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NRDC Comments to the
NTP CERHR Bisphenol A Expert Panel Report

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These comments are submitted by Natural Resources Defense Council (NRDC), who on behalf of our 1.2 million members and online activists, uses law and science to ensure a safe and healthy environment for all living things. NRDC has no financial interest in bisphenol A (BPA).

NRDC appreciates the significant amount of time spent by the NTP staff and its expert panel in the preparation of the BPA draft and final reports by the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR).[1]

NTP chemical assessments inform federal and state regulatory agencies

The NTP was established by Congress in 1978[2] to address the potential health harm from exposure to chemical pollutants in our environment.[3] It is the premier chemical evaluation program in the U.S., and possibly the world. The stellar reputation of the NTP and its products is hard-won through insistence on the highest standards of scientific performance. The NTP evaluations are an invaluable resource for regulatory agencies to wisely allocate resources towards the least burdensome and most effective strategies to protect human health.[4] Its reports and monographs are considered authoritative texts and have been relied upon by federal and state regulatory agencies, including in California to inform listings under Proposition 65.[5] Peer review by committees such as the CERHR expert committee is the method by which quality control is assured. We therefore ask that the expert committee and NTP staff consider seriously the concerns raised by NRDC and others in the final draft of the BPA report.

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[1] National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR). Bisphenol A. http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol-mtg.html

[2] The establishment of the NTP Wednesday, Nov. 15, 1978, Federal Register 43, No 221,4110-85-M

[3] National Toxicology Program website. About the NTP.
http://ntp.niehs.nih.gov/index.cfm?objectid=7201637B-BDB7-CEBA-F57E39896A08F1BB

[4] How NTP studies are used to protect human health.
http://ntp.niehs.nih.gov/index.cfm?objectid=03612A12-9F5F-C336-79B4709B8013F338

[5] The National Toxicology Program Processes in Relation to the Authoritative Bodies Mechanism in Proposition 65 http://www.oehha.ca.gov/prop65/policy_procedure/ntptechrev.html

NTP chemical assessments must be irreproachable and of the highest standard of scientific objectivity

Everyone agrees that it is extremely important that the BPA report is of the highest scientific quality, in both its depth of analysis and breadth of literature utilized. This chemical presents a challenge to the NTP to do a thorough and objective scientific analysis of the potential for harm from this widespread contaminant. There are large economic interests, whose short-term incentives are opposed to government regulation of BPA. To this end, the NTP must be given the protection of NIEHS and Congress to issue its scientific assessments without undue interference from parties that seek to protect their economic interests by stifling information on the potential hazards of their products.

BPA is a highly toxic, widespread contaminant. As a demonstration of its economic importance and toxicity, NTP provides the following summary: "Bisphenol A (CAS RN: 80–5–07) 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 to bisphenol A or by exposure to food or drink that has been in contact with a material containing bisphenol A. CERHR selected this chemical 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."[6]

NRDC has previously submitted comments of our concerns with the previous drafts of this document. While some of our concerns have been addressed by the committee, we have significant remaining concerns regarding some conclusions in this final draft.

1. **Biologically relevant studies have not been considered in this final analysis.**

   Specifically we are dismayed that the committee continues to refuse to utilize studies that did not use oral routes of BPA administration. We feel strongly that **routes of exposure other than oral administration should be considered of utility for the evaluation process, in particular for prenatal and immature animal studies.**

The expert panel acknowledges that immature animals (fetuses and neonates) are susceptible sub-populations because they have limited capabilities to de-toxify BPA by glucuronidation.[7] Therefore, immature animals are susceptible to the toxicity of

[6] Federal Register / Vol. 72, No. 115 / Friday, June 15, 2007.
http://cerhr.niehs.nih.gov/news/fedreg/CERHR_72_FR_115_BPA.pdf

[7] Section 2.6.7 in BPA CERHR final draft, "*Human findings were consistent with rodent studies that demonstrated no or limited glucuronidation capacity by fetuses (126, 150, 151) and lower glucuronidation capacity in immature than adult rats(2, 118, 151).* "

circulating free-BPA concentrations and studies that consider prenatal and neonatal exposures should be carefully considered. The potential for circulating free-BPA should be the gauge for determining the potential toxicity of BPA, regardless of the route of administration to achieve those levels. New scientific data support the argument that the route of administration does not affect levels of circulating free-BPA in immature animals. [8]

As previously noted by the expert panel, because of the evaluation criteria utilized, there are a relatively small number of studies considered to be of utility for evaluation. Appropriate inclusion of scientific studies that use non-oral routes of exposure will strengthen the analysis by NTP and allow for a more robust characterization of BPA effects in immature animals.

