Linda Adams
Agency Secretary
Cal/EPA

Department of Toxic Substances Control

Maureen Gorsen, Director
700 Heinz Avenue, Suite 200
Berkeley, California 94710-2721

Arnold Schwarzenegger
Governor

JAN 2 1 2007

December 26, 2006

Dr. Mike Shelby
CERHR Director
NIEHS
P.O. Box 12233
MD EC-32
Research Triangle Park, North Carolina 27709

RE: Bisphenol A (BPA) (Federal Register 71(238): 74534- 74536, Tuesday, December 12, 2006)

Dear Dr. Shelby:

In response to the NIEHS request for comment on the draft CERHR Report on the Reproductive and Developmental Toxicity of Bisphenol A, the following is intended to increase the clarity and rigor of the analyses and to lead to more accurate presentations of the exposure estimates.

At the outset, the document represents a heroic task and in general the working group has been charged with a tremendous amount of work to sort through literature that is often conflicting and often cannot be reproduced. Even accounting for differential designs and protocols and attempting to discern the skill of a particular laboratory, the discrepancies appear to remain. As a first step, the CERHR text should refrain from editorialization (e.g., page 155, lines 43-45) as such detracts from the science presented.

1. At pages 3-12, a great many publications concerning measurement of BPA in diverse media are cited. At page 12, boldface type directs the reader to discrepancies in the various concentration results. One aspect not covered in the review is the prevalent use of plastic labware and incidental BPA contamination by sample contact with polycarbonate plastic (e.g., page 39, lines 8 and 9). This problem can be increased by the extremely low levels that can be quantified by contemporary instruments; often (but not always) the study authors specify that all procedures were carried out using glass containers and other

contamination by sample contact with polycarbonate plastic (e.g., page 39, lines 8 and 9). This problem can be increased by the extremely low levels that can be quantified by contemporary instruments; often (but not always) the study authors specify that all procedures were carried out using glass containers and other materials to reduce the possibility of unintentional BPA contamination due to the ubiquitous presence of BPA-containing or derived materials in the laboratory. Neither the CERHR nor other authors (e.g., J.H. Kang et al. Toxicology 226: 79-89, 2006) appear to have taken the sample handling procedures into account when reporting BPA concentrations in environmental and tissue (including human) samples. The marked differences in reported BPA concentrations (e.g., Tables 5, 6, 13 and 18) suggest there are differences in reliability of BPA analytical techniques and the possibility of laboratory BPA contamination.

2. Please include a section (inserted preferably prior to Section 1.2) which conducts a critical review of the wide array of analytical methods that have been used to quantify BPA. For example, the first mention of the ELISA technique used by some laboratories (e.g., page 257, line 10 and page 258, lines 9 and 10) is made. Fukata et al. (Toxicology Mechanisms and Methods 16: 427-430, 2006) concluded: "ELISA is not suitable for BPA measurement in human samples because low levels of BPA in human samples, matrix effect and the specificity of anti-BPA antibody." However as the CERHR report is written, the Sakaki et al. (reference 51) ELISA results are presented as though they are of identical accuracy as those obtained using mass spectral-based methods (e.g., page 13, line 51). While lines 37-39 on page 13 contain a (rather weak) explanation of the problems associated with ELISA and its inability to distinguish BPA, the CERHR review would benefit from the addition of a section that reviews BPA analytical methods and identifies those methods the CERHR determines are reliable and reproducible. As written, the failure to evaluate critically the available analytical methods calls into questions the reliability of the data presented in Table 38 or those discussed at pages 257-259. As part of the analytical chemistry section, please include information on the chemical identity of substances other than the BPA molecule itself that can be found in commercially-available BPA (including those found in technical grade materials) used – apparently by most academic laboratories. It may be that some of the marked variability in results is due to the particular test article and since most papers do not report independent confirmation of the purity of the test article, it is difficult to determine whether materials other than BPA could have contributed to the discrepancies observed between similar protocols.
3. Fundamental to the practical use of the CERHR work, is a distinction between routes of exposure. As pointed out in Sections 3.2.6 and 4.3.3.4 (pages 46 and 77) of the WHO 1984 Environmental Health Criteria 30 (Principles for Evaluating Health Risks to Progeny Associated with Exposure to Chemicals During Pregnancy), "[test article] administration should be by the anticipates route(s) of human exposure" and on page 146 of the Canadian Ministry of Health and Welfare (The Testing of Chemicals for Carcinogenicity, Mutagenicity and Teratogenicity, 1975.): "If the population exposure to the chemical entity is by ingestion, then the compound will be administered orally". The CERHR Section

