Testimony

Before the Subcommittee on Consumer Affairs, Insurance, and Automotive Safety
United States Senate

Hearing on "Plastic Additives in Consumer Products"

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Summary of Testimony

The American Chemistry Council represents the leading business of chemistry. Products supplied by the chemistry sector are essential in manufacturing, agriculture, energy, transportation, technology, communications, health, education, defense, and virtually every aspect of our lives. Basic industrial chemicals are the raw materials for thousands of other products including plastics, water treatment chemicals, detergents, pharmaceuticals and agricultural chemicals. These applications include medicines and medical technologies that save lives, computers that expand our horizons, foods we eat, water we drink, cars we drive, homes in which we live, and clothes we wear.

We understand that recent media attention has created public concern and confusion about some of these chemicals – a family of compounds called phthalate esters, and another compound called bisphenol A. We are pleased to present this testimony to help address some of the confusion.

Bisphenol A is a single compound used primarily to make polycarbonate plastic and epoxy resins. It is also used to make resins used as dental sealants and composites. Only trace levels of residual bisphenol A remain in these materials and in consumer products made from these materials.

Phthalate esters describe a family of compounds used in many applications. The largest use is as an additive to plasticize, or soften, polyvinyl chloride. Before the addition of a plasticizer, polyvinyl chloride (vinyl) is actually a hard plastic.

These materials have been in use for decades. They have been subjected to extensive study worldwide, including by independent researchers as well as government agencies, and scientific review is ongoing. U.S. regulatory agencies charged with regulating these compounds in various applications, after reviewing the large body of scientific data, have reached conclusions supporting their safe use in important applications. The scientific evidence supports the continued use of these important materials.

Bisphenol A

Bisphenol A is a chemical building block used primarily to make polycarbonate plastic and epoxy resins. The safety of products made from these materials is supported by a 50 year safety track record of use and an equally long history of testing.

Polycarbonate is a lightweight, highly shatter-resistant plastic with optical clarity comparable to glass. Epoxy resins have an exceptional combination of toughness, chemical resistance and adhesion. The unique attributes of these materials make them ideal for use in a wide array of products, many of which improve the health and safety of consumers.

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

Typical Products Made From Polycarbonate Plastic and Epoxy Resins	
Health Care • Eyeglass lenses • Incubators • Critical components of medical devices (e.g., kidney dialyzers, blood oxygenators, drug infusion units)	**Electronic** • Digital media (CDs and DVDs) • Electronic product housings (e.g., cell phones, computers) • Printed circuit boards laminates
Security • Blast and bullet resistant shielding • Police shields • Protective visors	**Sports Safety** • Bicycle and football helmets • Sunglasses and visors • Skiing and diving goggles
Automotive, Marine, and Aerospace • Headlamp lenses, mirror housings and bumpers • Instrument panels • Primer coatings • Fiber reinforced composites	**Building and Construction** • Roof, skylight and greenhouse glazing • Corrosion resistant coatings for steel pipes/fittings, structural steel (e.g., bridges), concrete reinforcement bar • Decorative and industrial flooring
Home Appliances • Components of kitchen appliances (e.g., food processors, refrigerators) • Electrical appliance housings	**Food Containers** • Baby and water bottles • Home food storage containers and tableware • Food/beverage can coatings

In recent years, independent government and scientific bodies worldwide have examined the scientific evidence supporting the safety of bisphenol A. In every case, these assessments support the conclusion that bisphenol A is not a risk to human health at the extremely low levels to which people might be exposed.

Each of these assessments comprehensively examined the potential reproductive and developmental toxicity of bisphenol A. Based on the weight of evidence, these assessments uniformly demonstrate that bisphenol A is not a selective reproductive or developmental toxicant. The most recent evaluations of bisphenol A are briefly summarized below along with their key conclusions regarding reproductive and developmental toxicity.

Bisphenol A is Deemed Safe for Use by the U.S. Food and Drug Administration

FDA regulates the use of bisphenol A in food contact materials, such as polycarbonate used in baby bottles and water bottles, and in epoxy resins used to coat cans containing food products. The U.S. Food and Drug Administration (FDA) said in July 2007 that *"FDA is unaware of any specific study in which humans exposed to BPA through any food containers experienced miscarriages, birth defects or cancer. Furthermore, human exposure levels to BPA from its use in food contact materials is in fact many orders of magnitude lower than the levels of BPA that showed no adverse effects in animal studies."*

More recently (April 2008), in response to public confusion from media reports about bisphenol A, FDA formed an FDA-wide task force to review current research and new information on bisphenol A for all FDA-regulated products. FDA confirmed that it has been reviewing the emerging literature on bisphenol A on a continuous basis. FDA also confirmed that based on its ongoing review, it believes there is a large body of evidence that indicates that FDA-regulated products containing bisphenol A currently on the market are safe and that exposure levels to bisphenol A from food contact materials, including for infants and children, are below those that may cause health effects.

FDA's position is consistent with two risk assessments for BPA conducted by the European Food Safety Authority (EFSA) Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food and the Japanese National Institute of Advanced Industrial Science and

Technology. Each of these documents considered the question of a possible low-dose effect and concluded that no current health risk exists for bisphenol A at the current exposure level.

FDA said in April 2008 that it is NOT recommending that anyone discontinue using products that contain bisphenol A while FDA continues its risk assessment process. See http://www.fda.gov/oc/opacom/hottopics/bpa.html.

FDA's Conclusions are Consistent with Those of the European Food Safety Authority

The European Food Safety Authority (EFSA) was established by the European Parliament in 2002 to provide the European Commission, the European Parliament and the European Member States with a sound scientific basis for legislation and policies related to food safety. Included in the scope of EFSA's work are assessments of the safety of food packaging and other materials that contact food.

In January 2007, EFSA released a comprehensive assessment of bisphenol A that was conducted by an expert panel consisting of 21 independent scientific experts from across the European Union.[1] The assessment, which builds upon and updates an earlier assessment,[2] comprehensively evaluated studies on the toxicity, metabolism and pharmacokinetics, and dietary exposure of bisphenol A.

In general, the findings and conclusions of the EFSA assessment are consistent with those of the more recent CERHR evaluation (see below). The assessment established a Tolerable Daily Intake (TDI) of 50 µg/kg bw/day and concluded that "people's dietary exposure to BPA, including that of infants and children, is estimated to be well below the new TDI."

The TDI was based on the most sensitive no-effect-levels from multi-generation studies conducted in the rat and mouse (see below for more information on these studies). For both studies, the most sensitive no-effect-level was for systemic toxicity (e.g., liver effects) at 5 mg/kg bw/day. The no-effect-levels for reproductive and developmental effects in both studies were at a higher dose (50 mg/kg bw/day) that the dose at which systemic effects occurred. The EFSA panel further concluded that "low-dose effects" of bisphenol A in rodents have not been demonstrated in a robust and reproducible way.

Bisphenol A has been Extenstively Reviewed by the NTP Center for the Evaluation of Risks to Human Reproduction

The Center for the Evaluation of Risks to Human Reproduction (CERHR) was established by the U.S. National Toxicology Program and the National Institute of Environmental Health Sciences in 1998 to serve as an environmental health resource to the public and to regulatory and health agencies. A primary function of CERHR is to assess the potential for adverse effects on reproduction and development caused by agents to which humans may be exposed. This is accomplished through rigorous evaluations of the scientific literature by independent panels of scientists.

The CERHR evaluation comprehensively reviewed the large scientific database on bisphenol A, including:

- Chemistry, use and human exposure
- General toxicology and biological effects (including metabolism and pharmacokinetics)
- Reproductive toxicity
- Developmental toxicity

To reach its conclusions, the expert panel considered the quality, quantity, and strength of the scientific evidence that exposure to bisphenol A might cause adverse effects on human reproduction and/or development of the fetus or infant. The overall findings of the expert panel evaluation were announced at a public meeting in August 2007, and the final CERHR report was released in November 2007. Subsequently, NTP released a draft "Brief" based on the CERHR report on April 14, 2008.[3]

Based on the weight of scientific evidence, the expert panel found no serious or high level concerns for adverse effects of bisphenol A on human reproduction or development. The draft NTP Brief agreed with these conclusions: "the NTP has *negligible* concern that the exposure of pregnant women to bisphenol A will result in fetal or neonatal mortality, birth defects or reduced birth weight and growth in their offspring," and "the NTP concurs with the conclusion of the CERHR Expert Panel on Bisphenol A that there is *negligible* concern that exposure to bisphenol A causes reproductive effects in non-occupationally exposed adults, and *minimal* concern for workers exposed to higher levels in occupational settings." For several specific potential health effects (regarding neural and behavioural effects, and effects on the prostate gland, acceleration in puberty in females, and the mammary gland), the NTP draft

Brief expressed "some concern," but again no serious or high level concerns. Additional research was suggested by the NTP draft Brief, since data is inadequate to reach a firm conclusion.

