DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

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Re: FDMS Docket No. FDA-2008-P-0577-0001/CP

Dear Dr. Janssen & Mr. Colangelo:

This responds to your citizen petition,[1] received by FDA on October 28, 2008, requesting that the Commissioner of Food and Drugs issue a regulation prohibiting the use of bisphenol A (4,4'-isopropylidenediphenol or BPA) in human food and food packaging, and revoke all regulations permitting the use of any food additive that may result in BPA becoming a component of food. The agency appreciates your concern regarding the safety of BPA. We take this concern seriously; and, as discussed in further detail below, we are continuing to review scientific data concerning the safety of BPA, including its food contact uses, as such data become available.[2]

Under the Federal Food, Drug, and Cosmetic Act (the FD&C Act) and FDA's implementing regulations, FDA has the discretion to initiate the process for amending or repealing a food additive regulation. 21 U.S.C. § 348(d) and (i). FDA has carefully

1 In earlier litigation involving the petition at issue here, the D.C. Circuit conclusively established that your petition is a citizen petition, not a food additive petition. *In re NRDC*, 645 F.3d 400, 405-08 (D.C. Cir. 2011).

2 FDA continues to make its overall assessment public. See, for example, the January 2010 interim update on BPA [http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm064437.htm], in which FDA detailed its research and other activities related to the additive. FDA also opened a public docket (Docket No. - FDA-2010-N-0100) at: http://www.regulations.gov/#!docketDetail;D=FDA-2010-N-0100;dct=FR%252BPR%252BN%252BO%252BSR, to solicit information on BPA; this docket contains reviews of the available scientific literature and updated exposure assessments for infants, children, and adults.

reviewed your citizen petition and has determined that it failed to provide sufficient data and information to persuade FDA to initiate rulemaking under 21 U.S.C. § 348(d) and (i) and 21 CFR 171.130 to revoke regulations permitting the use of BPA in food contact materials. Because such uses remain authorized by FDA's regulations, FDA also denies your request to list BPA as a substance prohibited from use in human food under 21 CFR Part 189. Therefore, for the reasons set forth below, FDA is denying your citizen petition in its entirety. As a matter of science and regulatory policy, FDA has determined that its continued scientific study, including completion of studies in progress at FDA's National Center for Toxicological Research (NCTR), and supported by the National Toxicology Program (NTP), and review of all new evidence as it becomes available is the most appropriate course of action at this time.

I. Background on FDA's Framework for Safety Evaluation of BPA

In assessing the safety of a food additive, the central question of FDA's evaluation is whether the use is "safe," i.e., whether there is reasonable certainty that, in the minds of competent scientists, the substance is not harmful under the intended conditions of use [21 CFR 170.3(i)]. FDA has been reviewing and considering available studies for the purpose of providing a comprehensive, evidence-based evaluation related to the safety of BPA for its approved food additive uses. FDA's ongoing safety evaluation of BPA assesses whether there may be toxic effects from BPA; at what level of exposure such effects, if any, may be expected; and whether the exposure from the proposed use is likely to be below the level of concern. In its continuing review of scientific studies on BPA, FDA takes into consideration the following scientific principles when evaluating the scientific merits of the studies.[3] Although FDA takes these principles into account, FDA did not decline to review or consider studies for failure to satisfy these principles.

1. How does the route of administration of the test substance relate to oral exposure? Tests employing the oral route of administration are most relevant to the evaluation of dietary exposures. This is especially important in the case of BPA as BPA is known to be rapidly metabolized and excreted following oral administration.[4] Non-oral routes of administration bypass normal metabolic deactivation effects.[5] Thus, systemic exposures resulting from subcutaneous dosing at low levels may still be well above systemic exposures experienced as a result of higher oral dosing with BPA. Data are only now becoming available that may allow a quantitative comparison across different routes of administration. FDA is currently reviewing the newer studies.[6]

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3 See FDA's Redbook 2000, Testing for Human Health Guidance documents of the Organization for Economic Co-operation and Development, and Environmental Protection Agency guidelines. See also OFAS Review Memorandum dated August 31, 2009, Aungst and Twaroski Bisphenol A (CAS RN. 80-05-7); Review of Low Dose Studies, for further discussion of these criteria.

