CERTIFICAT DE COMPÉTENCES EN LANGUES DE L'ENSEIGNEMENT SUPÉRIEUR
CLES

Langue : ANGLAIS
Session : 2009
Niveau : CLES 3

Dossier documentaire (textes)

Document 1

Danger in Plastic Baby Bottles?

Common Plastics Chemical Linked to Genetic Damage, by Daniel J. DeNoon, WebMD
Adapted from: *Health News*

March 31, 2003 — A chemical used in plastic baby bottles—and many other food and beverage containers—causes genetic damage in mice, a new study suggests. But the plastics industry says there is no cause for alarm.

The damage is seen in egg cells of female mice. When these cells try to divide, their chromosomes don't line up right. In humans this results in spontaneous abortion, birth defects, or mental retardation, says genetic abnormalities expert Patricia A. Hunt, PhD, of Case Western Reserve University School of Medicine.

In studies published in the April issue of the journal *Current Biology*, Hunt and colleagues showed that very low doses of a common plastics ingredient may cause these effects. They also found that dangerous amounts of the chemical—known as BPA—can seep out of used plastic bottles.

"The effect we saw is pretty dramatic," Hunt tells WebMD. "We were stunned by how low a dose it took. I am becoming pretty convinced there are significant effects [of BPA] at pretty low exposures. I can't say how scared you should be because our studies don't say anything about humans. But that's why we study animals. We assume the processes are pretty well the same in humans."

The chemical is known as bisphenol A or BPA. It's found in all kinds of common products, mostly polycarbonate plastics. Nearly all plastic baby bottles in the U.S. are made of this kind. So are many common food containers, water storage bottles, aluminum can linings, and even some kinds of dental sealants.

Other animal studies have linked BPA to low sperm count, hyperactivity, early puberty, obesity, small testes size, and enlarged prostates. But Hunt's is the first study to suggest that BPA can affect future generations.

Frederick S. vom Saal, PhD, professor of biology at the University of Missouri in Columbia, has studied BPA for many years. He says that some 40 studies show that polycarbonate plastics are dangerous. Hunt's findings scare him most of all.

"What is so important about this finding is we are talking about something that causes spontaneous abortions of babies," vom Saal tells WebMD. "And then there is the horrifying fact that babies are born with these chromosomal abnormities. . . . This is a higher level of concern, a major new finding of a really profound adverse effect of this chemical in mice that were just drinking out of old baby bottles."

Document 2

Polycarbonate Plastics and Bisphenol A Release

Adapted from Bisphenol-A.org

Bisphenol A (BPA) is a key building block of polycarbonate plastic. In recent years a number of researchers from government agencies, academia and industry worldwide have studied the potential for low levels of BPA to migrate from polycarbonate products into foods and beverages. These studies consistently show that the potential migration of BPA into food is extremely low, generally less than 5 parts per billion, under conditions typical for uses of polycarbonate products.

Using these results, the estimated dietary intake of BPA from polycarbonate is less than 0.0000125 milligrams per kilogram body weight per day. This level is more than 4000 times lower than the maximum acceptable or "reference" dose for BPA of 0.05 milligrams per kilogram body weight per day established by the U.S. Environmental Protection Agency.

Stated another way, an average adult consumer would have to ingest more than 600 kilograms (about 1,300 pounds) of food and beverages in contact with polycarbonate every day for an entire lifetime to exceed the level of BPA that the U.S. Environmental Protection Agency has set as safe.

The European Commission's Scientific Committee on Food (SCF) has also recently confirmed the safety of polycarbonate plastic products for contact with foods and beverages. The SCF estimated total dietary intake of BPA from all food contact sources, including polycarbonate plastic products and epoxy resin coatings, to be in the range of 0.00048 to 0.0016 milligrams per kilogram body weight per day, which is below the Tolerable Daily Intake set by the SCF of 0.01 milligrams per kilogram body weight per day.

The study data and analyses show that potential human exposure to BPA from polycarbonate products in contact with foods and beverages is very low and poses no known risk to human health. The use of polycarbonate plastic for food contact applications continues to be recognized as safe by the U.S. Food and Drug Administration, the European Commission Scientific Committee on Food, the United Kingdom Food Standards Agency, the Japan Ministry for Health and Welfare and other regulatory authorities worldwide.

