STATE OF MARYLAND

DHMH

Maryland Department of Health and Mental Hygiene
201 W. Preston Street • Baltimore, Maryland 21201
Martin O'Malley, Governor – Anthony G. Brown, Lt. Governor – Joshua M. Sharfstein, M.D., Secretary

September 11, 2012

The Honorable Thomas McLain Middleton
Chairman, Senate Finance Committee
3 East Miller Senate Building
Annapolis, MD 21401

The Honorable Peter Hammen
Chairman, House Health and Government Operations Committee
Room 240 House Office Building
Annapolis, MD 21401

RE: Senate Bill 151\Chapter 189 and House Bill 4\Chapter 190 and of the Acts of 2011 – Report on Findings of Federal Research and Regulatory Activities Related to Bisphenol-A

Dear Chairmen Middleton and Hammen:

Senate Bill 151\Chapter 189 and House Bill 4\Chapter 190 of the Acts of 2011 prohibited the State from purchasing infant formula with more than 0.5 parts per billion of Bisphenol-A (BPA), and prohibits the manufacture, distribution, or sale of containers of infant formula with more than 0.5 parts per billion (ppb) of BPA. These prohibitions take effect July 1, 2014.

Chapters 189 and 190 require the Department to report to the House Health and Government Operations Committee and the Senate Finance Committee on the findings of federal research and regulatory activities related to BPA, including the availability and safety of substitutes for BPA used in food containers containing infant formula. The enclosed report addresses this requirement.

The report contains a review of recent scientific and regulatory developments related to BPA. Based on this review, the Department does not reach the conclusion that BPA in infant formula is unsafe. Given that substantial research is still ongoing, the Department cannot exclude a potential risk.

The Department agrees with the Food and Drug Administration (FDA) that families should not change the use of infant formula or foods, as the Department's judgment is that the benefit of a stable source of good nutrition outweighs the potential risk to an individual infant from BPA exposure. The Department recognizes that manufacturers are moving away from the use of BPA in packaging materials, in part because of public concerns about the potential health effects.

Under its latest contract, the Maryland's Women, Infants, and Children (WIC) program will only purchase infant formula that is manufactured in a BPA-free process. The rest of the market is moving quickly in this direction as well. Companies are developing new materials for packaging of infant food, which should be studied and reviewed prior to use.

One outstanding question is whether the imposition of the 0.5 ppb standard for testing in the formula could produce unforeseen adverse consequences. Given environmental sources of BPA, it is important that the testing method be specific to formula, credible, and reliable. The Department intends to seek public comments and input on the specific question of the use of the 0.5 ppb standard in the implementation of Maryland Code Annotated, Health-General § 24-304, and to ask for formal recommendations from the Children's Environmental Health and Protection Advisory Council.

We hope this information is useful to you. If you have any questions regarding this report, please contact Marie Grant, Director of Governmental Affairs, at 410-767-6481.

Sincerely,

Joshua M. Sharfstein, M.D.
Secretary

Enclosure

cc: Frances Phillips
Donna Gugel
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# REPORT TO THE MARYLAND LEGISLATURE

# REPORT ON
# BISPHENOL-A FREE INFANT FORMULA CONTAINERS

## IN ACCORDANCE WITH SB 151\CHAPTER 189
## AND HB 4\CHAPTER 190
## OF THE ACTS OF 2011

**Maryland Department of Health and Mental Hygiene**
**September, 2012**

## Introduction

Senate Bill 151\Chapter 189 and House Bill 4\Chapter 190 of the Acts of 2011, *Public Health – Containers of Infant Formula Manufactured with Bisphenol–A – Prohibition*, was signed by the Governor on May 10, 2011. The law (now Maryland Code Annotated, Health-General § 24-304) contains the following provisions:

1. On or after July 1, 2014, the State may not purchase infant formula in containers containing more than 0.5 parts per billion (ppb) of bisphenol-A (BPA);
2. A person may not manufacture, knowingly sell, or distribute in commerce a container of infant formula containing more than 0.5 ppb of BPA;
3. Substitutes for BPA used to comply with the above provisions must be safe and legal, and specifically may not be rated as Group A, B, or C carcinogens by the United States Environmental Protection Agency, or reproductive toxicants that cause birth defects, reproductive harm, or developmental harm as identified by the United States Environmental Protection Agency; and
4. Requires the Department of Health and Mental Hygiene (DHMH) to adopt regulations to carry out the above provisions.

