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February 6, 2006

Dr. Michael D. Shelby
CERHR Director, NIEHS
P.O. Box 12233
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Research Triangle Park, NC 27709

Sent as e-mail attachment to: Shelby@niehs.nih.gov

Re: Information and comments in regard to the CERHR expert panel evaluation of bisphenol A

Dear Dr. Shelby:

I am pleased to provide these comments on behalf of the Polycarbonate Business Unit (PCBU) of the American Plastics Council in regard to the upcoming CERHR expert panel evaluation of bisphenol A. The PCBU represents the leading global manufacturers of bisphenol A and polycarbonate plastic, who for many years have supported and conducted scientific research to understand whether bisphenol A has the potential to cause health or environmental effects and to support scientifically sound public policy.

We have also supported critical reviews by scientific experts of the many studies relevant to whether bisphenol A has the potential to cause health or environmental effects. When properly conducted, such reviews can be of high value to support public policy, guide future research and reduce controversy. Consequently, our comments are provided in the spirit of promoting a well-conducted and scientifically sound expert panel evaluation of the scientific evidence regarding the potential reproductive and developmental toxicity of bisphenol A.

Our comments are divided into two sections. The first section (Attachment 1) describes key aspects of a weight-of-evidence framework that we believe is essential for an evaluation of a scientifically complex data base, as is the case with bisphenol A. The second section (Attachment 2) provides scientific information on bisphenol A that is within the scope of CERHR's evaluation.

Please do not hesitate to contact me if I can be of further assistance to clarify any of the information provided or if additional information is needed. I can be reached at (703) 741-5588 or by e-mail at steve_hentges@plastics.org.

Regards,

Steven G. Hentges, Ph.D.
Attachments

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ATTACHMENT 1

Key Aspects of a Weight of Evidence Framework for the Evaluation of Bisphenol A

Submitted to the
National Toxicology Program, Center for the
Evaluation of Risks to Human Reproduction (CERHR)
in regard to the
CERHR Expert Panel Evaluation of Bisphenol A

February 6, 2006

Key Aspects of a Weight of Evidence Framework for the Evaluation of Bisphenol A

1. Introduction

A complete understanding of the potential risks of bisphenol A (BPA) to reproduction and development requires, at a minimum, detailed knowledge of several areas of research.

- Metabolism and pharmacokinetics
- Human exposure
- Reproductive and developmental toxicity

Bisphenol A is one of the best studied of all substances and each of these areas includes a large number of published studies, which vary substantially in size, scope, quality and relevance to human health. Considering the large number of studies it is not surprising that some inconsistent results have been reported, in particular from studies that examine low doses of BPA.

Given the large number and diversity of studies, it is of particular importance for the expert panel to apply a weight of evidence approach to systematically review and critically analyze the studies, leading to transparent conclusions based on all of the relevant evidence. The panel should be allowed adequate time to conduct a thorough and comprehensive evaluation rather than a cursory overview with inadequate analysis to support sound conclusions.

The need for a rigorous weight of evidence approach was highlighted in a November 2005 report from the EU Scientific Committee on Health and Environmental Risks, which noted that reported BPA low-dose effects have not been reproduced.[1] The committee recommended that "assessment of such effects requires a rigorous and science based weight-of-the-evidence approach, which needs to consider that the findings at low doses represent changes without, or, at best, unknown toxicological significance."

It is likely that the expert panel will evaluate many types of studies ranging from *in vitro* studies to multi-generational studies. The findings reported in these studies will likewise cover a wide range. The panel must distinguish between toxicological effects and other physiological responses that do not result in an adverse effect. The panel must also distinguish between studies that may be relevant to human health and those that are of little or no relevance.

[1] Scientific Committee on Health and Environmental Risks. Opinion on Endocrine Disrupting Chemicals: a Non-animal Testing Approach. November 25, 2005. Available on the Internet at http://europa.eu.int/comm/health/ph_risk/committees/04_scher/docs/scher_o_015.pdf.

2. Weight of Evidence Framework

A suitable weight of evidence framework includes the analytical elements described below.[2]

Elements Focused on Internal Validity

- Rigor – Studies should be evaluated for their proper conduct and analysis. Greater weight should be given to better-conducted studies. Some studies may have been performed so poorly that their results should be substantially or entirely discounted.

  Additional weight should be given to studies conducted under Good Laboratory Practice (GLP) regulations or principles, which would be followed by any studies submitted by industry for regulatory purposes. Extensive monitoring, auditing, and quality assurance are integral parts of the GLP process, resulting in increased reliability of data from GLP studies. Numerous other aspects of GLP should be part of any good scientific practice (e.g., written protocol with justification for the study design and test methods, standard operating procedures, data collection records, data retention procedures, confirmation of dose administered, independent quality assurance review). These aspects may not exist or may not be readily determined from published non-GLP studies.

- Power – The statistical power of an experimental design should be examined for its ability to detect effects of a given magnitude. Studies of higher statistical power should be given higher weight over studies of lower statistical power that are otherwise comparable.