April 28, 2008
Source: http://www.bisphenol-a.org/human/polyplastics.html

Document 3

Perspectives | **Editorial**

Bisphenol A: Where to Now?

doi:10.1289/ehp.12492

Recently, *Time* magazine published an article titled "The Year in Medicine: From A to Z" (Park et al. 2008). The letter "B" was represented by the controversy over bisphenol A, a ubiquitous chemical used in polycarbonate and polyvinyl chloride plastics and epoxy resins and found in the urine of > 90% of Americans. The debate over whether bisphenol A poses a threat to human health has been brewing for the better part of the past decade.

On 3 September 2008, the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) weighed in by releasing a report that significantly contributes to this ongoing discussion. The *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A* (NTP 2008a) identified evidence from experimental animal studies that raised "some concern" that current levels of exposure to human fetuses, infants, and children may result in developmental changes in the prostate gland and brain and diminish sexually dimorphic behaviors. "Some concern" represents the mid-point of a five-level scale of concern used by the NTP that ranges from "negligible" to "serious" concern. A lower level, "minimal concern," was also expressed for possible changes in development of the mammary gland and an earlier age of attaining puberty in females.

The NTP's opinion on the level of concern for effects of bisphenol A on human reproduction and development stemmed from a 2-year analysis of a very limited number of available human studies but nearly 1,000 studies in experimental animals. Many of the laboratory studies explored effects on offspring of pregnant rodents receiving "low doses" of bisphenol A (< 5 mg/kg body weight/day, and including studies performed with much lower doses) during critical periods of development. The NTP Board of Scientific Counselors (2008) provided peer review and suggestions for refinement of the NTP CERHR's conclusions (NTP 2008a), and the Science Board to the Food and Drug Administration (FDA 2008a, 2008b) also expressed agreement with the evaluation.

The NTP's evaluation of bisphenol A expressed "some concern" because many of the developmental effects reported in laboratory animals were observed at exposures to bisphenol A similar to those experienced by humans. Collectively, the findings could not be dismissed. Similar conclusions were reached by Health Canada (2008) and by participants at a workshop examining the potential relationship between bisphenol A and negative trends in human health (vom Saal et al. 2007). However, the NTP CERHR report (NTP 2008a), as well as other reviews, identified many areas of uncertainty and data gaps that should be addressed to fully understand bisphenol A's potential to harm human development.

In the months since release of the NTP-CERHR report (NTP 2008a), the literature on exposures and potential human health effects of bisphenol A has continued to grow (Calafat et al. 2008; Hugo et al. 2008; Lang et al. 2008; Leranth et al. 2008), raising public concern and generating more questions. Lists of research needs have been assembled (NTP 2008a; vom Saal et al. 2007). The NTP and the National Institute of Environmental Health Sciences (NIEHS) Division of Extramural Research and Training (DERT) recently issued a request for information

(RFI) to the scientific community seeking information to help focus future research and testing activities (NTP 2008b). The RFI seeks information about *a*) ongoing research on the health effects of bisphenol A; *b*) unmet research needs; and *c*) suggestions for collaboration and cooperation between investigators to improve efficiency and timeliness in filling the information gaps. Together, the NTP and DERT will carefully consider the responses to this RFI as we develop research programs and explore other ways to address these issues in the future.

The RFI (NTP 2008b) listed a number of general topics that scientists have consistently raised as areas where research is needed: *a*) the need to better understand sources of human exposures; *b*) the need to compare the metabolism of bisphenol A among rodents, nonhuman primates, and humans and understand how it changes with age; *c*) the need for physiologically based pharmacokinetic (PBPK) models to provide a scaffold for quantitatively assessing the consistency of outcomes across studies performed with widely different doses and designs; and *d*) the need for additional developmental toxicology studies of traditional design and power, but with modifications to provide the capability to detect the range of effects reported in academic studies as well as functional consequences as the animals age.

The NTP has begun work in several areas. In collaboration with the Centers for Disease Control and Prevention and academic investigators, we are facilitating an evaluation of exposures to bisphenol A in infants in neonatal care settings and in children < 6 years of age. Together with the FDA National Center for Toxicological Research, we have initiated studies to obtain the data for constructing PBPK models in rodents and nonhuman primates, and we are planning studies to explore the long-term consequences of perinatal exposure to bisphenol A in order to understand the potential impact to humans of the developmental changes reported in numerous laboratory animal studies. Collectively, the results of these studies should begin to chip away at the uncertainties and research gaps and provide a better perspective of the potential threat that exposure to bisphenol A poses to public health.

