GROCERY MANUFACTURERS ASSOCIATION
SCIENCE POLICY PAPER

Bisphenol A

A GUIDE FOR CONSUMERS, POLICYMAKERS AND THE MEDIA

GMA
The Association of Food, Beverage and Consumer Products Companies

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The **Grocery Manufacturers Association (GMA)** represents the world's leading food, beverage and consumer products companies. The association promotes sound public policy, champions initiatives that increase productivity and growth and helps to protect the safety and security of the food supply through scientific excellence. The GMA board of directors is comprised of chief executive officers from the Association's member companies. The $2.1 trillion food, beverage and consumer packaged goods industry employs 14 million workers, and contributes over $1 trillion in added value to the nation's economy. For more information, visit the GMA website at **www.gmaonline.org**.

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FOREWORD

This paper addressing Bisphenol A (BPA) is one in a series written by the Grocery Manufacturers Association (GMA) to explore some of the most important food-related science policy issues before consumers and policymakers.

The Grocery Manufacturers Association represents the world's leading food, beverage and consumer products companies. The Association promotes sound public policy, champions initiatives that increase productivity and growth, and helps to protect the safety and security of the food supply through scientific excellence. One of the Association's goals is to ensure that the laws and regulations governing food marketing and production are feasible, practical and based on sound information.

Each of our science policy papers includes a review of key scientific peer-reviewed published articles, regulatory considerations, food and beverage applications and market insights. The Association's goal in publishing these white papers is to provide current, scientifically accurate resources to journalists, health professionals, policy makers, interested consumers and other stakeholders.

For more information, visit the Grocery Manufacturers Association website at **www.gmaonline.org/science/index.cfm**. ■

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INTRODUCTION

At the heart of all good science, reproducibility of findings and consistency of diverse observations are vital.

The debate surrounding the safety of Bisphenol A (BPA) in consumer products follows two very different paths.

On one hand, a considerable, well-developed body of peer-reviewed and validated findings from reputable scientists and scientific organizations indicate that BPA is safe, indeed very safe (margins of safety in the tens of thousands) to children and adults. On the other hand, a small number of vocal critics present conclusions and opinions that are inconsistent with accepted scientific rigor and practice.

Their findings are embellished with hypotheses and conjectures suggesting — *without benefit of replication* — that BPA may be injuring exposed humans in many ways by somehow disrupting the proper functioning of the endocrine system.

BPA is a chemical used as a monomer in the manufacture of polycarbonates and epoxy resins. It is used in food contact material for a variety of purposes, including the prevention of corrosion of cans and contamination of foods when used as an epoxy can coating and increased heat resistance and durability when used in bottles. ■

EXECUTIVE SUMMARY

The overall health and safety data on Bisphenol A (BPA) are robust, reliable, reproducible, and consistent with understanding of the chemical's behavior in the body including interactions with reproductive organs and the developing offspring.

It is noteworthy that international organizations, such as the World Health Organization (WHO), when faced with all of the reliable data and taking into account the existence of non-replicable and non-replicated data, have so far found no basis to issue health warnings about BPA. In addition, the WHO has not generated major evaluative documentation about the risks and safety of BPA in society. The lack of concern by WHO may be based on evaluations of several international organizations reporting no concern that BPA might pose a health risk to consumers. In 2002, for instance, the Health and Consumer Protection Directorate of the European Commission published its "Opinion of the Scientific Committee on Food on Bisphenol A" (European Commission, 2002) which concluded that a Total Daily Intake (TDI) of 0.01 mg/kg body weight per day is considered safe. In 2003, the European Chemical Bureau of the European Union published in "Risk Assessment Report on Bisphenol A" in which it listed the margins of safety from assorted foods to range in the thousands to the tens of thousands as a measure of the safety of ingested BPA (European Chemicals Bureau, 2003). In 2006, the European Scientific Panel on Food Additives, Flavourings, Processing Aids, and Materials in Contact with Food reported its findings to the European Commission that the TDI of 0.01 mg/kg bw contained an adequate margin of safety (Scientific Panel, 2006). Finally, in 2007, the Japanese National Institute of Advanced Industrial Science and Technology (NAIST) reported on its thorough review of health and safety information on BPA that the "human risk of BPA exposure is below the level of concern" (NAIST, 2007). All of these panels of experts reached the same conclusions by examining the worldwide body of scientific evidence, including that which purports to claim that BPA is injuring human health, and have concluded such claims are based on unreliable data.

Furthermore, the Harvard Center for Risk Analysis convened a panel to evaluate the weight-of-evidence for the potential reproductive and/or developmental toxicity of BPA (Gray *et al.*, 2004). The panel stated the following conclusions:

> "No consistent affirmative evidence of low-dose BPA effects for any endpoint…Lack of adverse effects in two multiple-generation reproductive and developmental studies casts doubt on suggestions of significant physiological or functional impairment…Differences in the pattern of BPA responses compared to estradiol or diethylstilbestrol (DES) cast doubt on estrogenicity as a low-dose mechanism of action for BPA…There is indirect evidence that humans may be less sensitive to possible estrogenic effects from BPA exposure due to pharmacodynamic factors."

By contrast, the adverse finding of BPA critics has not been reproduced despite repeated attempts by not only the original investigators but also other investigators

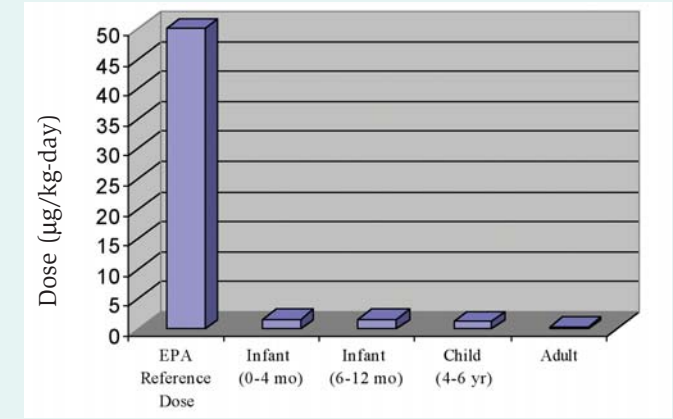
using different approaches and sophisticated methodologies. A major failing of the critics is that their findings frequently misrepresent the relevance of their conclusions for humans. Specifically, they make major leaps of faith in assuming that results of *in vitro* data are extrapolated directly to humans without taking the pains to validate the biological connection between experimental subjects exposed to unphysiological conditions and the more complex human organism. This approach leads inevitably to mischaracterization of the toxic potency and risk estimates for humans exposed to BPA in everyday life.