2. NTP should consider whether an adequate positive control was included when evaluating the strength of studies and apply this standard consistently.

The expert panel on p. 123 of the final draft states:

"*The Panel also examined the issue of data that would be expected to result when positive controls were employed. While we did not feel that positive controls were required for studies, when they were used, expected effects needed to be demonstrated to validate that the experimental model was capable of responding to a certain stimulus. This is of even more value when there is no response to the main exposure under study. When looking for estrogenic responses, investigators often use 17 estradiol or diethylstilbestrol. These must be used at adequate doses to produce the desired response. Inadequate challenge by the positive control, resulting in no response, leaves the reader uncertain whether the lack of response is due to the selection of too low a dose, or whether the experimental model is incapable of responding to a sufficient challenge. Even though the Panel, based on its own scientific experience, might conclude that inappropriately low doses had been selected and thus a lack of response is not surprising, the Panel was left with little choice in such situations but to give much less weight to studies where non-effective doses of a positive control compound were used.*"

Establishment of a positive control is essential for determining the quality of a research study and its ability to predict differences in treatment outcomes. Studies with no positive controls should be given less weight than studies that have no positive control. Even when applying the criteria outlined above by NTP, there are inconsistencies in how this criteria were applied in the final draft. For example, Cagen (339) the CERHR writes, "The lack of much effect with diethylstilbestrol treatment is a weakness." yet, in the end this study was considered adequate and of high utility.

These inconsistencies in applying criteria have been pointed out in detail by NRDC and others in previous comments. These inconsistencies result in an unbalanced evaluation of the science. The expert panel should ensure that significant weaknesses and strengths are

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[8] Taylor JA, Welshons WV, and vom Saal FS. *Available online 17 January 2008* No Effect of Route of Exposure (Oral; Subcutaneous Injection) on Plasma Bisphenol A throughout 24 hr after Administration in Neonatal Female Mice. Reproductive Toxicology.

consistently and uniformly identified in each study, especially those that are considered of high utility.

3. Newly-published scientific reports should be considered.

Several new studies have been published since this final draft was completed. These new studies should be considered by NTP in their final monograph.

1. Calafat AM, Ye X, Wong L-Y, Reidy JA, and Needham LL. 2008. Exposure of the U.S. Population to Bisphenol A and 4-*tertiary*-Octylphenol: 2003–2004. Environ Health Perspect. 2008 January; 116(1): 39–44.

Results from the CDC's NHANES 2003-2004 analysis of over 2,500 Americans found BPA in 93% of urine samples, at levels ranging from 0.4-149 microg/L. Females had significantly higher levels of BPA in their urine than males. Children had the highest levels, followed by teens and adults. Important ethnic differences also were noted with non-Hispanic blacks and whites having significantly higher levels than Mexican Americans. These findings support results from previous studies that have shown widespread exposure in the general public, with children being the most highly exposed. Of note, this analysis did not consider children younger than 6 years of age. Failure to consider pre-school aged children is a significant weakness of the database, given the strongly likelihood that of significant exposure to this age-group through baby bottles and food.