- Corroboration – The replication of findings among similar studies and the observation of similar effects under relevant conditions increases the confidence that the findings represent a real effect in experimental animals. Replication is a fundamental principle of the scientific process. Conversely, lack of corroboration is grounds to doubt the validity of single experimental results. In a multi-generational study, an exposure-related effect should appear across generations.

Elements Focused on External Validity

- Universality – The degree to which an effect is consistently reproduced in valid test systems increases the confidence that it applies to humans. In contrast, if an effect is restricted to a certain species, strain, or route of administration, the ability to generalize the response to other species or routes becomes more questionable.

[2] Gray, G. M., Baskin, S. I., Charnley, G., et al. 2001. The Annapolis accords on the use of toxicology in risk assessment and decision-making: An Annapolis Center workshop report. Toxicological Methods. 11(3):225-231.

- Proximity – When effects have been shown in a species similar to humans or at a dose level similar to that expected in humans, such results weigh more heavily than those in dissimilar species, by inappropriate routes, or at markedly different dose levels. In this regard, the significant differences in the metabolism and pharmacokinetics of bisphenol A between different routes of exposure and between rodents and humans must be taken into account. In humans, the oral route of exposure is most relevant. By this route, bisphenol A is subject to complete first-pass metabolism to a biologically inactive metabolite that is then rapidly eliminated in urine.

- Relevance – From what is known about the underlying biological basis for a toxic response in animals, it may be possible to judge (based on knowledge of animal and human physiology) whether similar metabolism, mechanisms of damage and their repair, and molecular targets of action should be expected to operate in humans. Confidence in applicability to humans can increase or decrease accordingly.

- Cohesion – The extent to which all of the data are consistent and are subject to a single, biologically plausible explanation increases weight compared to a situation where inconsistencies require ad hoc explanations and exceptions to general patterns. A common hypothesis is that bisphenol A acts via an estrogenic mode of action at low doses to cause adverse effects. The weight of evidence analysis must look for and demonstrate a replicable pattern of estrogenic effects across the many studies. Lack of a consistent pattern of effects significantly reduces the biological plausibility of the hypothesis that bisphenol A causes reproductive and developmental effects at low doses.

ATTACHMENT 2

Bisphenol A Safety Overview

Submitted to the
National Toxicology Program, Center for the
Evaluation of Risks to Human Reproduction (CERHR)
in regard to the
CERHR Expert Panel Evaluation of Bisphenol A

February 6, 2006

Bisphenol A Safety Overview

1. What Is Bisphenol A and How It Is Used

Bisphenol A (BPA) is a chemical building block used primarily to make polycarbonate plastic and epoxy resins. The unique attributes of these materials make them ideal for use in a wide variety of products, many of which improve the health and safety of consumers. Both materials have a long history of safe use, more than 50 years, and an equally long history of testing to support the safety of these products.

Polycarbonate is a lightweight, heat-resistant and nearly shatter-proof plastic that is as clear as glass. Examples of the many uses of polycarbonate include:

- Shatter-resistant food storage containers, bottles and tableware. The transparency of polycarbonate makes it easy to check on the contents or cleanliness of a container while eliminating the risk of injury from broken glass.
- Corrective eyeglass lenses are lightweight and virtually unbreakable.
- Sports safety equipment, such as bicycle helmets, visors and goggles, provide protection from injury while being lightweight and comfortable to wear.
- Many home appliances and electronic equipment, ranging from cell phones and computers to food processors and hairdryers are safer and more durable due to the shatter-resistance, heat-resistance and electrical insulating properties of polycarbonate. In addition, optical media (i.e., CDs, DVDs) are made from polycarbonate.
- Polycarbonate sheets are used as paneling and glazing wherever people and property need to be protected from injury and damage, for example factory safety guards, hockey rink sideboard panels, and bullet-resistant windows in banks.

Epoxy resins have an exceptional combination of toughness, chemical resistance and adhesion, which makes them particularly useful as protective coatings in a wide variety of applications. Most notably, epoxy resins provide an invaluable public health benefit as the coating on the interior surface of most metal food and beverage cans. The coating provides an essential public health benefit by preventing corrosion of the can and contamination of food. In addition to protecting contents from spoilage, these coatings make it possible for food products to maintain their quality and taste, while extending shelf life.

2. Government Bodies Worldwide Support the Safety of BPA

The scientific evidence supporting the safety of BPA has been repeatedly and comprehensively examined by government bodies worldwide in recent years. In each case, these assessments support the conclusion that BPA is not a risk to human health at the extremely low levels to which people might be exposed.

Key examples of the most recent government assessments are described below:

- **US Food and Drug Administration (FDA) - 2005**
  In response to a request from the California legislature, FDA provided their views on the safety of polycarbonate plastic and epoxy resins in contact with food and beverages[1] (emphasis added):

  > "However, **based on all the evidence available at this time**, FDA sees no reason to change its long-held position that **current uses with food are safe**."