Chapters 189 and 190 qualifies the above provisions by allowing the Secretary of Health and Mental Hygiene to suspend these provisions if the Secretary certifies "that the safety concerns for bisphenol-A are resolved by additional research or if implementation of [the provisions] would adversely affect the health or well-being of children or adults…"

Chapters 189 and 190 require that DHMH, on or before September 1, 2012, report to the House Health and Government Operations Committee and Senate Finance Committee, on the findings of federal research and regulatory activities related to BPA.

This report is submitted in fulfillment of the requirements of Chapters 189 and 190, and addresses the following issues:

- Federal research findings related to BPA and its potential alternatives;
- Recent Federal regulatory activities related to BPA;
- Recent scientific findings in the peer-reviewed literature on BPA and possible alternatives;
- Summary of findings relative to the safety concerns for BPA;
- Update on Maryland's purchase of BPA-free formula; and
- Summary and Chapters 189 and 190 analysis.

## Federal Research Findings Related to BPA and Potential Alternatives

A sizeable number of federally-funded studies have recently been published relating to BPA health effects. In particular, the National Institute for Environmental Health Sciences (NIEHS), part of the National Institutes of Health, has funded research that has produced more than 100 papers in a number

of areas (these can be found online at http://www.niehs.nih.gov/news/sya/sya-bpa/bpa-related/index.cfm):

- *Pharmacokinetics* – A number of studies compared the metabolism and elimination of BPA in different species (mice, monkeys) in order to determine how quickly BPA was removed after oral consumption, and in what chemical form.
- *Cancer* – Several studies looked at the possible effects of BPA as an estrogenic compound on prostate cell lines, in order to understand whether BPA might play some role in prostate cancer.
- *Reproduction* – There is considerable literature already on the potential reproductive effects of BPA, due to its estrogenic effects. More recent studies funded by NIEHS have focused on issues such as potential mechanisms of the effects (of BPA on DNA methylation, estradiol response, or oocyte or embryo quality during *in vitro* fertilization).
- *Cardiology* – There have been suggestions that BPA may influence development of cardiac tissue, particularly in the cardiac conduction system that determines heart rhythm.

The Food and Drug Administration's (FDA) assessment of recent research findings related to BPA does not significantly alter its earlier position regarding the safety of BPA. The FDA's National Center for Toxicological Research (NCTR) has been working with other agencies, particularly NIEHS, to develop a more complete understanding of the safety of BPA and possible alternatives. These studies are summarized in more detail below, but the findings, as described on FDA's website for consumers, are:

- "The level of BPA from food that could be passed from pregnant mothers to the fetus is so low that it could not be measured. Researchers fed pregnant rodents 100 to 1,000 times more BPA than people are exposed to through food, and could not detect the active form of BPA in the fetus eight hours after the mother's exposure.

- Exposure to BPA in human infants is from 84 to 92 percent less than previously estimated.

  NCTR researchers report that they were able to build mathematical models of what happens to BPA once it's in the human body. These models showed that BPA is rapidly metabolized and eliminated through feces and urine. They found that BPA is "exactly the opposite" from some other toxins, like dioxin, that can stay in the body's tissues for months or even years.

  The center's toxicology research has not found evidence of BPA toxicity at low doses in rodent studies, including doses that are still above human exposure levels."

Source: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm297954.htm, accessed August 9, 2012.

There are still a number of ongoing studies of BPA that should become available in the near future.

**Recent Federal Regulatory Activities Related to BPA**

To date, FDA has rejected efforts to further limit use of BPA in packaging. On March 30, 2012, the Food and Drug Administration (FDA) announced its decision to deny a petition from the Natural Resources Defense Council proposal to ban BPA in food-contact materials (Appendix A). FDA denied the petition in its entirety, stating: "The Food and Drug Administration's assessment is that the scientific evidence at this time does not suggest that the very low levels of human exposure to BPA through the diet are unsafe."

On July 18, 2012, FDA announced a ban on BPA in future production of baby bottles and infant feeding cups in the U.S. market, based on changes in manufacturing as suppliers have moved away from the use of BPA in these products. This action was not based on safety concerns. Previously, FDA decided on the following steps to reduce human exposure to BPA in the food supply. These steps include:

- Facilitating the development of alternatives to BPA for the linings of infant formula cans; and
- Supporting efforts to replace BPA or minimize BPA levels in other food can linings.

