

BISPHENOL A AND PUBLIC HEALTH

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WHAT IS BISPHENOL A?

Bisphenol A (called BPA for short) is a small molecule used to build polycarbonate plastics and to formulate epoxy resins. Polycarbonate plastics are used in manufacture of bicycle safety helmets, athletic shin guards and plastic beverage containers. The epoxy resins are used to line metal containers that store food and beverages. Because bisphenol A has some estrogen-like pharmacologic activity, it is one of a class of substances commonly known as “endocrine disruptors”.

WHY THE CONTROVERSY AROUND BISPHENOL A?

In the mid-1990s, one laboratory reported changes in the reproductive tract of male mice whose mothers were fed small (microgram per kilogram per day or $\mu\text{g}/\text{kg}\text{-day}$) doses of bisphenol A. Other investigators fed bisphenol A to pregnant mice at the same doses, but they were not able to reproduce the original observations. In a review of the original studies, Ashby (2001) concluded that a lack of attention to “methodological details makes it difficult to reconcile different endocrine disruptor assay outcomes for the

same chemical”. From there, the debate escalated (Witorsch, 2002; Purchase, 2004; vom Saal et al., 2005; Purchase, 2005).

Subsequently, research on bisphenol A exploded. By 2007, there were 4,263 published scientific papers on developmental toxicity, acute and chronic toxicity, carcinogenesis, immunotoxicity, neurobehavioral toxicity, genotoxicity, biochemical toxicology, epidemiology studies, studies with workers exposed to bisphenol A and analyses of its concentrations in food, water and soil (summarized in Goodman et al., 2006; United Kingdom Health and Safety Executive, 2007, Willhite et al., 2008).

One reason for the controversy concerns the route of administration. Many of the studies that show adverse effects in rodents given small doses of bisphenol A used subcutaneous injections. Most of the studies in rodents that did not show adverse effects even at high doses used the oral route. Keeping in mind that nearly all (99%) of a child’s bisphenol A exposure occurs via ingestion (Wilson et al., 2007), several agencies have published criteria and conclusions on this important point:

- “In routine tests, administration should be by the anticipated route(s) of human exposure. This is logical, since the amount and rate of a chemical that reaches the embryo varies according to the route of administration.” (WHO, 1984)
- “The route of exposure in these studies is usually oral, unless the chemical or physical characteristics of the test substance or pattern of human exposure suggests a more appropriate route of administration.” (US EPA, 1991)
- “The injection route of administration renders those studies of no utility for quantitative risk assessment as this is not a relevant route of exposure.” (CERHR in Boekelheide et al., 2004)

- “Section 6A. Route of Administration. If the population exposure to the chemical entity is by ingestion, then the compound will be administered orally.” (Health and Welfare Canada, 1975)

Since 99% of human bisphenol A exposure occurs via ingestion, only those laboratory studies that used the oral route are candidate key studies for human health risk assessment.

SHOULD BISPHENOL A BE BANNED?

Previous experience tells us about public fear of developmental toxins. Nowhere is this more evident than a mother’s fear of exposure to therapeutic drugs, pesticides, hair dyes, paints, varnishes, solvents or unidentified, exotic or difficult-to-pronounce industrial or environmental chemicals that could harm her baby (Koren et al., 1989).

History also provides us with examples of the actions taken by confused and/or paranoid government agencies, the courts and the popular press that increased public anxiety about developmental toxicants. Unfortunately, these actions increase human misery.

Two examples illustrate that point:

A) In 1973 the US Consumer Products Safety Commission (CPSC) banned the sale of certain spray adhesives and published national warnings that these products caused birth defects and chromosome damage. The CPSC warned all pregnant women who may have had contact with these sprays to see their physician and inquire about the chromosomes of their fetus. The minimum consequences of this action were: 1273 working days

logged by 130 US diagnostic and genetic counseling centers, at least 380 chromosome studies, 11 amniocenteses and at least 9 elective abortions out of concern for exposure to spray adhesives. Eight of these abortions were performed without diagnostic amniocentesis and one was performed in an expectant mother who had chromosome breaks in her amniotic fluid. The genetic counselor in the latter case informed the woman that he was unable to determine the health of her fetus with the information at hand; she elected abortion out of fear of possible birth defects and without telling the counselor of her decision. The aborted fetus was subject to a detailed autopsy. Not only was there no evidence for any abnormality, but the suspected chromosome change was found to be due to viral contamination of the sample. In those areas of the country where local newspapers gave the CPSC announcement the highest visibility, the larger were the numbers of pregnant women who had genetic testing. Six months later, the CPSC withdrew the ban because no toxicity of the substances in the spray could be demonstrated and the original observations on chromosome damage could not be confirmed (Hook and Healy, 1976) [Attachment]. Other examples of the dread instilled in pregnant women by sensational stories and hyperbole (Gunderson-Warner et al., 1990) and the consequences of that fear are well known (Koren et al., 1989; 1993; Trichopoulos et al., 1987).

B) In 1956, a drug known as Bendectin (Debendox) was first marketed to control nausea and vomiting. Its use was very common and 20-25% of all expectant mothers used the drug and a total of 30 million pregnancies were exposed over the 27 years that the drug

was available. The customary dose was 1-4 tablets per day, each containing 1-2 mg/kg-day of the active ingredient.