  Likewise, in regard to the proposed product bans, FDA stated:

  > "**Considering all the evidence**, including measurements by FDA chemists of levels found in canned foods or migrating from baby bottles, **FDA sees no reason at this time to ban or otherwise restrict the uses now in practice**."

- **Japanese Ministry of Economy, Trade and Industry (METI) – 2005**
  A comprehensive risk assessment report on BPA was published by the Research Center for Chemical Risk Management of the National Institute of Advanced Industrial Science and Technology, which is an independent institution associated with METI, in November 2005.[2] Based on a thorough review of safety and exposure information, **the key conclusions of the report confirm no risk of BPA to human health, including infants and children. A No Observed Adverse Effect Level of 50 mg/kg-bodyweight/day was established for reproductive and developmental toxicity based on the results of a multi-generation study in laboratory animals.** No adjustment was made for claimed low-dose effects because the findings in the low-dose studies were not robust, while those in negative studies were consistent. Based on this report, no risk management actions have been proposed for polycarbonate plastic or epoxy resin products.

- **Japanese Ministry of Environment (MOE) – 2005**
  After conducting their own tests on BPA, including a comprehensive reproduction test in laboratory animals, **MOE concluded there were no clear endocrine disrupting effects found at low doses and that no regulatory action is required to manage risks**.[3]

- **EU Risk Assessment Report – 2003**
  A comprehensive risk assessment report on BPA was published by the European Union in 2003.[4,5] Based on a thorough review of safety and exposure information,

the key conclusions of the risk assessment confirm low risk of BPA to human health, including use of polycarbonate plastic and epoxy resins in consumer products. The report established a No Observed Adverse Effect Level of 50 mg/kg-bodyweight/day based on the results of a multi-generation study in laboratory animals. Based on this report, no risk management actions have been proposed for polycarbonate plastic or epoxy resin products.

- **EU Scientific Committee on Toxicity, Ecotoxcity and the Environment (CSTEE) – 2002**
  The CSTEE is an independent expert scientific committee that reviews risk assessment reports before they are published in final form. **Their detailed opinion affirmed the key conclusions of the BPA risk assessment report**.[6] This independent scientific review confirms that the results of the risk assessment report are valid.

- **EU Scientific Committee on Food (SCF) – 2002**
  The SCF is an independent scientific committee that advises the European Union on food safety matters. In April 2002 the SCF published their detailed assessment of BPA focused on food contact applications of polycarbonate plastic and epoxy resins.[7] After comprehensively reviewing both safety and exposure information, the SCF concluded that worst-case human exposures to BPA are well below their Tolerable Daily Intake (TDI) for BPA. The TDI was conservatively based on the results of a multi-generation study in laboratory animals and is intended to protect against harmful effects over a lifetime. **These conclusions support the continued safe use of polycarbonate plastic and epoxy resins in contact with food and beverages.**

- **US National Toxicology Program (NTP) – 2001**
  The NTP conducted a scientific peer review of the evidence for reproductive and developmental effects from exposure to low doses of chemicals, specifically including BPA. The overall conclusion of this review confirmed that "**low-dose" effects for BPA have not been conclusively established as a general or reproducible finding**."[8] This conclusion, which supports the safety of BPA, has been affirmed in each of the more recent reviews described above.

3. Safety of Bisphenol A Confirmed by the Weight of Scientific Evidence

Along with more than 50 years of safe use, BPA has an equally long history of testing to support the safety of polycarbonate plastic and epoxy resins. **The weight of scientific evidence demonstrates that BPA is not a risk to human health at the extremely low levels to which people might be exposed.**

A complete understanding of the safety of BPA requires detailed knowledge of several areas of research: metabolism and pharmacokinetics, toxicity, and human exposure.

A. Metabolism and Pharmacokinetics

Pharmacokinetics describes the processes by which a substance is absorbed, distributed, metabolized and eliminated from the body. These parameters have a substantial influence on the potential for a substance to cause adverse health effects since they determine whether and where a substance is present in the body, in what form it is present, and for how long. For example, substances that are poorly absorbed or rapidly eliminated will have a lower potential to cause adverse health effects because the substance has only a limited presence in the body. Similarly, metabolism is often a way for the body to convert a potentially toxic substance into a non-toxic metabolite that can be readily eliminated, thus reducing the potential to cause adverse health effects while in the body.