FDA is also supporting recommendations from the Department of Health and Human Services for infant feeding and food preparation to reduce exposure to BPA.

FDA has not recommended that families change the use of infant formula or foods, as the Agency's judgment is that the benefit of a stable source of good nutrition outweighs the potential risk from BPA exposure.

FDA has revised its earlier 2008 estimates of exposure using "a probabilistic approach to exposure assessment that relies on new data from our laboratories on BPA concentrations in formula, data contained in publications on BPA concentrations in toddler and adult food and, studies on BPA concentrations in formula as a result of formula reconstitution in PC bottles. Breast milk was not considered in our analysis."(FDA, 2009) Based on this revised estimate, FDA has lowered its estimate of the amount of BPA to which infants are typically exposed. In addition, FDA has cited new animal studies and pharmacologic models studies as indicating that BPA is rapidly metabolized, and that *in utero* exposures may be low or not detectable (See *Bisphenol A (BPA): Use in Food Contact Application*, at: http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm064437.htm#current).

In addition, the European Food Safety Agency reported that "no new study could be identified, which would call for a revision of the current TDI. This TDI is based on the No-Observed-Adverse-Effect-Level (NOAEL) of 5 mg/kg b.w./day from a multi-generation reproductive toxicity study in rats, and the application of an uncertainty factor of 100. This factor is regarded as conservative based on all information on BPA toxicokinetics." (EFSA, 2010)

## Recent Scientific Findings in the Peer-Reviewed Literature on BPA and Possible Alternatives

Recent studies of BPA in the peer reviewed literature are consistent with previous findings that BPA has estrogenic effects *in vitro* and *in vivo*, including effects on reproduction, development, and possibly the neurologic system (Alonso-Magdalena et al., 2011). There is a suggestion that BPA has developmental effects in children, although the effect, if present, is subtle (Braun et al., 2011). Studies in the peer-reviewed literature have also suggested that the estrogenic effects of BPA may also influence metabolic disorders, particularly those involving the thyroid and pancreas (Wang et al., 2012; Sheng et al., 2012; Soriano et al., 2012).

Studies in the peer reviewed literature have also found levels of environmental BPA in material such as house dust. (Liao, 2012) This may complicate the use of a very strict measurement standard for BPA, because of the possibility of environmental contamination of samples or products.

Unfortunately, there is very little in the published literature concerning the safety of chemical alternatives to BPA that would replace it as a component in the resin coatings of cans.

## Summary of Findings Relative to the Safety Concerns for BPA

The DHMH Environmental Health Bureau has reviewed the recent publicly available research findings on BPA. According to the Bureau's chief, Dr. Clifford S. Mitchell, the findings indicate the following:

1. Regarding the chemical BPA: There is evidence that BPA can act biologically as an endocrine disruptor. Numerous studies show effects of BPA on reproductive and endocrine systems, although controversy remains over the dose response (particularly for some effects that do not appear to follow a typical dose response pattern). Other possible health effects remain unclear and the subject of investigation.
2. Regarding exposure to BPA: Estimates of BPA exposure are complex, and should take into account both the known food sources and the likelihood that exposure also occurs through other environmental sources. FDA and international agencies have used complex but generally accepted methods to calculate exposures for their safety estimates, but these estimates may not look at all environmental and food exposures.
3. Standards based on very strict measurement methods should take into account the presence of environmental sources of BPA.
4. The market in packaging for infant formula appears to be moving rapidly away from the use of BPA, although the health consequences of the proposed alternatives have not been widely described.

## Update on Maryland's Purchase of BPA-Free Formula

The Women, Infants, and Children (WIC) formula rebate was recently rebid through a multi-state contracting alliance, led by the State of Washington. Abbott Nutrition was awarded the contract for milk-based formula, and Mead Johnson was awarded the contract for soy-based formula. According to Abbott, all of their Similac® product packaging is being manufactured BPA-free as of October 1, 2011. This means that there is no BPA used in the manufacturing process. Other manufacturers have also committed to a BPA-free manufacturing process.

## Summary

Based on available scientific evidence, the Department does not reach the conclusion that BPA in infant formula is unsafe. Given that substantial research is still ongoing, the Department cannot exclude a potential risk.

