NATURAL RESOURCES DEFENSE COUNCIL

Dr. Michael D. Shelby, CERHR Director
National Institute of Environmental Health Sciences
Email: shelby@niehs.nih.gov

Dr. Barbara Shane, Executive Secretary for the NTP BSC
National Institute of Environmental Health Sciences
Email: shane@niehs.nih.gov

Submitted by electronic mail.

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NRDC Comments on the
Draft NTP brief on Bisphenol A
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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, use 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 and careful analysis done by the NTP staff in the preparing the draft brief on BPA, released April 14, 2008.[1] We are pleased that NTP has expanded the level of concern from the CERHR expert panel analysis to include additional developmental outcomes in fetuses, infants, and children related to current levels of exposures to BPA.

NTP has agreed with the CERHR Expert Panel that 'there is a sufficiently consistent body of literature to suggest that perinatal or pubertal exposure to "low" doses of bisphenol A causes neural and behavioral alterations in rats and mice, especially related to the development of normal sex-based differences between males and females ("sexual dimorphisms" or "sexually dimorphic")..' A significant departure from the NTP-CERHR report is that NTP has raised the level of concern for certain types of developmental toxicity in fetuses, infants and children. NTP expresses "some concern"

[1] National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR). Bisphenol A. http://cerhr.niehs.nih.gov/chemicals/bisphenol/BPADraftBriefVF_04_14_08.pdf

for bisphenol A exposure in these populations based on effects in the prostate gland, mammary gland, and an earlier age for puberty in females.

NRDC strongly agrees with NTP that BPA could cause developmental harm in fetuses, infants and children. We acknowledge that a designation of "some concern" for developmental toxicity in fetuses, infants and children is meaningful and signifies potential human harm. However, we feel strongly that the scientific evidence to date supports a higher level of concern and weight of evidence for developmental toxicity. In particular, NTP has been too dismissive of the significance of pre-cancerous lesions in reproductive tissues caused by BPA. Although more research for a deeper understanding of toxicity is always of interest, the current level of evidence is sufficient to issue a public health warning to reduce BPA exposure for prevention of adverse effects.

NTP's conclusions regarding BPA toxicity will be reviewed and used by regulatory agencies. Therefore, NTP's conclusions should be interpretable without ambiguity or confusion. As currently written there is considerable ambiguity and the conclusions have been interpreted in the lay press as indicative of both evidence that BPA is harmful to humans[2] and evidence that current levels of exposure are safe[3].

Pre-cancerous lesions in reproductive tissues should warrant greater concern.

The draft NTP brief is too dismissive of the importance of hyperplasia and carcinoma *in situ* and based on the relevance of animal models and the significance of pre-cancerous lesions in humans, NTP should have a higher level of concern for these effects.

In discussing mammary tissue, NTP notes that "the development of these lesions does not guarantee the formation of tumors or cancer…and that they are most appropriately interpreted as risk factors". However, the absence of long term studies demonstrating the development of mammary gland tumor should not be interpreted as an absence of adverse effects. Carcinoma *in situ* can and should alone be viewed as an adverse effect.

As noted by NTP, ductal carcinoma *in situ* (DCIS) increases the risk of developing invasive breast cancer by 8-10 fold. This increased risk is well-recognized and taken seriously by the medical community, such that if a woman is diagnosed with DCIS, the

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[2] "These findings of BPA's dangers are based on the totality of research around this chemical," said Rep. John D. Dingell, D-Mich., chairman of the House Committee on Energy and Commerce, in a Tuesday statement. "These assessments fly in the face of the FDA's determination that BPA is safe." **Plastic bottles could be hurting your baby. AP News, 4/15/08.**

[3] 'At the American Chemistry Council, Steve Hentges, executive director of the polycarbonate/BPA global group, said today that there's still no evidence of serious health risks or need to remove BPA from the market. This evaluation echoes many of the already published findings about BPA, Hentges said. "But the data as it currently stands does not indicate that there is a significant risk associated with bisphenol A."' **Plastic bottles could be hurting your baby. AP News, 4/15/08.**

standard of care for most patients is surgical removal (lumpectomy or mastectomy) followed by tamoxifen therapy and increase medical surveillance. Atypical hyperplasia also should be viewed as an adverse effect. This diagnosis also calls for increased monitoring and in some cases tamoxifen therapy. Clearly, these pre-cancerous lesions have economical, mental and physical impacts in the women who are diagnosed with them. Any chemical which causes these lesions should be viewed with serious concern.