The European Union Risk Assessment Supports Bisphenol A's Continued Safe Use

Under the EU Existing Substances Directive, the EU conducted a comprehensive risk assessment of bisphenol A that was published in 2003.[4] An updated risk assessment is in the final stages and is expected to be published in early 2008.

The EU risk assessment comprehensively evaluated studies on the toxicity, metabolism and pharmacokinetics, and exposure of bisphenol A. In general, the findings and conclusions of the EU risk assessment are consistent with those of the CERHR evaluation. The 2003 risk assessment established an overall no-effect-level of 50 mg/kg bw/day, which was based on the no-effect-level for reproductive and developmental effects in a multi-generation study conducted in the rat. The no-effect-level from the rat multi-generation study has subsequently been affirmed by the results of a multi-generation study in the mouse (see below for information on both multi-generation studies). The updated risk assessment, based on the most recent scientific information, retains the overall no-effect-level of 50 mg/kg bw/day, now based on both the rat and mouse studies.

The 2003 EU risk assessment was reviewed by the Scientific Committee for Toxicity, Ecotoxicity, and the Environment (CSTEE), which is an independent scientific advisory committee to the European Commission.[5] The CSTEE agreed with the overall no-effect-level and stated that "a number of high quality studies on the reproductive and developmental effects of bisphenol A are already available and do not support low-dose effects." The CSTEE further stated that **"**there is no convincing evidence that low doses of bisphenol A have effects on developmental parameters in offspring…"

The Japanese National Institute of Advanced Industrial Science and Technology's Review Supports the Continued Safe Use of Bisphenol A

The Japanese National Institute of Advanced Industrial Science and Technology (AIST), which is affiliated with the Japanese Ministry of Economy, Trade and Industry is Japan's largest public research organization. A comprehensive human health and environmental risk assessment on bisphenol A,

conducted by scientists at AIST's Research Center for Chemical Risk Management, was published in November 2005.[6]

Based on a thorough review of the toxicological profile of bisphenol A combined with estimates of human exposure, AIST concluded that "current exposure levels of BPA will not pose any unacceptable risk to human health."

Along with systemic toxicity, a key toxicological endpoint for the AIST assessment was reproductive toxicity. Similar to the EFSA assessment, the most sensitive no-effect-level was 5 mg/kg bw/day for systemic toxicity in a multi-generation study conducted in the rat. The no-effect-level for reproductive toxicity was 50 mg/kg bw/day, at which systemic effects also occurred. The AIST assessment further concluded that findings from studies claiming reproductive effects at much lower doses were not considered to be robust in comparison to the consistent findings from studies reporting no low-dose effects.

Health Canada's Recent Review is Supportive of Continued Use of Bisphenol A

In April 2008, Health Canada opened a comment period on a proposal to ban polycarbonate baby bottles. This event has been the subject of some confusion in the media, because the reviewing scientists concluded "that bisphenol A exposure to newborns and infants is below levels that may pose a risk." The Canadian government nevertheless proposed moving forward with a ban on polycarbonate baby bottles based on a policy decision that the "gap between exposure and effect is not large enough." Canada also proposed to set limits on BPA in infant formula and to work with industry on alternatives for food packaging.

Canada did not suggest that parents and caregivers stop using polycarbonate bottles while the proposal is being considered. Canada did not suggest that stores stop selling polycarbonate baby bottles while the proposal is being considered. Canada did recommend that parents and caregivers continuing to use polycarbonate baby bottles "do not put boiling water in them."

Recent, High Quality Studies Animal Studies Have Been Completed on Bisphenol A

The effects of bisphenol A on fertility and reproductive performance have been investigated in three high quality studies in rats and mice using internationally validated guidelines (two-generation and three-generation studies in the rat, two-generation study in mice) and in a continuous breeding study in mice. Developmental toxicity studies in rats and mice have also been conducted.

- No effect on fertility was seen in the rat two-generation study at the four low-dose levels tested (0.2-200 µg/kg bw/day). In the rat three-generation study, a reduction in litter size was seen only at the top dose of 500 mg/kg bw/day, which also produced clear parental systemic toxicity (significant body weight gain reduction in both sexes and renal tubule degeneration in females). No effects on reproduction or development were seen at the five lower doses tested (1 µg/kg bw/day to 50 mg/kg bw/day) and no parental systemic effects were seen at the four lowest doses (5 mg/kg bw/day and below).

- Consistent with the rat studies, bisphenol A produced parental systemic toxicity in the mouse two-generation study at the two highest doses tested (50 and 600 mg/kg bw/day), resulting in a NOEL of 5 mg/kg bw/day. The NOEL for reproductive and developmental effects was 50 mg/kg bw/day. No treatment related effects were seen at the four lowest doses tested (3 µg/kg bw/day to 5 mg/kg bw/day).

- In the continuous breeding study in mice, no effects on fertility were seen at 300 mg/kg bw/day. Fertility effects were only observed at doses of approximately 600 mg/kg bw/day and above, at which parental systemic toxicity was present.

- No evidence that bisphenol A is a developmental toxicant was observed in standard developmental studies in rats and mice. In rats, a maternal LOAEL and fetal NOAEL of 160 and 640 mg/kg bw/day, respectively, were identified. In mice, maternal and fetal NOAELs were 250 and 1,000 mg/kg bw/day, respectively.

Individually and collectively, these studies, these studies consistently demonstrate that bisphenol A is not a selective reproductive or developmental toxicant.

In addition, effects claimed to occur at low doses in small-scale unvalidated studies, have not been corroborated in the large-scale multi-generation studies conducted according to internationally validated guidelines. Additional detail on these studies is provided below.

<u>Three-Generation Reproductive Toxicity Study in CD Sprague-Dawley Rats</u>

The study followed the US EPA OPPTS test guideline 837.3800, with additional assessments beyond the guideline requirements, and was conducted under Good Laboratory Practice requirements.[7] Strengths of the study include:

- Oral route of administration, which is most relevant for human exposure

- Wide dietary dose range (6 dose groups ranging from 0.015 to 7500 ppm bisphenol A in the diet, corresponding to intakes of approximately 1μg/kg bw/day to 500 mg/kg bw/day)
- Large group size (30 animals per dose level)
- Multiple endpoints examined, including a thorough histologic evaluation

Parental systemic toxicity (a guideline requirement) was produced at the two highest doses, resulting in a NOAEL of 5 mg/kg bw/day. The NOAEL for reproductive and developmental effects was 50 mg/kg bw/day.

Two-Generation Reproductive Toxicity Study in CD-1 Swiss Mice

The study followed the internationally accepted OECD 416 test guideline, with additional assessments beyond the guideline, and was conducted under Good Laboratory Practice requirements.[8] The study was preceded by a full two-generation reproductive toxicity study on 17β-estradiol, which was then also used as a positive control in the bisphenol A study. Strengths of the study include:

- Oral route of administration, which is most relevant for human exposure
- Wide dietary dose range (6 dose groups ranging from 0.018 to 3500 ppm bisphenol A in the diet, corresponding to intakes of approximately 3μg/kg bw/day to 600 mg/kg bw/day)
- Large group size (28 animals per dose level)
- Multiple endpoints examined, including a thorough histologic evaluation

In addition, maternal and paternal toxicity (a guideline requirement) was produced at the two highest doses, additional F1 male offspring were retained for evaluation concurrent with F1 parental males, a positive control was used to demonstrate that the test system was responsive to a known estrogen, and two negative control groups were used to increase the baseline historical database in mice and to define the intrinsic variability in endpoints of interest.

Consistent with the three-generation study in rats, systemic toxicity was identified at the two highest doses, resulting in a no observed effect level (NOEL) of 5 mg/kg bw/day. The NOEL for reproductive and development effects was 50 mg/kg bw/day. Also consistent with the three-generation rat study, no treatment-related effects were found at doses ranging from 3μg/kg bw/day to 5 mg/kg bw/day and the study did not corroborate effects claimed to occur in this low dose range in small-scale studies.

Two-Generation Reproductive Toxicity Study in CD Sprague-Dawley Rats

In a third comprehensive study, bisphenol A has been tested in a two-generation reproductive toxicity study in CD Sprague-Dawley rats.[9] This study, which focused on low doses, followed the internationally accepted OECD 416 test guideline and was conducted under Good Laboratory Practice requirements. Strengths of the study include:

- Oral route of administration
- Large group size (25 animals per dose level)
- Wide variety of hormonally sensitive endpoints examined, including behavioral measurements

Consistent with the three-generation rat study and the two-generation mouse study, no treatment-related effects were found in the low-dose range from 0.2 to 200 µg/kg bw/day and the study did not corroborate effects claimed to occur in this low dose range in small-scale studies.