4 FDA Review Memorandum dated May 23, 2008, Division of Food Contact Notifications William L. Roth, Vanee Komolprasert, *Compact Summary of Bisphenol A (BPA) Pharmacokinetics*.

5 Ibid.

6 Pharmacokinetics of bisphenol A in neonatal and adult rhesus monkeys, Doerge D.R., Twaddle, N.C., Woodling, K.A., Fisher, J.W. Toxicology and Applied Pharmacology 248 (2010) 1–11; Pharmacokinetics of Bisphenol A in neonatal and adult CD-1 mice: Inter-species comparisons with Sprague-Dawley rats and

2. Is the substance tested on enough animals, under sufficiently controlled conditions, to provide a level of confidence that observed effects are due to treatment and not due to other unrelated factors such as normal biological variability or to chance?

3. Is the measured toxicity endpoint one that would be expected in a living organism under specific exposure conditions? Live animal (*in vivo*) experimentation, or where available, data related to human exposures, are typically used to facilitate identification of adverse endpoints that are most likely to be relevant to the living organism. *In vitro* testing (e.g. testing for potential effects on isolated cells or tissues in an artificial culture vessel) may sometimes be used as a valid indication of risk in a living organism, but only when the particular test has been accepted because it has been shown to be a valid marker for prediction of a known adverse effect.

4. Are a study's findings plausible in light of everything that is known about the test substance, and the effects observed for similar substances?

5. Have the study's findings been reproduced, both within the laboratory and across different laboratories? Findings that have been shown to be reproduced in a variety of different laboratories increase confidence in the study's conclusions. By contrast, when attempts to reproduce a particular finding are unsuccessful, the result is reduced confidence.

II. Claims in Your Citizen Petition

Your petition asserts that since FDA approved the use of BPA as a food-contact substance, new data have become available regarding both the toxicity and the human exposure to BPA through food. Your petition further asserts that the totality of available data now before the Agency both fails to establish that BPA is safe and demonstrates that BPA may cause serious adverse health effects in humans, especially infants and children.[7]

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rhesus monkeys Doerge D.R., Twaddle, N.C., Vanlandingham, M., Fisher, J.W. Toxicology Letters 207 (2011) 298– 305; Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague–Dawley rats Doerge D.R., Twaddle, N.C., Vanlandingham, M., Brown, R.P., Fisher, J.W. Toxicology and Applied Pharmacology 255 (2011) 261–270; Pharmacokinetic modeling: Prediction and evaluation of route dependent dosimetry of bisphenol A in monkeys with extrapolation to humans Fisher, J.W., Twaddle, N.C., Vanlandingham, M., Doerge D.R. Toxicology and Applied Pharmacology (2011) in press; Lactational transfer of bisphenol A in Sprague–Dawley rats Doerge D.R., Vanlandingham, M., Twaddle, N.C., Delclos, K.B. Toxicology Letters 199 (2010) 372–376; Quantification of deuterated bisphenol A in serum, tissues, and excreta from adult Sprague Dawley rats using liquid chromatography with tandem mass spectrometry Twaddle, N.C., Churchwell, M.I., Vanlandingham, M., Doerge D.R. Rapid Commun. Mass Spectrom. 2010; 24: 3011–3020; Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats Doerge D.R., Twaddle, N.C., Vanlandingham, M., Fisher, J.W. Toxicology and Applied Pharmacology 247 (2010) 158–165; Teeguarden, J. G., Calafat, A. M., Ye, X., Doerge, D. R., Churchwell, M. I., Gunawan, R. and Graham, M. K. (2011). Twenty-Four Hour Human Urine and Serum Profiles of Bisphenol A during High-Dietary Exposure. Toxicol Sci 123, 48-57.