The author declares he has no competing financial interests.

John R. Bucher
NTP, NIEHS
National Institutes of Health
Department of Health and Human Services
Research Triangle Park, North Carolina
Environmental Health Perspectives • volume 117 | number 3 | March 2009 A 9

Document 4

BPA may pose greater threat to newborns

by MARTIN MITTELSTAEDT
adapted from *Tuesday's Globe and Mail*
February 24, 2009 /ENVIRONMENT REPORTER

Bisphenol A, the controversial chemical used to make plastic, lingers far longer in the bodies of babies who ingest it than in adults because they lack a crucial liver enzyme needed to break it down, according to researchers at the University of Guelph.

The finding prompted one of the researchers to recommend that parents try to make sure their babies have no exposure to bisphenol A, and that pregnant women minimize what they ingest to protect their developing fetuses.

Last year Health Canada added BPA to its toxic-substances list and banned baby bottles made with the chemical. *(JONATHAN HAYWARD/THE CANADIAN PRESS)*

Len Ritter, professor at the university's department of environmental biology and the study's lead author, said infants "do appear to have significantly greater levels ... up to 11 times higher [than adults]. That's not trivial."

The study, published in Environmental Health Perspectives, is likely to put further pressure on Health Canada to step up its efforts to control bisphenol A (also known as BPA), a synthetic compound that has raised concerns because it mimics estrogen.

Bisphenol A is used to make polycarbonate and the linings of most food and beverage cans. It is also an additive in many types of plastic. Because it is not tightly bound in consumer packaging, trace amounts can leach into food and drinks.

Last year, the federal agency added the chemical to Canada's toxic-substances list and announced a ban on plastic baby bottles made from it, the first country in the world to take such actions.

Health Canada also said it wanted infant formula makers to minimize the amounts seeping out of can linings, but neither the companies nor the government have finalized control measures.

Health Canada said in a statement in response to questions from *The Globe and Mail* that it met last month with the U.S. Food and Drug Administration, infant formula makers and canning companies to develop a North American approach to the reduction of BPA in food products.

Health Canada believes pregnant women don't need to reduce their exposure, but said in the statement that pregnant or breastfeeding women with concerns can reduce exposure by using non-polycarbonate plastic containers to heat foods or using alternatives such as glass or stainless-steel containers.

Many researchers are worried that through exposure to BPA, people are getting what amounts to an extra dose of estrogen. Animal experiments have found the chemical is associated with hormonal conditions, such as earlier onset of sexual maturity in females, and breast cancer, particularly when exposure occurs during fetal or neonatal periods.

In the new study, Dr. Ritter used models based on animal and human experiments to estimate how long it would take babies to clear the chemical from their bodies, compared with adults, when both were given equivalent doses, adjusted for their differing body weights.

Adults have a well-developed capacity to metabolize BPA into a harmless form that is quickly excreted in urine. Dr. Ritter said this capacity isn't fully developed in newborns, allowing BPA to build up in their blood to 11 times what an adult would have.

Infants gradually gain the ability to detoxify BPA, and by three months would still have about double adult levels of the chemical, he said.

Researchers don't know precisely when infants gain a fully developed capacity to metabolize BPA.

http://www.theglobeandmail.com/servlet/story/RTGAM.20090224.wlbpa24/BNStory/specialScienceandHealth/home

Document 5

BPA Experts Find Hundreds of Errors in Government Assessment

August 6, 2007

Dr. Michael D. Shelby
Director
Center for the Evaluation of Risks to Human Reproduction
National Institute of Environmental Health Sciences
Department of Health and Human Services
P.O. Box 12233
MD EC-32
Research Triangle Park, NC 27709

Re: **Failure of CERHR Assessment of BPA to Meet Basic Scientific Standards.** Supplemental Comments on the Interim Draft NTP-CERHR Report on the Reproductive and Developmental Toxicity of Bisphenol A.

