Alternatives to Bisphenol A in Thermal Paper, Draft Report, July 31, 2012

Written comments received as of 10/18/2012

File Copy

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September 18, 2012

Cal Baier-Anderson, Ph.D.
Design for the Environment
US Environmental Protection Agency
1200 Pennsylvania Ave NW (7406M)
Washington, DC 20460-0001

Re: Bisphenol A Alternatives in Thermal Paper;
Nippon Soda Co., Ltd's Response to the July 2012 Draft for Public Comment

Dear Dr. Baier-Anderson,

Nippon Soda Co., Ltd. (Nisso) thanks the Environmental Protection Agency for the opportunity to comment on the July 2012 draft document titled Bisphenol A Alternatives in Thermal Paper. Nisso is a manufacturer of two alternative products, D-8 and D-90, listed in the draft assessment and we wish to respond to the draft in several areas.

D-8 [CAS No. 95235-30-6]

Genotoxic Potential

The draft document indicates that the genotoxicity potential for this compound is "moderate" (see page 4-350). Nisso believes a more appropriate category would be "low."

The July 2012 draft report states for the "gene mutation *in vitro*" parameter that professional judgement estimates a potential for mutagenicity. Nisso previously submitted a gene mutation *in vitro* study titled "Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of D-8" dated January 27, 1987 and authored by Eryl Jones and Lesley A. Fenner of Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England. This study was sent to the EPA as part of the Pre-Manufacture Notice for D-8 which was submitted on October 8, 1987. The authors of the study conclude that, "...no evidence of mutagenic potential of D-8 was obtained in this bacterial test system at the dose levels used." For your convenience a copy of the PMN documentation and the study is attached as Appendix 1a and 1b, respectively.

The Agency concludes in the July 2012 draft document that, "There is uncertain potential for genotoxicity due to the lack of data for this substance. Genotoxic effects cannot be ruled out." However, as mentioned above, actual data exists from the Ames study as well as from a previously submitted *in vitro* chromosomal aberration study that show the compound has a low potential for being genotoxic.

Repeat Dose Effects

The July 2012 draft document indicates that the potential for repeat dose effects from exposure to D-8 is "high" based on the analogy to bisphenol S (see page 4-353 in the draft).

The use of bisphenol S as a surrogate for D-8 is not necessary as Nisso does have empirical repeat dose data which shows the No Observable Effect Level (NOEL) for D-8 is 50 mg/kg bw/day based on a 90-day feeding study in Wistar rats. The "moderate" categorization as per the July 2012 draft document is an oral NOEL between 10 and 100 mg/kg bw/day (see page 4-6 in the draft). Therefore Nisso believes a more appropriate descriptor for categorization of D-8 repeat dose effects is "moderate" since the NOEL is 50 mg/kg bw/day.

The following repeat dose study is being submitted in Appendix 2:

Title:	90-Day Oral Toxicity Study with D-8 in the Rat;
Author:	Raluca Kubaszky, D.V.M., PhD.
Date:	September 22, 2009
Study No.:	08/775-101P
Lab:	LAB Research Ltd.
Address:	H-8200 Vezprem, Szabadsagpuszta, Hungary
Phone:	+36 88 545 300

Nisso approves including the summary information from this study in your public report on BPA alternatives in thermal paper. In order to do so, it is our understanding that Nisso must waive the TSCA Confidential Business Information (CBI) claim for those summary data. To serve this end, Nisso hereby waives the TSCA CBI claim for the summary information to be extracted from the enclosed study. This waiver is only for the summary information and all other CBI claims (i.e., for the complete study) remain in place.

D-90 [CAS No. 191680-83-8]

Bioaccumulation (BAF/BCF)

On page 4-371 of the draft document we note the Agency suggests the bioaccumulation factor (BAF) for D-90 is "high." Specifically the Agency states, "The estimated BAF value for the low MW oligomers with n = 2 is > 1,000 indicating that this component has the potential to bioaccumulate." Nisso believes that a more appropriate BAF category is "low."

Previously Nisso sent comments regarding the BAF of D-90 to the Agency in response to an earlier draft hazard assessment (see Appendix 3, letter to C. Baier-Anderson on October 21, 2011). These comments pointed to a previously submitted bioconcentration study. These data were submitted within the product's original Pre-Manufacture Notice (PMN) dated March 25, 1998.

The data are found in the *Bioconcentration Study of D-91 with Carp*, January 30, 1998, Study No. 7B284G, Mitsubishi Chemical Safety Institute, Ltd. which was authored by Ms. Midori Mino. D-91, as referenced in the study, is the code name for the low molecular oligomers (i.e., n=1 and n=2) of the D-90 compound and therefore represents the scenario of highest concern.

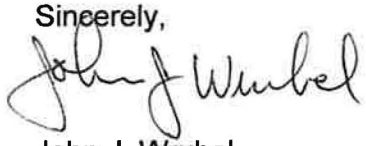
The results of the study show that the lower molecular weight oligomers of D-90 do not bioconcentrate in carp when tested at two (high and low) exposure levels. The bioconcentration factor (BCF) was < 2 for the high exposure level and < 19 for the low exposure level.

With a BCF of 19 or less we believe the bioaccumulation endpoint is more appropriately categorized as "low" according to the criteria in Table 4-2 in the draft document (see page 4-7).

Furthermore the log Pow for the n=1 and n=2 molecular weight oligomers of D-90 is 0.629 and 1.73, respectively, again based on empirical data that can be found in the original PMN for D-90. Octanol/water partitioning values such as these indicate a low potential for bioaccumulation.

In closing, Nisso thanks the Agency for the opportunity to comment on the July 2012 draft Bisphenol A Alternatives in Thermal Paper document. Please feel free to contact me at telephone number 212-490-0351 if you have any questions.

Sincerely,



John J. Wrubel
Regulatory Affairs Director

Encls.

APPLETON PAPERS' COMMENTS TO

BISPHENOL A ALTERNATIVES IN THERMAL PAPER

DRAFT FOR PUBLIC COMMENT, JULY 2012

DESIGN FOR THE ENVIRONMENT –EPA

Dear Dr. Baier-Anderson,

We have reviewed the "BISPHENOL -A ALTERNATIVES IN THERMAL PAPER" draft and do commend the DfE for their diligence and hard work in preparing such a thorough document. It is our belief that the final version of this document will be the first and most comprehensive report aimed at mapping the health and environmental profiles of the currently known Bisphenol A alternatives. Having access to the environmental and health information in a single document will be beneficial to all parties in the supply chain of the direct thermal industry as well as to the general public.

We have paid particular attention to the findings reported on Bis-S and TGSA. We have found the information presented in this draft on Bis-S and TGSA to be very detailed, albeit we do have some concerns on some of the ratings assigned to these developers based on the information and test data.

2,2'-DIALLYL -4,4'-SULFONYLDIPHENOL (CAS NO. 41481-66-7) PP: 4-305:307

Skin sensitization

- **Skin sensitization was rated "HIGH". On page 4-310, it is stated that " *there is concern that TGSA is a skin sensitizer based on experimental data indicating a potential for sensitization in guinea pigs".***

Appleton has reviewed the CERI (**C**hemicals **E**valuation and **R**esearch **I**nstitute, Japan, Kurume) report titled "Evaluation for Outcomes from different Skin Sensitizations Tests". This report was published in July of 2012. The objective of the report was to review and assess the skin sensitization potential of "2,2'-DIALLYL -4,4'-SULFONYLDIPHENOL" from different sensitization tests (GMPT, BT, and LLNA).

The findings in the CERI report are aligned with the information published on page 4-311 of the DfE report with respect to BT and LLNA skin sensitization tests. Essentially both the BT and LLNA were negative.

As far as the GMPT result, CERI reports that the test yielded a positive response. Indeed, the test results indicate a 70% incidence rate for a topical induction of 50% in arachis oil B.P. However, when using the categorization guidelines of the tests (see Table 1), 2,2'-DIALLYL -4,4'-SULFONYLDIPHENOL would be rated as a "WEAK" sensitizer and not as a "STRONG SENSITIZER", as reported on page 4-311.

Table 1. Categorization criteria based on the GMPT (Kimber et al. 2003)

	PERCENT INCIDENCE	
Topical induction	=30 to <60%	≥60%
< 0.1%	STRONG	EXTREME
≥0.1% to < 1%	MODERATE	STRONG
≥1% to <10%	WEAK	MODERATE
≥10% to 100%	WEAK	WEAK

Based on these findings, Appleton believes that the skin sensitization rating should be downgraded from HIGH to LOW and that such a rating would be in accordance with the interpretation guidelines of the GMPT test.

Respiratory sensitization

As far as respiratory sensitization, we noticed that only two developers were rated for that attribute. The rating was based solely on a professional judgment. The report states on 4-19 "At this time, there are no standard test methods for respiratory sensitization; as a result there was often no designation for this endpoint. " We are surprised that professional judgment was used in this situation considering there is no approved standard test method, let alone data. In addition, our understanding was that the evaluation of these developers would all be rated consistently for all alternatives. We believe there is no basis for singling out TGSA and MAE when no other developers were rated.

Since this is an area that seems to be largely based on professional opinions with no data to substantiate such ratings and since only two developers were rated, we believe that the whole classification "respiratory sensitization " should be left out of the report and revisited at a later point when more data is available.

Chronic aquatic toxicity:

- **The chronic aquatic toxicity of TGSA was rated HIGH on page 4-314. On page 4-314 it is stated that the rating "*HIGH*" is based *"on estimated ChV values for fish and algae that are in the range of 0.1-1.0mg/L. Experimental chronic toxicity values were located for daphnia but not for fish or algae. Experimental values for Daphnia are in the Moderate hazard range of 1-10mg/L. Without experimental values for fish or algae, a conservative approach using estimated values will be the basis for the hazard designation".***

Appleton has reviewed a study titled "A study of TGSH in Medaka" carried out and published by CERI (**C**hemicals **E**valuation and **R**esearch **I**nstitute, Japan, Kurume). The study was initiated in August of 2011 and completed/published in 2011. The objective of the study was to experimentally estimate the LOEC and NOEC by conducting a 28-day growth study of TGSH in medaka.The study was carried out in accordance with OECD Principles of Good Laboratory Practice (November 26, 1997, ENV/MC/CHEM(98)17) using test method

a) OECD Guidelines for Testing of Chemicals, No 215, Janurary 21, 2000, " Fish, Juvenile Growth Test"
b) OECD Guidance Document, No23, September 2000, "Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures".