3.4.2.1 makes an effort to separate results obtained after parenteral (e.g., intraperitoneal, intracisternal, subcutaneous) injections and those obtained after exposure routes relevant to humans (e.g., oral). While the parenteral routes may be of some use in hazard identification, most readers will be interested in those data collected after BPA ingestion. Therefore, it would be helpful to reorganize the narrative presentation to discuss all of the parenteral route studies together then in a separate section discuss all of the ingestion (e.g., dietary, gavage, micropipette) together. At the conclusion of the narrative, it is important CERHR differentiate between the results obtained and relative BPA potency observed after parenteral as contrast to ingestion exposure.

4. Some comment is needed concerning the comparative dose metric across different routes of exposure. Given the marked differences in BPA handling after ingestion as compared to parenteral exposure, accurate presentation of health risk (if any) depends on the parent circulating free BPA concentrations associated with each protocol. Unfortunately, the CERHR did not consider the absorbed BPA dose metric (and places emphasis on the administered dose regardless of route) which should be used to compare study results and assign relative potency across exposure routes. At Table 49, please amend the presentation to include the administered dose used in each study; as written, the CERHR conclusion at lines 30-33 on page 79 and at lines 14-16 on page 109 is not clear in that the CERHR definition of "high dose" (including duration and frequency of exposure) was not provided. Indeed, despite the voluminous BPA literature this may not be possible, but some acknowledgment of this important comparative tool should be made in the conclusion.
5. For each and every study presented in Section 3.2, please insert the purity of the test article (as seen at page 127, line 14) and if no mention is made of BPA purity, please indicate that is the case (as done at page 118, line 39).
6. The CERHR report should take care to highlight and exclude from further consideration those publications that used inappropriate statistical procedures or that failed to state clearly the experimental unit. For many years, the litter has been considered the experimental unit for statistical handling of developmental toxicity data (e.g., Am. J. Anat. 128: 185-192, 1970; Biometrics 37: 819-829, 1981). Goodman et al. (Crit. Rev. Toxicol. 36: 436, 2006) listed those studies reviewed by CERHR which either failed to define proper statistical handling of the data or (apparently) used an incorrect (individual offspring) experimental unit. Thus, all of the studies listed by Goodman et al. (2006) that employed incorrect statistical handling of the data should be so identified by CERHR; further, those incorrect evaluations should be eliminated from any further consideration during weight-of-evidence integration of the data.
7. At page 279 lines 14 and 15, the text should be revised to read "that the oral NOAEL for potential BPA-mediated effects on the adult rat reproductive system exceeds 200 mg/kg-day."
8. The CERHR can assist the reader by grouping all of the oral studies shown in Tables 97 to 99 together with table titles as such and grouping separately all parenteral (sc, ip, ic) studies into a separate set of tables.

While CERHR report finalization may be delayed by appointment of analytical chemists familiar with BPA measurement and quantification to the CERHR panel, the document would benefit from a critical review of laboratory procedures, analytical capability and accuracy and quality evaluation of the published BPA sediment, river and drinking water or biological concentration data. Please identify clearly those analytical method(s) the CERHR deems reliable and those the CERHR finds unreliable. Until the reader has a clear understanding of the possible contribution of BPA laboratory contamination (and the potential magnitude of that contribution) in studies of BPA kinetics, tissue residue and environmental media, it is very difficult to reconcile the widely differing reports. Until the CERHR review identifies papers that used inappropriate statistical procedures, it is very difficult to reconcile the widely differing reports.

Sincerely,

[Redacted]

Calvin C. Willhite, Ph.D.