National Toxicology Program Continuous Breeding Study in Mice

Bisphenol A was administered in the diet during a one-week pre-mating period and a 14-week mating trial to groups of twenty male and female CD1 mice (F0 generation) at concentrations of 0, 0.25, 0.5 or 1.0%; daily intakes of bisphenol A are estimated to have been 0, 300, 600 and 1200 mg/kg bw/day in males, and 0, 325, 650 and 1300 mg/kg bw/day in females.[10] In the continuous breeding phase, a statistically significant decrease in maternal body weight was observed after each litter (between 6 and 9%), at the top dose, on postnatal day 0 compared to controls. At study termination, a small but statistically significant decrease in body weight (4%) was observed in treated females compared to controls.

A subsequent one generation study to further evaluate parental toxicity of bisphenol A to CD1 mice observed significant parental toxicity at doses of 650 or 1300 mg/kg bw/day.[11] Key evidence of parental systemic toxicity was increased liver and kidney weights with hepatocellular hypertrophy and renal tubule degeneration/regeneration, reduced body weights and body weight gain. In the continuous breeding study, a statistically significant decrease compared to controls was observed in the number of litters produced per pair (4.5 and 4.7 compared to 5.0 for controls), litter size (6.5 and 9.8 compared to 12.2 for controls) and the number of live pups per litter (6.3 and 9.7 compared to 12.1 for controls) in the

high and mid-dose group. No effects on fertility were observed in the low-dose group. A statistically significant decrease in litter size (controls: 11.4, treated males: 9.1, treated females: 5.9) and number of live pups per litter (controls: 11.3, treated males: 8.4, treated females: 5.5) were observed in the cross-over mating. In the continuous breeding phase, a statistically significant decrease in live pup weight (6%) on postnatal day 0 was observed in females at the top dose after adjustment for litter size, including live and still births. In the continuous breeding phase a small but statistically significant decrease in body weight gain (4%) was only observed in treated females at study termination. No effect was observed on the sex ratio in the F1 generation. In the F1 litters used in the cross-over breeding experiment, post natal (day 0) pup weights were significantly increased in males (9-11%) and in females (8-10%) in the mid- and high-dose.

This study, conducted at high doses, is superseded by the more recent two generation study in mice.

National Toxicology Program Developmental Toxicity Study in Mice

Bisphenol A has been tested for developmental toxicity in a NTP study using CD-1 mice.[12] Two tests were performed and as the same signs of maternal toxicity were observed in both tests the data were combined. Groups of 29-34 time-mated female mice were gavaged with 0, 500, 750, 1000 or 1250 mg/kg bw/day in corn oil on days 6 to 15 of gestation. Animals were sacrificed on day 17 of gestation and the fetuses were subjected to routine external, visceral and skeletal examinations. Data were also provided on the additional dose level of 250 mg/kg bw/day, which was used only in the first test. Some maternal deaths were observed at doses of 750 mg/kg bw/day and above and a decrease in maternal body weight gain of 4-10% and 32-43%, for both the treatment and gestation period was observed at 1,000 and 1,250 mg/kg bw/day, respectively. Other significant signs of maternal toxicity were observed at 500, 750, 1000 or 1250 mg/kg bw/day as well as a dose-related statistically significant increase in mean relative liver weight (9-26%) was observed in dams in all bisphenol A treatment groups as compared to controls. At 1250 mg/kg bw/day a statistically significant increase was observed in % resorptions per litter (40% as compared to 14% in controls). A dose-related decrease in mean fetal body weight per litter was observed

in the bisphenol A treated groups that was statistically significant at 1,250 mg/kg bw/day when compared to the control value; 1%, 1%, 9% and 14% at 500, 750, 1,000 and 1,250 mg/kg bw/day, respectively. No statistically significant effect was observed on the number of implantation sites per dam, the number of live fetuses per litter and the sex ratio. Bisphenol A administration had no significant effect on the % of fetuses malformed per litter or the % of litters with malformations. Overall, a significant increase in resorptions and decrease in fetal body weight was observed only at 1,250 mg/kg bw/day in the presence of severe maternal toxicity.

National Toxicology Program Developmental Toxicity Study in Rats

Bisphenol A was studied for developmental toxicity potential in a NTP study.[13] In the main study, two trials were performed and the data from both tests were combined. In total, groups of 27-29 time-mated CD rats were gavaged with 0, 160, 320, 640 or 1,280 mg/kg bisphenol A in corn oil on days 6 to 15 of gestation. Animals were sacrificed on day 20 of gestation and the fetuses were subjected to routine external, visceral and skeletal examination. At 1,280 mg/kg, deaths were observed in 7/27 females and because of this high mortality rate, the top dose group was not included in statistical analyses. Compared to controls, a statistically significant decrease in mean maternal body weight gain was observed in dams at all dose levels for the treatment period (35-54%) and the gestation period (11-14%). No effect was observed on gravid uterine weights. When maternal body weight gain was corrected for gravid uterine weight a statistically significant decrease was still apparent at all dose levels (26-34%). Pregnancy rates were not affected by treatment with bisphenol A, nor was there any effect on the number of implantation sites per litter, % resorptions per litter, number of live fetuses per litter, sex ratio, mean fetal body weight per litter, % fetuses malformed per litter and % litters with malformed fetuses. In conclusion, this study provides no evidence of developmental toxicity in the rat at exposure levels which are toxic to the mother. A maternal NOEL could not be identified; instead a LOAEL of 160 mg/kg was identified for clinical signs of toxicity and a statistically significant decrease (26%) in body weight gain. No fetal effects were seen at the highest dose level evaluated, 640 mg/kg.

"Low-Dose" Studies are Unvalidated

Although bisphenol A has been shown to have some weak "estrogen-like" activity in a number of *in vitro* and *in vivo* screening assays, molecular biology studies[14] have demonstrated that bisphenol A does not act as a weak estrogen mimic but exhibits a distinct mechanism of action from estradiol at the estrogen receptor. Nevertheless, the potency of this activity in screening assays generally ranges from 3 to 5 orders of magnitude less than that of estradiol.

It should also be noted that many of the studies investigating endocrine modulating activity are essentially screening tests and many employ experimental protocols that have not been validated. This information in conjunction with the known extensive metabolism of bisphenol A to non-estrogenic metabolites (see below) provides a scientific basis for the lack of toxicological effects at low doses in the multi-generation studies described above. Effects claimed to occur at low doses in small-scale unvalidated studies have not been corroborated in the large-scale multi-generation studies conducted according to internationally validated guidelines.

The small-scale unvalidated studies have been evaluated in the comprehensive assessments described above. Each of these assessments applied a "weight-of-evidence" approach to evaluate the body of information available for bisphenol A. Each assessment relied on the results of the two- and three-generation studies described above for its overall conclusion.

Metabolism and Pharmacokinetics Data Supports Results from Animal Studies

The potential for a substance to cause reproductive or developmental toxicity is substantially influenced by metabolism and pharmacokinetics. These parameters have been very well characterized for bisphenol A in numerous animal studies (i.e., rodents and primates) and in several human volunteer studies.

Overall, these studies indicate that bisphenol A has a low potential to cause adverse health effects in humans and, in particular, effects mediated by an estrogenic mode of action. Key findings from these studies are summarized below:

- **Humans Efficiently Metabolize and Eliminate Bisphenol A from the Body**
  Human volunteer studies confirm that bisphenol A is efficiently metabolized to a glucuronide conjugate after oral exposure.[15,16,17] Studies in animals and with isolated liver cells have shown

that this metabolic process occurs in the intestinal wall[18] and in the liver,[19,20,21,22] both of which must be crossed before bisphenol A can enter into circulation in the body after oral exposure.

In the first human study, volunteers were treated with a single 5 mg oral dose of bisphenol A per person, which is approximately 1000 times greater than a typical daily intake of bisphenol A (see Section 6 below). No parent bisphenol A was found in blood at any time point and all bisphenol A was excreted in urine as the glucuronide. The elimination half-life for the glucuronide conjugate was approximately 4 hours, which means that any bisphenol A to which people are exposed should virtually all be eliminated from the body within approximately 24 hours.

- **Bisphenol A Has Low Bioavailability and Does Not Accumulate in the Body**
  The human volunteer studies confirm that bisphenol A has very low bioavailability (i.e., very little parent bisphenol A will reach target tissues) after oral exposure. The rapid elimination of bisphenol A indicates that bisphenol A has very low potential (if any) to bioaccumulate in the body.

  Low bioavailability, efficient metabolism of bisphenol to the glucuronide, and low potential to bioaccumulate have also been demonstrated in numerous studies on laboratory animals, some of which are cited here.[23,24,25,26,27,28,29] Included are studies that demonstrate that metabolism of bisphenol A is not altered during pregnancy[30] and that neonatal animals also efficiently metabolize bisphenol A from an early age in neonatal life.[31]

- **Bisphenol A Metabolites are Not Estrogenic**
  The primary metabolite of bisphenol A, the glucuronide, has been shown to exhibit no estrogenic activity.[32] The bisphenol A sulfate metabolite, which may be present at lower levels, has also been shown to exhibit no estrogenic activity.[33] These studies indicate that bisphenol A is not likely to cause estrogenic effects since the metabolites of bisphenol A that enter the body have no known biological activity and, in particular, have no estrogenic activity.

