints, noting "clear evidence of adverse effects" of "high dose developmental toxicity" only in studies in laboratory rats and mice that produced significant maternal toxicity (*e.g.,* the Tyl studies, referred to by footnote 1), and "limited evidence of adverse effects" of "low dose developmental toxicity" in the much-discussed "low-dose" studies.[3] Importantly, these are not the conclusions of the Brief, and do not lend themselves to determinations for purposes of Proposition 65 that NTP-CERHR has "formally identified" BPA as "causing reproductive toxicity." Rather, they merely characterize the strengths and weaknesses of the data from which the conclusions in the NTP Brief are drawn, which are illustrated in Figure 3. As you will recall, your Committee had similar observations about the high dose studies – the effects observed were secondary to maternal toxicity – and the low dose studies, which were interesting, but inconclusive.

You, as the State's Qualified Experts, implement the primary mechanism for listing chemicals under Proposition 65. The authoritative bodies process is a secondary mechanism designed to minimize the need for your committee (and the Cancer Identification Committee) to expend its limited resources to evaluate chemicals already evaluated by an authoritative body. In effect, the authoritative bodies are your designees. The authoritative bodies listing mechanism was not intended to effect a lower standard for listing than the standard used by your committee, or a different one. For that reason, your committee was mandated to designate authoritative bodies that would come to the same conclusion that you would since your committee represents the primary method for listing chemicals under Proposition 65. That is why your committee – and your committee alone – has authority under Proposition 65 to designate authoritative bodies.

There is something inherently wrong with the authoritative bodies process if the same chemical you declined to list can be proposed for listing six months later based on the same document you considered, and nothing more. Once a chemical is listed under the authoritative bodies provision, your Committee cannot reverse the decision, even if you decide your designation of the authoritative body was in error. We are asking you to correct this obvious problem by revisiting your designation of NTP-CERHR as an authoritative body.

This is not a criticism of NTP-CERHR or the NTP-CERHR Monographs. Rather, it is a recognition that the Monographs are intended to summarize and evaluate data and identify "levels of concern" – not to "formally identify" chemicals as "causing reproductive toxicity."

The solution is to clarify, refine or rescind the designation of NTP-CERHR as an authoritative body, and for the DARTIC to continue to use the Monographs as a primary resource in evaluating chemicals under the State's Qualified Experts mechanism. I urge you to consider this at your earliest opportunity, and thank you for considering my views.

Sincerely,

F. Jay Murray, Ph.D., DABT

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2 http://www.niehs.nih.gov/news/media/questions/mp3/bucher-key.mp3

3 http://ntp.niehs.nih.gov/ntp/ohat/bisphenol/bisphenol.pdf

cc: Ms. Cynthia Oshita
Carol Monahan-Cummings, Chief Counsel
Office of Environmental Health Hazard Assessment

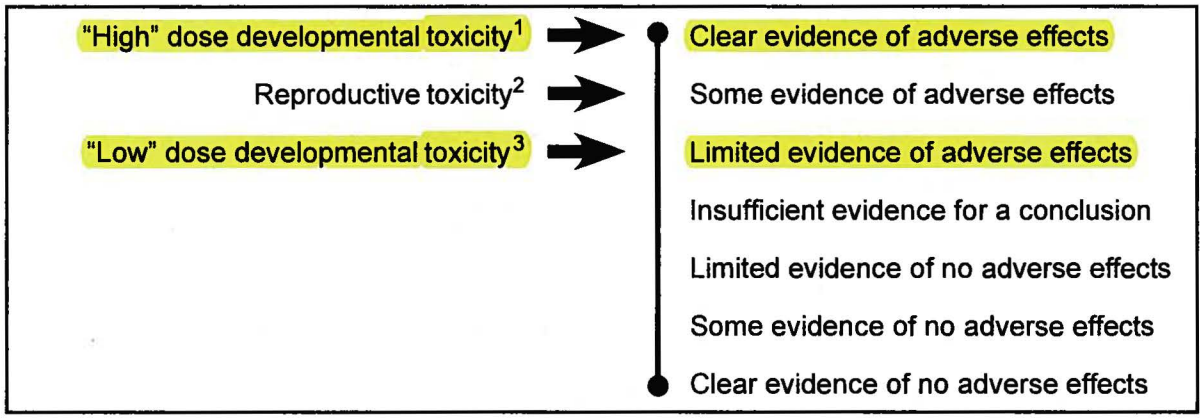
National Toxicology Program
U.S. Department of Health and Human Services