7 NRDC Petition, Page 6.

Moreover, you state that FDA's 2008 Draft Assessment of BPA for Use in Food-Contact Applications relies upon two studies that investigated traditional toxicological endpoints that are not, in your view, the endpoints of highest concern. You assert that the endpoints of highest concern are neurobehavioral changes and histopathological changes in the prostate or mammary gland, or other reproductive organs.[8]

Additionally, you assert that the levels of human exposure to BPA are unsafe. Specifically, you conclude that FDA's safety assessment of the food contact uses of BPA should be based on a lowest-observed adverse effect level (LOAEL) of 10 µg/kg-bw/day and a safety factor of 1000.[9] You assert that these levels are "well within the range of concern based on animal studies, which have found BPA to cause pre-cancerous changes in mammary tissue at levels as low as 2.5 µg/kg-bw/day, pre-cancerous lesions in the prostate at 10 µg/kg-bw/day, and neurobehavioral abnormalities at 10 µg/kg-bw/day."[10]

III. Data Presented in Your Petition

In support of your petition, you cite two categories of information: information on human exposure to BPA and information on studies intended to evaluate potential BPA toxicities. The human exposure information you cite includes reports of assays for BPA in food that establish that BPA is present in food, and reports of assays for BPA in biological samples of human origin, such as urine or other biological fluids, that establish that most Americans are exposed to BPA. The BPA toxicity citations include epidemiological, animal, and *in vitro* studies reporting a broad range of effects that you associate with exposure to BPA at doses near the estimated daily intake for BPA.

As explained in more detail below, your citizen petition does not provide information that persuades FDA to initiate rulemaking under 21 U.S.C. § 348(d) and (i) and 21 CFR 171.130. For a variety of reasons, the studies cited in your petition have limitations in their utility for assessing safety of dietary exposures to BPA. Nevertheless, we have considered these studies carefully and discuss below the utility and limitations of the studies you cited.

A. Data on Levels of Exposure

1. Levels of BPA in food

Your petition cites the previous FDA exposure estimates of 0.185 µg/kg bw/day for adults and 2.42 µg/kg bw/day for infants[11] as well as five sources of information to establish that BPA is present in certain foods.[12] FDA has reviewed these materials[13] and

8 NRDC Petition, Page 15.
9 NRDC Petition, Page 9.
10 NRDC Petition, Page 8-9.
11 NRDC Petition, page 9
12 NRDC Petition at pages 2, 7-8.

concurs that BPA migrates from certain food contact articles, becomes a component of food, and is therefore consumed.[14] Based on the totality of studies FDA has reviewed and based on the exposure estimation methodologies employed, FDA now estimates a revised age-dependent mean dietary intake to BPA resulting from its presence in food-contact articles to be 0.1-0.2 μg/kg-bw/day for children and adults, and 0.2-0.4 μg/kg-bw/day for infants.[15] The lower estimate for infant exposure, relative to our earlier assessment, is due mainly to the incorporation of information from a 2005-2007 Infant Feeding Practices Study (IFPS II).[16]

2. *Metabolism of BPA in Humans*

Your petition asserts that the majority of Americans are exposed to BPA, including fetuses and infants.[17] FDA has reviewed the biomonitoring studies[18] cited in your petition and other information, and agrees that most infants, children and adults, are exposed to low levels of BPA through the diet. These low levels of dietary exposure are due to residual BPA that can migrate from certain food packaging materials or other food-contact articles into food, and then be consumed in the diet.

FDA has also reviewed pharmacokinetic studies[19] and the reported findings from NCTR studies, which together establish that primates, including humans, quickly and efficiently metabolize BPA into its inactive form, BPA-monoglucuronide, which is then excreted.[20] Consequently, the amount of the *active* BPA circulating internally in humans and the degree to which various potential targets of any toxicity (e.g., cells and organs) are exposed is predicted to be significantly lower than the amount ingested, and even lower – much lower -- than seen after a similar exposure by typical non-oral routes (e.g., subcutaneous injections) used in many animal studies, including many of the studies cited in your petition. Furthermore, differences in the adsorption, distribution, metabolism, and excretion pathways seen in rodents are likely to result in higher internal exposures for rodents as compared to primates and humans for equivalent oral consumptions. That is, for a given amount of BPA in the diet, the actual exposure of potential internal target organs to the active form of BPA is predicted to be higher in rodents than in humans.