The following illustrations provide a powerful method that puts the discussion of possible human health risk in its proper context. Scientifically, the safety of BPA in foods may be shown by comparing actual doses to what U.S. Environmental Protection Agency (U.S EPA) considers a safe level of exposure, a Reference Dose (RfD). The RfD applies to total daily exposure from all sources, relies on the best toxicological science to estimate risk, and incorporates highly conservative approaches to account for uncertainties and to extrapolate findings from laboratory animal studies to the human population. This body of work is then peer-reviewed to assure its robustness.

The latest studies of assorted design provide no evidence to alter this conclusion of the EPA on the safe level of exposure of BPA.

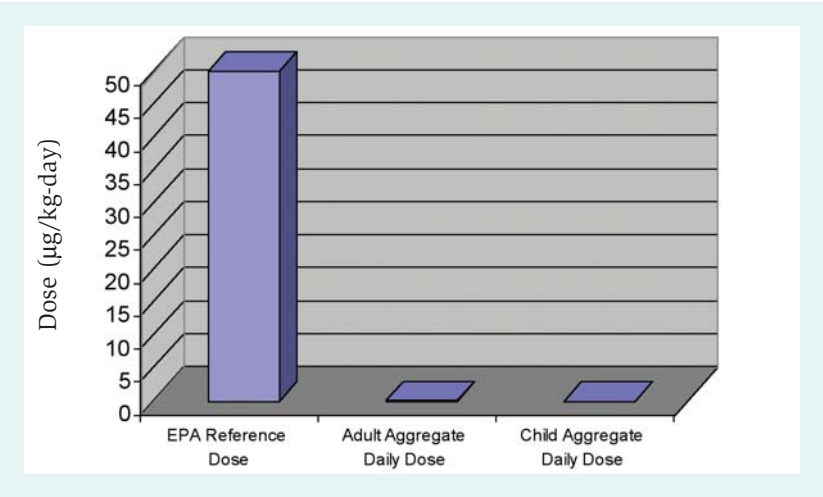
Comparing the RfD for BPA to the actual human doses from foods based on dietary intake, demonstrates a considerable safety margin to protect against any possible adverse effects, no matter how small, to human health is *more than 100 times greater than estimated human exposure to BPA* (*Figure 1*).

Figure 1. Comparison of RfD for BPA to the Daily Exposure to BPA *Dietary Intake* for Infants, Children and Adults (micrograms per kilogram body weight per day)



Recognizing that people can be exposed to BPA not only in foods but also via other media, the RfD can be compared to the measured aggregate exposure, estimated from urinary metabolite data, as is shown in *Figure 2*. Here also, one readily observes a considerable safety margin to protect against any possible adverse effects, no matter how small, to human health.

Figure 2. Comparison of U.S. EPA RfD for BPA to the *Aggregate Daily Exposure* to BPA for Children and Adults (micrograms per kilogram body weight per day)



A similar set of comparisons can be made using an RfD that was estimated for BPA by investigators from California's Department of Toxic Substances Control. Applying the RfD methodology to contemporary data on BPA, they derived an RfD equivalent that is one-third that of the RfD estimated by U.S. EPA in 1993 (Willhite *et al.*, 2008). This RfD equivalent, based on systemic toxicity and considered protective of any possible reproductive or developmental toxicity, obviously encompasses a substantial margin of safety for human exposure to BPA from dietary intake (*Figure 3*) and aggregate exposure estimated from urinary metabolite data (*Figure 4*).

Figure 3. Comparison of Willhite *et al.*, (2008) RfD equivalent for BPA to the Daily Exposure to BPA *Dietary Intake* for Infants, Children and Adults (micrograms per kilogram body weight per day)

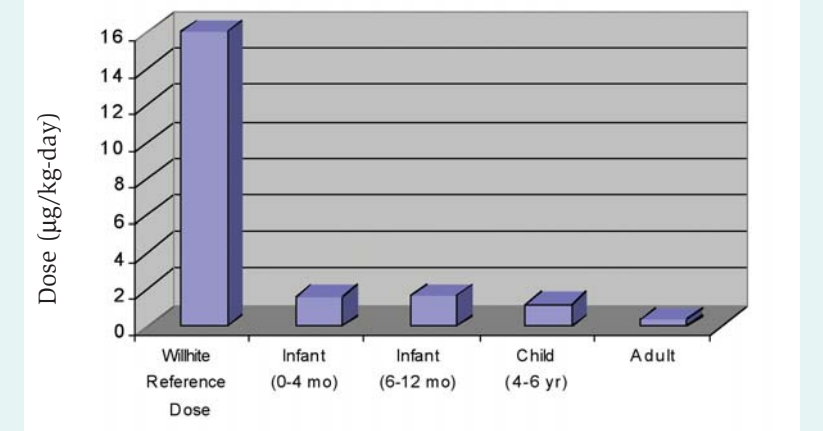
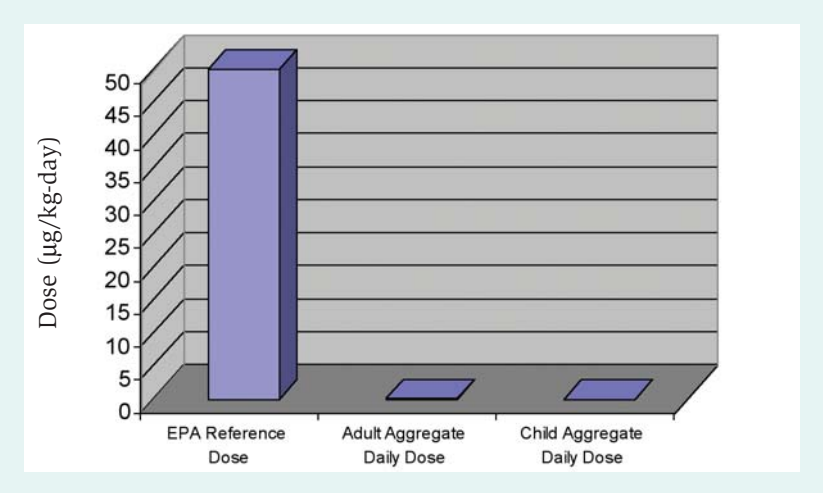


Figure 4. Comparison of Willhite *et al.* (2008) RfD equivalent for BPA to the *Aggregate Daily Exposure* to BPA for Children and Adults (micrograms per kilogram body weight per day)



In sum, the most up-to-date and highest quality science available demonstrates clearly that human exposures from BPA are so much smaller than regulatory levels widely acknowledged to be safe for all forms of toxicity. Relying on these data, therefore, one can reliably conclude that BPA presents no tangible danger to humans.