The pharmacokinetics and metabolism of BPA have been very well characterized in numerous animal studies (i.e., rodents and primates) and in several studies on human volunteers. **Overall, these studies indicate that BPA has a low potential to cause adverse health effects in humans and, in particular, estrogenic effects.**

Key findings from these studies are summarized below:

- **Humans Efficiently Metabolize and Eliminate BPA from the Body**
  Human volunteer studies confirm that BPA is efficiently converted to a metabolite (BPA-glucuronide) after oral exposure.[9,10,11] Studies in animals and with isolated liver cells have shown that this metabolic process occurs in the intestinal wall[12] and in the liver,[13,14,15,16] both of which are passed before BPA can enter into circulation in the body after absorption. As a result, **the human body has two layers of protection to prevent any significant amount of BPA from entering the body.**

  The efficiency of this metabolic process was highlighted by the first human study in which the volunteers were treated with 5 mg of BPA per person in a single dose. This dose is approximately 1000 times greater than a typical daily intake of BPA, which has been measured at approximately 1-2 µg/day or 0.001-0.002 mg/day (see below). Both blood and urine were monitored to determine the fate of BPA in the body. No parent BPA was found in blood at any time point and all BPA was excreted in urine as the glucuronide metabolite. **The half-life for**

elimination is approximately 4 hours, which means that any BPA to which people are exposed will be eliminated from the body within a day.[9]

- **BPA Does Not Accumulate in the Body and has Low Bioavailability**
  The human volunteer studies confirm that BPA has very low bioavailability in humans (i.e., very little, if any, BPA will reach tissues) since **little, if any, BPA actually enters circulation in the body. In addition, the rapid elimination of BPA indicates that BPA does not bioaccumulate in the body.**[9,10]

  Low bioavailability, efficient metabolism of BPA to the glucuronide, and low potential to bioaccumulate have also been demonstrated in numerous studies on laboratory animals, some of which are cited here.[17,18,19,20,21,22,23]

- **Human Metabolism and Elimination of BPA is More Efficient than Rodents**
  By excretion of the BPA-glucuronide metabolite into urine, humans more efficiently eliminate BPA from the body compared to rodents, which predominately excrete the metabolite in bile.[24,25] With biliary excretion into the intestine, BPA can be reabsorbed and pass through the body multiple times before eventual elimination, a phenomenon known as enterohepatic recirculation. In addition, studies on isolated liver cells from rodents and humans have shown that humans have significantly greater hepatic capacity to metabolize BPA to the glucuronide compared to rodents.[13]

  These differences indicate that humans are likely to be less sensitive, compared to rodents, to any potential effects from a given dose of BPA, which suggests caution in extrapolating from rodent toxicity tests to humans.

- **Metabolism of BPA is Not Altered during Pregnancy**
  The metabolism and pharmacokinetics of BPA in pregnant laboratory animals after oral dosing were not substantially different compared to non-pregnant animals.[26] These results indicate that pregnancy does not inhibit the efficient metabolism and rapid excretion of BPA, and that BPA does not bioaccumulate during pregnancy. Consequently, **pregnant women are not expected to be more sensitive to the potential effects of BPA.**

- **Neonates Efficiently Metabolize BPA**
  From early in neonatal life, BPA is efficiently metabolized by laboratory animals to the glucuronide metabolite.[27] These results indicate that **children are also capable of efficiently metabolizing and rapidly eliminating BPA**.

- **BPA Metabolites are Not Estrogenic**
  The primary metabolite of BPA, the glucuronide, has been shown to exhibit no estrogenic activity.[28] Although not expected to be present at any significant level, the BPA sulfate metabolite has also been shown to not exhibit estrogenic activity.[29] These studies indicate that **BPA is not likely to cause estrogenic**

effects since the metabolites of BPA that actually enter the body have no known biological activity and, in particular, have no estrogenic activity.

- **Non-Oral Routes of Exposure Are of Limited Relevance to Humans**
  Studies in laboratory animals show a significant difference in the bioavailability of BPA with oral exposure compared to non-oral routes of exposure (citations above). Since non-oral routes of exposure bypass the efficient metabolism of BPA in the intestinal wall and liver, bioavailability with non-oral routes is substantially higher than with oral exposure. Several additional metabolites are also observed after non-oral exposure of laboratory animals to BPA.[30] Since oral exposure is the most relevant route of exposure for humans, these studies indicate that **studies of toxicity or estrogenic potency involving non-oral routes of exposure in laboratory animals are of limited relevance for assessing the safety of BPA in humans**.

B. Human Exposure

As described in the section above on metabolism and pharmacokinetics, BPA is rapidly and entirely excreted by humans in urine in the form of the glucuronide metabolite. Thus, analysis of urine for this metabolite (i.e., biomonitoring) is the most direct way to measure human exposure to BPA. Because the half-life of BPA in the body is only about 4 hours, the amount of BPA found in urine represents recent exposure from the preceding 24 hours or less.

Numerous biomonitoring studies on BPA have been reported by researchers worldwide. These studies consistently indicate that human daily intake of BPA is extremely low and typically in the range of 20-30 nanograms/kg-body weight/day. These levels are about 1,000,000 times below levels where there were no adverse effects in multi-generation animal studies. Similarly, these levels are about 400-2,000 times below lifetime daily intake levels set by government bodies in the US and Europe that are expected to be without adverse effect.