Center For The Evaluation of Risks To Human Reproduction

NTP BRIEF ON BISPHENOL A

[CAS NO. 80–05–07]

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

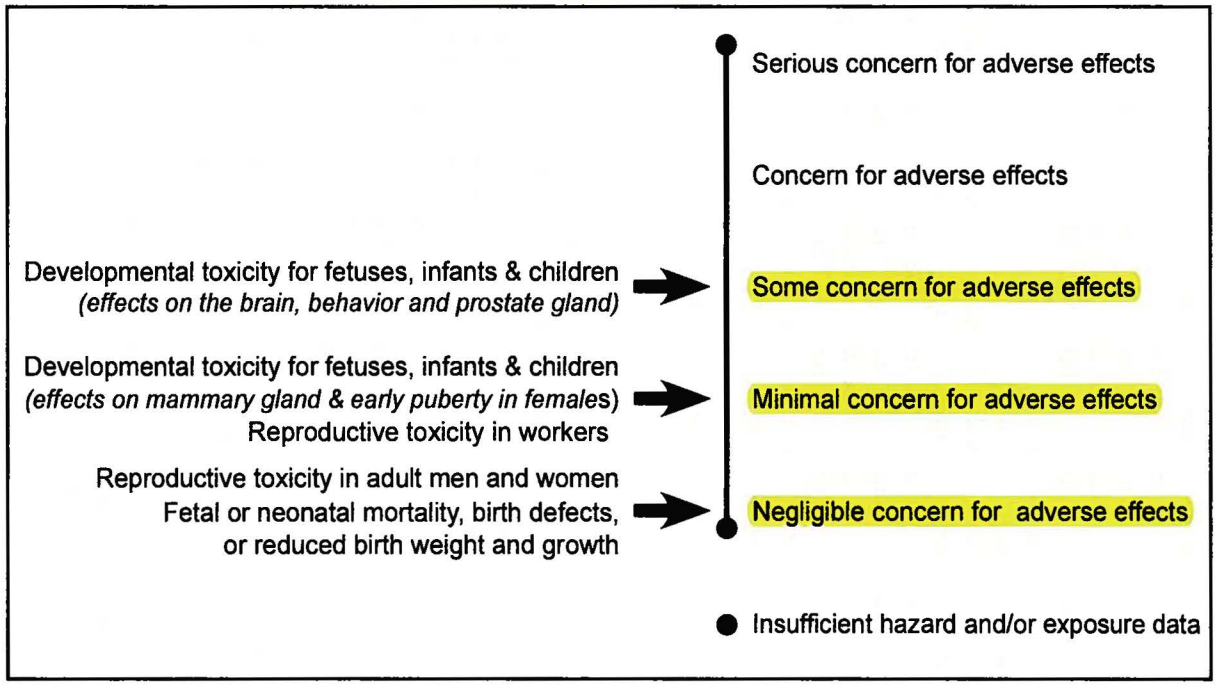


[1]Based on reduced survival in fetuses or newborns (≥500 mg/kg bw/day) *(36–40)*, reduced fetal or birth weight or growth of offspring early in life (≥300 mg/kg bw/day) *(36, 37, 41)*, and delayed puberty in female rats (≥50 mg/kg bw/day) and male rats and mice (≥50 mg/kg bw/day) *(37, 41–43)*.

[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)*.

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



NTP CONCLUSIONS

The NTP reached the following conclusions on the possible effects of exposure to bisphenol A on human development and reproduction. Note that the possible levels of concern, from lowest to highest, are negligible concern, minimal concern, some concern, concern, and serious concern.

The 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.