Dear Dr. Shelby:

You must be aware of the publication last week of a consensus statement on bisphenol A (BPA) signed by 38 independent specialists in BPA toxicity from around the world. These scientists concluded that BPA presents a clear risk to human health (CHCS 2007). The statement and the comprehensive review papers that accompany it underscore, by way of contrast, the hopeless corruption of the ongoing review of BPA being conducted by your Center, the Center for the Evaluation of Risks to Human Reproduction, or CERHR.

The Environmental Working Group (EWG) has conducted a detailed analysis of the comments by 9 scientists conducting BPA research at 5 laboratories in the U.S. and E.U., submitted to you as public comments in response to CERHR's interim draft BPA assessment (Vandenberg et al. 2007; Schonfelder 2007; Prins 2007; vom Saal 2007; Welshons 2007; Zoeller 2007). Our analysis shows that the CERHR panel's assessment of BPA utterly fails to meet basic, universally understood standards for scientific reviews and data quality, including those laid out in NIH policy and federal law.

These standards require that assessments be accurate, unbiased, consistent, complete, and conducted by those with the necessary expertise to ensure objectivity. Instead, our review of scientists' comments reveals that the CERHR assessment might contain nearly 300 errors of fact and interpretation; is biased, inconsistent, incomplete; and clearly fails to meet the most basic scientific standards. Among our findings, which are detailed in the attached table, are that the CERHR assessment is:

- **Inaccurate – 297 errors:** Reviewers identified 297 potential errors in documentation and analysis of study results, and in interpretation of the study findings and their significance, that are in conflict with the peer reviewed literature.
- **Incomplete – 195 instances of incomplete study reviews:** Reviewers documented 195 instances where the panel assessment is incomplete, including incomplete documentation of relevant test results or missing justifications for panel assertions.
- **Inconsistent – 48 basic inconsistencies:** Reviewers documented 48 instances in which the panel inconsistently applied criteria for study evaluation.

- **Biased.** The assessment heavily favors industry studies over government and independent studies. In its most recent assessment, the Panel rejected government and independent studies at nearly 3 times the rate of industry studies (Vandenberg et al. 2007).

Consider also the following, striking differences between the CERHR panel and the BPA panel which released the consensus statement last week (this panel convened in Chapel Hill, NC, and is referred to as the "Chapel Hill panel" for purposes of this document).

Both panels are funded by NIH, but are different in almost every other aspect:

- **The objectivity of the CERHR assessment is compromised by CERHR contractor's potential conflicts of interest.** CERHR panel members were selected by a contractor subsequently fired over potential conflicts of interest. The panel lacks members with expertise in BPA, and has just 12 members to assess over 500 BPA-related papers. The initial draft was prepared by the contractor who was fired over potential conflicts of interest, calling into question the validity of the contractor's work. In contrast, the Chapel Hill panel includes 38 of the world's most published BPA experts from top universities and government institutions.

- **The accuracy and consistency of the CERHR assessment is compromised by the panel's lack of organization.** Within the CERHR panel, study reviews were conducted independently by each scientist, prompting one panel member to state in a recent article in Risk Policy Report that "one thing that has plagued this review is that each reviewer was assigned a bunch of papers, and they reviewed them without any other input." In contrast, the Chapel Hill review was conducted in a highly structured, organized manner: 4 breakout groups were each asked to address 4 critical issues related to BPA, and only if there was consensus among all 4 groups were responses incorporated into the final consensus statement.

- **The objectivity, accuracy, and consistency of the CERHR assessment is compromised because it has not been subjected to a standard peer review.** The assessment of the CERHR panel has not been subjected to standard peer review. Hundreds of factual errors and errors of interpretation, inconsistencies, and completeness were found in current draft upon external review by BPA experts. In contrast, the work of the Chapel Hill panel was subjected to standard and comprehensive internal and independent external peer review…….

….The public has now paid for two assessments of BPA toxicity, the one conducted by your panel, which has failed to meet the most basic standards for the conduct of scientific reviews; and a peer reviewed assessment by a panel of BPA specialists (the Chapel Hill panel), which issued its final assessments last week. If you proceed with the CERHR panel process the public will have to pay for this assessment four times all told, because your assessment will require both a thorough peer review, and a complete revision from top to bottom of the current, corrupted document.
This is a high-stakes public health issue. Given the need to restore public confidence in your process after the conflict of interest concerns that have plagued it, we urge that, instead of trying to salvage the hopelessly broken work of CERHR on BPA, you instead dissolve your current panel and adopt the recommendations that the Chapel Hill panel issued last week.