Based on the results of this study, the LOEC and NOEC were >8.0mg/L and >= 8.0mg/L, respectively. A rating >1.0mg/L would be considered MODERATE based on the DfE's rating guidelines described on page 4-7.

Based on these results, Appleton's view is that a downgrade of the current rating from HIGH to MODERATE is warranted.

4,4'-DIHYDROXYDIPHENOL SULFONE (CAS NO. 80-09-1) PP: 4-276:278

Repeated Dose Effects

- **Repeated Dose Effects was rated "HIGH". On page 4-276, it is stated that "*Among two adequately-designed, repeated-dose oral studies in rats, one study identified a NOAEL of 10 mg/kg-day and a LOAEL of 60 mg/kg-day for systemic effects and the other study identified a NOAEL of 40 mg/kg-day and a LOAEL of 200 mg/kg-day for systemic effects. Based on uncertainty as to the potential systemic toxicity in the range of 40 to 60 mg/kg-day, a High hazard designation is selected. It should be noted that because the standard criteria thresholds are for 90-day studies, the 28-day study was evaluated using modified criteria at 3 times the threshold values.".***

The analysis of the data for this criteria clearly requires some extrapolation, since the duration of the studies was less than 90 days. We understand the logic of extending the threshold values by three times

as an approximation. The table below shows the stated thresholds for 90 days and our understanding of the extrapolated thresholds used to assess 4,4'-DIHYDROXYDIPHENOL SULFONE (CAS NO. 80-09-1).

Repeated Dose Effects	Very High	High	Moderate	Low	Very Low
Oral (mg/kg/day for 90 days)	-	<10	10-100	>100	-
Extraplolated Thresholds (3X)	-	<30	30-300	>300	-

All the LOAEL values for the studies cited fall into the Moderate extrapolated threshold. Only one NOAEL value fell into the High category. This would suggest to us that Moderate might be a more appropriate rating.

Based on this analysis we would recommend changing the Repeated Dose Effects rating to Moderate for 4,4'-DIHYDROXYDIPHENOL SULFONE (CAS NO. 80-09-1) PP: 4-276:278. We would also recommend that additional studies be conducted at the 90 day guideline duration to eliminate the need for extrapolation.

- ***On page 6-11, it is stated that "a significant use of thermal paper is for point of sales receipts. Every year, an estimated 9.6 million trees are cut down in the United States for receipts (Clifford, 2011), although many companies strive for sustainability through stewardship and management programs…E receipts could reduce paper waste and also limit exposure to BPA and other chemicals, making them an approach to be considered in alternatives discussions. A full examination of the relative merits of thermal paper versus e-receipts requires the consideration of lifecycle attributes, which is beyond the scope of this project".***

Appleton finds such comments to be misinterpreted by the general public leading the public to believe that:

a) the production of POS contributes to deforestation and that 9.6 million trees are cut down every year to satisfy the POS market need.

b) e-receipts offer a greener/healthier alternative than paper receipts because of less paper waste (and less cutting down of trees) and less of exposure to BPA/other chemicals.

A review of the relevant literature on deforestation and the environmental impact of digital technologies (see attached internal publications for more in depth information and references) indicate the following:

a) the pulp and paper and allied industry is not a major contributor to deforestation. Trees are a renewable resource and the industry is a great steward of the forests and plantations. Its efforts along with those of the US Forest Service have yielded increased timber growth due to expanded programs in forest fire control, tree planting and other forestry measures. The Food

and Agriculature Organization (FAO) of the United Nations reported on the total amount of forest Area in North America. In 1990, North America had 676.8 million hectares of forest area. That number increased to 677.1 million hectares in 2000 and increased again to 678.9 million hectares in 2010. For the USA, the corresponding figures are 296.3 million hectares, 300.2 million hectares, and 304 million hectares, respectively. Furthermore, it is estimated that the number of trees of in the United states is likely to be 526.6 billion trees and that in North America to approach 1.2 trillion trees.

Based on these estimates, cutting down 9.6 million trees to meet the demand of the POS market would represent 0.18% of the total estimated trees in the USA and 0.08% of the number of trees in North America-truly insignificant numbers with minimal impact on the forests and plantations. It has been reported that "the world's demand for paper can be permanently satisfied by the wood production of just 5% of the current forest cover. Plantations do not account for much of the overall forest area, and they actually help relieve pressure on natural forest, which still dominate more than 95% of the world's forests."

b) It is not clear that the switch to a digital technology will result in a greener/safer alternative to paper, paper containing BPA and/or other chemicals. In 2004, a UN University study reported that the average desktop computer and monitor use more than 10 times its weight in fossil fuels and chemicals. In that study, the United Nations called for worldwide action to halt the growth of high-tech trash. The study showed that the construction of a 24KG computer and a 27cm monitor requires at least 240KG of fossil fuel, 22 KG of chemicals and 1500 KG of water. Now consider that more than a 130 million computers are sold each year. This translates into significant need for fossil fuels and other chemicals. In addition, plastics are integral component in the construction of computers and electronic devices. It is well known that the plastic industry is a major user of BPA and/or analogues of BPA. Based on these arguments, it is not clear that substituting direct thermal paper receipts with e-receipts transmitted via electronic devices is a "greener" alternative. It is Appleton's opinion that BPA free and even a phenol free POS receipts will become ubiquitous long before plastics discover such alternatives and adopt them.

In addition to the environmental impact stemming from the manufacturing of electronic devices one need to consider the environmental impact from a carbon footprint and energy consumption point of view.

Apple reports that over its lifetime an Ipad will generate 130Kg of CO_2 equivalent. Ipad sales are expected to top 66 millions by end of 2012. This would translate in over 8.6 billion Kg of CO_2. In contrast, the production of 66 million books would translate into a carbon foot print of 265 million Kg of CO_2.

Devices, such as Ipads, laptops, desktops, and other electronic devices require and use additional electronic services, such as websites, email, etc. All of these services require the use

of massive data centers which house computers and drive space. These servers and data centers consume significant amount of energy. In 2007, the EPA reported to Congress, that the nation's servers and data centers consumed in 2006, 61 billion kilowatt-hours (KWh) (1.5% of total US electricity consumption) with a cost tag of ~4.5 billion dollars. The consumption of electricity in 2006 had more than doubled when compared to the consumption in 2000. These numbers have been updated since that report. Johnathan Koomey updated the EPA report based on data gathered from 2005-2010 and reported a 36% increase in the USA.

It is also important to note that the paper industry is also energy intensive but it does a remarkable job in generating energy from renewable sources rather than fossil fuels. The DOE reported that in 1972, the paper and allied product industry was self generating 40.3% of total energy needs with renewable byproducts such as bark, spent pulping liquor, and in some locations, hydroelectric power. The burning of biomass is preferred over fossil fuels since the Co2 released from wood burning is part of a natural cycle and is offset by growing trees.

While the industry's overall energy use increased by 4% from 1972-2000, its self generated energy capacity grew by approximately 40% and production grew by 70%. The DOE reports that the paper manufacturing sector generates more electricity than any other industry. In 2002, the pulp and paper industry generated 51,208 million Kilowatt hours. This represents 38% of total US industry onsite generation of electricity.

The industry has also been a pioneer and leader in combined heat and power technology to generate electricity. This technology uses fuels much more efficiently to produce electricity than conventional electricity generation technologies and as a result fewer greenhouse gases are emitted.

The above discussion points clearly indicate that there is no real evidence that the digital technologies are truly "greener" than paper and paper-based products, whether direct thermal or traditional paper.

Lastly, the stated purpose of the DfE BPA Alternatives in Thermal Paper was and has been to evaluate alternatives to BPA in current thermal products. We believe the referenced comments on page 6-11 are off topic and deal more with the merits of thermal paper in general versus competing technologies. This was not the stated purpose of this committee and would likely be best treated in an independent study.

Based on the factual arguments presented above, and the point that this argument is outside the scope of this effort, Appleton is requesting the removal of the closing paragraph of section 6.7 on page 6-11 and an invitation to industry, governmental agencies and academia to collaborate, innovate and promote "greener" developer technologies than BPA and its analogues.

The Chemical Company

September 28, 2012

Dr. Caroline Baier-Anderson
Design for the Environment
U.S. Environmental Protection Agency
Washington, DC

Dear Dr. Baier-Anderson,

Re: Comments on EPA Draft Report for *Bisphenol A Alternatives In Thermal Paper* published July, 2012

BASF is submitting comments on the Draft Report for *Bisphenol A Alternatives In Thermal Paper* published in July, 2012. Comments are focused on the alternative Pergafast 201 which was reviewed in the report. Overall, BASF feels that assessment of Pergafast 201 should be more favorable than that stated in the Draft Report and outlines its reasons why it believes a more favorable assessment of Pergafast 201 is justified. The following comments are offered to help clarify some aspects of the report that may be confusing or may not completely portray the hazards.

Lack of overall rating needs to be more transparent. While the report provides adequate justification for the process used in the assessment and explanation of the hazard categories used, the Agency has not indicated any overall rating. BASF agrees with this approach; however, BASF has already observed that some readers are confused into thinking that there is a list of recommended substances where one is not apparent. It should be emphasized in the preface of the document that the EPA report on BPA alternatives does not represent a ranking but an overview on available BPA alternative substances and their properties.

Furthermore, the color coding of substances in Table 4-4 suggests a rank when there is none. BASF believes that the use of different background colors in table 4-4 Screening Level Hazard Summary should be defined. It is assumed that these colors represent chemical similarity of the substances; however, another interpretation is that Blue signalizes a comparatively low hazard whereas orange or violet colored substances are more hazardous. This is confusing to the reader and is too easily misinterpreted. BASF recommends that the color coding be explained.

Identification of NOAEL for Reproductive Toxicity is confusing. BASF suggests a change in the wording for the NOAEL for reproductive toxicity of Pergafast 201 as stated on the Table on Page 4-387. Currently, the NOAEL is identified as “NOAEL (F1 pups): ≥200 mg/kg bw-day”. BASF believes that this can be misread to relate to developmental effects, which are described on the following page and indicate a NOAEL of 100 mg/kg based on F1 pups. The two statements appear to conflict. BASF believes that clarity can be achieved by changing to NOAEL for reproductive toxicity to “NOAEL: > 200 mg/kg bw-day based on fertility”.