These comparisons indicate a substantial margin of safety between actual and safe exposure levels. **Overall, the biomonitoring data on bisphenol A supports the conclusion that exposure to bisphenol A is extremely low and poses no known risk to human health**.

Key findings from these studies are summarized below:

- **Human Exposure to BPA Confirmed to be Very Low**
  Recently published studies in which human urine samples were analyzed for BPA indicate that exposure to BPA is extremely low, in the range of 1-2 micrograms/day, or 20-30 nanograms/kg-bodyweight/day.

Included are two studies in which urine samples were collected over 24-hour periods.[31,32] The amount of bisphenol A excreted in a 24-hour period is a good estimate of bisphenol A daily intake because of the short half-life of bisphenol A in the body. In one of these studies, the median level of BPA excreted by 36 males was estimated as 1.2 micrograms/day. This study also examined day-to-day variation by collecting 24-hour urine samples for 5 consecutive days for 4 males and 1 female. Although some day-to-day variation was observed, the median value was 1.3 micrograms/day. A second study reported the average level of BPA excreted by 11 males and 11 females to be 1.68 micrograms/day.

Numerous other studies conducted in Japan[33,34,35,36,37], Korea,[38,39] Europe,[40] and the US[41,42,43,44,45,46,47] have reported measurements of BPA in spot samples of urine. The largest study was conducted in the US by the Centers for Disease Control and Prevention. Estimates of daily BPA intake based on these spot sample measurements are generally very consistent with each other and with the 24-hour urine measurements.

Overall, these studies consistently indicate that **typical long-term human exposure to bisphenol A is extremely low and likely to be in the range of 20-30 nanograms/kg-bodyweight/day.**

- **Children's Exposure to BPA is Very Low**
  The results of a study on exposure of preschool children to various chemicals from all environmental sources, including food and beverages, indicate that children are exposed to very low levels. The mean estimated aggregate exposure to BPA was 43 nanograms/kg-bodyweight/day.[48]

- **Consumer Products Contain Very Little BPA**
  The manufacturing processes to make polycarbonate plastic and epoxy resins convert virtually all of the BPA into the plastic or resin, leaving behind only trace levels of residual BPA, typically less than 50 parts per million (0.005% by weight), in the finished material. **Consumers frequently benefit from products made from polycarbonate or epoxy resins, but come into contact with very little BPA from use of these products**.

- **Migration Studies Show Low Potential for Human Exposure**
  Numerous studies have been conducted to examine the potential for BPA to migrate from polycarbonate plastic containers into a food or beverage. Of particular interest are the many studies on polycarbonate baby bottles. The Dutch national Food and Consumer Product Safety Authority recently published their study of the migration of BPA from new and used polycarbonate baby bottles.[49] Their results on new bottles, which represent a wide range of bottles on the market, show no migration from any bottle with a limit of detection of less than 4 parts per billion. The same testing on bottles collected from households where they were used for up to three years showed no detectable migration from most of

the bottles, and only a trace level of migration (3-5 parts per billion) in a few of the bottles.

These levels are far below the safe limits established by the Dutch and EU regulatory authorities and the findings are consistent with many other studies that have been published around the world, of which several examples are cited here, including studies conducted by FDA and UK government researchers.[50,51,52,53,54]

- **Exposure to BPA Poses No Known Risk to Human Health**
  To put the biomonitoring data into perspective, it is helpful to compare typical daily intakes to acceptable daily intakes set by government bodies. These acceptable daily intakes are derived from toxicity studies to which conservative safety factors are applied to estimate lifetime exposure levels that are expected to be without adverse effects.

  The US Environmental Protection Agency has set a Reference Dose of 50 micrograms/kg-bodyweight/day[55] and the European Commission's Scientific Committee on Food has set a Tolerable Daily Intake of 10 micrograms/kg-body weight/day.[7] **A typical daily bisphenol A intake is about 400-2,000 times lower than the levels considered to be safe to government bodies, which indicates a large margin of safety**.

  Typical daily intake values can also be compared directly to doses that have been shown to cause no adverse effects in toxicity studies. **A typical daily intake is about 1,000,000 times lower than levels shown to cause no adverse effects in multi-generation animal studies, which also indicates a large margin of safety.**

  It is notable that actual human exposure levels are well below the "low doses" claimed to cause endocrine effects in animal studies. The "low doses" tested in animal studies are almost all at the level of 1000 nanograms/kg-bodyweight/day or higher, compared to typical human exposure levels of 20-30 nanograms/kg-bodyweight/day.

C. Toxicity and Endocrine Disrupting Effects

A very large number of studies have been reported that examine the potential for BPA to cause toxic effects and, in particular, endocrine disrupting effects. These studies cover a very wide range of study types, sizes and designs. The relevance of many of the reported studies to human health is limited, for example by use of an inappropriate route of exposure. In general though, high-quality comprehensive studies have been conducted that allow a thorough assessment of the potential risk to human health from exposure to BPA.