(…)

Sincerely,

Anila Jacob, M.D., M.P.H, Senior Scientist/ Jane Houlihan, Vice President for Research

Source URL: http://www.ewg.org/node/22696

Document 6

THE GREENER ISSUE

In Praise of Plastic

By Keith O'Brien | *The Boston Globe*, September 28, 2008

Plastic—symbol of a bankrupt consumer society from its maxed-out credit cards to its obsession with in-bulk acquisition—is about as popular these days as an oil spill. People love to hate plastic for the petroleum used to produce it, for the litter it becomes, for the space it takes up in landfills, and the damage it can do in oceans. At one point this year in the United States alone, the plastics industry faced some 400 pieces of anti-plastics legislation, including one on Beacon Hill and another in Plymouth. Plastic bags—for the plastic-haters, anyway—are especially evil. The goal of most of the proposed laws is taxing the use of plastic bags or banning them outright. And though most have failed or wound up tabled, the anti-plastics people have had their victories, too. Namely, Seattle.

In July, the city of Seattle banned polystyrene takeout food packaging (think Styrofoam coffee cups or soup bowls) and placed a 20-cent tax on plastic bags that is set to go into effect January 1. The City Council's vote, supported by the mayor, shook a plastics industry that was still reeling from a panic in the spring. Parents concerned over the use of a possibly harmful chemical called bisphenol A, found in some clear plastic baby bottles among other things, ditched the bottles in droves, and some stores and manufacturers did the same. Then there was the phthalate ban, enacted by Congress over the summer, singling out yet another worrisome chemical often found in plastic toys.

Overall, it has been a bad year for plastics. But, quietly, the plastics industry, plastics engineers, and plastics lovers—yes, they do exist—are making a case for what may be a misunderstood touchstone of our times. "We see the legislative debates as an opportunity to tell the story of plastics," says Steve Russell, managing director of the plastics division at the American Chemistry Council, the group that represents the plastics industry. " Plastics, Russell and others argue, aren't just durable, convenient, and inexpensive to manufacture; innovative new plastic packaging is actually more energy-efficient than other alternatives and helps users reduce, not increase, their carbon footprints. Replacing the plastic packaging that is in use today, according to one European study, would use four times as much material from other sources, like paper or aluminum. The key reason why: Plastic is lightweight. Less packaging means less waste and less energy spent on transport—and packaging is hardly the only application for plastic.

Builders use plastic to wrap new homes, cutting down on heat loss and increasing energy efficiency. Boeing's new 787 Dreamliner, which relies so heavily on carbon fiber reinforced plastic (a type of acrylic) construction that some have dubbed it the "plastic plane," uses 20 percent less fuel than any other airplane of its size.

There are these benefits, the plastics industry points out, and then there's the obvious one: Plastics are recyclable, able in most cases to be used over and over again. The problem is, Americans, even as global warming becomes an accepted truth, don't take recycling seriously. In 2006, Americans consumed more than 29 million tons of plastic, but recycled just 2 million tons of it, a paltry 7 percent. And as much as supposed Boston liberals driving their

hybrid cars and toting their canvas grocery bags might like to blame this failure on the Red States, that argument simply doesn't fly.

PLASTIC HAS BEEN THROUGH TOUGH TIMES BEFORE. In March 1987, a barge ferrying more than 3,000 tons of garbage left Long Island bound for a landfill in North Carolina. But officials there turned the garbage barge away. And with nowhere else to go, the barge wandered for months from port to port. It was ultimately turned away by six states and three foreign countries. No one wanted New York's trash.

So New York finally took it back. That September, the garbage was burned in a Brooklyn incinerator. The barge, called Mobro 4000, became a symbol for American waste, and much of the vitriol, right or wrong, fell on the plastics industry. Within weeks, lawmakers from New York to California were threatening to ban or tax certain kinds of plastics.

Frank Ackerman remembers the scandal—he could relate to the backlash. As a researcher in the early 1990s ,Ackerman believed, like many people, that plastic packaging had to be worse for the environment than, say, glass. It just seemed like common sense. Plastic products are made with oil and natural gas, finite resources, while glass, for example, is made primarily with sand, "which the world," Ackerman says, "is not going to run out of any time soon."