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13 FDA Review Memorandum dated November 19, 2009, Karen Hatwell, *Natural Resources Defense Council (NRDC). Petition to establish a regulation prohibiting the use of BPA in human food and in the manufacture of food contact materials*. Submission received 10/21/08 (receipt date 10/28/08).
14 In October 2009, FDA documented an intake assessment that included data from 33 studies and assays of over 1300 samples. FDA Review Memorandum dated October 22, 2009, Division of Food Contact Notifications, Bailey, Hatwell, and Mihalov, *Exposure to Bisphenol A (BPA) for infants, toddlers and adults from the consumption of infant formula, toddler food and adult (canned) food.*
15 *Ibid.*
16 Grommer-Strawn, L. M.; Scanlon, K. S.; Fein, S. B. Infant feeding and feeding transitions during the first year of life. *Pediatrics* 2008, 122 *Suppl* 2, S36-S42.
17 NRDC Petition at page 8.
18 These biomonitoring studies are assays that identify bisphenol A in human urine and other biological fluids.
19 Pharmacokinetic studies evaluate the absorption, distribution, metabolism, and elimination of the test substance.
20 See Footnote 5

Biomonitoring studies can be used to determine the level of ingested BPA, but these studies often measure only total BPA and do not distinguish inactive BPA-monoglucuronide from active BPA. Models based on the pharmacokinetic studies can permit estimation of actual internal exposure to the active form of BPA which is relevant to evaluating BPA's human toxicity.[21] The findings of these pharmacokinetic studies, together with negative findings of other studies reviewed in FDA's ongoing safety evaluation of BPA, confirm that FDA's current safety assessment identifying a no-observed adverse effect level (NOAEL) of 5 mg/kg bw/day and use of a 1000 fold safety factor is an appropriate safety level relevant to human dietary exposures and public health. While this is FDA's current assessment, FDA continues to assess BPA both through ongoing research in its laboratories and evaluation of studies performed elsewhere as they become available.

B. Data on Toxicity

Your petition cites the study by Ho, S.M. et al. 2006, and the NTP-CERHR Monograph to support your assertion that FDA should base its safety assessment on a LOAEL of 10 µg/kg-bw/day, and a safety factor of 1000.[22] Your petition also cites information on a broad range of possible health effects that you suggest have been associated with BPA exposure.

1. Ho, S.M. et al. 2006, and NTP-CERHR Monograph

FDA evaluated both the Ho, S.M. et al. 2006 study and the NTP Monograph upon which your petition relies. FDA disagrees that this data supports 10 µg/kg bw/day as a suitable LOAEL on which to base a safety assessment for dietary exposures to BPA.

For example, FDA discussed the Ho, S.M. et al. 2006[23] study in the 2008 Draft Assessment of BPA for Use in Food Contact Applications (pages 60-62). In that Assessment, FDA concluded that although this study "provides an interesting protocol for the examination of early exposure to environmental compounds and subsequent challenge with hormones, the relevance of this study to a direct effect of BPA treatment alone and an increased incidence in tumor formation or a clear progression of the findings is unclear."

Moreover, the interpretation of the results for a human safety evaluation of dietary exposures to BPA was limited by certain design aspects of this study. For example, the

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21 Pharmacokinetic Modeling: Prediction and Evaluation of Route Dependent Dosimetry of Bisphenol A in Monkeys with Extrapolation to Humans. Fisher, J.W., Twaddle, N.C., Vanlandingham, M., Doerge D.R. Toxicology and Applied Pharmacology (2011).

22 NRDC Petition, Page 9.

23 Ho, S.M. et al. 2006, Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase Type 4 Variant 4, *Cancer Research* 66: 5624-5632.

internal dose experienced by the test animals following subcutaneous administration of BPA is expected to be many times higher than the internal dose experienced after oral administration of an equivalent amount of BPA.[24] However, it is the internal dose resulting from oral administration of BPA that is relevant to the safety of dietary exposures in humans. In addition, the authors did not provide information on the background variation of the observed pre-cancerous lesions in this strain of rats, or on the experimental variation of testosterone and estradiol-induced, pre-cancerous lesions. The subcutaneous administration of the test substance, the small sample size, and the limitations in the controls preclude reliance on these data to establish the safety levels of BPA.