The Department agrees with FDA that families should not change the use of infant formula or foods, as the Department's judgment is that the benefit of a stable source of good nutrition outweighs the potential risk to an individual infant from BPA exposure. The Department recognizes that manufacturers are moving away from the use of BPA in packaging materials, in part because of public concerns about the potential health effects.

Under its latest contract, Maryland's WIC program will only purchase infant formula that is manufactured in a BPA-free process. The rest of the market is moving quickly in this direction as well. Companies are developing new materials for packaging of infant food, which should be studied and reviewed prior to use.

## Chapters 189 and 190 Analysis

Chapters 189 and 190 of the Acts of 2011 require the Secretary to assess the impact of BPA on the health and well-being of children. The WIC program and the market are moving to BPA-free manufacturing, accomplishing the legislative goal of reducing BPA in formula and containers available in Maryland.

One outstanding question is whether the imposition of the 0.5 ppb standard for testing in the formula could produce unforeseen adverse consequences. Given environmental sources of BPA, it is important that the testing method be specific to formula, credible, and reliable. The Secretary proposes to seek public comments and input on the specific question of the use of the numeric standard of 0.5 ppb in the implementation of Maryland Code Annotated, Health-General § 24-304.

With this report, the Secretary is releasing a request for comments in the *Maryland Register*. Comments will be received by the Department and evaluated by the Children's Environmental Health and Protection Advisory Council, with subsequent recommendations by the Council to the Secretary.

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# Appendix A

March 30, 2012, Denial by the U.S. Food and Drug Administration of a Petition by the Natural Resources Defense Council Requesting a Prohibition of the Use of Bisphenol A in Human Food and Food Packaging

30 MAR 2012

Sarah Janssen, M.D., Ph.D., M.P.H.
Natural Resources Defense Council
111 Sutter Street, 20th Floor
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Aaron Colangelo
Natural Resources Defense Council
1200 New York Ave., NW, Suite 400
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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

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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 Pharmacol 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.

human health.[33] FDA also believes the question of relevance to human health is critical because, for example, certain of the neurological effects observed in rodent studies occur in portions of the rodent brain for which there exists no homologous structure in the human brain (NTP Monograph, page 20), or potentially through mechanisms that are much more important in rodent development than in human development. (NTP Monograph, pages 20-21). Due to these uncertainties, FDA is unable to find adequate scientific basis in the NTP Monograph for establishing a no-observed adverse effect level for BPA at 10µg/kg-bw/day, or for concluding that the current dietary exposure levels resulting from the regulated food additive uses of BPA pose an unacceptable risk based on observations of neurobehavioral abnormalities.

You also cite Leranth C, et al.[34] as supportive evidence of neurobehavioral abnormalities. The finding of antagonism of hormone induced synaptogenesis cannot be determined to be an adverse event, a toxicity endpoint, or detrimental to the organism. This study also contained some limitations in design elements: for example, the use of implanted pumps and neutering (ovariectomizing) test animals.

The study by Kaneko[35] is severely limited in utility for a safety evaluation as it was performed *in vitro* using non-mammalian cells. Such *in vitro* screening studies do not provide information on the concentration that may cause an effect in humans. Application of BPA directly on the tissue bypasses metabolism; therefore, we cannot ascertain the comparable oral exposure of BPA. Also, this study addresses a potential mechanism of action, but it does not provide a link to an adverse toxicity endpoint.

Your petition cites Palanza P, et al.,[36] which is a publication that reviews and summarizes a series of previously published studies and contains no new data. FDA has reviewed each of the studies cited in this review and concludes that the interpretation of these studies with regard to the safety evaluation of BPA is highly uncertain and that the studies do not support derivation of a LOAEL of 10 µg/kg-bw/day, nor do they provide sufficient evidence to change FDA's previous safety determination regarding the regulated uses of BPA to manufacture food-contact articles.

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33 NTP-CERHR Monograph, page 38: *"The NTP also concurs with the CERHR Expert Panel on Bisphenol A that additional research is needed to more fully assess the functional, long-term impacts of exposures to bisphenol A on the developing brain and behavior. Overall, the current literature cannot yet be fully interpreted for biological or experimental consistency or for relevance to human health."*

34 Leranth C, et al. Bisphenol A prevents the synaptogenic response to estradiol in hippocampus and prefrontal cortex of ovariectomized nonhuman primates. *Proc Natl Acad Sci.* 2008 Sep 16;105(37): 14187-91.