The NTP concurs with the conclusion of the CERHR Expert Panel on Bisphenol A that the scientific evidence supports a conclusion of *some concern* for exposures in fetuses, infants, and children based on a number of laboratory animal studies reporting that "low" level exposure to bisphenol A during development can cause changes in the brain and behavior. In addition, the NTP has *some concern* for exposures to these populations based on effects on the prostate gland observed in laboratory animals. This level of concern for effects on the prostate gland is higher than that expressed by the Expert Panel and is based primarily on new supportive data related to (1) the interpretation of studies that use a non-oral route of administration in neonatal rodents, and (2) an additional publication reporting subtle cellular changes in the prostate gland. These reports were not published when the Expert Panel completed its deliberations. These studies in laboratory animals provide only limited evidence for adverse effects on development and more research is needed to better understand their implications for human health. However, because these effects in animals occur at bisphenol A exposure levels similar to those experienced by humans, the possibility that bisphenol A may alter human development cannot be dismissed.

The NTP has *minimal concern* for effects on the mammary gland and an earlier age for puberty for females in fetuses, infants, and children at current human exposures to bisphenol A.

The NTP concurs with the conclusion of the CERHR Expert Panel on Bisphenol A that the scientific evidence supports a conclusion of *minimal concern* for exposures in fetuses, infants, and children based on a number of laboratory animal studies reporting that "low" level exposure to bisphenol A during development can alter the timing of events related to sexual maturation in females. In addition, the NTP has *minimal concern* for exposures to these populations based on effects on the mammary gland observed in laboratory animals. This level of concern for effects on the mammary gland is higher than that expressed by the Expert Panel and is based primarily on (1) information received through public comments and (2) a new supportive study reporting subtle changes in the undifferentiated structures of the mammary gland. These studies in laboratory animals provide only limited evidence for adverse effects on development and more research is needed to better understand their implications for human health. However, because these effects in animals occur at bisphenol A exposure levels similar to those experienced by humans, the possibility that bisphenol A may alter human development cannot be dismissed.

The NTP has *negligible concern* that exposure of pregnant women to bisphenol A will result in fetal or neonatal mortality, birth defects, or reduced birth weight and growth in their offspring.

The NTP concurs with the conclusion of the CERHR Expert Panel on Bisphenol A that there is *negligible concern* that exposure of pregnant

women to bisphenol A will result in fetal or neonatal mortality, birth defects or reduced birth weight and growth in their offspring. In laboratory animals, exposure to very high levels of bisphenol A during pregnancy can cause fetal death and reduced birth weight and growth during infancy. These studies provide clear evidence for adverse effects on development, but occur at exposure levels far in excess of those experienced by humans. Two recent human studies have not associated bisphenol A exposure in pregnant women with decreased birth weight or several other measures of birth outcome. Results from several animal studies provide evidence that bisphenol A does not cause birth defects such as cleft palette, skeletal malformations, or grossly abnormal organs.

The NTP has *negligible concern* that exposure to bisphenol A will cause reproductive effects in non-occupationally exposed adults and *minimal concern* for workers exposed to higher levels in occupational settings.

The NTP concurs with the conclusion of the CERHR Expert Panel on Bisphenol A that there is *negligible concern* that exposure to bisphenol A causes reproductive effects in non-occupationally exposed adults and *minimal concern* for workers exposed to higher levels in occupational settings Data from studies in humans are not sufficient to determine if bisphenol A adversely affects reproduction when exposure occurs during adulthood. A number of studies, when considered together, suggest a possible effect on reproductive hormones, especially in men exposed to higher levels of bisphenol A in the workplace. Laboratory studies in adult animals show adverse effects on fertility, estrous cycling, and the testes at exposure levels far in excess of those experienced by humans. A number of other effects, such as decreased sperm counts, are reported for the reproductive system at lower doses in animals exposed only during adulthood, but these effects have not been shown to be reproducible. Laboratory animal studies consistently report that bisphenol A does not affect fertility.

These conclusions are based on information available at the time this brief was prepared. As new information on toxicity and exposure accumulates, it may form the basis for either lowering or raising the levels of concern expressed in the conclusions.