Bisphenol A Presents Very Low Potential for Human Exposure

Numerous studies have been conducted to directly measure human exposure to bisphenol A by urinary biomonitoring and to indirectly estimate human exposure by analysis of potential sources of exposure. These data consistently indicate that human exposure to bisphenol A is essentially all through the diet and is extremely low. Typical human exposure to bisphenol A is less than 0.1 µg/kg bw/day. Key findings from these studies are summarized below:

- **Biomonitoring Studies Confirm Extremely Low Human Exposure**
  Since the glucuronide metabolite of bisphenol A is rapidly and completely eliminated into human urine, human exposure can readily be estimated by urinary biomonitoring for bisphenol A (after hydrolysis of conjugates). Numerous studies conducted worldwide indicate that typical human exposure to bisphenol A is less than 0.1 µg/kg bw/day.

  The largest study was conducted by the US Centers for Disease Control and Prevention as part of their NHANES 2003-2004 program.[34] This study reported urinary bisphenol A data for more than 2500 individuals ranging in age from 6-85. Due to the study design, the data is representative of the US population. In this study, the median concentration of bisphenol A in

urine (after hydrolysis) was 2.8 ng/ml. Based on this data, the typical daily intake of bisphenol A for the population is estimated to be approximately 0.05 µg/kg bw/day.

Many smaller-scale studies from Japan[35,36,37,38,39], Korea,[40,41] Europe,[42] and the US[43,44,45,46,47,48,49] have reported similar results. Included are two studies in which urine samples were collected over 24-hour periods.[50,51]

- **Potential Exposure From Consumer Products is Very Low**
  Consumer products made from polycarbonate plastic or epoxy resins contain only trace levels of bisphenol A, typically less than 50 parts per million (0.005% by weight), which limits potential exposure to bisphenol A from use of products. Human exposure to bisphenol A is essentially all through the diet[52] and numerous studies have been conducted to examine the potential for bisphenol A to migrate from polycarbonate plastic or epoxy resins into a food or beverage. Of particular interest are the many studies on polycarbonate baby bottles[53,54,55,56,57,58] and canned foods and beverages.[59]

  Calculated human exposure estimates based on measured migration data combined with consumption patterns[62k,60] are generally consistent with exposure estimates directly measured by biomonitoring. Both confirm that human exposure to bisphenol A from all sources, including from use of consumer products, is extremely low.

- **Exposure to Bisphenol A Is Within Government-Set Safe Limits**
  The European Food Safety Authority recently established a Tolerable Daily Intake for bisphenol A of 50 µg/kg bw/day based on an up-to-date scientific review.[2] This value is identical to the Reference Dose set by the US Environmental Protection Agency.[61] The typical daily intake of bisphenol A is approximately 1,000 times lower than these acceptable levels and poses no known risks to human health.

Phthalate Esters

The dozen or so phthalates in use today have thousands of applications. Their chief use is to make vinyl soft and flexible, without sacrificing its durability. They are used as softeners (or plasticizers) in toys, cars and products found in the home and in hospitals. For example, they are an important ingredient in life-saving and life-supporting vinyl medical devices. One member of the phthalate family is used in perfumes and other personal care products to make their fragrances last longer. Another type of phthalate is used in items such as tool handles and nail polish to help resist chipping.

Recent discussion regarding phthalates has focused on its use in toys and child care items. An extensive body of research on phthalates, including several recently completed U.S. and EU risk assessments, demonstrates that the use of phthalates, and in particular diisononyl phthalate (DINP), as a plasticizer in toys and objects used by children poses little to no risk to children.

With respect to toys and children's products, discussion typically focuses on the use of six phthalates: di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), and butyl benzyl phthalate (BBP) – in the materials used in manufacturing toys or objects used by children, and another three – diisononyl phthalate (DINP), diisodecyl phthalate (DIDP) and di-n-octyl phthalate (DnOP) – in such products that children can put in their mouths.[62] This discussion apparently occurs because, despite the conclusions of the European risk assessments on phthalates, the EU acted to limit the uses of these phthalates in toys before the risk assessments were final.

In the late 1990's, a question arose as to whether use of phthalates in vinyl toys might present a health risk to children. The concern was based primarily on effects in rats that were treated with very high oral doses of phthalates, and on the knowledge that some phthalate could migrate out of vinyl toys if and when they were mouthed by children, and thus be ingested. At the time, information was sparse and uncertain regarding how much phthalate actually would migrate out of mouthed toys and the amount of time children actually mouthed toys. Initial calculations using very conservative assumptions for these parameters showed that exposure to phthalates would be lower than the levels at which effects are seen in

animal studies, but that the margin of safety (MOS) might be less than considered desirable for DINP and DEHP.

In 1999, the EU instituted an emergency temporary ban on DBP, BBP, DnOP, DEHP, DINP and DIDP in toys intended to be put in the mouths of children under three, and began considering more permanent legislative measures.[63] At the same time, actions were initiated to bring more certainty to the science. The European Commission's Joint Research Center (JRC), the Netherlands' TNO Nutrition and Food Research Institute, the United States Consumer Product Safety Commission (CPSC), and the Canadian Ministry of Health (Health Canada) collaborated to develop a reliable method for measuring phthalate migration from mouthed vinyl toys. In the meantime, The EU was in the process of conducting in-depth and comprehensive risk assessments of DBP, BBP, DEHP, DINP and DIDP as part of its effort to evaluate and control risks from existing substances. In the U.S., the CPSC undertook an exhaustive assessment of the risks posed by DINP in children's toys, which included a state-of-the-art study of children's mouthing behaviors and migration testing using the method developed by the European/North American collaboration.

By 2003, these efforts had revealed that the risk posed by the use of DINP in children's toys – even those that are mouthed – is insignificant. The CPSC found that PVC toys and other items intended for children under five posed "***no demonstrated health risk***."[64] The European Union's risk assessment for DINP concluded: "***The end products containing DINP (clothes, building materials, toys and baby equipment) and the sources of exposure (car and public transport interiors, food and food packaging) are unlikely to pose a risk for consumers (adults, infants and newborns) following inhalation, skin contact and ingestion***."[65]

Paradoxically, at the same time the science was providing reassurance about the use of phthalates in children's products, European politicians were urging more and more stringent restrictions on such use, resulting in the permanent ban in 2005 on the use DEHP, DBP and BBP in toys, and DINP, DIDP and DnOP in toys intended to be mouthed. Since 1999, the risk assessments conducted by the CPSC and the EU have provided high-quality scientific evidence that the use of most phthalate plasticizers, in particular

DINP, in toys and children's articles poses little to no risk to children. Contrary to assertions made by some, there is little uncertainty about these conclusions. There are always remaining questions to be addressed by science; however, phthalates are among the best studied compounds in the world, and the risk assessments are based on recent, state-of-the-art studies.

In the meantime, early concerns from the 1990's about DEHP with respect to carcinogenicity observed in rodents following high dosing were investigated and addressed following additional research. In 2000, based on its judgment that the rodent results were not relevant to humans, the arm of the World Health Organization called the International Agency for Research on Cancer (IARC) - the international authority on cancer – changed its classification for DEHP to "not classifiable" as a human carcinogen. Regulatory agencies in Europe and Canada have also reached the same conclusion.

Accordingly, based on the science and the use patterns for phthalates, no restriction on the use of phthalates in toys and childcare articles is warranted at this time.

The United States Consumer Products Safety Commission Risk Assessment for Vinyl Toys Containing Phthalates Found Minimal to No Risk to Children Five Years of Age or Under

In late 1998, The National Environmental Trust and other organizations petitioned the US Consumer Product Safety Commission (CPSC) to ban the use of polyvinyl chloride (PVC or vinyl) in products intended for children five years of age or under. A reason asserted for the ban was alleged health effects from the phthalate used as a plasticizer in vinyl children's products – diisononyl phthalate (DINP). The CPSC therefore undertook an intensive investigation of the toxicology of DINP and of potential exposure of children to DINP from vinyl products.[66]

For its review, CPSC convened a Chronic Hazard Advisory Panel (CHAP) – a seven-member panel of independent scientific experts who conducted a detailed review of the potential health hazards posed by DINP in products mouthed by children. The CHAP met three times over the course of a year and accepted voluminous comments from representatives of both industry and public interest groups. The 160-page CHAP report was published on June 15, 2001 and is available on the CPSC website.[67]

The CHAP found that 120 μg/kg/day was an Acceptable Daily Intake (ADI) of DINP for humans – i.e., the amount of chemical a person can be exposed to on a daily basis over an extended period of time (up to a lifetime) with a negligible risk of suffering adverse effects. Based on this ADI, the CHAP concluded that a young child would have to routinely mouth DINP-plasticized toys for 75 minutes or more per day in order to pose a possible DINP exposure risk. However, finding no evidence that children mouth such toys for such extensive periods, the Report concluded that exposure to DINP for toys containing phthalates poses little or no risk of injury to children.