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Characterization of algal toxicity should be modified. BASF believes that the characterization of the environmental hazard based on algal toxicity is incorrectly identified as *Very High*. Two separate reports were provided to the Agency on algal toxicity: one in which algae were exposed to Pergafast 201 under static conditions according to the OECD 201 Testing Guideline, and a second in which algae were exposed to Pergafast 201 in the presence of sediment to mimic realistic conditions (described as second study listed for Green Algae – confidential submission). It is highly unlikely that algae would be present in a natural system that does not include sediment as well as suspended solids (organic carbon) in the water column. These matrices could attenuate the toxicity of Pergafast 201 to algae. The sediment was constituted per OECD Guideline 219. During the test period of 96 hours, the test substance concentrations in the water decreased. At the end of the test, 54 to 61% of the nominal values were found. The report states that the decrease was due to the adsorption of the test item into the sediment surfaces and algae. The biological results are based on the nominal test concentrations, since adsorption to surfaces as occur in the water-sediment system will also occur under natural conditions, i.e., the study reflects more realistic environmental exposure conditions in the aquatic environment. The toxicity of Pergafast 201 to the algae was over an order of magnitude lower in the presence of sediment than in the absence. BASF suggested that it is this study better represents the environmental hazard and using those results would change the assessment from *Very High* to ***Moderate***. We urge the Agency to re-evaluate this endpoint based on the information that was provided.

Heavy reliance on calculated values rather than experimental ones. BASF is concerned about the extensive use of ECOSAR calculations rather than experimental data. For example, for long-term toxicity to algae calculated ChV values were used to assign hazard ratings rather than just experimental data. BASF strongly objects to this approach and would rather use experimental data only when they are available. ECOSAR model calculations should only be used in form of a Weight of Evidence approach in combination with other endpoint information. The stand-alone use of ECOSAR should be avoided because of a low reliability of the estimated toxicity values, e.g., the calculated acute toxicity value for marine invertebrates (LC_{50} = 29.89 mg/L) is much low than the calculated chronic toxicity value for marine invertebrates (ChV = 640 mg/L). In Table 1 (see below), a comparison is made for the ecotoxicological endpoints between the available data from the Pergafast 201 material safety data sheet and the data presented in the EPA BPA alternatives draft report.

Growth rate is more universally accepted than biomass to evaluate toxicity to algae. There is evidence that the average growth rate as the basic response variable for algal growth should preferably be used for the consistent assessment of toxicity to algae[1]. In the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) of the United Nations, it is clear stated that "[…] *The preferred observational endpoint in this study is algal growth rate inhibition because it is not dependent on the test design, whereas biomass depends both on growth rate of the species as well as the test duration and other elements of test design*. […]" (GHS[2], Annex 9, A9.3.2.7.1 Test

[1] Ratte, H. T., M. Hammers-Wirtz & M. Cleuvers (1998): Influence of the growth pattern on the EC50 of cell number, biomass integral and growth rate in the algae growth inhibition test. Umweltbundesamt, Project No. 36003010.

[2] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) - fourth revised edition (2011). United Nations.

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in algae). Therefore, BASF suggests using the experimental short- and long-term algae toxicity data based on growth rate and not based on algal biomass.

Data for toxicity to terrestrial plants are available. BASF has data on the effect of Pergafast 201 on terrestrial plants (*Avena sativa*, *Pisum sativum*, and *Brassica napus*). Exposure to 1000 mg/kg soil dw was without effect on seedling emergence or growth over 21 days. While EPA does not include an assessment of terrestrial plant toxicity, BASF feels that this study further demonstrates the lack of impact of Pergafast 201 on the environment.

Respectfully submitted,

Raymond M. David, Ph.D., DABT
Manager, Toxicology

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Table 1: Comparison of ecotoxicological endpoint data for Pergafast 201 presented in the EPA draft report on BPA alternatives and on the BASF Material Safety Data Sheet (2012) for Pergafast 201.

Endpoint	Reference in EPA BPA draft report	BASF data available for Pergafast 201
Acute toxicity to fish	NICNAS 2004, Estimated (ECOSAR), BASF 2010	Yes, (OECD TG 203)
Acute toxicity to Daphnia	NICNAS 2004, Estimated (ECOSAR)	Yes, (OECD TG 202)
Saltwater invertebrate	Estimated (ECOSAR)	No
Acute toxicity to algae	NICNAS 2004, Submitted confidential study, Estimated (ECOSAR)[3]	Yes, (OECD TG 201)
Chronic toxicity to fish	Estimated (ECOSAR), Submitted confidential study	Yes, (OPPTS Draft Guidline 850.1400)
Chronic toxicity to Daphnia	NICNAS 2004, Estimated (ECOSAR), BASF 2010, Submitted confidential study	Yes, (OECD TG 211)
Chronic saltwater invertebrate	Estimated (ECOSAR)	No
Chronic toxicity to algae	Estimated (ECOSAR)	Yes, (OECD TG 201)
Earthworm subchronic toxicity	Estimated (ECOSAR)	Yes, (OECD TG 222)
Terrestrial non-target plants	No information available	Yes, (OECD TG 208)
Biodegradation	NICNAS 2004, BASF 2010, Submitted confidential study	Yes, (OECD TG 301F, 302B)
Hydrolysis	NICNAS 2004	Yes, (OECD TG 111)
Bioaccumulation	NICNAS 2004, Submitted confidential study	Yes, (OECD TG 305)

[3] The conclusion was drawn based on biomass and NOT on growth rate. Using growth rate as endpoint basis rather than biomass, changes the assessment from “Very High” (threshold: <1 mg/L) to “High” (threshold: 1-10 mg/L).

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From:	Laura Weinberg
To:	Caroline Baier-Anderson/DC/USEPA/US@EPA
Cc:	gelb@chelseaofficesystems.com; PenPalette@nycap.rr.com; MAM18@aol.com; friends@hbcac.org; andiglad@lightlink.com
Subject:	Response from the NYSBCN regarding the EPA BPA Thermal Receipt Report
Date:	10/01/2012 10:41 AM

Dear Cal Baier-Anderson:

We thank you and the EPA for working on and releasing the Report on Alternatives to BPA in Thermal Cash Receipts that covers many important concerns and issues. Thank you also for describing BPA in the Introduction of the report as "interacting with estrogen receptors" as opposed to it being a "weak estrogen" as described in one of the original drafts.

However, members of our New York State Breast Cancer Network (NYSBCN) are disappointed that "Endocrine Activity" is not being recognized in the Report as an adverse health effect or endpoint in Table 4.1 where other adverse health effects are prominently listed. The EPA Report states that endocrine disruption is not an endpoint but instead a means to an endpoint. In several instances though, the report inconsistently refers to endocrine disruption as an endpoint or a human health hazard. (Chapter 6.1.1) It is important to note that endocrine disruption is viewed as a human health hazard in the 2009 Endocrine Society Review. The Endocrine Society has a worldwide membership of 14,000 medical and health professionals.

Moreover, NYSBCN had previously stated in our letter to the EPA in November 2011, that "because of the strong proven links to breast cancer risk, our agenda includes reduction of the vast amount of toxins in our environment, especially those that are carcinogenic or show endocrine activity, and those that fall under the category of estrogen mimickers." During November 2011 we were told that Endocrine Activity was not listed in Table 4.1 because there were not enough studies that showed endocrine disruption caused adverse health effects. However, the EPA Report lists an ample number of studies on endocrine disruption for several of the reviewed chemicals. This is another inconsistency in the report that needs to be addressed or explained.

An additional concern regarding the EPA Report on Alternatives to BPA are the "Data Gaps". Data on endocrine activity is available for

BPA and for 10 of the 20 alternatives included in the report. For chemicals without available data on endocrine activity, this was acknowledged with a "no data available" entry.

Aside from endocrine activity, there are many data gaps for the chemicals being assessed for all of the various health endpoints listed. Due to the many data gaps, there needs to be more research done on the potential adverse health effects of the 19 chemicals being assessed before any are used in thermal cash receipts; otherwise we may be replacing one hazardous substance for another. Of additional concern to the breast cancer community, data was also missing in the categories of carcinogenesis for many of the chemicals being assessed.

The EPA is to be commended for mentioning non-chemical approaches to using BPA in thermal sales receipts such as the implementation of electronic receipts and looking to green chemistry for safer alternatives.

Thank you for including the New York State Breast Cancer Network in the EPA/DFE Partnership for this committee.

Sincerely yours,

NEW YORK STATE BREAST CANCER NETWORK
Laura Weinberg, Great Neck Breast Cancer Coalition
Karen Miller, Huntington Breast Cancer Action Coalition
Margaret Roberts, Capital Region Action Against Breast Cancer
Roberta Gelb
Environmental Committee Members

September 30, 2012

Cal Baier-Anderson
Environmental Protection Agency
Design for the Environment Program
Washington DC 20009

Re: Comments on Draft Report on Bisphenol A Alternatives in Thermal Paper

Environmental Working Group is writing to comment on the draft hazard evaluation of thermal paper produced by EPA's Design for the Environment (DfE) program for chemical-coated thermal paper used to print store receipts and other documents that people handle daily, including food labels, parking and lottery tickets and medical images. The synthetic estrogen bisphenol A (BPA) is a common color developer used on thermal paper, a use that poses unacceptable risks for human exposure and environmental contamination. Our comments on the July 2012 draft are largely unchanged from comments we submitted September 2011.

The DfE program launched its thermal paper evaluation in 2010 with a commitment to examining the full range of chemicals that could be used as a replacement to BPA, but its draft summary document doesn't go far enough to interpret the available evidence for thermal paper developers. In its nearly 500 page document EPA exhaustively catalogs the existing data for BPA and 19 alternative chemicals and estimates toxicity endpoints for chemicals lacking experimental data. Yet this two-year research effort offers little tangible guidance to manufacturers seeking safer developers, and obscures an important finding that many alternatives pose similar risks to BPA in thermal papers. EPA should clearly rank or bin the chemicals by level of concern and highlight the data gaps and missing tests for the most promising alternatives to BPA.