35 Kaneko M, et al. Bisphenol A acts differently from and independently of thyroid hormone in suppressing thyrotropin release from the bullfrog pituitary. *Gen Comp Endocrinol.* 2008 155(3):574-80

36 Palanza P., et al. Effects of developmental exposure to bisphenol A on brain and behavior in mice. *Envy Res* 2008, 108: 150-1 57.

Similarly, Brown J.S. Jr.'s study[37] is also a review article that contains no new data. Here, the authors survey available studies and present a hypothesis for the involvement of BPA in schizophrenia. FDA previously reviewed the studies cited by Brown which were relevant for the safety evaluation and concluded that these studies did not support the hypothesis. Examples of methodological and interpretation limitations in these studies include: subcutaneous or high concentration dosing and uncertainties in translating rodent results to primates, including humans. FDA also reviewed additional developmental neurotoxicity studies[38] which had minimal limitations. These studies provided contradictory evidence to the studies cited in the Brown 2008 review.

c. Data on Metabolic and Cardiovascular Effects

Although your petition does not rely on data relating to metabolic endpoints to support your claim that FDA should use 10 µg/kg-bw/day as the LOAEL in its BPA safety assessment, you cite several sources of information on reported metabolic effects of low doses of BPA in your petition.

For example, you cite the Hugo ER, et al. study[39] to support a claim that research in primates shows associations between BPA exposure and insulin resistance. However, this is not a study in primates; rather, it is an *in vitro* study of effects on isolated explanted human tissue samples outside of any living animal. Although such studies can provide potential mechanistic data and/or information suggesting possible toxicity endpoints, the study design (e.g., bypassing the metabolic effect, inadequate evidence of toxic effects, or relevance and predictive value of the effects observed in explanted tissue to the living human) precludes at present the use of these data to support conclusions relating to dietary exposures to BPA.

You also cite an epidemiology study[40] based on data from the National Health and Nutrition Examination Survey 2003-2004. The authors reported that higher urinary BPA concentrations were associated with cardiovascular disease (angina, coronary heart disease, or heart attack), diabetes, and elevation of three liver enzymes (γ-glutamyltransferase (GGT), alkaline phosphatase, and lactate dehydrogenase). Because of the cross-sectional design of this study (i.e., a single measurement of exposure made at the same time biological data were collected), a possible causal association between levels of BPA concentrations and development of disease cannot be determined.[41]

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37 Brown J.S., Jr. Effects of Bisphenol-A and Other Endocrine Disruptors Compared With Abnormalities of Schizophrenia: An Endocrine-Disruption Theory of Schizophrenia. *Schizophr Bull.* 2008 Jan 31.
38 Ema M, Fujii S, Furukawa M, Kiguchi M, Ikka T, Harazono A (2001) Rat two-generation reproductive toxicity study of bisphenol A. *Reprod Toxicol.* 15(5): 505-523; and,
Stump, *et al.*, Developmental Neurotoxicity Study of Dietary Bisphenol A in Sprague-Dawley Rats *Toxicological Sciences* 115(1): 167–182 (2010).
39 Hugo ER, et al. Bisphenol A at Environmentally Relevant Doses Inhibits Adiponectin Release from Human Adipose Tissue Explants and Adipocytes. 2008. *Environ Health Perspect.* 116(12):1642-7.
40 Lang, *et al.* Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. 2008. *JAMA.* 300(11):1303-10.
41 Other limitations of the epidemiology study include the self reported health status and the lack of dietary

Therefore, these data do not call into question the safety of the regulated uses of BPA in food-contact articles.

d. Hormonal Effects

Although your petition does not rely on data relating to hormonal endpoints to support your claim that FDA should use 10 µg/kg-bw/day as the LOAEL in its BPA safety assessment, you cite two sources of information on reported hormonal effects of low doses of BPA.[42] You state that these studies suggest that low dose BPA exposure is associated with an early onset of puberty. However, the small degree of early onset of puberty observed by Honma is of questionable significance (~ 1 day), and the study employed subcutaneous administration, which as noted before, is of questionable relevance for an oral exposure assessment. Moreover, FDA has reviewed other studies that are more relevant for safety evaluations in humans, which report negative findings for this endpoint at low doses.[43]

You also cite Rubin BS, et al.[44] Although this study was designed to assess the effects of perinatal BPA exposure on birth weight, estrous cyclicity, and hormone levels in rats, the sample sizes were small, the statistical approach was inappropriate, and the BPA exposure was estimated by determining the amount of treated water consumed, which can lead to inaccurate estimates of dose. Notably, the NTP characterized this study as inadequate, finding that actual exposures are poorly defined, particularly postnatally. FDA agrees with NTP and has further concluded that the data could not support the determination of a no-observed adverse effect level.[45]

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intake information in relation to BPA concentrations.