Research initiatives are to be encouraged, not so much because of the presence or suspicion of a danger, but rather to advance knowledge about how a chemical like BPA functions in the body of humans and other species. ■

DISCUSSION:

RISK SCIENCE

Sources of concern from some members of the scientific community that BPA at very low doses causes injury to human health are not credible.

Concerns have been raised by a few groups and a relatively small yet vocal fraction of investigators (most notably Frederick vom Saal and co-workers) in this field about the potential for a relationship between Bisphenol A (BPA) and alleged trends in human health outcomes in recent decades (*e.g.*, abnormal penile/urethra development in males, early sexual maturation in females, an increase in neurobehavioral deficits such as attention deficit hyperactivity disorder and autism, an increase in childhood obesity and Type II diabetes, a regional decrease in sperm count, and an increase in hormone-mediated cancers, such as prostate and breast cancers (vom Saal *et al.*, 2007)).

The basis of these concerns stems from only two published animal studies (Nagel *et al.*, 1997; vom Saal *et al.*, 1998) reporting a questionable relationship between treatment with "low" doses of BPA and effects on the male reproductive system indicative of an estrogenic mode of action as reported in vom Saal *et al.* (2007)[1]. In addition, experimental animal studies and *in vitro* mode-of-action studies have been cited by these same investigators to postulate molecular mechanisms that they believe could perhaps mediate such effects; and these same investigators have reported that these events are occurring within the range of exposure (*i.e.*, µg/kg body weight) to BPA of the so called "typical" human living in a developed country such as the U.S. *It is important to note that no one has yet replicated their original findings; and no one has reported evidence in support of their hypotheses.*

These particular investigators have engaged in making quantum leaps of at least two types: (1) from broadly based information about endocrine disruptors to BPA; and (2) from *in vitro* and *in vivo* laboratory studies of questionable scientific rigor and of suspect relevance to humans to definitive statements about causation in humans.

1 Also known as the Chapel Hill Census Statement.

The definition of "low" dose of BPA in this and other scientific documents refers to administration of doses to laboratory animals below those that had been used in traditional toxicity studies conducted in support of risk assessments for humans. Prior to the past few years, the lowest dose of BPA examined and found to be relevant for human health risk assessment was *50,000 µg/kg body weight per day*, from rat and mouse chronic (103 week; rodent lifespan) studies conducted by the National Toxicology Program (NTP, 1982). Based on this earlier information, the U.S. EPA established a RfD for BPA of *50 µg/kg body weight per day* based on reduced body weight gain [and with no pathology reported in estrogen-sensitive tissues] in male and female rats ingesting 50,000 µg BPA/kg body weight per day, adjusted by an uncertainty factor of 1000 (a conservative value commonly applied by U.S. EPA).

The estrogen-mimicking ability of BPA had been known since the 1930s, when research efforts were underway to synthesize non-steroidal chemicals with estrogenic-like activity for potential therapeutic use. This activity led to the discovery of BPA, which showed *weak* estrogenic activity to relatively high concentrations of BPA in the rodent uterotrophic assay[2] (Dodds and Lawson, 1936)

A few years later, the potency of BPA in eliciting estrogenic responses was found to be quite weak and considerably less than that of naturally occurring estrogen:

- *In vitro* studies indicated that BPA was approximately *15,000 times less potent* than 17β-estradiol, the most potent natural estrogen found in the human body (Gaido *et al.*, 1997).
- BPA was shown to interact with the estrogen receptors with a binding affinity and potency approximately *10,000-fold less* than that of 17β-estradiol.
- BPA produced an estrogen-like effect in the rat uterotrophic assay following a subcutaneous injection, with a potency of *10,000-fold less* than that of

2 The uterotrophic assay is used to evaluate whether chemicals or substances have the same physiological effect on the uterus in the body as estrogen, which is to promote the menstrual cycle. In this assay, normal cyclic estrogen levels in the rat are eliminated by using young, prepubertal (immature) animals or by removing the ovaries, which produce the cyclic production of estrogen. If a substance has estrogenic activity, it would promote the menstrual cycle in the rat, which can be measured by the increase in uterine weight. Furthermore, as far back as 1993, BPA had been shown to leach in tiny amounts from autoclaved polycarbonate flasks, confounding experiments that had been designed to investigate whether yeasts cells produce estrogen (Krishnan *et al.*, 1993). This assay is considered a particularly sensitive tool for screening substances that have estrogenic activity, raising hypotheses as to whether such effects might be present in whole animals ingesting the test substances.

17β-estradiol.

- BPA was shown by several investigative groups to produce an estrogenic effect (*i.e.* premature vaginal opening, increased uterine and vaginal weight, and reduced duration of estrous cycle) on the reproductive organs of female rats at high oral or subcutaneous doses (Ashby and Tinwell, 1998; Cook *et al.*, 1997; Kim *et al.*, 2001; Laws *et al.*, 2000).

For any chemical such as BPA, the presence of an estrogen-mimicking ability raises the possibility that it may also alter reproductive function in exposed females and males. In the 1970s and 1980s, BPA was tested in animal reproductive toxicity studies using internationally accepted protocols of one-generation (rat) or two-generation continuous breeding (mouse) study designs (Morrissey *et al.*, 1989; Wazeter and Goldenthal, 1984a,b) to ascertain whether BPA did indeed impair reproductive function. These studies showed that BPA produced no selective reproductive toxicity (*i.e.*, in the absence of systemic toxicity) at high dietary concentrations. Furthermore, in internationally accepted protocols designed to detect developmental toxicity (*i.e.*, anatomical birth defects) in the absence of general systemic toxicity, high oral doses of BPA produced no adverse affects in the fetuses (Morrissey *et al.*, 1987).