Our review of the draft report finds little assurance that the DfE program is drawing the appropriate conclusions about the safety of BPA and alternative thermal paper developers. In particular:

- In its assessment of 20 thermal paper developers EPA scientists and collaborators found that every chemical alternative to BPA was found to pose a "high" or "very high" hazard in at least one area of concern for health or the environment.

- Only 11 of the 20 chemicals studied have test data for hormone disruption, and 9 of these suggest some endocrine activity. The remainder of BPA replacements have not been tested.

- On page 480 EPA states somewhat enigmatically, "Several chemicals included in this analysis appear to have more preferable profiles, with low human health and ecotoxicity endpoints." (EPA 2012a) But doesn't name these chemicals. Furthermore the report

clarifies that these determinations were not based on empirical data, rather modeling and expert judgment.

- Overall EPA fails to clearly interpret the nearly 400 pages of hazard information for thermal paper developer, leaving manufacturers to do as they please in selecting the appropriate chemicals to use in this multi-million dollar industry.
- In light of these challenges DfE should declare that BPA in thermal paper poses an unnecessary risk to consumers and the environment, and name a group of additional chemicals that shouldn't be used as substitutes. It appears that no suitable alternatives can be fully validated at this point. But EPA should identify promising chemicals and the empirical tests needed to confirm their safety. In the meantime EPA should guide industry to accepting alternative printing technologies or modifications to thermal paper production that would decrease the likelihood of human exposure and environmental harm.

Problems with thermal paper

The use of BPA in thermal paper poses an unnecessary health risk to the public. Trace BPA exposure disrupts the endocrine system and triggers a wide variety of disorders including reproductive system abnormalities, impaired brain and neurological development, increased susceptibility to reproductive system cancers and resistance to chemotherapy (NTP 2008 Jenkins 2009, LaPensee 2009, Prins 2011). In 2010, EWG-commissioned tests of store receipts found that major retailers using BPA-containing receipts included McDonald's, CVS, Whole Foods, WalMart, Safeway and the U.S. Postal Service. These and other tests show thermal papers to be up to 3 percent BPA by weight (EWG 2010, Mendum 2011).

BPA or replacement color developers are coated on the exterior of thermal paper in relatively large amounts but are not bound tightly to the paper surface. A recent study estimates that 25 percent of BPA that rubs off paper can penetrate human skin (Zalko 2011). As a result, BPA in thermal paper poses serious risks for merchants and consumers who handle the paper as well as for workers in production facilities. Furthermore, the recycling of thermal paper contaminates products made from it and disposal of virgin or recycled products pollutes the environment.

The DfE report provides virtually no information about the magnitude of chemical use for the thermal paper market in the United States, but reports that 9.6 million trees are cut in the United States alone to supply receipt paper. The largest U.S. maker of thermal paper, Appleton Paper, announced that it had switched from BPA to bisphenol sulfone in 2006.

Hormone disruption data for alternatives must be clearly presented

One significant gap in the draft report is the lack of analysis of the threat of hormone disruption by BPA and the 19 potential replacement chemicals. DfE staff reviewed and summarized this information for the 20 chemicals in individual hazard assessments but did not include it in DfE's

final summary Table 4-4 (EPA 2012a). Its absence in this crucial table creates the impression that hormone disruption is not a top concern for alternatives to BPA in thermal paper, when in fact the opposite is true. We are deeply concerned that the absence of hormone disruption data in this table and in the evaluation process could lead to faulty conclusions about the relative hazards of other developers in thermal paper.

Many of the potential replacements for BPA are molecules with a phenolic structure similar to BPA's and are suspected to have similar toxicological risks. Given that the DfE assessment program was prompted by BPA's hormone-disrupting properties and widespread human exposure, this endpoint must be a high priority in assessing the alternatives and must be reflected clearly in the agency's summary and conclusions.

The thermal paper project marks the first attempt by the DfE program to include information about hormone disruption, a toxicological endpoint that lacks standardized guidelines for determining whether a chemical poses a "low," "medium," "high" or "very high" hazard to human health or the environment. In its 2010 kick-off meeting, DfE announced that it intended to identify chemicals with "potential endocrine activity" (EPA 2010). However, the draft documents fall short of this goal. DfE staff has invested significant energy in summarizing available data for color developers in the narrative but did not characterize the risks of potential for endocrine effects. Both EWG and NRDC have urged EPA to draw clearer conclusions about the potential for endocrine disruption, and it appears our concern is shared by officials at NIEHS as well (EPA 2011).

The DfE program typically makes hazard determinations for chemicals based on nationally and internationally standardized criteria for interpreting data on toxicity or environmental fate. These criteria are not available for hormone disruption.

DfE hazard summaries indicate that data on hormone disruption is available for BPA and 11 of 19 replacement chemicals. Nine of 11 chemicals with available test data have been shown to interfere with hormone systems in at least one study. The remaining 9 alternatives have not been tested, and their ability to stimulate or inhibit responses of thyroid or sex hormones remains uncharacterized.

Based on these summaries, however, we believe that there is sufficient evidence to flag the 9 tested chemicals for "potential endocrine activity" in Table 4-4. Several of the untested chemicals are phenols that are structurally similar to bisphenol A. We recommend DfE examine the untested chemicals using read-across data and expert judgment and flag any that might have "potential endocrine activity" in Table 4-4, and that this data be used to clarify overall hazard levels for the 20 potential developers.

Replacement chemicals for thermal paper

The outcome of DfE's thermal paper project is of utmost concern to EWG because of the large quantity of color developers used on thermal paper and the likelihood of widespread consumer exposure. Although major thermal paper manufacturers have recently switched from BPA to

alternative chemicals, the DfE draft documents reveal significant concerns over the potential of these replacement developers to have human heath effects, aquatic toxicity or environmental persistence or bioaccumulation. EPA's draft assessment rates each of the 19 alternatives as "high" or "very high" concern for at least one human health or ecological endpoint (EPA 2012), raising the question of whether there is any suitable way to make thermal paper.

Industry commonly complains that DfE alternative assessments do not provide clear guidance about environmentally preferred alternatives. We sympathize with industry's perspective and believe that instead of leaving the test results open to interpretation, the ultimate goal of DfE assessments should be to clearly identify chemicals that achieve a higher level of safety, as was recently done in the review of alternatives for nonylphenol ethoxylates (EPA 2012b). Some of the alternative developers are sufficiently similar to BPA and should be given failing grades.

EPA mentioned that several chemicals appear to have a favorable toxicity profile based on modeling and expert judgment (EPA 2012 pg. 480). EPA should clearly state these chemicals identities and which types of empirical data are needed to confirm their potentially benefits. Finally EPA should explore in more detail whether process innovations to thermal paper could achieve an acceptable solution.

In our opinion the evidence suggests that the best alternative to BPA is to abandon thermal paper production completely. Stores commonly use ink jet printers for coupons. Electronic receipts and sale records can replace thermal paper, don't require chemical coatings and don't carry any of the inherent hazards that the agency has identified for the chemicals it assessed. We urge DfE to promote the use of alternative printing technologies as an intrinsically safer method for sales records, labels and images.
Sincerely,

Sonya Lunder, MPH
Senior Analyst

David Andrews, Ph.D.
Senior Scientist

Environmental Working Group
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Washington DC 20009

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October 15, 2012

Cal Baier-Anderson, Ph.D.
Design for the Environment
US Environmental Protection Agency
1200 Pennsylvania Ave NW (7406M)
Washington, DC 20460-0001

Re: Comments on Draft Alternatives Assessment Report on Bisphenol A in Thermal Paper

Dear Dr. Baier-Anderson:

The Polycarbonate/BPA Global Group of the American Chemistry Council[1] respectfully submits the attached comments on EPA's Design for the Environment draft alternatives assessment report on bisphenol A (BPA) in thermal paper. The Polycarbonate/BPA Global Group represents the leading global manufacturers of BPA and polycarbonate plastic. For many years the group has sponsored scientific research to understand whether BPA has the potential to cause health or environmental effects and to support scientifically sound policy.

Please do not hesitate to contact me if I can be of further assistance to clarify any comments or if additional information is needed. If it would be helpful, we would also be willing to meet with EPA staff to discuss our comments. I can be reached at (202) 249-6624 or by e-mail at steve_hentges@americanchemistry.com.

Regards,

Steven G. Hentges, Ph.D.
Polycarbonate/BPA Global Group

Attachment

[1] The American Chemistry Council represents the leading companies engaged in the business of chemistry. Council members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. The Council is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a $435 billion enterprise and a key element of the nation's economy. It is the nation's largest exporter, accounting for ten cents out of every dollar in U.S. exports. Chemistry companies invest more in research and development than any other business sector.

Comments of the Polycarbonate/BPA Global Group on EPA's Design for the Environment Draft Alternatives Assessment Report on Bisphenol A in Thermal Paper

October 15, 2012

1. Summary

In the guidance document for EPA's Design for the Environment program ("Design for the Environment Program Alternatives Assessment Criteria for Hazard Evaluation"),[3] EPA has set rigorous goals and requirements for the conduct of DfE alternatives assessments. These include specific requirements for data quality and program rigor:

- "DfE has carefully chosen the criteria … with the goal of creating a rigorous and useful system …"
- "DfE uses the best information available, both experimental and modeled"
- "When gathering data for evaluation under these criteria, a review of the open literature including published peer-reviewed studies and government reports as well as any confidential business information will be conducted"
- "When available and appropriate, the results of benchmark dose modeling will also be considered"
- Use of existing data should follow the EPA HPV Challenge Program and OECD HPV Program data adequacy guidelines"

In the case of the draft assessment of alternatives to bisphenol A (BPA) in thermal paper though, EPA has failed to follow its own guidelines and, as a result, has not produced a rigorous and useful work product. The draft report does not include the best information available, including readily available studies from the peer-reviewed literature, did not use the results of readily available benchmark dose modeling, and apparently did not follow its own data adequacy guidelines. Rather than rely on clear criteria from EPA's own guidance document to set hazard designations, EPA appears to rely in some cases on qualitative "concerns" and "uncertainty."

As discussed in these comments, the carcinogenicity, reproductive and developmental endpoints are particularly problematical. The proposed hazard designations for each of these endpoints are overrated and not supported by the scientific evidence provided in the hazard profile or by the best information available. Consistent with EPA's guidelines, these endpoints must be corrected and the hazard profiles should reflect the best information available.