Given the number and range of studies reported, it is not appropriate to base conclusions on any single study. Rather, a rigorous and science-based weight of evidence assessment is required to fully evaluate the potential for BPA to cause adverse health effects. Such assessments have been conducted by government agencies worldwide, as described in Section 2 of the overview. In addition to the reviews by government agencies, the weight of evidence assessments discussed below are of particular relevance for potential endocrine disrupting effects.

Overall, these many studies and weight of evidence assessments demonstrate that BPA is not a risk to human health at the very low levels of BPA to which humans are exposed. As discussed in the overview, this conclusion is supported by government bodies worldwide.

Key findings from these studies are summarized below:

- **Low Oral Toxicity**
  In general BPA has low oral toxicity in acute, subchronic and chronic studies, with No-Observed-Adverse-Effect-Levels (NOAEL) values at 50 mg/kg/day and higher for repeat dose studies.[4,5]

- **Not Carcinogenic or Mutagenic**
  Life time studies in rats and mice conducted by the US National Toxicology program indicate that BPA is not carcinogenic.[56] The European Union risk assessment report[4,5] concluded "Taking into account all of the animal data available the evidence suggests that bisphenol-A does not have carcinogenic potential" and "Considering all of the available genotoxicity data … it does not appear that bisphenol-A has significant mutagenic potential *in vivo*."

  Similarly, the EU Scientific Committee on Toxicity, Ecotoxicity and the Environment[6] concluded "Based on the overall evaluation of the available data, including those from repeated dose and mutagenicity studies, the CSTEE agrees ... that bisphenol A does not have a significant carcinogenic potential" and "The CSTEE, therefore, agrees with the overall conclusion that bisphenol A has no significant mutagenic potential *in vivo*."

  A recent comprehensive weight-of-evidence review of the potential carcinogenicity of BPA published in a peer-reviewed journal[57] concluded that "BPA is not likely to be carcinogenic to humans" and "BPA is without genotoxic or mutagenic activity *in vivo*." More recently, one study claimed that BPA exposure causes meiotic aneuploidy in the female mouse. However, those results have not been replicated in a comprehensive series of studies sponsored by the EU.[58]

- **Not Teratogenic or a Selective Reproductive Toxicant**

Studies conducted in rats and mice by the US National Toxicology Program indicate that BPA is not teratogenic, meaning it does not cause birth detects or malformations.[59]

As demonstrated by several studies, BPA is not a selective reproductive toxicant. These studies include a continuous breeding study in mice conducted by the US National Toxicology Program,[60] which was confirmed in an abbreviated one-generation study in mice,[61] a three-generation reproductive toxicity study in rats,[62] a two-generation study in rats sponsored by the Japanese Ministry of Health, Labor and Welfare,[63] and, most recently, a one-generation study in rats conducted by the Japanese Ministry of Environment.[64]

- **Estrogenic Effects at Low Doses Not Confirmed**
  BPA has long been known to be weakly estrogenic with estrogenic potency versus estradiol being ~1,000-100,000 times weaker. Estrogenic potency is determined in screening assays that measure a biological property but do not assess whether the substance causes adverse health effects in laboratory animals at relevant exposure levels.

  In recent years, various reproductive and developmental effects have been reported to occur at very low doses in small-scale studies. However, **attempts to replicate key studies reporting low-dose effects have not found the reported effects in independent laboratories**, even though the repeat studies have generally been larger, high quality studies.[65]

  More importantly, **low-dose findings have not been found in the much larger-scale multi-generation studies that follow internationally accepted guidelines and are conducted under Good Laboratory Practices.**[62,63,64] These studies, which follow laboratory animals through multiple generations, are designed to detect adverse health effects and are the studies relied upon by regulatory agencies worldwide to assess safety.

- **Weight of Scientific Evidence Does Not Support Low-Dose Effects**
  In November 2005, the EU Scientific Committee on Health and Environmental Risks (SCHER, which is an independent scientific advisory committee), noted that reported BPA low-dose effects have not been reproduced.[66] The committee recommended that "**assessment of such effects requires a rigorous and science based weight-of-the-evidence approach**, which needs to consider that the findings at low doses represent changes without, or, at best, unknown toxicological significance."

  Consistent with the SCHER recommendation a weight-of-the-evidence evaluation of low-dose BPA reproductive and developmental effects was conducted by an expert scientific panel convened by the Harvard Center for Risk Analysis.[67] The panel reviewed all published studies through April 2002 that examined reproductive and developmental endpoints in laboratory animals at low

doses.[62,63,65a-d,68] The review followed a rigorous analytical framework that considered a series of aspects to evaluate internal validity (i.e., rigor, power, corroboration) and external validity (i.e., universality, proximity, relevance, coherence).

In their overall conclusion, the panel stated **"the weight of evidence for low-dose effects is very weak,** and **"the panel found no consistent affirmative evidence of low-dose BPA effects for any endpoint."**

Between April 2002 and November 2005, more than 50 additional studies that examined reproductive and developmental endpoints in laboratory animals at low doses have been published.[65e,69,70,71,72] These studies have been reviewed using the same rigorous analytical framework used in the initial evaluation.