In contrast to these "high" dose studies (>30,000 µg/kg), Nagel *et al.* (1997) and vom Saal *et al.* (1998) reported that (1) prostate gland weight was increased and (2) daily sperm production (DSP) per gram testis was decreased in male CF-1 mice offspring that had been exposed *in utero* to very low oral doses of BPA (2 and 20 µg/kg). Although prostate weight development is dependent on serum androgen (*i.e.*, testosterone) levels in the body, it was hypothesized, but never proven, by the investigators that estrogens might modulate the action of androgen in regulating prostate differentiation and weight.

To rationalize their observations, vom Saal and coworkers proposed that estrogen and estrogen-like substances, such as BPA, have a non-monotonic inverted-U shaped relationship between dose and response (Nagel *et al.*, 1997; vom Saal *et al.*, 1998). In other words, they claimed that the previous animal studies on BPA were conducted at doses that were too high to see an effect compared to low doses. *However, this supposed dose-response relationship of theirs is contradictory to a fundamental principle of toxicology that, as the dose increases beyond the effectiveness of bodily defense mechanisms, the toxic responses increase (*i.e.*, an S-shaped curve) — that is, "the dose makes the poison!"*

An essential element of the scientific method is the reproducibility of initial observations. The uniqueness of the low-dose findings of Nagel *et al.* (1997) and of vom Saal *et al.* (1998) has led to several attempts to replicate their work and to test the sensitivity of their hypothesis, and all are without success:

- More robust studies designed with larger number of animals and the same doses (Ashby *et al.*, 1999) produced no corroborating evidence.
- Adding lower and higher doses (Cagen *et al.*, 1999a) did not produce the same results such as the alleged U-shaped curve.
- Testing the statistical significance of the decreased daily sperm production per gram testis reported in male CF1 mice exposed *in utero* at BPA dose 20 µg/kg, the data from Ashby *et al.*, (1999) could not be confirmed (NTP, 2001).
- Sharpe *et al.*, (1995) reported significantly reduced testes weights in male offspring of female Wistar rats exposed to approximately 100 to 400 µg BPA/kg per day (1 ppm BPA in their drinking water) for eight to nine weeks during pre-breeding, mating, gestation, and lactation, however these same authors *could not reproduce their own initial findings* (Sharpe *et al.*, 1998).
- In addition, Cagen *et al.* (1999b) were also unable to reproduce the study by Sharpe *et al.* (1995) using the same exposure route, timing, and strain of rat, but with a larger number of doses, and/or parental routes of administration (*i.e.*, higher experimental power).
- Two comprehensive *multi-generation* reproductive toxicity studies — one in Sprague-Dawley rats and the other in CF-1 mice — recently conducted using internationally standardized test protocols and performed using Good Laboratory Practice (GLP) guidelines failed to find any "low"-dose effects of BPA (Tyl *et al.*, 2002; Tyl *et al.*, 2006).
- Furthermore, a Crj:CD(SD)IGS rat *two-generation* reproductive toxicity study conducted by Ema *et al.* (2001) also showed no evidence of a low-dose effect of BPA.
- The type of feed used in some of the studies may have affected the results also has been raised as a possible confounding factor; the studies of Cagen *et al.* (1999a,b) and Tyl *et al.* (2002) have been criticized for using a commercial animal feed that has been reported to be variable in its estrogenic activity, presumably from naturally occurring phytoestrogens in the feed (Thigpen *et al.*, 2003); however, no compelling evidence indicates that the type of feed administered in the studies by Ashby *et al.* (1999) and Cagan *et al.* (1999) can explain the negative results reported.
- In the studies of Ashby *et al.* (1999) and Cagen *et al.*

(1999a,b), the positive control diethylstilbestrol failed to show a difference from the negative controls, indicating a major deficiency in the experimental system; the rat three-generation reproductive toxicity study by Tyl *et al.* (2002) did not include a positive control, also a major limitation in attempting to ascertain the significance of their findings.

- Recent studies, which have taken into account animal strain, feed, and use of positive controls, do *not* show "low" dose reproductive effects, again *failing to reproduce the original studies of vom Saal and coworkers*. The mouse two-generation reproductive toxicity study by Tyl *et al.* (2006) used the sensitive mouse strain CF-1 and estradiol as a positive control — which showed the expected estrogenic effects. The USEPA, conducted a "low"-dose exposure study of male rat offspring that had been exposed to BPA *in utero* (pregnant rat dams were given oral doses of BPA) and during lactation through milk, and found *no* adverse effects on the reproductive organs or epididymal sperm counts, whereas effects were observed with the positive control, ethinyl estradiol (Howdeshell *et al.*, 2008).
- Other factors that have been evaluated *unsuccessfully* to explain the contradictory nature of these studies conducted on BPA have been: (1) statistical power; (2) age of the animal when terminated in the study; (3) inadequate control for confounders like body weight of individual animals; (4) individual versus group housing of test animals; and (5) failure to account for potential effects of intrauterine position (variations in natural hormonal exposures due to proximity to males or females during prenatal development) (Gray *et al.*, 2004).

Considerable debate has ensued on the validity of the studies by Nagel *et al.* (1997) and vom Saal *et al.*, (1998) and why others could *not reproduce* these results. Questions have been raised concerning the animal strains used, with the possibility that some studies used animals that are naturally more sensitive to BPA's effects than other strains. It is noteworthy that Nagel *et al.* (1997) and vom Saal *et al.* (1998) used mice bred in-house (University of Missouri) for over two decades, and that this strain no longer exists. The possibility exists that due to genetic drift, the mice used by Nagel *et al.*/vom Saal *et al.* had become more sensitive to estrogenic effects than the commercially used strains in those studies that reported negative findings, raising serious concerns about the relevance of these data for humans as genetic variability would be the opposite of the highly inbred test strain. Variation in strain sensitivity to estrogenic effects, as well as increased sensitivity due to inbreeding, have been well documented (Spearow *et al.*, 1999; 2001).