Of particular concern is that EPA has failed to take advantage of extensive and detailed assessments of BPA that have been conducted by experts at government agencies around the world. Most importantly, although EPA has acknowledged in its BPA Action Plan that "FDA has the lead in making human health judgments on BPA," the draft BPA alternatives assessment is inconsistent with FDA's more comprehensive assessment and there is no indication that FDA

was consulted or involved with EPA's assessment at all. With limited federal government resources, this duplication of effort is wasteful and has resulted in a substandard draft report.

The problems with the draft report do not end with the BPA assessment since the hazard assessments for a variety of alternatives are apparently based on BPA as a surrogate. While this approach may have conceptual appeal, its success depends on the integrity of the underlying assessment of BPA. Because the problems with the BPA assessment appear to be pervasive across other alternatives, we request that this draft report be withdrawn and replaced, when appropriate, with a more rigorous draft that conforms more closely to EPA's guidelines.

2. The Carcinogenicity Hazard Designation (Moderate) Is Not Supported by EPA's Hazard Evaluation Criteria and Is Not Consistent with Worldwide Regulatory Agency Conclusions

The EPA carcinogenicity hazard profile for BPA includes the four elements listed below that apparently are intended to support the proposed Moderate hazard designation. The Moderate hazard designation is also summarized at the top of the carcinogenicity hazard profile (page 4-38).

- An estimated moderate rating from OncoLogic;
- Summary results from the NTP 2-year dietary studies in rats and mice;
- Conclusions from a 2010 FAO/WHO review of BPA; and
- Conclusions from a 2007 review paper by a small group of academic researchers.[2]

The information and evidence provided in these four elements must be evaluated against the carcinogenicity criteria provided in EPA's hazard evaluation criteria document for the DfE program[3] to determine which hazard designation is appropriate. In particular, the criterion for a Moderate carcinogenicity rating requires "Limited or marginal evidence of carcinogenicity in animals (and inadequate evidence in humans)." In addition, the hazard evaluation criteria document defines the term "carcinogenic" in reference to a chemical that "is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity."

Notably, the carcinogenicity criterion requires evidence of carcinogenicity in animals and the carcinogenic definition provides specific examples of the type of evidence that is required. Actual evidence of carcinogenicity, as specified in the definition, is quite different from the type of information that is available from studies that evaluate potential mechanisms, modes of action, or predisposition to neoplasia. In the absence of actual evidence of carcinogenicity, these types of studies cannot by themselves support a carcinogenicity hazard designation. Each of the four

[2] Keri, R. A., Ho, S.-M., Hunt, P. A., Knudsen, K. E., Soto, A. M., and Prins, G. S. 2007. An evaluation of evidence for the carcinogenic activity of bisphenol A. Reproductive Toxicology. 24(2):240-252.
[3] Design for the Environment Program Alternatives Assessment Criteria for Hazard Evaluation. Version 2.0. August 2011.

elements that apparently support EPA's proposed Moderate designation is evaluated below against this criterion.

As discussed in this section, the evidence provided in EPA's hazard profile for BPA, and available from other sources, can only support a Low carcinogenicity hazard designation. A Low hazard designation is consistent with numerous government agencies worldwide that have more comprehensively reviewed the scientific evidence.

a. The BPA Hazard Profile Does Not Provide the Necessary "Evidence of Carcinogenicity" to Support a Moderate Hazard Designation

As noted in EPA's hazard evaluation criteria document,[3] "Evaluation of chemicals under these criteria will be based on the best available data. In general, DfE will use data in the following order of preference: 1) measured data on the chemical being evaluated, 2) measured data from a suitable analog, and 3) estimated data from appropriate models." Based on this hierarchy, the estimated moderate rating from OncoLogic is of little or no relevance to the BPA hazard assessment since high quality measured data is available for BPA itself. The OncoLogic result should be deleted from the report and not used to support a hazard rating.

As described in the BPA hazard profile, the results of both NTP 2-year studies in rats and mice provide no convincing evidence of a carcinogenic effect for BPA. Both studies were designated as adequate for data quality. These studies provide the best available data for assigning a carcinogenicity hazard designation for BPA. According to EPA's hazard evaluation criteria document,[3] the results of these studies support a Low hazard designation. If BPA was a true tumor promoter, increases in estrogen receptor related tumors (e.g., breast, uterus, ovaries, liver) would have been obvious, but they were not present in the NTP studies. Furthermore, artificial animal models employing continuous release of testosterone and estrogen in relatively young animals, where it has been purported that BPA enhances pre-cancerous lesions, provide insufficient proof needed to support a Moderate hazard designation.

In contrast, no studies are cited that provide "evidence of carcinogenicity" as defined for the term "carcinogenic." For example, the FAO/WHO review, which is more recent than the 2007 review paper discussed below, clearly concludes that "there is currently insufficient evidence on which to judge the carcinogenic potential of BPA." Studies that might have been relevant are characterized as suffering "from one or more deficiencies in design or execution that prevent a definitive evaluation of its potential as a carcinogen." It is inconceivable that "insufficient evidence" is good enough for EPA to support a hazard designation.

Similarly, the 2007 review,[2] which is characterized as a "consensus statement," does not provide the necessary "evidence of carcinogenicity" to support a Moderate hazard designation. The conclusions from this review indicate that the authors are confident of endocrine activity and estrogenic properties of BPA, and the carcinogenic properties of estradiol-17β. None of these

conclusions provide evidence of carcinogenicity for BPA. Other conclusions in the review are characterized as "likely but requiring more evidence." Looking at the review in more detail, the only evidence for carcinogenicity that is discussed (in section 2 of the review) is from the NTP 2-year studies that provide no convincing evidence of a carcinogenic effect. Section 3 of the review, which presumably supports the "likely but requiring more evidence" conclusions, discusses "potential carcinogenic modes of action" of BPA, but does not provide actual evidence of carcinogenicity. Consequently, this review does not provide the necessary evidence of carcinogenicity and does not satisfy the criterion for a Moderate hazard designation.

It should also be noted that the consensus reached in the 2007 review is limited to the small number of authors of the review. As discussed further below, numerous agencies worldwide that have reviewed BPA have all reached different conclusions on the carcinogenic potential of BPA.

In addition to the four items from the hazard profile that are discussed above, the summary paragraph at the top of the carcinogenicity section refers to "concern for carcinogenicity" and "uncertainty." However, EPA's hazard criteria document provides no basis to use "concern" or "uncertainty" to assign a hazard designation. In fact the term "uncertainty" is not used anywhere in EPA's hazard designation criteria document, and the document uses the term concern only in other contexts. The summary paragraph also asserts that "carcinogenicity cannot be ruled out at this time." However, the criterion for carcinogenicity designations does not require that carcinogenicity be ruled out. Rather it requires evidence for carcinogenicity, meaning that carcinogenicity must be ruled in, not out. In the absence of any criteria, a Moderate designation based on "concern" and "uncertainty" is entirely arbitrary.

b. EPA's Carcinogenicity Designation for BPA is Inconsistent with Numerous Agencies Worldwide That Have Comprehensively Reviewed the Scientific Evidence

EPA's carcinogenicity hazard designation is based on what appears to be a limited and cursory evaluation of the available scientific evidence. In recent years, numerous government and scientific bodies worldwide have examined the scientific evidence supporting the safety of BPA and many of these assessments comprehensively examined the potential carcinogenicity of BPA. Each of these assessments applied a "weight-of-evidence" approach to evaluate the body of relevant information available for BPA.

As detailed below, these assessments consistently demonstrate that BPA is not a carcinogenic hazard or risk, which clearly supports a Low hazard designation. No other government or scientific body has reached a different conclusion. Several key evaluations of BPA are briefly summarized below along with their overall conclusions regarding the potential carcinogenicity and mutagenicity/genotoxicity of BPA.

Of particular note is the evaluation conducted by the U.S. Food and Drug Administration (FDA). As noted in EPA's Action Plan on BPA,[4] "Given that human exposures from TSCA uses of BPA are minor compared with human exposures from uses under FDA jurisdiction, EPA considers that FDA has the lead in making human health judgments on BPA." (emphasis added) As part of their evaluation, FDA has carefully reviewed the studies that presumably support EPA's Moderate carcinogenic hazard designation and general statements of "concern." Accordingly, EPA should follow FDA's lead, which is consistent with the conclusions of other government and scientific bodies worldwide, and assign a Low carcinogenicity hazard designation for BPA.

- **U.S. Food and Drug Administration**

The U.S. Food and Drug Administration (FDA) is currently undertaking a comprehensive assessment of the safety of BPA in FDA-regulated products such as food containers and medical devices. As part of the ongoing assessment, FDA issued a comprehensive draft report in 2008[5] and updated their views as recently as March 2012.[6] Similar to the EU Risk Assessment discussed below, FDA has comprehensively evaluated studies on the toxicity, metabolism and pharmacokinetics, and exposure of BPA. The overall FDA conclusion for carcinogenicity is presented below.

> "As part of this safety assessment, CFSAN's Cancer Assessment Committee (CAC) evaluated BPA based on the available bioassay data and recent peer-reviewed publications on BPA, specifically those that reported evidence of pre-neoplastic and neoplastic changes in animal models that were administered BPA orally at various dose levels. The CAC concluded that the findings reported in the 1982 NTP study on BPA do not provide any evidence that BPA is carcinogenic to F344 rats or B6C3F1 mice of either sex as tested under the conditions of this bioassay."
>
> "Because of these limitations [referring to limitations of the recent peer-reviewed publications referenced in the paragraph above], the CAC concluded that the totality of the information contained in these reports is of questionable usefulness for a determination of potential enhancement of neoplastic effects of BPA on the rodent prostate and mammary gland."

[4] Bisphenol A Action Plan. U.S. Environmental Protection Agency. March 29, 2010.
[5] Draft Assessment of Bisphenol A for use in Food Contact Applications. Draft 2008 report available at http://www.fda.gov/ohrms/dockets/AC/08/briefing/2008-0038b1_01_02_FDA%20BPA%20Draft%20Assessment.pdf.
[6] See http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm297954.htm.

- **European Union Risk Assessment**

Under the European Union (EU) Existing Substances Directive, the EU conducted a comprehensive risk assessment of BPA that was initially published in 2003 and updated in 2008.[7] These assessments comprehensively evaluated studies on the toxicity, metabolism and pharmacokinetics, and exposure of BPA. The overall conclusions for carcinogenicity and mutagenicity from the 2003 report and 2008 updates are presented below.