But in a study Ackerman completed for the US Environmental Protection Agency 1992, examining the environmental impact of different types of packaging, he came to exactly the opposite conclusion. "The biggest difference," he says, "turned out to be how heavy a package was." The lighter, the better. "A smaller, lighter package," Ackerman says, "just uses less raw material." Plastic, not glass, was a winner. "We were astonished," Ackerman says. "Our guess was all wrong."

Newer studies have supported Ackerman's early findings. A 2007 analysis—performed by an independent research firm but paid for by the American Chemistry Council—looked closely at the environmental impact of half-gallon milk jugs, and again plastic fared well. The typical high-density polyethylene, or HDPE, jug was lighter than other alternatives, required less energy to produce, and generated in its life cycle (including shipping) less than half the greenhouse gas emissions of glass and 25 percent less than paper milk cartons. The study confirmed that plastic's major benefit is the fact that it's lightweight.

The American Chemistry Council, representing the $268 billion plastics industry, has used these sorts of arguments to make a case for the industry in recent years. It's true, says Kevin Swift, the council's chief economist, that about 169 million barrels of oil were used to make plastic in the United States last year. But that was less than 3 percent of our total oil consumption, he says, "a rather modest amount."

This durable, convenient product keeps food from spoiling, allowing individuals to make fewer, more efficient trips to the grocery store. Applying a thin layer of polyethylene wrap to just one newly constructed house, they say, will save the equivalent of roughly 8,300 gallons of gasoline over the next 30 years.

Instead of banning plastic, proponents argue, governments should increase recycling efforts. In many cases, this would be a relatively simple solution.

Document 7

Adapted from: *Environ. Health Perspect*. 2005 August; 113(8): 926–933. PMCID: PMC1280330
Published online 2005 April 13.

An Extensive New Literature Concerning Low-Dose Effects of Bisphenol A Shows the Need for a New Risk Assessment

By vom Saal, F., Hughes, C.

The Definition of "Low Dose"

The U.S. EPA considers "low-dose" effects of environmental endocrine-disrupting chemicals to refer to effects being reported for chemicals at doses lower than those used in traditional toxicologic studies conducted for risk assessment purposes. For BPA, the lowest dose studied for risk assessment purposes was 50 mg/kg/day, which is the currently accepted lowest observed adverse effect level (LOAEL) that was used to calculate a reference dose of 50 µg/kg/day based on experiments conducted in the 1980s (IRIS 1988).

BPA is often described as a very "weak" estrogen because in a few assay systems, such as MCF-7 breast cancer cells in culture, the dose of BPA required to stimulate cell proliferation (~ 10^{-7} M or 23 ppb) is roughly 100,000 times higher relative to estradiol, which stimulates cell proliferation at approximately 10^{-12} M (Welshons et al. 1999). This contrasts, however, with the stimulation by BPA of calcium influx in MCF-7 cells that was significant at the lowest dose tested, which was 10^{-10} M or 23 ppt (Walsh et al. 2005). BPA also stimulated calcium influx and prolactin secretion in rat pituitary tumor cells at the lowest dose tested (10^{-12} M or 0.23 ppt), and the magnitude of the response to BPA was similar to the response to the same dose of estradiol (Wozniak et al. 2005). It is difficult to conceive how a chemical that can alter cell function at concentrations < 1 ppt can be characterized as a "weak" endocrine disruptor.

Low-dose effects of endocrine-disrupting chemicals such as BPA are mediated by endocrine-signaling pathways that evolved to act as powerful amplifiers, with the result that large changes in cell function can occur in response to extremely low concentrations (Welshons et al. 2003). Thus, information concerning the *in vivo* potency of estradiol is critical with regard to predicting the *in vivo* bioactivity of chemicals such as BPA. *In vivo* potency of estrogenic chemicals is determined by the affinity of the chemical for the specific type of estrogen receptor (ER) that mediates the effect, the rate of absorption and metabolism, and binding of the chemical to plasma estrogen-binding proteins. The initial interest in low-dose effects of BPA was based on the observation that BPA showed limited binding to plasma estrogen-binding proteins (Nagel et al. 1997), which results in higher free plasma BPA relative to estradiol. It is well known that it is the free hormone level in blood that is predictive of biologic activity (Nagel et al. 1999). A much higher free BPA concentration in blood relative to estradiol would not be taken into account in predicting its *in vivo* potency based simply on cell culture studies conducted in culture medium.