Since the publication of the work of vom Saal and coworkers, two other published review papers have reported effects of BPA at "low" doses in experimental animal models and in *in vitro* cell systems (Richter *et al.*, 2007; Wetherill *et al.*, 2007). Although the focus of most of these studies has been on BPA's estrogenic activity, investigators have reported that BPA also interacts with other hormone-response systems *in vitro* (such as the androgen and thyroid hormone receptor signaling systems), as well as effects on the male and female reproductive system, the brain and behavior, pancreatic cells, and the immune system (NTP, 2007; Richter *et al.*, 2007). Findings from these studies are difficult to interpret in the context of human and animal disease because they were conducted under grossly unphysiological conditions. Many of the *in vitro* studies are highly mechanistic in nature, with few, if any, studies linking the observed changes to any clinical disease. Hence, in the absence of any correlation between molecular changes and actual disease or physiological impairment, the relevancy to human health cannot be established

While BPA can be demonstrated and replicated to produce changes in cellular systems, without clinically adverse effects that can be replicated in standardized *in vivo* animal studies, the relevance of these biochemical findings cannot be established even in the test species much less in humans. A significant issue that has not been addressed in considering the relevance of these *in vitro* and animals studies, including the original vom Saal studies, is the generalization of the effects to health outcomes in humans. For example, no consistent correlation exists between changes in prostate size and either prostate pathology or prostate cancer in the animal models. *None* of the studies reporting alleged low-dose effects of BPA (and estradiol and DES) reported any pathological or tissue damage, making it impossible to establish a link between changes in organ weight and pathologic outcome.

The question of reproducibility, as well as the problem of generalizing the results from laboratory experiments, particularly *in vitro* studies, to human disease and definitive sounding conclusions, has plagued this area of research on "low" dose biological effects of BPA. The vom Saal *et al.* studies are not the only ones to not be replicated, the findings of a study by Hunt *et al.* (2003) also have not been reproduced. Hunt *et al.* (2003) reported that injecting[3] female mice with BPA resulted in a significant increase in meiotic abnormalities in the oocytes when exposure was pre-puberty. This effect was also observed in mice that were housed in polycarbonate bottles that had been damaged by exposure to a harsh detergent dur-

[3] Results in much higher blood levels and tissue concentrations that could be achieved via ingestion.

ing washing. The exaggerated implications of this study drawn by the investigators are that exposure of women to low dose of BPA before puberty may lead to infertility in mature females. *Yet again, attempts to reproduce the study have been unsuccessful, even when mice were fed a diet low in the possible confounders (namely, phytoestrogens)* (EFSA, 2006). *As a result, the original findings cannot be used to infer or conclude that the observed effects are relevant to humans exposed to low doses of BPA found in foods.*

While human data are lacking, laboratory animal carcinogenicity assays have noted no cancer risks (European Commission, 2002; European Chemicals Bureau, 2003; Scientific Panel, 2006; NAIST, 2007). Recently published exploratory molecular and cellular studies have further examined the carcinogenic possibility of BPA (Ho *et al.*, 2006; Prins *et al.*, 2008, Dairkee *et al.*, 2008). The findings do not alter the original conclusion because these studies reflect changes observed at the molecular and, therefore, are as yet of uncertain relevance to humans or human cancer.

Kinetic data (that decide a chemical's behavior in the body) indicate that BPA at levels found in foods is unlikely to injure human health

Major species differences exist between rodents and humans in the way that BPA is handled in the body (*i.e.*, kinetics). For example, major differences are known in the disposition of BPA–glucuronide, an inactive form of BPA from conjugation of BPA with glucuronic acid in the intestinal wall and liver, due to different pathways of elimination from the liver in rodents and humans. In humans, BPA is rapidly absorbed from the gastrointestinal tract, and is conjugated with glucuronic acid in the wall of the small intestine and in the liver (Vandenberg *et al.*, 2007). The BPA-glucuronide, which is devoid of estrogenic activity, is rapidly excreted in urine resulting in a terminal elimination half-life of BPA of less than six hours. In rodents, however, the BPA glucuronide formed is excreted from the liver with bile into the gastrointestinal tract. Enterohepatic circulation of BPA result from cleavage of BPA-glucuronide in the intestinal tract; and reabsorption of BPA from the intestine results in slow elimination of BPA in rodents. This quantitative difference in the elimination of BPA between humans and rodents means that *much higher doses of BPA are needed to produce effects in humans compared with rodents*, a fact overlooked by vom Saal and co-workers.

To date, the kinetic studies that have been conducted on BPA have used single, acute exposure and not continuous, low-level exposures. It has been argued that, because BPA is rapidly eliminated from the body and because measurable levels of free, unconjugated BPA are known empirically to be present in human blood and urine, two potential explanations / hypotheses have been raised (Welshons *et al.*, 2006):

1) BPA intake in humans may be actually much higher than had been suggested, and/or

2) Long-term, daily intake leads to bioaccumulation of BPA — only if exposure were continuous and intake were greater than excretion — leading to steady-state levels that are not represented by any of the current models for BPA metabolism, which are based on single, acute administration (Teegarden *et al.*, 2005).

Vandenberg *et al.* (2007) have stated that the "low" dose effects of BPA reported in experimental animal studies, as well as in *in vitro* systems, occur at circulating levels of unconjugated BPA below median current human exposures of approximately 1–3 ng/ml serum. This argument is based on an *unsubstantiated extrapolation* of the results from existing animal metabolic studies in which high oral doses were compared to the oral exposure levels used in the "low"-dose studies (a difference of > 10,000-fold). This approach allows for estimates of the circulating levels of parent, unconjugated BPA in animals that showed adverse effects in low-dose *in vivo* studies, despite not being measured directly in any study of oral toxicokinetics. The estimate of the ranges of circulating levels of BPA that are active in "low"-dose animal studies were compared to current measurements of circulating levels of parent, unconjugated BPA that have been measured in human blood and tissues, and to the concentrations of BPA that are active in human and animal cell culture studies *in vitro*. It was concluded by Vandenberg *et al.*, (2007), improperly, that the presumed adverse effects of "low" doses of BPA in laboratory animals exposed both during development and adulthood occur at levels that have been found in humans. This hypothesis remains unproven with no supporting or corroborating data.