Carcinogenicity Conclusions

"Taking into account all of the animal data available the evidence suggests that BPA does not have carcinogenic potential." (2003)

"Overall, therefore, the new information on the potential carcinogenic and/or promoting effects of BPA in prenatal and neonatal rat models supports the original conclusion from the published report that BPA does not possess any significant carcinogenic potential." (2008)

Mutagenicity Conclusions

"Considering all of the available genotoxicity data, and the absence of significant tumour findings in animal carcinogenicity studies, it does not appear that BPA has significant mutagenic potential *in vivo*." (2003)

"Therefore, the original conclusion from the published assessment that BPA has no significant mutagenic potential *in vivo*, is still valid." (2008)

- **Japanese National Institute for Advanced Industrial Science and Technology**

In 2005, the Japanese National Institute for Advanced Industrial Science and Technology (AIST) issued a comprehensive risk assessment of BPA, with an English translation made available in 2007.[8] A thorough update of the assessment, which considered research published since the original 2005 report, was very recently released in July 2011.[9] The AIST assessments evaluated studies on toxicity, metabolism and pharmacokinetics, and exposure of BPA. The overall AIST conclusions for carcinogenicity and genotoxicity from the 2005 report and 2011 update are presented below.

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[7] European Union Risk Assessment Report – 4,4'-isopropylidenediphenol (Bisphenol-A). Available at http://esis.jrc.ec.europa.eu/doc/existing-chemicals/risk_assessment/SUMMARY/bisphenolasum325.pdf (2003 summary) and http://esis.jrc.ec.europa.eu/doc/existing-chemicals/risk_assessment/REPORT/bisphenolareport325.pdf (combined 2003 full report and 2008 update).

[8] Bisphenol A Risk Assessment Document. English version available at http://unit.aist.go.jp/riss/crm/mainmenu/e_1-10.html.

[9] Updated Hazard Assessment of Bisphenol A. English version available at http://www.aist-riss.jp/main/modules/product/index.php?content_id=73&ml_lang=en.

Carcinogenicity and Genotoxicity Conclusions

"Carcinogenicity studies in F344 rats and B6C3F1 mice both produced negative results (NTP 1982). Results of cell transformation assays using cultured cells (*in vitro* carcinogenicity tests) were negative too (see, for example, Jones *et al*. 1988, European Commission 2003)." (2005)

"Following a weight-of-evidence approach recommended by IARC and US EPA, Haighton *et al.* (2002) concluded that BPA is not likely to be a human carcinogen. We consider that this conclusion is appropriate." (2005)

"Overall, taking the above results into account, it does not appear that BPA has positive genotoxic potential" and "BPA is unlikely to have genotoxic or carcinogenic potential." (2005)

"Following a weight-of-evidence approach, it has been concluded that BPA is not likely to be carcinogenic to humans (Haighton, 2002). This was due to the fact that; a) BPA did not cause gene mutations or chromosomal aberrations in bacteria/fungi/mammalian cells in standard in-vitro genetic tests, b) BPA was negative in in-vivo chromosomal aberrations tests, and c) BPA was negative in all of the bone-marrow micronucleus tests in mice, dominant lethal tests in rats, and carcinogenicity study in rats and mice. None of the new information supported overturning this conclusion." (2011)

- **Joint FAO/WHO Expert Meeting**

In November 2010, the World Health Organization (WHO) and the UN Food and Agriculture Organization (FAO) jointly organized an Expert Meeting to assess the safety of BPA. The full report from the meeting was released at the beginning of September 2011.[10] The overall conclusions for carcinogenicity, which is partially included in EPA's draft hazard assessment, and genotoxicity are presented below.

Carcinogenicity Conclusion

"In the traditional rodent cancer bioassay (NTP, 1982), BPA at doses of approximately 75–150 mg/kg bw per day gave, at best, weak evidence of carcinogenic activity, but it is questionable whether the chemical was adequately studied. The United States National Toxicology Program (NTP) bioassay did not include exposures during the perinatal period, which would appear to be a critical window of exposure. Studies that included perinatal (gestational and/or lactational) exposures to BPA (oral doses to the dam from ~10 to 250 µg/kg bw per day) have reported, among other lesions, proliferation of mammary ductal

[10] Toxicological and Health Aspects of Bisphenol A. Report of Joint FAO/WHO Expert Meeting. See http://www.who.int/foodsafety/chem/chemicals/bisphenol/en/index.html for full documentation on the meeting.

epithelium and squamous metaplasia of prostatic epithelium in offspring, conditions thought by many to predispose to neoplasia (Timms et al., 2005; Moral et al., 2008). Additional treatments with initiating or promoting agents have led to earlier onset of mammary tumours (Jenkins et al., 2009) or prostatic intraepithelial neoplasia (Prins et al., 2011).

However, the studies that included exposures to BPA during the appropriate periods all suffered from one or more deficiencies in design or execution that prevent a definitive evaluation of its potential as a carcinogen. These include 1) lack of consideration of litter effects, 2) small numbers of animals, 3) insufficient study duration to determine whether developmental conditions thought to enhance cancer susceptibility actually did so and 4) additional treatment with a strong initiating or additional promoting agent(s). In the absence of additional studies addressing these deficiencies, there is currently insufficient evidence on which to judge the carcinogenic potential of BPA."

Genotoxicity Conclusion

"In conclusion, BPA is not a mutagen in in vitro test systems, nor does it induce cell transformation. BPA has been shown to affect chromosomal structure in dividing cells in in vitro studies, but evidence for this effect in in vivo studies is inconsistent and inconclusive. BPA is not likely to pose a genotoxic hazard to humans."

- **Haighton et al., Regulatory Toxicology and Pharmacology (2002)**

A seminal evaluation of the potential carcinogenicity of BPA was published in 2002 by Haighton et al.[11] The evaluation included carcinogenicity and genotoxicity studies, along with various other toxicity, metabolism and exposure studies, and followed weight-of-evidence guidelines for assessment of carcinogenicity from the International Agency for Research on Cancer (IARC) and the U.S. Environmental Protection Agency. The overall conclusion of this evaluation was:

"Following a weight-of-evidence approach as recommended by IARC and U.S. EPA, it was concluded that BPA is not likely to be carcinogenic to humans. The bases for this conclusion included: (a) the results of an NTP study which provided no substantive evidence to indicate that BPA is carcinogenic to rodents; (b) the lack of activity of BPA, at noncytotoxic concentrations, in standard *in vitro* genetic toxicity tests; (c) the lack of genotoxic activity of BPA in a GLP-compliant *in vivo* mouse micronucleus assay; and (d) the results of metabolism studies showing BPA is rapidly glucuronidated without evidence of formation of potentially reactive intermediates, except possibly at high doses that could saturate detoxication pathways."

[11] Haighton, L.A., Hlywka, J.J., Doull, J., Kroes, R., Lynch, B.S., and Munro, I.C. 2002. An evaluation of the possible carcinogenicity of bisphenol A to humans. Regulatory Toxicology and Pharmacology. 35:238-254.

3. The Weight of Evidence Supports a Moderate or Low Reproductive Toxicity Hazard Designation

The EPA reproductive toxicity hazard summary apparently supports a High hazard designation based on NOAELs of 4.75 mg/kg bw-day and 47.5 mg/kg bw-day for male and females rats, respectively. These values are attributed to the "conclusions of NTP (2008)."[12] However, a complete review of the record related to these values does not support the use of the specific values or the High hazard designation.

The draft hazard assessment document also provides no other basis to support the proposed High hazard designation. To the contrary, the "best information available," which EPA asserts is to be used as the basis for hazard designations, supports at most a Moderate reproductive toxicity hazard designation.

a. Primary Study Data Supports a Moderate Reproductive Toxicity Hazard Designation

The NOAELs cited in the EPA hazard summary are derived from a three-generation reproduction study in rats reported by Tyl et al. (2002).[13] As a dietary study, the precise exposure values were reported as parts per million of BPA in the diet (i.e., 0, 0.015, 0.3, 4.5, 75, 750 and 7500 ppm). Actual intakes of BPA were reported by the authors as a range of 37.6 to 167.2 mg/kg bw-day (for male rats at the 750 ppm dietary dose) since intake "was dependent on the age and sex of the animals and the phase of the study." The 750 ppm dose level was reported by the authors as ~50 mg/kg bw-day and the value 47.5 mg/kg bw-day does not appear anywhere in the published paper. Rather, the NTP-CERHR expert panel reported the value as 47.5 mg/kg bw-day. Neither the NTP-CERHR expert panel report nor EPA's draft hazard assessment report provide any basis to support the 4.75 and 47.5 mg/kg bw-day values, an explanation of how they were derived, or any basis to justify why these values should override the values derived in the study itself. Given the inherent imprecision of the intake values, there is no sound basis to deviate from the intake values reported by the authors of the study or to suggest a more precise intake value.

For male reproductive toxicity, the authors reported a NOAEL of 750 ppm (~50 mg/kg bw-day), not 75 ppm (~5 or 4.75 mg/kg bw-day) as indicated in the EPA hazard summary. As noted in the published paper and the NTP-CERHR expert panel report, preputial separation (PPS) was

[12] NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. National Toxicology Program, U.S. Department of Health and Human Services, Center for the Evaluation of Risks to Human Reproduction, NIH Publication No. 08-5994. September 2008.

[13] Tyl, R.W., Myers, C.B., Marr, M.C., Thomas, B.F., Keimowitz, A.R., Brine, D.R., Veselica, M.M., Fail, P.A., Chang, T.Y., Seely, J.C., Joiner, R.L., Butala, J.H., Dimond, S.S., Cagen, S.Z., Shiotsuka, R.N., Stropp, G.D., and Waechter, J.M. 2002. Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. Toxicological Sciences. 68(1):121-146.

reported to be delayed at the 750 ppm dose only in the F1 generation, but not in the F2 or F3 generation. Because the observation was not replicated between generations, the study authors assigned the male reproductive NOAEL as 750 ppm rather than 75 ppm.