To verify these conclusions, the CPSC then conducted a state-of-the-art study of the amount of time children mouth objects, and it conducted additional studies of the rate of migration of DINP from vinyl when mouthed, using a methodology developed and validated by the TNO Nutrition and Food Research Institute, CPSC, Canada Health and the European Commission's JRC.[68] On September 23, 2002, the CPSC released a briefing package, summarizing the CPSC staff investigation of the potential risks of DINP in children's vinyl products.[69] The executive summary of that package states:

> Based upon the observation study, staff concludes it is very unlikely that children will mouth soft plastic toys for more than 75 minutes a day.[70]
> …
> The staff concurs with the CHAP conclusion that exposure to DINP from DINP-containing toys would be expected to pose a minimal to non-existent risk of injury for the majority of children. The new data from the behavioral observation study not only confirm this conclusion, but also demonstrate that children are exposed to DINP at lower levels than the CHAP assumed when it reached its conclusion. Also, since children mouth other products even less than they mouth toys and dermal exposure is expected to be negligible, there would be no justification for taking action against other products intended for children five years old and younger.

CPSC estimated that the most highly exposed group of children (those aged 3-12 months) had mean exposures to DINP of 0.07 μg/kg/day with a 95th percentile value of 0.44. This is well below the CHAP and CPSC conservative ADI of 120 μg/kg/day. CPSC also estimated worst case exposures hypothetically assuming that all toys, teethers and rattles were made with DINP-plasticized vinyl (in reality, only a portion of toys are made with soft plastic, only about a third of the soft plastic toys contain DINP, and no rattles or teethers contain DINP). Even under these conservative conditions, the estimated

DINP exposures for children 3-12 months were 2.91 μg/kg/day (mean) and 10.71 μg/kg/day (95th percentile), still well below the ADI. Additional detail on the CPSC analysis is provided in Appendix 1.

The overall CPSC staff risk assessment information and conclusions have been published in the peer reviewed literature.[71] The authors conclude that "***oral exposure to DINP from mouthing soft plastic toys is not likely to present a health hazard to children***."[72]

On February 21, 2003, the CPSC Commissioners voted unanimously to deny the petition.[73] As indicated in the denial letter to petitioners, the Commissioners denied the petition based on the finding of CPSC that "***there is no demonstrated health risk posed by PVC toys or other products intended for children five years of age and younger.***"[74]

The CPSC evaluation considered the conditions most likely to result in exposures of DINP to children and used very conservative (i.e., health-protective) assumptions. CPSC considered children in those age groups that most often mouth items; it considered exposure from such mouthing, which would be expected to exceed that which could occur by dermal contact; and it conservatively evaluated situations in which DINP was assumed to be used to a much greater extent in children's products than it actually is. As explained in Appendix 1, the acceptable daily intake (ADI) used by CPSC also was quite conservative – a value 100 times below levels at which no effects have been observed in animal studies. Even with such conservatism, the potential exposures were still well below the ADI. Thus, the CPSC concluded no restrictions on the use of DINP in children's articles are warranted.

EU Risk Assessments Demonstrate That The Use of Phthalates in Vinyl Toys and Childcare Articles Poses Little or No Risk to Children

Like the CPSC assessment, the EU's risk assessments of phthalates support the safety of the use of phthalate esters in toys and children's products. As part of its existing chemicals program, the EU has published risk assessments for three of the six phthalates typically noted as of concern for children's products, DBP,[75] DIDP[76] and DINP,[77] and has completed draft assessments of BBP[78] and DEHP.[79] The remaining of the six phthalates, DnOP, has apparently not been the subject of an EU risk assessment because the production of this particular plasticizer ceased more than 10 years ago. The EU risk

assessments, which incorporate the most modern and up-to-date data and methodology available to the EU, specifically include a consideration of risks to children from all potential sources, including toys and childcare articles.

The EU Risk Assessment for DINP Concurs With the CSPC Assessment, Finding No Likely Risk to Children

The most relevant EU risk assessment – that for DINP – was published in 2003. Unlike the CPSC risk assessment, which was intended only to determine the risk to children from mouthing objects, the EU assessment included an investigation of the risk to newborns, infants, children and adults from all routes of exposure. The EU assessment explicitly considered exposures of newborns, infants and children from multiple sources, including food and food-related uses, toys and baby equipment, car and public transport interiors, and building material and furniture. The EU risk assessment found no likely risk to humans under any exposure scenario. As stated in the risk assessment summary document with respect to consumer exposures:

> The end products containing DINP (clothes, building materials, toys and baby equipment) and the sources of exposure (car and public transport interiors, food and food packaging) are unlikely to pose a risk for consumers (adults, infants and newborns) following inhalation, skin contact and ingestion.[80]

The EU risk assessment also found no likely risk to adults, children or infants from environmental exposures, or from combined consumer and environmental exposures. The EU's finding of no risk to children under three was based on several calculated MOSs (Margins of Safety), all of which are above the CSTEE's recommended MOS of at least 100. The EU risk assessment reported the following MOSs with respect to children:

- 176 (kidney effects) and 552 (fertility effects) for infants and newborns exposed to DINP from multiple consumer pathways, including toys;
- 107 (kidney and liver effects) and 336 (testicular effects) for infants for combined environmental and consumer exposures, including toys.

Thus, the most advanced and up-to-date EU risk assessment for DINP concurs with that of the CPSC: DINP exposure from the mouthing of soft plastic toys poses no likely risk to children. Further, the

EU risk assessment for DINP demonstrates that exposure to DINP from other potential sources also poses no likely health risk. Under such circumstances, prohibiting the use of DINP in toys and childcare articles, whether or not they can be mouthed, is wholly scientifically unfounded.

U.S. National Toxicology Program Risk Assessments Support the Use of Phthalate Esters

The National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (NTP) has completed extensive risk assessments on the six phthalates that are the subject of various legislative inquiries with respect to toys and children's articles. The NTP assessed risks to human reproduction and development by creating a 16-member independent panel of scientific experts that reviewed the toxicity and exposure information related to each phthalate. After three public meetings at which the key studies and issues were discussed, the expert panel issued a report to NTP for each phthalate. Based on the expert panel reports, NTP then published a Brief for each phthalate, in which it reported its level of concern that the various phthalates cause developmental or reproductive effects in humans. The NTP Brief, expert panel report and responses to public comments were combined in a Monograph published for each phthalate.[81] The NTP's conclusions for each phthalate were:

- For DINP, the NTP found "***minimal concern***" for developmental or reproductive effects in children;
- For DIDP, the NTP found "***minimal concern***" for developmental effects in fetuses and children;
- For BBP, the NTP found "***minimal concern"*** for developmental effects in fetuses and children;
- For DBP, the NTP did not express a concern level for fetuses and children, primarily because of the low possibility of exposure from toys, but found "***minimal concern"*** for developmental effects when pregnant women are exposed to average levels of DBP;
- For DnOP, the NTP did not express a concern level for fetuses and children, also based on the low possibility of exposure, but expressed "***negligible concern***" for effects on adult reproductive systems;
- For DEHP, the NTP expressed "***serious concern***" only for critically ill male prematurely born infants with very high medical exposures, "***concern***" for infants of mothers with intensive medical treatments, and "***some concern***" for children older than one year, based on very high assumed exposures from all sources.

In sum, the NTP risk assessments typically expressed minimal concern for adverse developmental effects in fetuses and children, in particular for DINP, the phthalate most commonly used in toys. The only concern above "minimal" expressed by NTP was for very high exposures to DEHP, which is not

used in the manufacture of children's articles intended to be mouthed and therefore unlikely to approach these exposure levels.

An extensive body of research on phthalates, including several recently completed US and EU risk assessments, demonstrates that the use of phthalates as a plasticizer in toys and objects used by children poses little to no risk to children.

Additivity is Not a Concern

Some have expressed concern that exposures to phthalates could be added up and that this total could present a health hazard. Currently, reports of human hazard associated with aggregate or cumulative exposures to phthalates are limited, and no reproducible evidence of human hazard has been reported. However, based on recent U.S. Centers for Disease Control (CDC) biomonitoring data, humans are exposed to extremely low levels of several phthalates simultaneously (the detection of multiple phthalate metabolites in the urine confirms exposure, but does not inform considerations of hazard or risk). Exposure data published by the CDC indicate that levels of phthalates to which humans are exposed are much lower than doses with which additivity has been demonstrated in rodents.