As reviewed in the draft NTP brief, studies which have adequately examined mammary tissue after BPA exposure have found pre-cancerous lesions after peri-natal exposure. In addition, a recently published study of the effects of BPA in human breast cells provides further evidence that BPA promotes the development of breast cancer. Dairkee et al exposed normal human breast tissue to low, environmentally relevant levels of BPA and found changes in gene expression consistent with those found in a highly aggressive type of breast cancer and associated with poor survival.[4] This study adds further weight of evidence for the ability of BPA to cause changes in mammary tissue that are associated with the development of cancer.

Finally, as noted in previous comments to the NTP by Dr. Gail Prins, PIN lesions in rodent models are relevant for studying human prostate cancer.[5] According to this consensus statement, PIN lesions in rodents with invasive properties have clear significance and relevance to human PIN lesions. Moreover, the development of PIN lesions in humans is clearly an adverse effect as high grade PIN lesions are highly predictive for the development of cancer. Studies have found one-third to one-half of men with high grade PIN on biopsy will develop cancer on follow-up biopsy.[6,7]

Based on the relevance of animal models and the significance of pre-cancerous lesions as predictive factors for the development of invasive cancer, NTP should raise the level of concern for BPA's ability to cause these effects.

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[4] Dairkee SH, Seok J, Champion S, Sayeed A, Mindrinos M, Xiao W, Davis RW, Goodson WH. Bisphenol A induces a profile of tumor aggressiveness in high-risk cells from breast cancer patients. Cancer Res. 2008 Apr 1;68(7):2076-80.

[5] Cancer Research 64:2270, 2005. entitled "Prostate Pathology of Genetically Engineered Mice: Definitions and Classification. The Consensus Report from the Bar Harbor Meeting of the Mouse Models of Human Cancer Consortium Prostate Pathology Committee".

[6] Kronz JD, Allan CH, Shaikh AA, Epstein JI Predicting cancer following a diagnosis of high-grade prostatic intraepithelial neoplasia on needle biopsy: data on men with more than one follow-up biopsy. Am J Surg Pathol. 2001 Aug;25(8):1079-85.

[7] Park S, Shinohara K, Grossfeld GD, Carroll PR. Prostate cancer detection in men with prior high grade prostatic intraepithelial neoplasia or atypical prostate biopsy. J Urol. 2001 May;165(5):1409-14.

NTP chemical assessments inform federal and state regulatory agencies

The NTP was established by Congress in 1978[8] to address the potential health harm from exposure to chemical pollutants in our environment.[9] 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.[10] 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.[11] Peer review by committees such as the CERHR expert committee is the method by which quality control is assured. We therefore ask that the Board of Scientific Counselors and NTP staff consider seriously the concerns raised by NRDC and others for this draft brief.

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 consideration. 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

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

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

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

[11] 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

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."[12]

Based on the widespread exposure, especially in vulnerable populations, and the existing data and comments made above, BPA should be considered a hazard to human development and reproduction with clear evidence of adverse effects. BPA has been demonstrated to have multiple developmental toxicities at low and environmentally relevant doses in a number of well-designed studies. In addition, the relevance of animal models and significance of pre-cancerous lesions for human disease is clear and warrants a stronger statement from NTP on the adverse effects of BPA.

NRDC appreciates the opportunity to make comments on the draft NTP brief of bisphenol A.

Respectfully,

/s Sarah Janssen, MD, PhD, MPH
Science Fellow, Natural Resources Defense Council
111 Sutter Street, 20th floor
San Francisco, CA 94104
(415) 875-6100 (telephone); (415) 875-6161 (fax)
sjanssen@nrdc.org

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