Human observations do not support the contention that "low" doses of BPA injure, or are likely to injure, human health

Only five epidemiology studies exist in the published literature on BPA exposure and effects in humans (Takeuchi *et al.*, 2002; Hanaoka *et al.*, 2002; Takeuchi

et al., 2004; Hiroi *et al.*, 2004; Sugiura-Ogasawara *et al.*, 2005). In Takeuchi and Tsutsumi (2002), a cross-sectional descriptive study assessed BPA serum concentrations and hormone status in two small groups of women (14 healthy women in mid-follicular phase of menstrual period and 16 women with polycystic ovary syndrome (PCOS)) and one small group containing 11 healthy men. Compared to normal women, serum BPA concentrations were significantly higher in women with PCOS and healthy men. Additionally, serum BPA concentrations reported a significant positive association with total and free testosterone in all groups, but not with any other hormone, however, no confounders were taken into account during the analytical process, raising question about the reliability of the findings.

Hanoaka *et al.*, (2002) conducted a small cross-sectional study among 42 male workers occupationally exposed to BPA diglycidyl ether with a matched control of non-exposed workers. Urinary BPA concentrations were measured and assessed with respect to hormone levels. No association between urinary BPA concentrations and plasma testosterone and luteinizing hormone was reported, but an insignificant correlation was reported between urinary BPA concentrations and decreased levels of plasma follicle stimulating hormone (FSH). When data were adjusted for alcohol ingestion, a significant association between urinary BPA concentrations and the decrease in plasma FSH concentrations was observed. These findings show no association between BPA ingestion and specific clinical conditions.

Hiroi *et al.*, (2004) compared serum BPA concentrations in women with endometrial hyperplasia and a control group in a small cross-sectional study. Serum BPA levels were significantly decreased in women with complex endometrial hyperplasia compared with those with simple endometrial hyperplasia and the control group. In addition, serum BPA levels in postmenopausal women with endometrial cancer were also significantly lower than both the control group and women with simple endometrial hyperplasia. Despite the fact that the authors suggest an association between BPA and complex endometrial hyperplasia and endometrial cancer, it is impossible to determine whether BPA exposure preceded the disease from these data.

In the study by Takeuchi *et al.* (2004), a small cross-sectional descriptive study assessed 73 women with respect to serum BPA, hormone concentrations, and their clinical condition at a single point in time. Women were categorized clinically as normal (either obese or nonobese), or having various ovarian functions[4] (again either obese or nonobese). The six groups in the study each contained as many as 19 subjects (nonobese control group) and as few as six subjects (PCOS obese group). Serum BPA was reported to be higher in women with PCOS (both obese and nonobese) and obese normal women versus normal women who were nonobese. This study has been interpreted by vom Saal and Hughes (2005) and Environmental Working Group (2007) to suggest an association between blood levels of BPA and clinical disease (*i.e.*, obesity) in women. This, however, is not the case. Given the study design, it is not possible to determine whether the exposure preceded the clinical condition or whether the clinical condition affected the individual's level of exposure.

Similarly, the study by Sugiura-Ogasawara *et al.* (2006) reported a statistically significant ($p < 0.024$) relationship between blood levels of BPA and recurrent miscarriage[5] in Japanese women. Recurrent miscarriage is an unusual medical condition that is believed to be due to genetic factors, infections, anatomical malformations,; the only reported chemical-related association has been with smoking, alcohol, selenium (deficiency only), and pentachlorophenol (a chemical used as a timber preservative). Further studies are needed to determine whether BPA is specifically associated with either ovarian disease or miscarriage.

Relevance of Exposures to BPA via Foods and Environmental Sources

In November 2007, the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) released an expert panel report on the reproductive and developmental toxicity of BPA as consumed through the human diet. That expert panel reviewed the relevant laboratory animal, *in vitro*, and human data to evaluate the weight-of-evidence to determine whether BPA can be considered a reproductive or developmental toxicant for humans who ingest it as part of everyday life.

The expert panel also reviewed literature and data on exposure, BPA food migration, oral intake and urinary excretion and assessed the daily exposure estimate the child and adults. This expert panel determined that ingestion of food products that have been in contact with epoxy resin coatings and polycarbonate tableware or bottles (rather than environmental exposure, such as soil contact)

4 Hyperprolactinemia, hypothalamic amenorrhea, or polycystic ovary syndrome.

5 Recurrent miscarriage is defined as 3 or more consecutive miscarriages during the first trimester (Sugiura-Ogasawara *et al.*, 2006).

provide the greatest potential for human exposure to BPA. In addition, the data evaluated by CERHR generally represented realistic exposure scenarios to provide more accurate estimates of daily exposure. These data are presented in *Table 1*.

TABLE 1. Estimates of United States General Population Intake of BPA

Exposure Source	Population	BPA (µg/kg-day bw)	Notes
Estimates Based on Intake			
Formula	Infant	1	Assumes 4.5 kg bw, 700 ml formula at 6.6 µg/L BPA (U.S. canned formula max)
Breast Milk	Infant	1	Assumes 4.5 kg bw, 700 ml at 6.3 µg/l (U.S. breast milk max)
Food	Infant (0–4 mo)	1.6	European Commission data
	Infant (6–12 mo)	0.8–1.65	European Commission data
	Child (4–6 yrs)	1.2	European Commission data
	Adult	0.37 (canned food) 0.48 (canned food + wine)	European Commission data
Aggregate	Child (1.5–5 yrs)	0.04–0.07	Max 0.07–1.57 assumes 50% absorption
Estimates Based on Urinary Metabolites			
Aggregate	Child	0.07	U.S. 6–8 yr old girls (max 0.00217)
	Adult	0.026	U.S. population 95th percentile 0.00159

"Aggregate" = all foods, air, dust, and soil (Table 104 from NTP 2007)

Using estimated oral intake data, the CERHR Expert Panel calculated the potential BPA exposure for infants on formula (1 µg/kg-day) and breast milk (1 µg/kg-day). For BPA intake from canned food, the panel relied on European Commission data, because the European estimates of BPA concentrations were comparable, although slightly higher, to those in the United States. The European data were based on food migration studies and conservatively assumed 100 percent oral absorption. For infants, BPA exposure was calculated to be 1.6 µg/kg-day for 0–4 months of age and 0.8–1.65 µg/kg-day for infants 6–12 months of age.