It is also seen from the CDC data that maximum exposure in the most sensitive human subpopulations are still orders of magnitude less than doses with which additivity has been demonstrated in rodents.[82] Since the current reference dose for DBP (EPA IRIS) is 0.3 mg/kg/day, the estimated theoretical toxicity threshold for combined exposure to the most potent phthalate rodent toxicants DEHP, DBP, DiBP, and BBP would also be orders of magnitude higher than the RfD for DBP based on the simple dose addition model. It should be noted that synergistic effects – where the the presence of one chemical enhances the effects of the second – do not appear to be seen in tests.

Recent Human Studies Contain Serious Flaws and Do Not Suggest a Need for Action

Several recent statistical studies have been cited as supporting the view that phthalates may pose risks of reproductive health risks to humans from phthalates. These studies, however, while suggesting areas where additional scientific inquiry is desirable, are by no means dispositive, and in some cases contradict earlier findings in rodent studies.

Main Study

Danish researcher Katharina Main and co-authors of the study, "Human Breast Milk Contamination with Phthalates and Alterations of Endogenous Reproductive Hormones in Infants Three Months of Age," have suggested that exposure to phthalates affect reproductive hormones in baby boys.[83] Main's study involved taking breast milk samples during the first three post-natal months from the mothers of 130 boys and analyzing the samples for various phthalate esters metabolites. Sixty-two of the boys exhibited cryptorchidism, and 68 did not. The study, however, does not support Main's claims because it found no association between phthalate monoester levels and cryptorchidism. In addition, there was no significant correlation between MEHP and serum samples of gonadotropins, sex-hormone binding globulin (SHBG), testosterone and inhibin B.

Hauser Study

A second frequently cited study, conducted by Hauser et al. (2006), did not demonstrate an association between semen quality and levels of DEP metabolites in the urine.[84] The subjects were 463 males from subfertile couples and a group of control men. In general, the above statistical study provides results that are anecdotal in nature. They show a statistical association between a common chemical, or class of chemicals often used in personal care products, and a selected reproductive parameter. However, there is no causal relationship established, and there is no evaluation of other common, non-phthalate environmental chemicals. The latter evaluation would be necessary to establish that the increases in phthalate levels were not simply a biomarker of exposure to environmental chemicals in general, as opposed to a specific toxicant.

Swan Study

A third study which has been reported to associate phthalates with reproductive health risks was conducted by Shanna Swan *et al.*[85] This study was intended to test the hypothesis that *in utero* exposure to phthalic acid diesters blocks the action of testosterone in the male human fetus as reflected by changes in the anogenital distance (AGD), adjusted for body weight. Testosterone inhibition alters this parameter in reproductive tract studies of laboratory animals. This study examines statistical associations between

physical genital measurements in 85 boys, up to 28 months of age, and a corresponding set of measurements of phthalate monoester metabolites in single spot urine samples collected from their mothers during the pregnancy. The hypothesis of Swan *et al.* i.e., that exposures in the environment to several phthalates pose a hazard to male reproductive development, is not supported, however, due to five major flaws in the study:

> (1) The urine samples collected from the pregnant women are neither reliable nor valid for measuring their exposure to phthalates. The samples taken were not adjusted for variable fluid intake, were not adjusted for the time of day the samples were taken, and otherwise did not follow standard procedures, making the samples useless for obtaining accurate measurements of phthalate exposures.
>
> (2) The anogenital distance (AGD) measurement is of no known significance in humans. It is not a standard measurement in the practice of medicine and has never been related to any reproductive system problems. It is also difficult to measure accurately. Twenty per cent of the boys measured were dropped from the analysis because the researchers judged that reliable measurements could not be obtained for those boys. It is quite possible that many of the measurements on the remaining 80 percent also were not accurate.
>
> (3) Converting the AGD to an anogenital index (AGI) was an attempt to correct for varying weight and age, but ignores the fact that while the AGD does change with those two variables, the changes are not linear, and the correction is therefore incorrect. Also, the researchers did not compensate for other variables, like height or premature birth, in the infant's history.
>
> (4) In addition to the normal variations in weight and age, some measured infants were pre-term or even premature (which could well affect variables such as AGD, and genital effects), but were not excluded from the study.
>
> (5) It appears the researchers used the wrong statistical model to get their results. The statistical association claimed by the researchers is based on a model that predicts a relatively rapid decrease in AGI at low phthalate levels and much smaller decreases at higher levels. But this relationship is not biologically plausible; it should be the other way around. Thus, there is some question regarding the results of a study based on a possibly incorrect model.

The Swan study has been widely criticized as having significant flaws, and it is also noted as having been misreported by the press:

> [We] examined this study carefully and found some methodological problems, as well as a clear misinterpretation of the results by the press. The baby boys were not "demasculinized" in any way: the boys had a smaller anogenital index, which is a measure of the distance from the anus to the scrotum, adjusted for weight. In rats, under high doses of phthalates, this anatomical change also occurs, as does damage to the reproductive systems of the rats. In humans, no damage to the reproductive system was measured at all. And the shortened anogenital distance was well within

normal ranges for baby boys. (See http://www.stats.org/stories/WSJ_gives_skewed_phtha_oct05_05.htm)

Colon Study

A Puerto Rican study measured blood levels of a variety of substances – including phthalates – in young Puerto Rican girls with a condition called thelarche, or premature breast development.[86] Reporting of the study results appeared to have caused confusion. In fact, the authors of the study stated that phthalate esters "cannot be interpreted as the cause of premature thelarche in Puerto Rican girls." Several key points in support of this conclusion follow:

> (1) Phthalates have been tested for their ability to act as estrogens. The weight of the scientific evidence demonstrates that these substances are not estrogenic.[2] Without a strong indication that phthalates could induce an estrogenic response in laboratory animals, it is unscientific speculation to suggest that estrogen-induced effects, such as thelarche, could be produced by phthalates.
>
> (2) The authors observe the possibility for multiple causes of thelarche: "It may well be that the etiology of the various manifestations of premature sexual development (including thelarche) on this island is multifactorial."
>
> (3) Thelarche has been studied for years. Researchers have identified numerous possible causes and the authors themselves note: "The following have already been associated with premature sexual development in Puerto Rico: the presence of anabolic steroids in poultry and consumption of soy-based formula with a high phytoestrogen content by Puerto Rican infants."
>
> (4) There is a considerable body of scientific research that indicates phthalates do not affect the female endocrine system. In a recent review of the data on phthalates, the National Toxicology Program Center for Evaluation of Risks to Human Reproduction (CERHR) Expert Panel expressed no concern related to developmental effects in girls from phthalate exposures.

The apparent high incidence of thelarche in this population seems unusual and warrants continued investigation. The Colon study does not show phthalates to be a causative factor and, for the reasons stated above, believes it is highly unlikely that phthalates are a factor for thelarche.

In general, the above statistical studies provide results that are anecdotal in nature. They show a statistical association between a common chemical, or class of chemicals used in personal care products, and a selected reproductive parameter. However, there is no causal relationship established, and there is

no evaluation of other common, non-phthalate environmental chemicals. The latter evaluation would be necessary to establish that the increases in phthalate levels were not simply a biomarker of exposure to environmental chemicals in general, as opposed to a specific toxicant. Significantly, EPA has found that Swan and other epidemiological studies purporting to show a correlation between phthalate exposure and reproductive effects are unsuitable for use in the risk assessment process because they cannot demonstrate causation.[87]

Conclusion

From a toxicological perspective, BPA and phthalates are among the most well defined chemicals on earth. They have been the subject of hundreds of studies in lab animals and numerous government-sponsored assessments. Accordingly, based on the science and the use patterns for these compounds, no restriction on their uses in current applications is warranted at this time.

APPENDIX 1

EXTENDED SUMMARY OF THE UNITED STATES CONSUMER PRODUCT SAFETY COMMISSION RISK ASSESSMENT OF THE PHTHLATE ESTER, DINP

In 1998, the United States Consumer Product Safety Commission (CPSC), in response to a petition from several organizations to ban the use of PVC in products intended for children five years of age or under, undertook a rigorous investigation of the toxicology of DINP and of potential exposure of children to DINP from vinyl products. As part of its investigation, CPSC convened a Chronic Hazard Advisory Panel (CHAP) – a seven-member panel of independent experts who conducted a detailed review of the potential health hazards posed by DINP in products mouthed by children. The CHAP report, which was published on June 15, 2001,[88] came to the following conclusions regarding overall risk from exposure to DINP:

- "The CHAP concludes that humans do not currently receive DINP doses from DINP-containing consumer products that are plausibly associated with a significant increase in cancer risk."
- "[T]he risk to reproductive and developmental processes in humans due to DINP exposure is extremely low or non-existent."
- "There may be a DINP risk to young children who routinely mouth DINP-plasticized toys for 75 minutes per day or more. For most children, exposure to DINP from DINP-containing toys would be expected to pose a minimal to non-existent risk of injury."