Although the NTP-CERHR expert panel created the 4.75 and 47.5 mg/kg bw-day dose levels, and reported PPS results for each generation, NTP itself did not follow this approach. The NTP report stated "Delayed puberty in male rats treated during development has also been reported at oral doses of ≥ 50 mg/kg bw/day *(37, 42)*." The key citation supporting this statement is (37), which is the Tyl et al. (2002) study.[13] Thus, NTP agreed with the study authors that the appropriate NOAEL for male reproductive toxicity in this study is 50 mg/kg bw-day.

In addition to NTP, various regulatory agencies that have reviewed the Tyl et al. (2002) study in detail have all accepted the 50 mg/kg bw-day NOAEL for male reproductive toxicity. These include the European Food Safety Authority,[22] the European Union risk assessment,[7] and the Japanese risk assessment.[8] Perhaps most notably, since EPA has acknowledged that FDA has the lead in making human health judgments on BPA, FDA has accepted the 50 mg/kg bw-day NOAEL for male reproductive toxicity, stating "FDA calculated the following NOAELs for the study…Reproductive: 750 ppm (50 mg/kg bw/day)."[5] In fact, even the EPA Action Plan[4] acknowledges this NOAEL by stating "There is general agreement that BPA is a reproductive and developmental toxicant at doses in animal studies of > 50 mg/kg-bw/day (delayed puberty in male and female rats and male mice)."

The reproductive toxicity summary and hazard profile should be corrected to show NOAELs for male and female reproductive toxicity of 50 mg/kg bw-day. Based on EPA's hazard identification criteria document, these values justify at most a Moderate hazard designation. Since LOAELs and NOAELs are both considered, this value might also support a Low hazard designation since the LOAEL that corresponds to the 50 mg/kg bw-day NOAEL falls in the Low hazard designation according to EPA's hazard evaluation criteria document.[3]

b. Benchmark Dose Analysis Supports a Moderate Reproductive Toxicity Hazard Designation

It should also be noted that the NTP-CERHR expert panel calculated benchmark dose (BMD) values for the various endpoints in the Tyl et al. (2002) study. For the preputial separation (PPS) endpoint (F1, F2 and F3 generations), the various BMD values range from 163 to 547 mg/kg bw-day. As noted in EPA's hazard evaluation criteria document, "When available and appropriate, the results of benchmark dose modeling will also be considered." The BMD values calculated by the NTP-CERHR expert panel would support at most a Moderate hazard designation for reproductive toxicity. Regardless of whether NOAEL, LOAEL or BMD values are used, the weight of evidence supports a reproductive toxicity hazard designation that is no higher than Moderate.

EPA's hazard identification criteria document[3] calls for reliance on "… the best information available, both experimental and modeled." As an example, the criteria document states: "When available and appropriate, the results of benchmark dose modeling will also be considered." In light of these statements, it is quite surprising that EPA completely ignored an array of benchmark dose (BMD) values for the Tyl et al. (2002) study that were reported in the NTP-CERHR expert panel report on BPA.

The Tyl et al. (2002) study is based on a comprehensive and rigorous experimental design, including an approximate 6-orders of magnitude dose range. However, limiting the reproductive effects designation to only dose-specified NOAEL values fails to take advantage of the superior BMD methodology for establishing a more accurate estimate of the no adverse effect level. The BMD methodology is well suited for this purpose and therefore must be utilized over the NOAEL approach since it better informs decision making.[14,15]

> "The benchmark dose (BMD) approach…incorporates and conveys more information than the No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect level (LOAEL) process traditionally used for noncancer health effects."[14]

EPA's BMD approach has relied heavily upon Allen et al. (1994a and 1994b), who reported that the BMD_{05} estimates were comparable to NOAELs for developmental endpoints. As explained below, the NOAEL estimates taken from Tyl et al. (2002)[13] are somewhat uncertain due to issues around pre-selected and fixed dose spacing and the fact that monotonic changes in reproductive parameters do not begin until well after the 47.5 mg/kg/day dose level.[16] As explained by EFSA (2009):[15] "The BMD approach is of particular value for i) situations where the identification of a NOAEL is uncertain,"

Because of the dose-spacing and the high-dose (e.g., 475 mg/kg/day) biological response to BPA, there exists significant uncertainty in simply selecting a NOAEL based only on the nominal dosage. The true point of departure probably lies between the no effect and the adverse effect levels and is higher than the available NOAEL values. In fact, the NTP-CERHR expert panel apparently recognized this issue and provided BMD estimates (see following table taken from the NTP-CERHR expert panel report).

In regard to the data in the following table, as noted above, none of the NOAEL or LOAEL values appear in the published study. Rather the specific values were reported by the NTP-CERHR expert panel report and neither the NTP-CERHR expert panel report nor EPA's draft

[14] Benchmark Dose Technical Guidance. Risk Assessment Forum. EPA/100/R-12/001. June 2012.
[15] European Food Safety Authority. Scientific Opinion. Use of the benchmark dose approach in risk assessment. Guidance of the Scientific Committee. The EFSA Journal. 1150:1-72.
[16] Note that the doses cited in this section (4.75, 47.5 and 475 mg/kg bw-day) are taken from the NTP-CERHR expert panel report. As discussed in the previous section, the correct doses reported in Tyl et al. (2002) study are slightly higher (5, 50, and 500 mg/kg bw-day).

hazard assessment report provide any basis to support these values, an explanation of how they were derived, or any basis to justify why these values should override the values derived in the study itself. The most appropriate NOAEL and LOAEL values are those from the study itself, which were reported as 5, 50, or 500 mg/kg bw-day.

Reproductive Endpoints, NOAELs, LOAELs, and BMD/BMDL Estimates

	Dose (mg/kg/day)					
Endpoint	**NOAEL**	**LOAEL**	**BMD_{10}**	**$BMDL_{10}$**	**BMD_{1SD}**	**$BMDL_{1SD}$**
Live F2 pups/litter	47.5	475	268	192	559	394
Live F2 pups/litter	47.5	475	422	152	459	294
Live F3 pups/litter	47.5	475	236	174	376	286
F1 BODY WEIGHT, PND4	47.5	475	406	283	561	400
F1, F2 or F2 body weight PND7	47.5	475	217-328	183-257	265-410	218-313
F1, F2 or F2 body weight PND14	47.5	475	183-243	163-209	177-227	153-191
F1, F2 or F2 body weight PND21	47.5	475	208-252	166-226	223-267	175-220
↑ Age at F1 vaginal opening	47.5	475	394	343	206	176
↑ Age at F2 vaginal opening	47.5	475	404	336	277	228
↑ Age at F2 vaginal opening	47.5	475	471	401	396	203
↑ Age at F1 preputial separation	4.75	47.5	466	411	188	163
↑ Age at F2 preputial separation	47.5	475	300	255	241	203
↑ Age at F3 preputial separation	47.5	475	547	473	222	189
Mating, fertility, pregnancy, or gestational indices; precoital interval, postimplanation loss, estrous cyclicity and reproductive organ histopathology and organ histopathology; sperm count, morphology or motility;	>475 (high dose)					

The NTP-CERHR report provided two BMD estimates:

1. The BMD based on a 10% response rate (BMD_{10}/$BMDL_{10}$)
2. BMD 1-Standard Deviation based on the point of departure that differs from the controls (BMD_{1SD}/$BMDL_{1SD}$).

The "L" in both estimates stands for the lower confidence interval for the BMD estimate and typically extends the BMD estimate below the no effect level.

Typically, the BMD is set at a specified benchmark response rate and is employed for quantal data. When the $BMDL_{10}$ is selected for increased age of preputial separation for the F1 pups, the point of departure was 411 mg/kg/day. For the other endpoints, where multiple 47.5 mg/kg/day NOAELs were reported as for female pups, the $BMDL_{10}$ ranged from 152 to 473 mg/kg/day. Because the developmental endpoints occur over a range of days, a continuous approach assessed by the $BMDL_{1SD}$ is appropriate. Because the top BPA dose just begins to enter the monotonic range, and that the maximal response upon which a benchmark response rate depends has not been achieved, the $BMDL_{1SD}$ may be superior in that it is based on the control and no-effect responses. For delayed F1 preputial separation the $BMDL_{1SD}$ is 163 mg/kg/day. For the other collection of endpoints with a NOAEL of 47.5 mg/kg/day, the $BMDL_{1SD}$ ranged from 153 to 400 mg/kg/day. These BMDL estimates support a Moderate hazard designation reflecting a range of dose-response points of departure between 50 and 250 mg/kg. Finally, as an added measure of conservatism, the BMD/BMDL estimates are corroborated by 4 to 5 dosage levels below the estimated POD where no apparent changes in reproductive parameters were observed.

c. "Uncertainty" Provides No Basis for a Reproductive Toxicity Hazard Designation

Similar to the summary paragraph for the carcinogenicity section discussed in Section 2 above, the summary paragraph for the reproductive effects section of the BPA hazard profile refers to "considerable uncertainty" regarding effects reported in recent studies at oral doses < 5 mg/kg bw-day. As for carcinogenicity, uncertainty is not the same as hazard and provides no basis for any reproductive toxicity hazard designation.

4. The Weight of Evidence Supports a Moderate or Low Developmental Toxicity Hazard Designation

The EPA developmental toxicity hazard profile apparently supports the proposed High hazard designation based on "suggestive evidence" for neural and behavioral alterations, as reported in the NTP-CERHR and FAO/WHO reports. The specific comments from these reports clearly indicate effects reported at low doses in certain studies are associated with a high level of

uncertainty. The hazard designation is then characterized as "High concern, with a lower confidence."

However, the meaning of "High concern, with a lower confidence" is not at all clear, nor is it clear on what it is based. The EPA hazard evaluation criteria document[3] does not have such a designation. Furthermore, the criteria document sets general requirements for use of the GHS criteria and data evaluation approach, EPA risk assessment guidance, and EPA HPV Challenge Program and OECD HPV Programme data adequacy guidelines. With application of these requirements, it is not clear how "suggestive evidence" with high uncertainty can support any hazard designation. Indeed, no regulatory agency worldwide that has reviewed BPA in detail has concluded with a developmental toxicity NOAEL/LOAEL that would justify a High hazard designation. From the documentation provided in the draft alternatives assessment report, it is likewise clear that EPA cannot justify a High hazard designation either.

a. EPA's Draft Hazard Profile for BPA is Outdated and Fails to Incorporate Recent and Highly Relevant Studies

As noted in EPA's hazard evaluation criteria document,[3] "DfE uses the best information available," and "When gathering data for evaluation under these criteria, a review of the open literature including published peer-reviewed studies and government reports … will be conducted." It is apparent from the BPA developmental effects hazard profile, at least, that EPA has failed to use the best information available and has not reviewed readily available published studies and government reports.