After review of more than 70 studies plus extensive additional relevant information, a scientific panel of experts drawn from the Harvard panel and elsewhere stated **"Taken together, we conclude that the weight of evidence does not support the hypothesis that low oral doses of BPA adversely affect human reproductive and developmental health."**[73]

All of the data reviewed by the scientific panel is summarized in the attached two tables, which include all available published data on low-dose BPA reproductive and developmental endpoints. In these tables, the symbol "0" indicates a datapoint where no effect was observed. The data is split between oral and non-oral routes of exposure. Since the most relevant route of exposure for humans is oral, and because of the significant pharmacokinetic differences between the different routes of exposure, studies with non-oral exposures are of limited relevance for assessing the safety of BPA for humans. Note that the exposure levels examined in these "low-dose" studies are much higher than actual human exposure, typically by several orders of magnitude.

It can be seen at a glance that **the vast majority of available data shows no effect whatsoever**. There are no endpoints with marked or consistently repeatable effects that occur in a consistent pattern between dose groups and evaluation times. In addition, there is no common pattern of effects among endpoints that would be expected if BPA were functioning with an estrogenic mode of action.

The depth and rigor of these two weight-of-evidence evaluations stand in stark contrast to more simplistic approaches that suggest BPA acts as an endocrine disruptor to cause adverse health effects at low doses. For example, attempts to simply characterize entire studies as "positive" or "negative" ignore most of the data within the studies.[74] Without a thorough evaluation of all available data with a weight-of-evidence approach, as recommended by SCHER, mistaken conclusions are likely to be reached.

The conclusions of these weight-of-evidence evaluations are consistent with the conclusion of an earlier scientific panel convened by the US National Toxicology Program (NTP). In 2001, NTP issued a report on the findings of a peer review panel that examined the scientific evidence for low-dose effects, with a particular focus on BPA. In regard to the potential for low-dose effects from BPA, the panel concluded (emphasis added): "There is credible evidence that low doses of BPA can cause effects on specific endpoints. However, due to the inability of other credible studies in several different laboratories to observe low dose effects of BPA, and the consistency of these negative studies, **the Subpanel is not persuaded that a low dose effect of BPA has been conclusively established as a general or reproducible finding**. In addition, for those studies in which low dose effects have been observed, the mechanism(s) is uncertain (i.e., hormone related or otherwise) and the biological relevance is unclear."[8]

In addition, as described in Section 2, multiple government agencies worldwide have reviewed, but not accepted, the validity of low-dose effects for BPA. Based on the weight of scientific evidence, no regulatory body worldwide has accepted low-dose effects for BPA as the basis for regulatory action.

- **No Confirmed Endocrine Disrupting Effects From BPA Have Been Found in Humans**
  Only a few limited studies have attempted to look for endocrine effects from BPA in humans and each suffers from critical study design flaws that prevent any meaningful conclusions from being drawn.[75,76] The few studies reported are quite small and have not been confirmed in larger-scale studies with appropriate methodology. A particular study design flaw is the use of an inappropriate analytical method that is incapable of measuring BPA.

Outcome by Dose for Rat and Mouse Studies – Oral Administration

Endpoint	Dose (mg/kg–day) Order of Magnitude					
	$\leq 10^{-5}$	10^{-4}	10^{-3}	10^{-2}	10^{-1}	1
Body and Organ Weights						
Body	0000	000000	+0000000 00000000 –++– –00	0000000000 0000000000 0000– –00	0000000+00 000000– – 000	0000000000– 0000000
Male						
Epididymis	00	00–0	0000– 0000–0	000000 0– 0000000+0	0000000000– 0	00000
Preputial gland			00+0	0000	000	0
Prostate and ventral prostate	00	00+0	000000+0 00+	000000 0+00–000+	000000000+	00000
Seminal vesicles	00	0000	00000–0– 000– –	0000000000 0000–	000000000000	0000
Testes	0000	000–00	0000000– 0000+00–	0000000– –00– 0000+00	0000000+00 0000	0000000– –
Female						
Cervix			0	000	00	
Ovaries		0	00000	00000000	000000+	00
Uterus		0	0000000	000000000+	0000000++	00000
Vagina			0	000	00	
Organ Morphology/Cytology						
Male		– –	–0	– –0000	00+00	0000–
Female			00	0–00	00+0+– – –	0000000
Sperm Characteristics						
Sperm characteristics	000000	000– – – 000000–	0000– – – –0 00000– +–	000– –0–00– –00000000– 00–000–00+	000– 000000000– 0–0000	00–000–000
Perinatal						
AGD	00	00	000	000000	00000+	0
Puberty						
Male						
Preputial separation date	00	000	000	00000	0000	
Testis descent date		0	0	00	00	
Female						
Time until first estrus			–	00	00	
Vaginal opening date		0	00000	000000	00000	
Other Reproductive Endpoints						
Sex ratio		0	0000	0000000	000	000
Pup survival		0	00–0	000	000	00
Fertility	00	–00	00000000 00000+	0000000000 0000–0+++	000000000– +++	000000
Estrous cycle		00	00000	00000	0–000	–000