The European intake estimates for children (1.2 µg/kg-day) were described as *realistic worst-case scenarios* for food and drink intake relative to body weight. The panel relied upon data from two U.S. diet studies for child aggregate intake exposure data. The BPA concentrations in food determined in those U.S. studies were slightly lower than the European data, but considered comparable, so the European data were used for the food alone estimates. The adult exposure estimate calculated from European intake data was 0.37 µg/kg-day for canned food alone and 0.48 µg/kg-day for canned food in combination with wine.

The aggregate (*i.e.*, food, air, dust and soil) intake exposure estimates for children were reported to be 0.04-0.07 µg/kg-day and were calculated assuming 100 percent absorption and took ventilation rates, time spent indoors (home and daycare)/outdoors, body weight, dust and soil ingestion (assumed data), and total weight of food consumed was taken into consideration. The authors reported that 99 percent of exposure of BPA occurred through dietary ingestion, with food and beverage containers, such as cans and infant bottles, as the greatest source of human exposure to BPA.

Aggregate exposure for children and adults was also estimated using data from urinary metabolite excretion studies. It has been shown that nearly 100 percent of BPA will be excreted in urine within 24 hours after a single exposure (NTP, 2007), which allows BPA exposure to be estimated either through actual measurements or with the powerful Monte Carlo simulation models. The CERHR panel relied upon data from a study that evaluated the urinary metabolites of 90 U.S. girls (6–8 yrs) to calculate the child aggregate exposure estimate of 0.07 µg/kg-day, while the adult aggregate exposure estimate (0.026 µg/kg-day) was determined from a study that utilized the U.S. Government's NHANES III survey data (*Table 1*). A high degree of concordance between the child aggregate exposure estimates calculated by either intake or urinary metabolite data was reported.

SAFETY OF BPA FOR CONSUMERS UNDER CONDITION OF USE

Characterizing the safety and health risk of BPA and other compounds in foods requires a balanced and objective assessment of all relevant data. Human studies must be evaluated for their quality and relevance to conditions of ingestion. Laboratory animal studies must be closely examined to determine the quality of their performance, the predictability of the species to humans, the suitability of the dosing regimen to the human exposure circumstances, and adequacy of the information for precise extrapolation of toxic potency from test animals to humans.

In addition, the weight of evidence needs to comport to essential scientific norms, specifically reproducibility of key pathologic events and modes of action leading to them, consistence of findings, concordance of all evidence, and biological plausibility of suspected causal links.

The U.S. EPA has performed just such a thorough analysis in its estimation and promulgation of a RfD for oral exposure of humans to BPA. The Agency has concluded, relying on conservative methodologies and inferences, that 50 micrograms per kg body weight per day can be consumed safely every day throughout people's lifetime.

Using the RfD as a reliable measure, the safety of BPA in foods can be shown by comparing actual doses to U.S. EPA's RfD. When comparing the RfD for BPA to the actual human doses from foods, as is portrayed in *Figure 1*, one can readily observe that a considerable safety margin exists to protect against any possible adverse effects, no matter how small, to human health.

Recognizing that people can be exposed to BPA not only in foods but also via other media, the RfD can be compared to the measured aggregate exposure as is shown in *Figure 2*. Here also, one readily observes that a considerable safety margin exists to protect against any possible adverse effects, no matter how small, to human health.

It warrants mentioning that investigators from California's Department of Toxic Substances Control have applied the RfD methodology to contemporary data on BPA and derived an RfD equivalent of 16 µg/kg body weight per day [one-third that of the RfD estimated by U.S. EPA in 1993], from which they estimated a total allowable concentration (TAC) of 100 µg/liter of tap water (Willhite *et al.*, 2008). This RfD equivalent, based on systemic toxicity and considered protective of any possible reproductive or developmental toxicity, obviously encompasses a substantial margin of safety for human exposure to BPA from foods. U.S. EPA has yet to address this particular evaluation.

VIEWS OF HEATH AND REGULATORY AUTHORITIES

BPA has been used as a plasticizer since the 1950s, and its safety to human has been extensively evaluated by regulatory agencies. The following is a discussion of regulatory evaluations and viewpoints on BPA.

The U.S. Food and Drug Administration (U.S. FDA) has not set any regulatory limit or restrictions on BPA, since they have found no evidence or data in the scientific literature that would deem such restrictions necessary. Indeed, in 2005, U.S. FDA (2005) said *"based on all the evidence available to us at this time, FDA sees no reason to change its long-held position that current uses with food are safe"* in response to the California Assembly proposed Bill AB 319 to ban BPA and phthalates (a plasticizer) in children's products, which did not pass the assembly. The U.S. FDA (2005) further stated *"Considering all the evidence, including measurements by FDA chemists of levels found in canned food or migrating from baby bottles, FDA sees no reason at this time to ban or otherwise restrict the uses now in practice."* More recently, the deputy director of the U.S. FDA's Office of Food Additive Safety was quoted in an article in *Chemical & Engineering News* as saying *"FDA absolutely still considers BPA safe for uses in food containers,"* (Hileman, 2007).

In December 2007, an FDA official stated *"An infant would have to ingest over 7,100 times more than the current daily dietary exposure to BPA before there would be the potential for an adverse toxic effect,"* (Burkholder, 2007). FDA has reported that they actively review safety and toxicity data on BPA and *"sees no reason to ban or restrict its use in formula cans"* (Burkholder, 2007), which implies that they have not seen any scientific evidence that would justify changing their 2005 viewpoint on BPA.

The U.S. EPA in 1993 calculated an oral RfD of 50 µg/kg-day for BPA, which contains a margin of safety of approximately 100. The RfD is defined as an ingested dose obtained from all sources (food, water, soil) and at and below which any individual may be exposed daily for an entire lifetime with no likelihood of health impairment. U.S. EPA and other authoritative bodies rely on the RfD to estimate safe levels of exposure to a chemical for specific circumstances and media such as drinking water standards and occupational health limits.