Specifically regarding the "suggestive evidence for neural and neurobehavioral alterations," significant studies have been conducted subsequent to the completion of the NTP-CERHR report, including data from EPA's own laboratory. None of these studies are included in the developmental effects hazard profile. For neural and neurobehavioral effects, which appears to be the basis for a High developmental toxicity hazard designation, the new data would support a Low hazard designation.

Research conducted by EPA was designed to address concerns related to potential induction of sexually dimorphic changes attributable to BPA exposures of rats in the low dose range.[17] In addition to a wider range of test endpoints, one of the relevant features of this study was the use of well-characterized sexually dimorphic behaviors that are influenced by estrogens during development of female offspring. Exposure of rat dams to 0, 2, 20 or 200 µg/kg bw/day of BPA by oral gavage during gestation and lactation did not affect sexually dimorphic behavior (saccharin preference, lordosis, locomotory activity) in female offspring. There were also no effects on age of puberty (anogenital distance; vaginal opening), fertility or on malformations of

[17] Ryan, B. C., Hotchkiss, A. K., Crofton, K. M., and Gray Jr., L. E. 2010. 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. Toxicological Sciences. 114(1):133-148.

the external genitalia indicative of estrogen-mediated effects. These findings indicate that regardless of whether histological changes in sexually dimorphic endpoints can be demonstrated in rats at this dose range, such findings do not appear to hold any behavioral or reproductive consequences.

Of particular note with respect to EPA's hazard criteria document is a recently published developmental neurotoxicity study (DNT) on BPA.[18] This DNT study, conducted in accordance with harmonized OECD/US EPA guidelines, administered BPA at dietary concentrations of 0, 0.15, 1.5, 75, 750 and 2250 ppm daily from gestation day 0 to lactation day 21. There were no treatment-related effects on parameters of the Functional Observational Battery, learning and memory, and brain and nervous system neuropathology and brain morphometry in the offspring of Sprague Dawley rats. Thus, there was no evidence that BPA was a developmental neurotoxicant in rats. The NOAEL was the highest dose tested (164 and 410 mg/kg bw/day) for the gestation and lactation phases, respectively. According to EPA's hazard designation criteria, this study supports a Low hazard designation.

A second high quality study is a two-generation reproduction study that included behavioral tests on offspring.[19] No effects were found on any of the behavioral parameters tested. Although the study examined low doses only (0.2-200 µg/kg/day), these results are consistent with the results of the guideline DNT study and provide strong supporting evidence for a Low hazard designation.

Most recently, investigators with the US FDA laboratory at NCTR focused their investigation on examination of developmental effects that may manifest during the early pre-weaning[20] and postweaning[21] periods. Sprague Dawley rats were orally gavaged on gestational days 6-21 with 2.5 or 25 µg/kg/day BPA. Offspring were orally administered the same dose that the dam received on postnatal days 1 – 21. The authors conclude "These results add to the literature indicating that developmental BPA treatment at these doses has no effects on gestational or lactational body weight, offspring anogenital distance, preweaning behaviors or hormone levels, and whole and regional brain weights measured at weaning."[20] and "[i]n summary, oral BPA treatment during gestation followed by direct oral treatment of the offspring until weaning had no consistent or dose-related effects on those behaviors typically assessed in developmental neurotoxicology studies. ... These results add to a growing body of literature

[18] Stump, D. G., Beck, M. J., Radovsky, A., Garman, R. H., Freshwater, L. L., Sheets, L. P., Marty, M. S., Waechter, J. M., Dimond, S. S., Van Miller, J. P., Shiotsuka, R. N., Beyer, D., Chappelle, A. H., and Hentges, S. G. 2010. Developmental neurotoxicity study of dietary bisphenol A in Sprague-Dawley rats. Toxicological Sciences. 115(1):167-182.

[19] Ema, M., Fujii, S., Furukawa, M., Kiguchi, M., Ikka, T., and Harazono, A. 2001. Rat two-generation reproductive toxicity study of bisphenol A. Reproductive Toxicology. 15:505-523.

[20] Ferguson, S. A., Law, C. D., and Abshire, J. S. 2011. Developmental treatment with bisphenol A or ethinyl estradiol causes few alterations on early preweaning measures. Toxicological Sciences. 124(1):149-160.

[21] Ferguson, S. A., Law, C. D., and Abshire, J. S. 2012. Developmental treatment with bisphenol A causes few alterations on measures of postweaning activity and learning. Neurotoxicology and Teratology. In Press.

indicating that oral BPA treatment during development does not have substantial behavioral effects in rodents."[21]

These studies, robust in design and conducted largely in response to concerns expressed by the NTP-CERHR report, substantially mitigate the concerns that "BPA causes neural and behavioral alterations related to disruptions in normal sex differences in rats and mice (0.01 – 0.2 mg/kg bw-day)." These studies support a Low developmental hazard designation and must be included in the BPA hazard profile.

a. EPA's Developmental Toxicity Designation for BPA is Inconsistent with Numerous Agencies Worldwide That Have Comprehensively Reviewed the Scientific Evidence

As noted previously, FDA has the lead in making human health judgments on BPA and FDA's lead should also be applied to the developmental hazard designation. From FDA's extensive documentation, a NOAEL of 50 mg/kg bw-day would result in a Moderate developmental hazard designation. This value is also consistent with the many regulatory agencies worldwide that have reviewed BPA in detail (e.g., European Food Safety Authority, European Union risk assessment, Japanese risk assessment).

As with carcinogenicity, neurodevelopmental toxicity has been comprehensively reviewed by several regulatory agencies worldwide. For example, the overall conclusion from the European Union risk assessment, as updated in 2008,[7] states:

> "Overall, taking together the low confidence in the reliability of the developmental neurotoxicity studies and the lack of consistency in the results of behavioural testing, no conclusions can be drawn from these studies. This opinion is very similar to that of EFSA (2006), who reviewed nine of the developmental neurotoxicity studies."

More recently, the European Food Safety Authority also comprehensively evaluated all available relevant evidence[22] and concluded:

> "The Panel also stated that the data currently available do not provide convincing evidence of neurobehavioural toxicity of BPA."

5. New Data Should Be Incorporated Into the Hazard Profile

While it is understood that the hazard profile is not intended to be an all-inclusive report, the profile and resulting hazard designations would benefit from inclusion of certain significant new studies. EPA's failure to include significant studies that were readily available when the draft report was released is further evidence that EPA is not relying on "the best information

[22] See http://www.efsa.europa.eu/en/topics/topic/bisphenol.htm.

available" and has not "reviewed the open literature" as stated in EPA's alternatives assessment criteria document.[3]

Along with several studies discussed in the sections above, one example is the updated Japanese risk assessment,[9] which should be included in the Risk Assessment section on page 4-33 of the draft alternatives assessment report. Another section that would benefit from new data is the section on Adsorption, Distribution, Metabolism & Excretion (ADME), on page 4-36. In particular the recent studies conducted by FDA should be included here,[23,24,25,26,27,28,29] along with a recent PBPK model study.[30] The findings from these studies should be incorporated into the ADME hazard profile section.

In contrast to the studies that should be included, but were not, one secondary source of information was included, but should not have been. Specifically, in both the Acute and Chronic Toxicity sections of the Ecotoxicity hazard profile, Wright-Walters et al. (2010)[31] is frequently cited as the source of data presented in these sections. As described in a recent letter to the editor,[32] this paper has numerous flaws and mistakes and should not be cited at all in the BPA hazard profile. It should be removed.

[23] Doerge, D. R., Twaddle, N. C., Vanlandingham, M., and Fisher, J. W. 2010. Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats. Toxicology and Applied Pharmacology. 247(2):158-165.
[24] Doerge, D. R., Vanlandingham, M., Twaddle, N. C., and Delclos, K. B. 2010. Lactational transfer of bisphenol A in Sprague-Dawley rats. Toxicology Letters. 199(3):372-376.
[25] Doerge, D. R., Twaddle, N. C., Woodling, K. A., and Fisher, J. W. 2010. Pharmacokinetics of bisphenol A in neonatal and adult rhesus monkeys. Toxicology and Applied Pharmacology. 248(1):1-11.
[26] Doerge, D. R., Twaddle, N. C., Vanlandingham, M., Brown, R. P., and Fisher, J. W. 2011. Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague-Dawley rats. Toxicology and Applied Pharmacology. 255(3):261-270.
[27] Doerge, D. R., Twaddle, N. C., Vanlandingham, M., and Fisher, J. W. 2011. Pharmacokinetics of bisphenol A in neonatal and adult CD-1 mice: Inter-species comparisons with Sprague-Dawley rats and rhesus monkeys. Toxicology Letters. 2-7(3):298-305.
[28] Doerge, D. R., Twaddle, N. C., Vanlandingham, M., and Fisher, J. W. 2012. Pharmacokinetics of bisphenol A in serum and adipose tissue following intravenous administration to adult female CD-1 mice. Toxicology Letters. 211(2):114-119.
[29] Fisher, J. W., Twaddle, N. C., Vanlandingham, M., and Doerge, D. R. 2011. Pharmacokinetic modeling: Prediction and evaluation of route dependent dosimetry of bisphenol A in monkeys with extrapolation to humans. Toxicology and Applied Pharmacology. 257(1):122-136.
[30] Mielke, H., Partosch, F., and Gundert-Remy, U. 2011. The contribution of dermal exposure to the internal exposure of bisphenol A in man. Toxicology Letters. 204(2-3):190-198.
[31] Wright-Walters, M., Volz, C., Talbott, E., and Davis, D. 2011. An updated weight of evidence approach to the aquatic hazard assessment of bisphenol A and the derivation a new predicted no effect concentration (Pnec) using a non-parametric methodology. Science of the Total Environment. 409(4):676-685.
[32] Hentges, S., Caspers, N., Klecka, G. M., Mihaich, E. M., Ortego, L., and Staples, C. A. 2012. Letter to the editor (Wright-Walters et al., 2011). Science of the Total Environment. In Press.