Before conducting the first low-dose *in vivo* study with BPA, vom Saal et al. (1997) found that an increase in size of the fetal mouse prostate occurred in response to an experimental increase in free serum estradiol in fetuses of 0.1 pg/mL serum (0.1 ppt or 0.4×10^{-12} M), from 0.2 pg/mL in control fetuses to 0.3 pg/mL free serum estradiol in estrogen-exposed fetuses. Although this finding was initially controversial, other *in vivo* and *in vitro* studies have since confirmed that very low doses of the estrogenic drug diethylstilbestrol (DES) stimulate an increase in size of the fetal mouse prostate (Gupta 2000; Timms et al. 2005). Nagel et al. (1997) predicted the dose of BPA (fed to pregnant mice) that should be biologically active in

mouse fetuses based on a comparison of BPA and estradiol in terms of both the relative affinity for nuclear ERs and binding to serum estrogen-binding proteins that effectively restrict estradiol (but not BPA) uptake into cells. This has been referred to as a "physiologic approach" to dose selection (vom Saal et al. 1998). Nagel et al. (1997) chose the fetal prostate growth bioassay to test the physiologically based prediction of low-dose estrogenic activity of BPA, although the prediction was that any estrogenic response would be altered by exposure to BPA during early development. Nagel et al. (1997) reported finding an enlarged prostate in male offspring after feeding pregnant mice 2 or 20 μg/kg/day BPA. Because these doses are below the current reference dose, this finding received a considerable amount of attention.

The findings by Nagel et al. (1997) raised a critical question: Why were the estrogenic effects that they observed below the current reference dose not predicted based on traditional toxicologic studies that focused on the toxic effects of very high doses of BPA (Morrissey et al. 1987)? The toxicologic approach involves dose selection based on the maximum tolerated dose, which can be described as "top-down dose selection," whereas the physiologic approach used by Nagel et al. (1997) can be described as "bottom-up dose selection" (Welshons et al. 2003). We show below that there is now overwhelming evidence demonstrating that these different experimental approaches lead to very different conclusions of safety with regard to the current reference dose for BPA of 50 μg/kg/day. Findings based on low-dose studies thus present a strong challenge to the assumptions that form the basis for chemical risk assessments.

Why Did the APC Contract with the HCRA to Write a Report on Low-Dose Effects of BPA?

The controversy created by reports of findings for BPA and other chemicals at "low doses," and studies funded by chemical corporations that quickly disputed these findings, resulted in the U.S. EPA asking the National Toxicology Program (NTP) to host a meeting in October 2000 on the low-dose issue. The final NTP Low Dose Peer Review report (NTP 2001) was summarized by the co-chairs and session organizers (Melnick et al. 2002).

In contrast to today, at the time of the NTP low-dose meeting there were relatively few published low-dose studies with BPA. However, the NTP report (NTP 2001) was critical of some of the industry-funded studies of BPA. […]

When the initial report of the NTP panel was released, the APC quickly issued a public letter in which the conclusion of the NTP panel—that there was "credible evidence of low-dose effects"—was described as "troubling . . . if not erroneous" (Bisphenol A Global Industry Group 2000). The APC then contracted with the HCRA in 2000, which established a panel of scientists (including coauthor C.H.) to perform a weight-of-the-evidence evaluation of available data on the developmental and reproductive effects of exposure to BPA in laboratory animals. In turn, the HCRA panel focused on 19 published studies of the available 47 publications and, particularly, on the effects of low doses of BPA on development of the reproductive system in male rodents. The conclusions in the panel's published report (Gray et al. 2004) were directed to this portion of the literature that was intensively scrutinized, but the wording was promptly interpreted by plastic industry trade organizations as suggesting that a far more complete survey of the BPA literature had been encompassed by the panel's review process (APM 2005; vom Saal 2005). As of April 2002, there were 47 available publications that could have been examined in a comprehensive review of all low-dose effects of BPA in all species. Because of the charge to the HCRA panel and its response to that charge, it reviewed 7 of 9 (78%) of the industry-funded published studies, but reviewed only 12 of 38 (38%) of the government-funded studies that were available in the published literature.