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Expert Panel Report

NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A

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Preface

The National Toxicology Program (NTP)[1] established the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) in June 1998. The purpose of the CERHR is to provide timely, unbiased, scientifically sound evaluations of the potential for adverse effects on reproduction or development resulting from human exposures to substances in the environment. The NTP-CERHR is headquartered at NIEHS, Research Triangle Park, NC, and is staffed and administered by scientists and support personnel at NIEHS.

Bisphenol A is a high-production volume chemical used in the production of epoxy resins, polyester resins, polysulfone resins, polyacrylate resins, polycarbonate plastics, and flame retardants. Polycarbonate plastics are used in food and drink packaging; resins are used as lacquers to coat metal products such as food cans, bottle tops, and water supply pipes. Some polymers used in dental sealants and tooth coatings contain bisphenol A. Exposure to the general population can occur through direct contact with bisphenol A or by exposure to food or drink that has been in contact with a material containing bisphenol A. CERHR selected bisphenol A for evaluation because of (1) high production volume; (2) widespread human exposure; (3) evidence of reproductive toxicity in laboratory animal studies; and (4) public concern for possible health effects from human exposures.

Relevant literature on bisphenol A was identified from searches of the PubMed (Medline) and Toxline databases through February 2007 using the term "bisphenol" and the bisphenol A CAS RN (80-05-7). References were also identified from databases such as REPROTOX, HSDB, IRIS, and DART, from the bibliographies of the literature reviewed, by members of the expert panel, and in public comments.

CERHR convened a 12-member, independent panel of government and non-government scientists to evaluate the scientific studies on the potential reproductive and developmental hazards of bisphenol A. The expert panel met publicly on March 5–7, 2007 and August 6–8, 2007. The Expert Panel Report on Bisphenol A is intended to (1) interpret the strength of scientific evidence that bisphenol A is a reproductive or developmental toxicant based on data from in vitro, animal, or human studies; (2) assess the extent of human exposures to include the general public, occupational groups, and other subpopulations; (3) provide objective and scientifically thorough assessments of the scientific evidence that adverse reproductive and developmental health effects may be associated with such exposures; and (4) identify knowledge gaps to help establish research and testing priorities to reduce uncertainties and increase confidence in future evaluations. This report has been reviewed by members of the expert panel and by CERHR staff scientists. Copies of this report have been provided to

[1]NTP is an interagency program headquartered in Research Triangle Park, NC, at the National Institute of Environmental Health Sciences, a component of the National Institutes of Health.

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There is sufficient evidence in rats and mice that bisphenol A causes male reproductive toxicity, characterized as delayed preputial separation, with subchronic or chronic oral NOAEL of 4.75 mg/kg bw/day and a LOAEL of 47.5 mg/kg bw/day (Tyl et al., 2002b).

There is inconsistent evidence in rats and mice that bisphenol A alters testosterone and gonadotropin levels in males after oral postnatal exposure.

There is inconsistent evidence in male and female mice that bisphenol A produces aneugenic effects in germ cells after exposure.

5.0 SUMMARIES, CONCLUSIONS, AND CRITICAL DATA NEEDS

5.1 Developmental Toxicity

No data on the effects of human developmental exposure to bisphenol A are available. There is a large literature describing studies in rodents and some work in other species. A large experimental animal literature was reviewed, assessed for its utility, and weighed based on the criteria established by this Panel.

From the rodent studies we can conclude that bisphenol A:

- Does not cause malformations or birth defects in rats or mice at levels up to the highest doses evaluated: 640 mg/kg/day (rats) and 1250 mg/kg/day (mice).
- Does not alter male or female fertility after gestational exposure up to doses of 450 mg/kg bw/day in the rat and 600 mg/kg bw/day in the mouse (highest dose levels evaluated).
- Does not permanently affect prostate weight at doses up to 475 mg/kg/day in adult rats or 600 mg/kg/day in mice.
- Does not cause prostate cancer in rats or mice after adult exposure at up to 148 or 600 mg/kg/day, respectively.
- Does change the age of puberty in male or female rats at high doses (ca. 475 mg/kg/day).