Outcome by Dose for Rat and Mouse Studies – Non–oral Administration

Endpoint	Dose (mg/kg–day) Order of Magnitude					
	10^{-5}	10^{-4}	10^{-3}	10^{-2}	10^{-1}	1
Body and Organ Weights						
Body	0	–00	0	0000000000	00000000+ 00000000	00000000– – 0000
Male						
Epididymis				00000	0000	00000
Preputial gland				000	00	0
Prostate and ventral prostate				0000	000	+0
Seminal vesicles				00000	000000	00000
Testes				0000000	0000000	000000
Female						
Ovaries	0	0		000	+00	00+00
Uterus	000	00–0	0	0000+	0+0000	00000000000
Vagina	00	–0				
Organ Morphology/Cytology						
Male		0	0	+–+0+0	+– +0+++00	0000+0
Female	00000000++ +–00	–00000+– ++0–+0	0	000++++00	0++0+++0 0+++0000+ 0–+00	+00000000
Sperm Characteristics						
Sperm characteristics				0–+000– 0000	– –+00– – – –0000++	–0–000+00– –00+
Perinatal						
AGD			0	000	0	
Puberty						
Female						
Mammary gland maturation date	+					
Age at first estrus			0	–		
Vaginal opening date	0	0	0	–	0+	00–
Other Reproductive Endpoints						
% of time in diestrus					+	
Sex ratio	0	0	0	00000	00000	000
Pup survival		–		0	00	0
Fertility	0	00	0–0	000000000	0000000000	000000
Estrous cycle (offspring)	+	+	0+	+	+	

4. Planned and Ongoing Studies

Two studies of particular relevance are underway or in press.

A. Two-Generation Reproductive Toxicity Study of Bisphenol A in CD-1 Mice

As described in the protocol,[77] the objectives of this study are to evaluate the potential of a wide range of dietary BPA concentrations to produce alterations in parental fertility, maternal pregnancy, and growth and development of offspring for two offspring generations with one litter per generation in mice. The study will also examine the potential for BPA to produce possible parental and offspring systemic toxicity. The BPA dietary concentrations used in this study range from approximately 0.018 - 3500 ppm (approximately 0.003 – 600 mg/kg/day).

In addition, the study includes a single dietary concentration of 0.5 ppm 17β-estradiol (approximately 100μg/kg/day) as a positive control to confirm the sensitivity of the mouse model to a potent endogenous estrogen. The study further includes two vehicle control groups to increase the baseline historical database in mice and to define the intrinsic variability in the endpoints of interest.

The study is being conducted at RTI International with Dr. Rochelle Tyl as the Study Director. The in-life phase of the study has been completed and an audited draft final report is expected by November 2006. The study is being conducted according to OECD Good Laboratory Practice guidelines.

The two-generation study on BPA was preceded by an equivalent two-generation reproductive toxicity study of 17β-estradiol in CD-1 mice. One of the objectives of this study was to develop a baseline by which to judge possible xenoestrogen effects in mice. The study also led to identification of a suitable dose of 17β-estradiol for use as a positive control in the BPA two-generation study. The study was conducted under OECD Good Laboratory Practice guidelines. The final report for this study and the corresponding rangefinder study[78] are complete and manuscripts are in preparation.

B. Updated Weight of the Evidence Evaluation of Reproductive and Developmental Effects of Low Doses of Bisphenol A

As noted above in Section 3C, the weight of evidence evaluation of low-dose reproductive and developmental effects of BPA originally conducted by an expert scientific panel at the Harvard Center for Risk Analysis has been updated. The original and updated evaluations include more than 70 studies that examine *in vivo* reproductive and developmental toxicity in mammals at low doses.

The updated evaluation applied the same systematic and rigorous analytical framework used by the original Harvard panel and builds upon the evaluation results of the Harvard panel. The updated evaluation is in press and will be provided as soon as it is available.

5. Conclusions

The safety of BPA has been evaluated in a very large number of studies that examined metabolism and pharmacokinetics, human exposure, and toxicity. In particular the potential for BPA to cause endocrine effects at low doses has been extensively studied.

Overall, **the weight of scientific evidence from the many studies summarized above demonstrates that BPA is not a risk to human health at the extremely low levels to which people might be exposed.** This conclusion is supported by multiple weight-of-evidence assessments conducted recently by scientific and government bodies worldwide. Notably, each of these assessments has included or specifically focused on claims that BPA can cause adverse health effects at low doses by disruption of natural hormonal processes. In every case, these assessments have found that the scientific evidence does not support the validity of low-dose health effects from BPA.

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