The RfD for BPA was calculated using an uncertainty factor of 100 and the lowest observed adverse effect level (LOAEL) of 50,000 µg/kg-day as reported in a 1982 National Toxicology Program technical report (U.S. EPA,

1993). Currently, the U.S. EPA has set no other regulatory limit or guideline, including drinking water Maximum Contaminant Level Goals or health advisories, for BPA.

The World Health Organization (WHO) has published neither an IARC nor Environmental Health Criteria monograph on BPA. In addition, BPA has not been evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). As with the U.S. EPA, WHO has not included BPA in their guidelines for drinking water quality (current edition published in 2006). If a genuine concern existed that BPA poses a threat to human health, surely WHO and IARC would have initiated major reviews of the toxicological and other health data.

The National Toxicology Program (NTP), in 1982, published a technical report on the carcinogenesis bioassay of BPA in rats and mice. NTP concluded that there was no convincing evidence of carcinogenicity of BPA in either species or sex (NTP, 1982). Since that time, no evidence has surfaced suggesting that BPA might cause cancer or genotoxicity in any species including humans.

The NTP CERHR in 2007 convened an expert panel to evaluate BPA with the goals to:

1) Interpret the strength-of-evidence that BPA is a reproductive/developmental toxicant;

2) Assess the extent of human exposure;

3) Assess objectively and thoroughly the scientific evidence of the reproductive/developmental toxicity of BPA associated with exposure; and

4) Identify knowledge gaps.

After a public comment period, the expert panel concluded that there is minimal risk associated with low dose effects, a possible association between bisphenol A and neurobehavioral effects for pregnant women and infants/children, and negligible concern for adverse effects from BPA exposure in adults (NTP, 2007).

NTP is a division of the National Institute for Environmental Health Science (NIEHS). Integrity, objectivity and transparency are principles that NIEHS strongly stresses in their own research and review and in extramural research within their associated institutions. Policies, including guidelines for expert panels and conflict of interest statements, are often updated, reviewed and created to ensure that integrity and objectivity continues with the evolving scientific community. Since the NTP was established in 1978, the integrity of the organization and its expert panels has rarely been questioned. The NTP expert panels, including CERHR, have specific guidelines that must be followed to ensure the transparency and integrity of the process. In the CERHR Expert Panel Guidelines, it states *"that all members serve as individual experts in their specific areas of expertise, not as representatives of their employer or other organization."* All members of the expert panels are required to sign strict conflict of interest agreements (NTP, 2005).

A public concern expressed that the BPA expert report had excluded relevant articles in the deliberations and findings. In response, NTP conducted an audit of the literature cited and fidelity of the changes to the draft BPA expert report, and concluded that the BPA expert panel had included consideration of all relevant references and dutifully included changes by the expert panel members. NTP has shown that when even the slightest hint of question about the integrity of its expert panels is raised, they will take immediate action to investigate the claims and make any changes, if necessary, to improve the process. The reputation of NTP is one of integrity and objectivity.

Health and Consumer Protection Directorate of the European Commission published in 2002 its "Opinion of the Scientific Committee on Food on Bisphenol A" (European Commission, 2002) which concluded that a Total Daily Intake (TDI) of 0.01 mg/kg bw per day is considered safe.

European Chemical Bureau of the European Union published in 2003 in "Risk Assessment Report on Bisphenol A" in which it listed the margins of safety from assorted foods to range in the thousands to the tens of thousands as a measure of the safety of ingested BPA (European Chemicals Bureau, 2003).

European Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food reported in 2006 its findings to the European Commission that the TDI of 0.01 mg/kg bw contained an adequate margin of safety (Scientific Panel, 2006).

Japanese National Institute of Advanced Industrial Science and Technology reported in 2007 on its thorough review of health and safety information on BPA that the "human risk of BPA exposure is below the level of concern" (NAIST, 2007).

Since the publication of the BPA reviews and reports discussed above, additional studies on the reproductive and/or developmental toxicity of BPA have been published including:

- Kiguchi *et al.*, (2007), "Behavioral Responses to Methylphenidate and Apomorphine in Rats Exposed Neonatally to Bisphenol-A";
- Padmanabhan *et al.*, (2008), "Maternal Bisphenol-A Levels at Delivery: A Looming Problem?";
- Okada and Kai (2008), "Effects of Estradiol-17β and Bisphenol A Adminstered Chronically to Mice Throughout Pregnancy and Lactation on the Male Pups' Reproductive System";
- Kiguchi *et al.*, (2008), "Behavioral Characterisation of Rats Exposed Neonatally to Bisphenol-A:

Responses to a Novel Environment and to Methylphenidate Challenge in a Putative Model of Attention-Deficit Hyperactivity Disorder"; and

- Patisaul and Batement (2008), "Neonatal Exposure to Endocrine Active Compounds or an ER Agonist Increases Adult Anxiety and Aggression in Gonadally Intact Male Rats."

No significant effects on the reproductive/developmental endpoints were observed in three of the recent studies (Kiguchi *et al.*, 2007; Padmanabhan *et al.*, 2008; Kiguchi *et al.*, 2008), while the other two demonstrated minor significant effects at high doses with uncertain human relevance (Okada and Kai, 2008; Patisaul and Bateman, 2008). Thus, the recent data provide further evidence corroborating the health and safety assessments of BPA.

SUMMARY

1. Internationally accepted protocols of reproductive and developmental assays have reported no reproductive toxicity or adverse effects on the fetus at high doses, in the absence of general systemic toxicity.
2. Kinetics data indicate that the quantitative difference in the elimination of BPA between humans and rodents means that much higher doses of BPA are needed to produce effects in humans compared with rodents.
3. *The reference dose calculated by the EPA to be protective of the public health is more than 100 times greater than estimated human exposure to BPA.*
4. The FDA and WHO have not set any regulatory guidelines for BPA, as they have not deemed any restrictions necessary and the NTP recently concluded that there is minimal risk associated with BPA.
5. Data purporting to demonstrate "low"-dose effects on the male reproductive system by BPA have not been successfully replicated and, therefore, are not credible to estimate human health risks and safety in light of the weight of a large body of evidence to the contrary.

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