42 Honma S, *et al.* Low dose effect of *in utero* exposure to bisphenol A and diethylstilbestrol on female mouse reproduction. 2002. *Reprod Toxicol.* 16:117-22; and Howdeshell KL, *et al.* Exposure to bisphenol A advances puberty. 1999. *Nature* 401:763-4.

43 Tyl RW, Myers CB, Marr MC, Sloan CS, Castillo NP, Veselica MM, Seely JC, Dimond SS, Van Miller JP, Shiotsuka RN, Beyer D, Hentges SG, and Waechter JM Jr (2008) Two-generation reproductive toxicity study of dietary bisphenol A (BPA) in CD-1 (Swiss) mice. *Tox Sci* 104(2):362-384.

Tyl RW, Myers CB, Marr MC, Thomas BF, Keimowitz AR, Brine DR, Veselica MM, Fail PA, Chang TY, Seely JC, Joiner RL, Butala JH, Dimond SS, Cagen SZ, Shiotsuka RN, Stropp GD, Waechter JM (2002) Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. *Toxicol Sci.* 68(1): 121-146.

Ema M, Fujii S, Furukawa M, Kiguchi M, Ikka T, Harazono A (2001) Rat two-generation reproductive toxicity study of bisphenol A. *Reprod .Toxicol.* 15(5): 505-523.

Ryan BC, Hotchkiss AK, Crofton KM, Gray LE Jr. (2009) In utero and lactational exposure to bisphenol A, in contrast to ethinyl estradiol, does not alter sexually dimorphic behavior, puberty, fertility and anatomy of female LE rats. *Toxicol Sci.* 114(1) 133-148.

44 Rubin BS, et al. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. 2001. *Environ Health Perspect* 109: 675-80.

45 FDA has reviewed other studies of high utility for safety evaluations in humans which report negative findings for the endpoint of birth weight and/or estrous cyclicity (e.g., Tyl *et al.* (2008) Two-generation reproductive toxicity study of dietary bisphenol A (BPA) in CD-1 (Swiss) mice. *Tox Sci* 104(2):362-384; Tyl *et al.*, (2002) Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. *Toxicol Sci.* 68(1): 121-146; and Stump, D.G., A Dietary Developmental Neurotoxicity Study of Bisphenol A in Rats; WIL Research Laboratories, LLC, WIL-186056, Dated 09/30/2009)

Additionally, you cite Markey CM, et al.[46] The authors conclude that BPA causes an early onset of puberty based on a finding that vaginal opening occurs an average of a day earlier in dosed pups than in controls. However, FDA cannot conclude that an effect was observed because the findings were not statistically significant. Moreover, FDA has concerns with the study design which limit interpretability of the data. These concerns include the use of a non-oral route of administration, low sample size, and use of the solvent pure dimethyl sulfoxide as the vehicle in the osmotic mini-pump.[47] Lack of proper sampling and the statistical methods used also limit the ability to utilize this study.

e. Reproductive Effects

Your petition cites the Newbold, RR, et al. 2007 study[48] to support a claim that neonatal exposure to BPA at levels as low as 10 µg/kg bw/day is associated with uterine fibrosis and cystic ovaries later in life. FDA concludes that there were several significant limitations of this study. For example, the study used subcutaneous dosing, the randomization method was unclear, and the pathology interpretation was subjective.

In addition, you cite the Sugiura-Ogasawara M, et al. study[49] to assert that higher serum BPA levels are associated with repeated human miscarriages. FDA reviewed this study and determined that scientific conclusions cannot be drawn from this study because it lacked appropriate controls (control subjects had no history of live birth or infertility and were not epidemiologically similar to the test subjects), had inadequate statistical analysis, employed a sample size too small to provide confidence in the conclusions, and used an inappropriate sampling methodology.