The CHAP based its conclusions regarding children's risk on a plausible upper-bound estimate of DINP exposure of 0.28 mg/kg/day for 0-18 month old children, assuming those children mouth soft plastic toys for 3 hours every day.[89] However, in reaching its conclusion, the CHAP emphasized the uncertainty associated with available DINP migration rate data, and questioned the robustness of existing mouthing behavior studies relied upon to calculate the upper-bound estimate, stating that "important covariates such as developmental age, physical condition, ethnicity, and other sociodemographic indicators are not reported."[90] Because of these uncertainties, the CHAP described its estimated child DINP exposures as "preliminary at best."[91]

To more accurately estimate potential child exposures to DINP, the CPSC conducted an extensive, state-of-the-art study to quantify the cumulative time per day that young children spend mouthing all objects, including toys, and conducted additional migration rate studies. The child mouthing study, described in Greene (2002)[92] and Kiss (2001),[93] was conducted in two phases, in which more than 550 children ranging in age from 0 through 36 months were observed and their mouthing behaviors recorded. In Phase 1, the mouthing behaviors of 491 children ages 0 through 81 months were observed and recorded to the nearest minute by their parents or legal guardians for four 15-minute periods over two days. In Phase 2, a trained observer observed and recorded the mouthing behaviors of 169 children (109 of whom had participated in Phase I) ages 3 through 26 months for a total of four hours on at least two different days. The observer conducted the observations at different times of the day, and if the child attended a child care facility outside the home, attempts were made to observe the child there as well. Children were selected to ensure that the subjects were reasonably representative of the overall population with regard to race, income, type of child care and gender.

The CPSC's mouthing study revealed that for all objects other than pacifiers, which do not contain DINP, estimated average daily mouthing times were:

- 70 minutes for children between 3 months and 1 year of age;

- 48 minutes for children between 1 year and 2 years; and
- 37 minutes for children between 2 and 3 years of age.

For all soft plastic items other than pacifiers, which comprise the items that could contain DINP, estimated average daily mouthing times were only;

- 1.3 minutes for the 3-12 month olds
- 1.9 minutes for the 1-2 year olds; and
- 0.8 minutes for the 2-3 year olds.

Significantly, these data show that for even the youngest children, who typically mouth the most, the average mouthing time for all objects other than pacifiers is below the 75 minutes per day potential risk threshold identified by the CHAP. More importantly, the average amount of time children spend mouthing soft plastic toys, the objects that could contain DINP, is less than two minutes per day – far below CHAP's 75 minutes per day threshold, and far below prior mouthing estimates. In addition, these mouthing times are significantly lower than the times estimated by the Dutch Consensus Group study relied upon by the EU, which found average mouthing times for "plastic toys" of 17 minutes for 0-18 month olds.[94] As stated by the CPSC in its Executive Summary "[t]hese new mouthing data are much lower than earlier estimates and show an even smaller risk of exposure to DINP for children mouthing and chewing soft plastic toys."

In addition to the mouthing study, the CPSC also performed a migration rate study[95] using a modified head over heals (HoH) method developed and validated by the TNO Nutrition and Food Research Institute, CPSC, Canada Health and the European Commission's JRC.[96] CSPC tested 41 children's products that, according to their labeling, could be mouthed, sucked or chewed. Using the HoH method, the release of DINP was found to range from 1.05 to 11.09 μg/min/10cm^2.

Assuming that a child mouths a typical variety of objects and toys, the CPSC estimated that the most highly exposed group of children (those aged 3-12 months) had mean exposures to DINP of 0.07 μg/kg/day with a 95th percentile value of 0.44 μg/kg/day. These mean and 95th percentile exposure levels are, respectively, more than 1,700 and 270-fold below CHAP and CPSC's Acceptable Daily Intake (ADI) of 120 μg/kg/day.

The ADI is an estimate of the amount of chemical a person can be exposed to on a daily basis for an extended period of time (up to a lifetime) with a negligible risk of suffering deleterious effects. The ADI for DINP was calculated using a Benchmark Dose (BD_{05}) of 12 mg/kg/day and dividing by a 100-fold safety factor. The BD_{05} is generally considered more robust than a NOAEL, whose value is tied to an arbitrarily chosen dose level, because it takes into account all available dose response data. For DINP, the CPSC calculated the BD_{05} by fitting a mathematical model to pooled dose response data from two chronic exposure studies (Lington et al. 1997[97]; Moore 1998[98]). In this case, the BD_{05} of 12 mg/kg/day is not only more robust than a NOAEL from a single study, but is more conservative, as its value is lower than either of the two studies' reported NOAELs. Thus, the CSPC data indicate that a typical child's exposure to DINP from soft plastic toys is well below the ADI, a conservative estimate of safe exposure levels of DINP.

In addition to estimating exposure to a typical child, the CPSC also conducted a worst-case exposure estimate, hypothetically assuming that all toys, teethers and rattles that the children mouthed were made with DINP-plasticized vinyl, when in reality, only a portion of toys are made with soft plastic, only about a third of soft plastic toys contain DINP, and no rattles or teethers contain DINP. Even applying these very conservative assumptions, the estimated DINP exposures for children 3-12 months

were only 2.91 μg/kg/day (mean) and 10.71 μg/kg/day (95th percentile), still well below the CPSC's conservative ADI of 120 μg/kg/day.

On September 23, 2002, the CPSC released a briefing package that summarized the CPSC staff investigation of the potential risks of DINP in children's vinyl products. [99] The executive summary of that package states:

> Based upon the observation study, staff concludes it is very unlikely that children will mouth soft plastic toys for more than 75 minutes a day.[100]
>
> …
>
> The staff concurs with the CHAP conclusion that exposure to DINP from DINP-containing toys would be expected to pose a minimal to non-existent risk of injury for the majority of children. The new data from the behavioral observation study not only confirm this conclusion, but also demonstrate that children are exposed to DINP at lower levels than the CHAP assumed when it reached its conclusion. Also, since children mouth other products even less than they mouth toys and dermal exposure is expected to be negligible, there would be no justification for taking action against other products intended for children five years old and younger.

The overall CPSC staff risk assessment information and conclusions have been published in the peer reviewed literature.[101] In this publication, the authors state that they "conclude that oral exposure to DINP from mouthing soft plastic toys is not likely to present a health hazard to children."[102]

On February 21, 2003, the CPSC Commissioners voted unanimously to deny the petition to ban the use of PVC in products intended for children five years of age or under.[103] As indicated in the denial letter to petitioners, the Commissioners denied the petition based on the finding of CPSC that "there is no demonstrated health risk posed by PVC toys or other products intended for children five years of age and younger."[104]

[1] European Food Safety Authority. January 29, 2007. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) related to 2,2-BIS(4-HYDROXYPHENYL)PROPANE. A summary report and full report are available at http://www.efsa.europa.eu/en/science/afc/afc_opinions/bisphenol_a.html.

[2] European Commission. April 17, 2002. Opinion of the Scientific Committee on Food on Bisphenol A. Available at http://ec.europa.eu/food/fs/sc/scf/out128_en.pdf.

[3] Information on the CERHR evaluation, including the April 14 NTP draft brief, is available at http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol.html. The final report will also be posted on this site.

[4] European Union Risk Assessment Report – 4,4'-isopropylidenediphenol (Bisphenol-A). 2003. Available at http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/SUMMARY/bisphenolasum325.pdf (summary) and http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/bisphenolareport325.pdf (full report).

[5] European Commission. May 22, 2002. Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE); Opinion on the results of the Risk Assessment of: Bisphenol A; Human Health Part. Available at http://ec.europa.eu/health/ph_risk/committees/sct/documents/out156_en.pdf.

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END OF BISPHENOL A ENDNOTES * BEGINNING OF PHTHALATE ESTERS FOOTNOTES**

[62] Phthalates are a group of chemicals with a variety of uses, and not all phthalates are used in the same applications. Of the six phthalates typically discussed, DnOP, DEHP, DIDP and DINP are used principally to plasticize – i.e., soften and make less brittle – vinyl (or PVC). However, DnOP, DEHP and DIDP are used much less often in vinyl toys than DINP. Similarly, BBP also is used in vinyl products, but almost exclusively in vinyl flooring. Dibutyl phthalate (DBP) currently is not used in vinyl; it is used primarily in latex adhesives and cellulose plastics and as a solvent for dyes. DINP is by far the phthalate most commonly used in vinyl toys and children's products. Child safety is a primary reason for manufacturing flexible vinyl toys, as they are soft and durable, so will not break and form small pieces that are a choking hazard or have sharp edges.