Rodent studies suggest that bisphenol A:

- Causes neural and behavioral alterations related to disruptions in normal sex differences in rats and mice. (0.01–0.2 mg/kg/day).

The data on bisphenol A are insufficient to reach a firm conclusion about:

- A change in the onset of puberty in male rats or mice at doses up to 475–600 mg/kg/day.
- An acceleration in the age of onset of puberty at a low dose in female mice at 0.0024 mg/kg/day, the only dose tested.
- Whether Bisphenol A predisposes rats toward prostate cancer or mice toward urinary tract deformations.

5.2 Reproductive Toxicity

There are insufficient data to evaluate whether bisphenol A causes male or female reproductive toxicity in humans. A large experimental animal literature was reviewed, assessed for its utility, and weighted based on the criteria established by this expert panel, including an evaluation of experimental design and statistical procedures. These animal data are assumed relevant for the assessment of human hazard.

Female effects: There is sufficient evidence in rats and mice that bisphenol A causes female reproductive toxicity with subchronic or chronic oral exposures with a NOAEL of 47.5 mg/kg bw/day and a LOAEL of ≥475 mg/kg bw/day.

Male effects: There is sufficient evidence in rats and mice that bisphenol A causes male reproductive toxicity with subchronic or chronic oral exposures with a NOAEL of 4.75 mg/kg bw/day and a LOAEL of ≥47.5 mg/kg bw/day.

5.3 Human Exposures

Bisphenol A is FDA-approved for use in polycarbonate and epoxy resins that are used in consumer products such as food containers (e.g., milk, water, and infant bottles) food can linings (Staples et al., 1998; SRI, 2004) and in dental materials (FDA, 2006). Resins, polycarbonate plastics, and other products manufactured from bisphenol A can contain trace amounts of residual monomer and additional monomer may be generated during breakdown of the polymer (European-Union, 2003).

Environmental Exposures: Bisphenol A emitted from manufacturing operations is unlikely to be present in the atmosphere in high concentrations. However, it was found in 31–44% of outdoor air samples with concentrations of <LOD (0.9) to 51.5 ng/m^3 (Wilson et al., 2006). Indoor air samples found concentrations ≤29 ng/m^3 (Rudel et al., 2001, 2003; Wilson et al., 2003). Limited U.S. surface water sampling found bisphenol A in 0–41% of samples ranging from <0.1 to 12 ug/L (Kolpin et al., 2002; Boyd et al., 2003). Twenty-five to 100% of indoor dust samples contained bisphenol A with concentrations of <detectable to 17.6 μg/g (Rudel et al., 2001, 2003; Wilson et al., 2003, 2006).

Exposures Through Food: The highest potential for human exposure to bisphenol A is through products that directly contact food such as food and beverage containers with internal epoxy resin coatings and through the use of polycarbonate tableware and bottles, such as those used to feed infants (European-Union, 2003). Studies examining the extraction of bisphenol A from polycarbonate infant bottles in the U.S. found concentrations <5 μg/L. Canned infant formulas in the U.S. had a maximum levels of 13 μg/L in the concentrate that produced a maximum of 6.6 μg/L when mixed with water (FDA, 1996; Biles et al., 1997a). Breast milk studies in the U.S. have found up to 6.3 μg/L free bisphenol A in samples (Ye et al., 2006). Measured bisphenol A concentrations in canned foods in the U.S are <39 μg/kg (FDA, 1996; Wilson et al., 2006). Limited drinking water sampling in the U.S. indicates that bisphenol A concentrations were all below the limit of detection (<0.1 ng/L) (Boyd et al., 2003).