f. Data on Potential Association with Breast Cancer

Although your petition does not rely on data relating to breast cancer endpoints to support your claim that FDA should use 10 µg/kg-bw/day as the LOAEL level in its BPA safety assessment, you cite Dairkee SH, et al.[50] as a source of information on reported breast cancer effects of low doses of BPA. You cite this study to support a claim that research in primates shows associations between BPA exposure and breast cancer. This *in vitro* study compared gene expression profiles from hormones plus BPA treatments of breast cells grown in culture. Cells were taken from a small number of patients and the description of the methodology employed in the study was unclear. The study results do not

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46 Markey CM, et al. Mammalian development in a changing environment: exposure to endocrine disruptors reveals the developmental plasticity of steroid hormone target organs. 2003. *Evol Dev* 5:67-75.
47 The use of dimethyl sulfoxide as a vehicle is not recommended by the manufacturer and could have caused pump failure leading to inaccurate BPA dosing, thus decreasing confidence in accurate dosing.
48 Newbold, RR, WR Jefferson, and EP Banks. 2007. Long-term Adverse Effects of Neonatal Exposure to Bisphenol A on the Murine Female Reproductive Tract. *Reproductive Toxicology* 24:253-258.
49 Sugiura-Ogasawara M, et al. Exposure to bisphenol A is associated with recurrent miscarriage. 2005. *Hum Reprod* 20(8):2325-9.
50 Dairkee SH, et al. Bisphenol A induces a profile of tumor aggressiveness in high-risk cells from breast cancer patients. *Cancer Res.* 2008. 68(7):2076-80.

demonstrate progression to or increased risk of tumor formation. The in vitro study design (e.g., bypassing the metabolic effect, inadequate evidence of toxic effects, and unclear relevance and predictive value of the effects observed in explanted cells to living humans) precludes at present the use of these data to support conclusions relating to dietary exposures to BPA.

g. Data on Genetic Effects

Although your petition does not rely on data relating to genetic endpoints to support your claim that FDA should use 10 µg/kg-bw/day as the LOAEL in its BPA safety assessment, you cite several sources of information on reported genetic effects of low doses of BPA.[51] You cite these studies to support your assertion that BPA exposure has been shown to disrupt meiosis.[52] In Susiarjo, the authors report that their results indicate that BPA can influence early meiotic events and, indicate that the oocyte itself may be directly responsive to estrogen during early oogenesis. Lenie S, et al. state that BPA exposure in a mouse follicle culture reveals dose dependant effects. The inability to link the *in vitro* dose to an *in vivo* exposure is one limitation of this study. Moreover, for both of these studies, the NTP noted, in the NTP Monograph (p. 16, 33 & 39), that meiotic effects, such as those reported, would be expected to produce adverse effects on fertility, and that "breeding studies in laboratory animals exposed to bisphenol A do not present results consistent with such effects." FDA has reviewed numerous other studies that are more relevant for evaluating safety of BPA in humans, which report a lack of effect on fertility at low doses.[53]

Additionally, you assert that possible BPA effects may occur across generations through epigenetic mechanisms, like changes in DNA methylation patterns.[54] You support your

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51 Susiarjo M, Hunt P. Bisphenol A exposure disrupts egg development in the mouse. *Fertil Steril.* 2008 Feb;89(2 Suppl):e97, and Lenie S, et al. Continuous exposure to bisphenol A during *in vitro* follicular development induces meiotic abnormalities. *Mutat Res.* 2008 Mar 12:65 1 (1-2):7 1-8 1.

52 Meiosis is a type of cell division that is necessary for sexual reproduction. In animals, the cells produced by meiosis are sperm and egg cells. The outcome of meiosis is four genetically unique haploid cells, compared with the two genetically identical diploid cells produced from normal 'life-cycle' cell division processes. An oocyte is an immature ovum, or egg cell.

53 Tyl RW, Myers CB, Marr MC, Sloan CS, Castillo NP, Veselica MM, Seely JC, Dimond SS, Van Miller JP, Shiotsuka RN, Beyer D, Hentges SG, and Waechter JM Jr (2008) Two-generation reproductive toxicity study of dietary bisphenol A (BPA) in CD-1 (Swiss) mice. *Tox Sci* 104(2):362-384.

Tyl RW, Myers CB, Marr MC, Thomas BF, Keimowitz AR, Brine DR, Veselica MM, Fail PA, Chang TY, Seely JC, Joiner RL, Butala JH, Dimond SS, Cagen SZ, Shiotsuka RN, Stropp GD, Waechter JM (2002) Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. *Toxicol Sci.* 68(1): 121-146.