2. The **consensus statement and associated articles from the Chapel Hill bisphenol A expert** panel (Reproductive Toxicology, Aug-Sept 2007). This series of articles resulted from an NIEHS-sponsored workshop of scientific experts with extensive knowledge about BPA. The consensus statement from thirty-eight participants reads:

> *"The published scientific literature on human and animal exposure to low doses of BPA in relation to in vitro mechanistic studies reveals that human exposure to BPA is within the range that is predicted to be biologically active in over 95% of people sampled. The wide range of adverse effects of low doses of BPA in laboratory animals exposed both during development and in adulthood is a great cause for concern with regard to the potential for similar adverse effects in humans. Recent trends in human diseases relate to adverse effects observed in experimental animals exposed to low doses of BPA. Specific examples include: the increase in prostate and breast cancer, uro-genital abnormalities in male babies, a decline in semen quality in men, early onset of puberty in girls, metabolic disorders including insulin resistant (type 2) diabetes and obesity, and*

> *neurobehavioral problems such as attention deficit hyperactivity disorder (ADHD).*"[9]

Notably, unlike the CERHR panel, all of these experts have done research on BPA and have no industry affiliations with producers or users of BPA. This represents a different but important view of the science surrounding BPA and should be seriously considered in the final NTP analysis.

3. Taylor JA, Welshons WV, and vom Saal FS. *Available online 17 January 2008* No Effect of Route of Exposure (Oral; Subcutaneous Injection) on Plasma Bisphenol A throughout 24 hr after Administration in Neonatal Female Mice. Reproductive Toxicology.

This article demonstrates that BPA exposure levels during the neonatal period were equivalent after both sc and oral administration. This study strongly suggests that the NTP should reconsider utilizing developmental studies with non-oral routes of exposure in their final analysis.

4. Howdeshell KL, Furr J, Lambright CR, Wilson VS, Ryan BC and Gray LE, Jr. (in press). Gestational and Lactational Exposure To Ethinyl estradiol, But Not Bisphenol A, Decreases Androgen-dependent Reproductive Organ Weights and Epididymal Sperm Abundance In The Male Long Evans Hooded Rat. ToxSci Advance Access published December 20, 2007

This study investigated the effects of developmental exposures to BPA and the synthetic estrogen, ethinyl estradiol (EE), in Long-Evans rats. The route of administration was by gavage with the chemicals dissolved in corn oil. This study analyzed hormone levels and male reproductive morphology. The study found permanent disruption of the male reproductive tract at doses above 50 microg/kg/day of EE but did not find any effect at lower doses nor did the investigators find any effects of BPA treatment, although a wide range of doses was not investigated. This study adds further to our knowledge of the effects of xenoestrogen exposure in LE rats.

However, this study should not be used to preclude utilization of other low dose effect BPA studies by NTP. There are a number of significant differences between this study and other low dose studies including species of animal tested (rat v. mouse), vehicle (corn oil v. DMSO), route of administration (gavage v. subcutaneous), and differences in laboratory protocol including types of cages, bedding material, and feed. Of note, a similar study in LE rats using a gavage of BPA dissolved in corn oil vehicle did find effects of BPA at similar doses, including changes in hormone levels and male

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[9] Chapel Hill Bisphenol A Expert Panel Consensus Statement: Integration of Mechanisms, Effects in Animals and Potential to Impact Human Health at Current Levels of Exposure. Reproductive Toxicology, Reproductive Toxicology, Volume 24, Issue 2, August-September 2007, Pages 131-138.

reproductive organ weights.[10] The reason for differences between these two studies is not clear but should be considered by NTP when considering the utility of this study in their analysis.

Conclusion

NTP has been tasked with developing a timely and comprehensive report on the potential risks associated with real-world exposures to BPA. Given the limitations of this panel and in light of new scientific evidence, the challenge for NTP is to now take a step back and re-visit this report, specifically focusing on non-oral routes of exposure in immature animals. NTP also should take into serious consideration the low dose exposures as outlined by the Chapel Hill group.

NRDC appreciates the opportunity to make comments on the expert panel committee final draft review of bisphenol A.

Respectfully,

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On behalf of our 1.2 million members and online activists, NRDC advocates for disclosure of information, regard for scientific inquiry and facts, justice for disempowered people, honesty by government, and corporate accountability. We seek to establish sustainability and good stewardship of the Earth as central ethical imperatives of human society (www.nrdc.org)

[10] Akingbemi BT, Sottas CM, Koulova AI, Klinefelter GR, Hardy MP. Inhibition of testicular steroidogenesis by the xenoestrogen bisphenol A is associated with reduced pituitary luteinizing hormone secretion and decreased steroidogenic enzyme gene expression in rat Leydig cells. Endocrinology 2004; 145: 592-603.