Biological Measures of Bisphenol A in Humans: The panel finds the greatest utility in studies of biological samples that use sensitive and specific analytical methods (LC-MS or GC-MS) and report quality control measures for sample handling and analysis. The panel further focused on biological monitoring done in

U.S. populations. In the U.S, adult urine concentrations of free bisphenol A are <0.6 μg/L and total bisphenol A concentrations are <19.8 μg/L (Calafat et al., 2005; Liu et al., 2005; Ye et al., 2005). The 95th percentile total bisphenol A concentration for 394 adult volunteers (males and females; 20–59 years old) from the NHANES III survey was 5.18 μg/L (Calafat et al., 2005). Girls age 6–9 in the U.S. have concentrations of total bisphenol A <54.3 μg/L, with median concentrations ranging from 1.8–2.4 μg/L (Liu et al., 2005; Wolff et al., 2006). No U.S. studies have examined blood or semen concentrations of bisphenol A. Amniotic fluid total bisphenol A concentrations in the U.S are <1.96 μg/L. Dental sealant exposure to bisphenol A occurs primarily with use of the dental sealant bisphenol A dimethylacylate. This exposure is considered an acute and infrequent event with little relevance to estimating general population exposures.

Bisphenol A Intake Estimates: The panel found that previous oral intake estimates for infants fed formula and breast milk did not use levels reported for the U.S. population, so the panel estimated intake based on typically-used parameters. The panel found the food intake estimates made by the European Commission (2002) used concentrations of bisphenol A comparable to U.S. food concentrations in their intake estimates, so have included these estimates as well (Table 104). Estimates from duplicate diets in U.S. children (Wilson et al., 2003, 2006) found lower bisphenol A concentrations in foods than those estimated by the European Commission, therefore the aggregate estimates of intake by Wilson et al. were somewhat lower than those estimated by the European Commission. However, the aggregate intake estimates by Wilson et al. (2003, 2006) are in line with the estimates based on urinary metabolite measurements for children described above.

Estimates of intake based on occupational air concentrations of bisphenol A from U.S. powder paint workers suggest exposures up to 100 ug/kg bw/day (USEPA, 1988). Estimates of intake based on urinary metabolite levels among Japanese workers spraying epoxy coatings resulted in a mean estimate of exposure of 0.043 μg/kg bw/day (<0.002 pg to 0.45 μg/kg bw/day) (Hanaoka et al., 2002).

5.4 Overall Conclusions

The panel spent a considerable amount of time attempting to interpret and understand the inconsistent findings reported in the "low dose" literature for bisphenol A. Conducting low dose studies can be challenging because the effects may be subtle and small in magnitude and therefore more difficult to statistically distinguish from background variability. The inherent challenge of conducting these types of studies may be exacerbated with bisphenol A because the endpoints of concern are endocrine-mediated and potentially impacted by factors that include phytoestrogen content of the animal feed, extent of bisphenol A exposure from caging or water bottles, and the alleged sensitivity of the animal model to estrogens. The Panel believed that high-dose studies are less susceptible to these types of influences because the toxicologic response should be more robust and less variable. While the Panel did not necessarily expect a specific effect to display a monotonic dose response (e.g., consistently increasing organ size), many members of the panel expected the high-dose studies with bisphenol A to detect *some* manifestation of toxicity (e.g., altered weight, histopathology) in tissues reported to be affected at low doses even if the study could not replicate the reported low dose effect. There are several large, robust, well designed studies with multiple dose groups using several strains of rats and mice and none of these detected any adverse reproductive effects at low to moderate dosage levels of BPA administered via the relevant route of human exposures. Further, none of these studies detected changes in prostate weight, age at puberty (rat), pathology or tumors in any tissue, or reproductive tract malformations. For this reason, Panel members gave more weight to studies that evaluated both low- and high-doses of bisphenol A compared to low-dose-only studies in cases where the target tissues were comparably assessed.