Ema M, Fujii S, Furukawa M, Kiguchi M, Ikka T, Harazono A (2001) Rat two-generation reproductive toxicity study of bisphenol A. *Reprod .Toxicol.* 15(5): 505-523.

Ryan BC, Hotchkiss AK, Crofton KM, Gray LE Jr. (2009) In utero and lactational exposure to bisphenol A, in contrast to ethinyl estradiol, does not alter sexually dimorphic behavior, puberty, fertility and anatomy of female LE rats. *Toxicol Sci.* 114(1) 133-148.

54 NRDC Petition Page 11.

claim by referencing the Dolinoy, et al.[55] study that used a high dose of BPA (50 mg/kg bw/day) to examine epigenome modulation. The reported results of this study demonstrate the complexity of regulation of methylation. The reported changes in methylation due to high dose BPA treatment, high variation in controls, and complex treatment interactions reinforce contemporary concerns that slight changes in the distribution of methylation at reporter sites in this model system may not be a meaningful endpoint for adverse outcomes. The data from this study are neither intended nor useful for an evaluation of BPA through low dose human exposure in foods.

h. Chapel Hill Bisphenol A Expert Panel Consensus Statement

You also cite the Chapel Hill bisphenol A expert panel consensus statement,[56] which, based on an assessment of selected studies and review articles, expresses the opinion of a group of scientists, many of whom had contributed to the literature reviewed. Many studies or reviews included were not directly relevant to human oral exposures: for example, use of *in vitro* assays that do not take into account metabolism, use of non-mammalian species that have limitations in study design and relevance to humans, and use of non-oral routes of exposure. Relevant information cited in the Chapel Hill bisphenol A expert panel consensus statement was considered by FDA; however, our review of such data concluded that there was insufficient information to persuade us to issue a regulation prohibiting the use of BPA in human food and food packaging or to revoke all regulations permitting the use of any food additive that may result in BPA becoming a component of food.

## IV. Summary of FDA's Ongoing Review of Data on BPA

As part of FDA's ongoing review of the safety of BPA, FDA has reviewed many other studies[57] that employ BPA as a test substance and that were intended to test hypotheses relating to possible mechanisms of action, or to probe for various systemic effects across a broad range of possible end points. Certain of these studies became available after the date of your petition and were conducted for the purpose of quantifying oral doses at which effects attributable to BPA may be observed, others were designed simply to determine whether effects could be observed and generally associated with the presence of BPA. FDA has critically reviewed these studies both for their potential importance to and utility in assessing the safety of BPA as a food additive, and to obtain an overall understanding of the available science regarding potential health effects of BPA. Other

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55 Dolinoy DC, Huang D, Jirtle RL. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. *Proc Natl Acad Sci U S A*. 2007. 104(32):13056-61.

56 NRDC Petition, pages 3, 10.

57 FDA 2008 *Draft Assessment of Bisphenol A for Use in Food Contact Applications*; OFAS Review Memorandum dated August 31, 2009, Aungst and Twaroski Bisphenol A (CAS RN. 80-05-7): Review of Low Dose Studies; OFAS Review Memorandum dated November 10, 2009, Aungst and Twaroski Bisphenol A (CAS RN. 80-05-7): Response to reviewers of 'Review of Low Dose Studies' and update of the assessment.

studies are ongoing at NCTR. FDA will continue to make public its reviews of these studies.

Although FDA is not persuaded by the data and information in your petition to initiate rulemaking to revoke the food additive approvals for BPA, FDA will continue in its broader and more comprehensive review of emerging data and information on BPA.

## V. Conclusion

FDA has determined, as a matter of science and regulatory policy, that the best course of action at this time is to continue our review and study of emerging data on BPA. Because the information provided in your petition was not sufficient to persuade FDA, at this time, to initiate rulemaking to prohibit the use of BPA in human food and food packaging, or to revoke all regulations permitting the use of any food additive that may result in BPA becoming a component of food, FDA is denying your petition in accordance with 21 CFR 10.30(e)(3). FDA is performing, monitoring, and reviewing new studies and data as they become available, and depending on the results, any of these studies or data could influence FDA's assessment and future regulatory decisions about BPA.

Sincerely,

David H. Dorsey
Acting Associate Commissioner for Policy and Planning

cc: HFA-224 HFS-200 HFS-275 HFS-205 HFS-246 HFS-206 HFS-255
Letter No. 8Z4777 Denial