For the same reasons, the NTP's Center for the Evaluation of Risks to Human Reproduction (CERHR) also concluded, in its Expert Panel Report on BPA, that this study was of limited utility for the identification of hazards associated with dietary exposures of BPA.[25] Similarly, the NTP Monograph concludes that *"[t]he evidence is not sufficient to conclude that bisphenol A is a rodent prostate gland carcinogen or that bisphenol A presents a prostate cancer hazard to humans"*[26] and that "*additional studies are needed to understand the effects of bisphenol A on the development of the prostate gland and urinary tract.*"[27]

Furthermore, FDA has reviewed each of the relevant studies cited in the NTP Monograph. FDA's evaluation of this data determined that there was insufficient scientific evidence in the NTP Monograph for establishing a LOAEL for BPA at 10 µg/kg-bw/day, and insufficient evidence raising safety concerns about the authorized food contact uses of BPA to support amending or repealing our food additive regulation.

2. *Other Studies in the Petition*

Your petition also cites several other studies reporting findings relating to BPA. FDA has reviewed all the publications and information cited in your petition. These studies presented one or more of the following limitations: a dosing method that cannot currently be compared to oral exposure for BPA, an inadequate sample size, an inappropriate statistical analysis, or failure to establish relevance to a human health effect. We critically evaluated all of the studies cited in your petition both for utility in a quantitative safety evaluation and to develop an overall understanding of the science relating to potential health effects of dietary exposures to BPA.

a. Prostate and Male Reproductive Endpoints

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24 See footnote 7.
25 NTP Expert Panel Report, page 275, line 27.
26 NTP Monograph, page 24, column 1.
27 Ibid. page 25, column 2, line 15.

With respect to potential effects of dietary exposure to BPA on the prostate, you cited Prins, G.S., et al.[28] This publication is a review article that contains no new data. The authors summarize, among other work, the findings of Ho et al. 2006 (described above), and hypothesize that exposure to BPA during an early developmental period may increase the risk of developing prostate cancer later in life. This hypothesis has not been proven.

You also cite studies that present epidemiologic data associating prostate intraepithelial neoplastic lesions with the development of prostate cancer.[29] However, these studies did not examine any questions relating to BPA exposure, and do not provide data upon which to base any conclusions relating BPA exposure to prostate intraepithelial neoplasia.

Your petition also cites Richter CA, et al.[30] to support your position that BPA exposure has been associated with testicular toxicity. This publication is a review article that contains no new data. The authors conclude that there is evidence that adult exposure to BPA has adverse consequences for testicular function in male rats and mice. Studies cited in this review that are relevant to the safety evaluation of BPA from oral exposure, as well as other studies examining testicular endpoints but not cited in this review, were examined in FDA's 2008 safety assessment of BPA. In that assessment, FDA concluded that a lowest no-observed adverse effect level for reproductive effects, including testicular effects, could be determined to be 50 mg/kg-bw/day oral exposure.[31] No data have been presented in your petition to warrant a change in FDA's conclusion on this issue. Furthermore, the NTP Monograph concludes there exists negligible concern that exposure to BPA will cause reproductive effects.[32]

b. Data on Neurobehavioral Abnormalities

With respect to potential neurobehavioral effects of low doses of BPA, the NTP Monograph concludes that there exists some concern for effects on brain and behavior, but that additional research is needed to understand the implications or relevance to

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28 Prins, G.S., et al. Perinatal exposure to oestradiol and bisphenol A alters the prostate epigenome and increases susceptibility to carcinogenesis. *Basic Clin Pharniacol Toxicol.* 2008 102(2): 134-8.
29 See 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;
Park S, Shinohara K, Grossfeld GD, Carroll PR. Prostate cancer detection in men with prior high grade prostatic intraepithelial neoplasia or atypical prostate biopsy. 3 Urol. 200 1 May; 165(5): 1409-14; and Enokida H, Shiina H, Urakami S, Igawa M, Ogishiina T, Li LC, Kawahara M, Nakagawa M, Kane CJ, Carroll PR, Dahiya R. Multigene methylation analysis for detection and staging of prostate cancer. Clin Cancer Res. 2005 Sep 15;11(18):6582-8.
30 Richter CA, et al. *In vivo* effects of bisphenol A in laboratory rodent studies. *Reprod Toxicol.* 2007 Aug-Sep;24(2): 199-224
31 FDA 2008 *Draft Assessment of Bisphenol A for Use in Food Contact Applications.*
32 NTP-CERHR Monograph, page 39.