Every chemical that produces low dose cellular and molecular alterations of endocrine function also produces a cascade of effects increasing in severity resulting in clearly adverse alterations at higher doses, albeit the effects can be different from those seen at low doses. With these endocrine disrupters, but not BPA, the low dose effects are often causally linked to the high-dose adverse effects of the chemical. This is true for androgens like testosterone and trenbolone, estrogens like DES, 17β-estradiol and ethinyl estradiol, xenoestrogens like methoxychlor and genistein, and antiandrogens like vinclozolin, for example. Hence, the failure of BPA to produce reproducible adverse effects via a relevant route of exposure, coupled with the lack of robustness of the many of the low dose studies (sample size, dose range, statistical analyses and experimental design, GLP) and the inability to reproduce many of these effects of any adverse effect strains the credibility of some of these study results. They need to be replicated using appropriate routes of exposures, adequate experimental designs and statistical analyses and linked to higher dose adverse effects if they are to elevate our concerns about the effects of BPA on human health. The lack of reproducibility of the low dose effects, the absence of toxicity in those low-dose-affected tissues at high-doses, and the uncertain adversity of the reported effects led the panel to express "minimal" concern for reproductive effects.

In contrast, the literature on bisphenol A effects on neural and behavioral response is more consistent with respect to the number of "positive" studies although it should be noted that the high-dose studies that proved to be the most useful for evaluating reproductive effects did not adequately assess neural and behavioral responses. In addition, even though different investigators assessed different neural and behavioral endpoints, the Panel concluded that the overall findings suggest that bisphenol A may be associated with neural changes in the brain and behavioral alterations related to sexual dimorphism in rodents. For this reason, the Panel expressed "some" concern for these effects even though it is not clear the reported effects constitute an adverse toxicological response.

Concerns are expressed relative to current estimates of general population exposure levels in the U.S.

1. *For pregnant women and fetuses*, the Expert Panel has different levels of concern for the different

developmental endpoints that may be susceptible to bisphenol A disruption, as follows:

- For neural and behavioral effects, the Expert Panel has some concern;
- For prostate effects, the Expert Panel has minimal concern;
- For the potential effect of accelerated puberty, the Expert Panel has minimal concern; and
- For birth defects and malformations, the Expert Panel has negligible concern.

2. *For infants and children*, the Expert Panel has the following levels of concern for biological processes that might be altered by Bisphenol A, as follows:

- Some concern for neural and behavioral effects; and
- Minimal concern for the effect of accelerated puberty.

3. *For adults*, the Expert Panel has negligible concern for adverse reproductive effects following exposures in the general population to Bisphenol A. For highly exposed subgroups, such as occupationally exposed populations, the level of concern is elevated to minimal.

5.5 Critical Data Needs

1. *Neural and behavioral endpoints.* 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. This effort should include molecular and cellular studies to ascertain the sensitivity of the developing brain to bisphenol A-induced structural and biochemical alterations. The association between bisphenol A and neural and behavioral endpoints should also be examined in longitudinal studies of pregnancy and child development in humans.
2. *Human exposure assessment.* Additional data are needed to clarify bisphenol A exposures and internal dosimetry in the general population, newborns, and occupationally-exposed individuals. Available data demonstrate that a large fraction of children and adults have detectable levels of bisphenol A metabolites in their urine. What are needed are duplicate diet studies to identify in detail the sources and routes of exposure of bisphenol A. For example, while research suggests diet is the major source of BPA for U.S. infants and young children, the detailed analysis of BPA levels has primarily focused on polycarbonate baby bottle leachates and canned food. The contributions of non-canned food and drinking water routes of exposure for U.S. youth and adults not occupationally-exposed to BPA remain unknown and in need of further study. Levels of BPA in residential drinking water wells and community water sources have not been systematically studied. Also unknown is the impact of landfill leachates on levels of bisphenol A in U.S. drinking well waters and whether chlorinated congeners of bisphenol A are found in U.S. municipal water supplies. Finally, more measurement are needed of free and total bisphenol A, its glucuronide conjugate, and other metabolite concentrations from maternal, fetal, and neonatal tissues or fluids (i.e., placenta, amniotic fluid, breast milk, urine, serum). These data would provide insight into the roles of metabolism and exposure route on internal dose.
3. Human studies relating adult exposure to reproduction and development, including effects on hormone levels.
4. *Physiologically-based pharmacokinetic (PBPK) models.* PBPK models are needed to facilitate the interpretation and applicability of animal studies, including rodents and nonhuman primates, for human risk assessment.
5. *Effects on prostate and mammary gland development.* Additional data are needed to understand the susceptibility to disruption of prostate and mammary gland development in humans and animals by bisphenol A exposure. Laboratory animal studies should initially focus on the oral route of exposure and should be informed by any new knowledge about human exposure and human internal dosimetry. A particular data need is an improved understanding of the biology of PIN (prostatic intraepithelial neoplasia) in animal models and its relationship to prostate cancer. Similarly, bisphenol A-induced alterations in mammary gland development and their potential relationship to mammary cancer should be investigated across a broad range of internal concentrations and external doses.
6. *Altered puberty.* The robustness and biologic basis for altered puberty following bisphenol A exposure should be evaluated in mouse, rat, and gerbil. In laboratory animals, this evaluation should be performed following combined gestational and lactational exposure, and following pubertal exposure alone, and should include an assessment of any changes in hormonal responsivity at later ages, and all related to internal and tissue concentrations of bisphenol A. In addition, longitudinal cohort studies examining the potential modulation by bisphenol A of the onset, progression, and control of puberty in humans should be performed.
7. *Biological mechanism for low-dose-only effects.* Most useful would be data that provided a biologically-plausible explanation for effects that appear at low doses but not higher doses. This might involve the membrane-bound estrogen receptor and its possible activation by bisphenol A.
8. More work directed toward urinary tract morphological and histologic changes after developmental exposure would be helpful to determine the robustness and relevance of the limited report of these effects in one study.
9. *Inter-laboratory replication of studies.* Inter-laboratory replication of critical findings is a sine qua non for enhancing confidence in experimental results. Such studies should be supported by funding agencies, and should be facilitated by the open sharing of experimental details and approaches. The future reproducibility should also be considered by investigators as they design their studies.