[63] *See* ENDS Environment Daily, EU phthalate ban decision postponed, November 22, 1999, available at: www.environmentdaily.com/articles/index.cfm?action=article&ref=6501. At that time, members of CSTEE questioned whether the science supported a finding of an immediate risk and expressed their disagreement with the imposition of the emergency ban.

[64] CPSC, Petition Denial at 3 (quoting Memorandum from Marilyn L. Wind to the Commission, Response to Petition HP 99-1 (August 13, 2002), at 16-17).

[65]European Chemicals Bureau (2003). 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich and di-"isononyl" phthalate (DINP), CAS Nos: 68515-48-0 and 28553-12-0, EINECS Nos: 271-090-9 and 249-079-5, Summary Risk Assessment Report, Special Publication I.03.101, p. 18, available at http://ecb.jrc.it/.

[66]A more extensive summary of the CPSC report is Attached to these comments.

[67]CHAP (2001). Report to the US Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Diisononyl Phthalate (DINP), June 2001, *available at* http://www.cpsc.gov/LIBRARY/FOIA/Foia01/os/dinp.pdf.

[68]*See* Simoneau, C (2000) Standard Operation Procedure, "Determination of release of diisonylphthalate (DINP) in saliva stimulant from toys and childcare articles", JRC, European Commission, November 11, 2000.

[69] CPSC (2002). Response to Petition Requesting Ban of Use of PVC in Products (HP 99-1). US Consumer Products Safety Commission, Bethesda, MD, ("CPSC Risk Assessment") available at http://www.cpsc.gov/library/foia/foia02/brief/briefing.html (This url takes you to Commission briefing packages for

Fiscal Year 2002. The first seven links on that page are the complete staff briefing package on PVC/DINP. The first link (Part 1) contains the staff memo with the substance of their conclusions and recommendations. The remainder of that link and the other links provide supporting documentation.).

[70] CPSC's mouthing study found that children's mouthing times for soft plastic objects was less than two minutes per day. *Id.*

[71] Babich, M., Chen, S-B., Greene, M., Kiss, C., Porter, W., Smith, T., Wind, M. and Zamula, W. (2004). Risk assessment of oral exposure to diisononyl phthalate from children's products. Regulatory Toxicology and Pharmacology 40: 151-167.

[72] *Id.* at 165.

[73] Letter from Todd A. Stevenson, Secretary, CPSC, to Jeffrey Becker Wise, Policy Director, National Environmental Trust (February 26, 2003) (Petition Denial); available at http://www.cpsc.gov/library/foia/foia03/petition/Ageunder.pdf.

[74] CPSC, Petition Denial at 3 (quoting Memorandum from Marilyn L. Wind to the Commission, Response to Petition HP 99-1 (August 13, 2002), at 16-17).

[75] European Chemicals Bureau, European Union Risk Assessment Report: Dibutyl Phthalate, CAS No: 84-74-2, EINECS No: 201-557-4, Risk Assessment, with Addendum to the Environmental Section – 2004, 1st Priority List, Volume 29 (2003).

[76] European Chemicals Bureau, European Union Risk Assessment Report: European Chemicals Bureau, European Union Risk Assessment Report: 1,2-Benzenedicarboxylic Acid, Di-C9-11-Branched Alkyl Esters, C10-Rich and Di-"Isodecyl" Phthalate (DIDP), CAS Nos: 68515-49-1 and 26761-40-0, EINECS Nos: 271-091-4 and 247-977-1, Risk Assessment, 2nd Priority List, Volume 36 (2003).

[77] European Chemicals Bureau, European Union Risk Assessment Report: 1,2-Benzenedicarboxylic Acid, Di-C8-10-Branched Alkyl Esters, C9-Rich and Di-"Isononyl" Phthalate (DINP), CAS Nos: 68515-48-0 and 28553-12-0, EINECS Nos: 271-090-9 and 249-079-5, Risk Assessment, 2nd Priority List, Volume 35 (2003).

[78] European Chemicals Bureau, European Union Risk Assessment Report: Benzyl Butyl Phthalate, CAS No: 85-68-7, EINECS No: 201-622-7. Final Report of Norwegian Pollution Control Authority (2006).

[79] European Union Risk Assessment Report: Bis(2-ethylhexyl) phthalate, CAS No: 117-81-7, EINECS No: 204-211-0. Final Report of the Swedish Chemical Inspectorate (2006).

[80] European Chemicals Bureau, DINP Risk Assessment at 18.

[81] The NTP Monographs are available at: http://cerhr.niehs.nih.gov/reports/index.html.

[82] Maximum estimated human daily exposure to one of the most commonly used phthalates, DEHP, was calculated from measurements in children aged 3-14 (3.1 ug/kg/d).

[83] K. M. Main et al., "Human Breast Milk Contamination with Phthalates and Alterations of Endogenous Reproductive Hormones in Infants Three Months of Age," *Environmental Health Perspectives* 114 (2006).

[84] R. Hauser et al., Altered Semen Quality in Relation to Urinary Concentrations of Phthalate Monoester and Oxidative Metabolites," *Epidemiology* 17, no 6 (2006).

[85] S. H. Swan et al., "Decrease in Anogenital Distance among Male Infants with Prenatal Phthalate Exposure," *Environmental Health Perspectives* 113 (2007).

[86] Ivelisse Colon, Doris Caro, Carlos J. Bourdony, and Osvaldo Rosario, "Identification of Phthalate Esters in the Serum of Young Puerto Rican Girls with Premature Breast Development," Environmental Health Perspectives, Vol. 108, No. 9 (Sept. 2000).

[87] See, EPA Draft Toxicological Review of Dibutyl Phthalate (Di-n-Butyl Phthalate): In Support of the Summary Information in the Integrated Risk Information System(IRIS), available at: http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=457421.

[88] CHAP (2001). Report to the US Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Diisononyl Phthalate (DINP), June 2001, available at http://www.cpsc.gov/LIBRARY/FOIA/Foia01/os/dinp.pdf.

[89] The 3 hour upper bound exposure estimate was based on mouthing time data reported in a Dutch Consensus Group study. RIVM (1998). Phthalate Release from Soft PVC Baby Toys. National Institute of Public Health and Environmental Protection (RIVM), Report from the Dutch Consensus Group. RIVM Report 31 3320 002, Könemann WH (ed), Bilthoven, The Netherlands.

[90] *Id.* at 30.

[91] *Id.*

[92] Greene, MA (2002) Mouthing times among young children from observational data. US Consumer Products Safety Commission, Bethesda, MD.

[93] Kiss, C (2001) A mouth observation study of children under 6 years. Consumer Products Safety Commission, Bethesda MD.
[94] *See* CHAP (2001). Report to the US Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Diisononyl Phthalate (DINP), June 2001, p. 20.
[95] See Chen, SB (2002) Screening of toys for PVC and Phthalates Migration. US Consumer Products Safety Commission, Bethesda MD.
[96] *See* Simoneau, C (2000) Standard Operation Procedure, "Determination of release of diisonylphthalate (DINP) in saliva stimulant from toys and childcare articles", JRC, European Commission, November 11, 2000.
[97] Lington AW, Bird MG, Plutnick RT, Stubblefield WA, Scala RA (1997) Chronic toxicity and carcinogenic evaluation of diisononyl phthalate in rats. Fundam Appl Toxicol 36: 79-89.
[98] Moore MR (1998) Oncogenicity study in mice with di(isononyl)phthalate including ancillary hepatocellular proliferation and biochemical analyses. Covance Laboratory Report 2598-105, January 29, 1998.
[99] CPSC (2002). Response to Petition Requesting Ban of Use of PVC in Products (HP 99-1). US Consumer Products Safety Commission, Bethesda, MD, (CPSC Risk Assessment) available at http://www.cpsc.gov/library/foia/foia02/brief/briefing.html (This url links to Commission briefing packages for Fiscal Year 2002. The first seven links on that page are the complete staff briefing package on PVC/DINP. The first link (Part 1) contains the staff memo with the substance of their conclusions and recommendations. The remainder of that link and the other links provide supporting documentation.).
[100] CPSC's mouthing study found that children's mouthing times for soft plastic objects was less than two minutes per day. *Id.*
[101] Babich M., Chen S-B., Greene M., Kiss C, Porter W., Smith T., Wind M. and Zamula W. (2004). Risk assessment of oral exposure to diisononyl phthalate from children's products. Regulatory Toxicology and Pharmacology 40: 151-167.
[102] *Id*. at 165.
[103] Letter from Todd A. Stevenson, Secretary, CPSC, to Jeffrey Becker Wise, Policy Director, National Environmental Trust (February 26, 2003) (Petition Denial); available at http://www.cpsc.gov/library/foia/foia03/petition/Ageunder.pdf.
[104] Petition Denial at 3 (quoting Memorandum from Marilyn L. Wind to the Commission, Response to Petition HP 99-1 (August 13, 2002), at 16-17).