Actions on the Draft NTP Brief on Bisphenol A by the NTP Board of Scientific Counselors (BSC), June 11, 2008

The BSC agreed with the following conclusions in the Draft NTP Brief on Bisphenol A as written:

- The BSC accepted unanimously (12 yes, 0 no) that the scientific evidence cited in the draft NTP Brief on Bisphenol A supports the NTP conclusion of *some* concern* for neural and behavioral effects of bisphenol A in fetuses, infants, and children at current human exposures.

- The BSC accepted (10 yes, 2 no) that the scientific evidence cited in the draft NTP Brief on Bisphenol A supports the NTP conclusion of *some* concern for bisphenol A exposure in fetuses, infants, and children at current human exposures based on effects in the prostate gland.

- The BSC accepted (11 yes, 1 no) that the scientific evidence cited in the draft NTP Brief on Bisphenol A supports the NTP conclusion of *negligible* concern that exposure of pregnant women to bisphenol A will result in fetal or neonatal mortality, birth defects or reduced birth weight and growth in their offspring.

- The BSC accepted unanimously (12 yes, 0 no) that the scientific evidence cited in the draft NTP Brief on Bisphenol A supports the NTP conclusion of *negligible* concern that exposure to bisphenol A causes reproductive effects in non-occupationally exposed adults.

- The BSC accepted (11 yes, 0 no, 1 abstention) that the scientific evidence cited in the draft NTP Brief on Bisphenol A supports the NTP conclusion of *minimal* concern for workers exposed to higher levels of bisphenol A in occupational settings.

The BSC recommended changing the level of concern in the Draft NTP Brief on Bisphenol A from "some" to "minimal" for effects in the mammary gland and an earlier age for puberty in females. The Board recommended the following conclusions:

- The BSC accepted (7 yes, 4 no, 1 abstention) that the scientific evidence cited in the draft NTP Brief on Bisphenol A supports the conclusion of *minimal* concern for bisphenol A exposure in fetuses, infants, and children at current human exposures based on effects in the mammary gland.

- The BSC accepted (7 yes, 4 no, 1 abstention) that the scientific evidence cited in the draft NTP Brief on Bisphenol A supports the conclusion of *minimal* concern for bisphenol A exposure in fetuses, infants, and children at current human exposures based on an earlier age for puberty in females.

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* The five levels of concern used by NTP are from highest to lowest: serious concern, concern, some concern, minimal concern, and negligible concern.