In the September 1979 issue of *The National Enquirer*, the following appeared:

“Experts Reveal...Common Drug Causing Deformed Babies. In a monstrous scandal that could be far larger than the thalidomide horror, untold thousands of babies are being born with hideous defects after their mothers took an anti-nausea drug (Bendectin) during early pregnancy.”

Then in the November 1980 issue of *Mother Jones* (“The Bendectin Coverup”), the magazine advised pregnant women to use – instead of Bendectin- “natural alternatives” including 100 mg of pyridoxine (a dose 10 times that of the same compound in Bendectin).

As of 1987, at least 300 lawsuits had been filed contending that Bendectin caused birth defects (primarily of the limbs). Given the spontaneous or “background” rate of all types of congenital malformations in the United States (~3%), it would be expected that 900,000 malformed babies would be born to those 30 million mothers even in the absence of Bendectin use. Given the United States background rate for limb defects (1 per 3000 births), 10,000 such defects would be expected in the absence of any Bendectin exposure.

Bendectin does not cause birth defects in animals (including non-human primates), but delayed maturation of the fetal skeleton in laboratory studies can be seen at doses 250-400 times those that were used in clinical medicine. There are at least 14 cohort and 18 case control epidemiology studies on Bendectin in addition to one (conducted by the NIH) in which the occurrence of congenital malformations was prospectively studied in

31,564 newborns. The results of the NIH study, just like those of the others, found the odds ratio for any of 58 major categories of malformations and Bendectin exposure was 1.0 – exactly that expected by chance alone. Of those categories with a ‘trend’ or ‘suggestive’ positive associations, the magnitude of those associations was as great as that from vomiting during pregnancy with Bendectin use as without Bendectin use.

Bendectin was withdrawn from the market not because it lacked efficacy or because it caused toxicity, but because of the excessive litigation costs incurred by the manufacturer in defending the drug. Let it also be known that at least 7 women elected to terminate their pregnancies after reading the *National Enquirer* article (reviewed in Brent, 1995).

IS BISPHENOL A SAFE?

To answer that question, one must keep in mind that what is considered “safe” by one person is not necessarily considered “safe” by another person. Therefore, we must rephrase that question and ask:

What is the Bisphenol A Margin of Exposure?

To determine the relative hazard or safety associated with any chemical in air, soil, food or water, one compares the exposure (measured here as microgram per kilogram of body weight per day or $\mu\text{g}/\text{kg}\text{-day}$) for a particular age group or gender to a “tolerable daily intake” (TDI) or a “reference dose” (RfD). The Europeans use the term TDI and the US EPA uses the term RfD, but these are synonyms. The difference between the total

daily exposure and the RfD (or the TDI) is called the “Margin of Exposure”. The larger the margin of exposure, the greater the level of safety.

In order to determine the margin of exposure, we need to be able to compare the particular exposure to a “benchmark” value or limit. These limits are exemplified by the Health Advisories and Maximum Contaminant Levels (MCLs) promulgated by State and Federal agencies to control public exposure to contaminants in drinking water. To derive a limit value for bisphenol A, we first need to have an oral reference dose (RfD). After we have our RfD, then we can compare the measured human exposures for that chemical to the RfD. In that way we can calculate the margin of exposure for a particular product, for groups of people with different characteristics or people with different exposure patterns. Margins of exposure differ depending on the specific substance and how people encounter the substance.

WHY IS NSF INTERNATIONAL INTERESTED IN BISPHENOL A?

NSF International is a private not-for-profit public health and safety company. Among its many activities, it offers voluntary certification of various kinds of products after testing those products to rigorous standards. In 1988, US EPA terminated its drinking water additives program and it was replaced by NSF Standards 60 and 61. Among the many products evaluated are those that contact drinking water (e.g., faucets, meters, pipe, valves, and tank liners). As there is no Federal drinking water Health Advisory or Maximum Contaminant Level (MCL) for bisphenol A, NSF conducted a human health risk assessment on bisphenol A so it could be used to facilitate its certification activities.

REFERENCE DOSE

In the United States, the U.S. FDA regulates bisphenol as an indirect food additive (21 CFR 17.105). As noted above, there is no drinking water MCL for bisphenol A and the RfD developed by US EPA was derived in 1987. Using new information, the European Commission (2006) updated its TDI for bisphenol A to 50 µg/kg-day and in 2008, NSF International derived an oral RfD for bisphenol A of 16 µg/kg-day (Willhite et al., 2008) [Attached]. Both the European Commission oral TDI and the NSF oral RfD are based on the audited multi-generation Good Laboratory Practice (GLP) reproduction studies with rats and mice fed bisphenol A (Tyl et al., 2002; 2008). Auditors from the US EPA (OPPT) and the German Federal Institute for Health Protection and Veterinary Medicine found the laboratory facility in which the study was conducted and the rat data complied with Good Laboratory Practice regulations; an external audit of the mouse study was conducted by Toxicology/Regulatory Services (Charlottesville, Virginia) with identical findings.

Differences between the European Commission and NSF results are due to the application by NSF of an 'extra' safety factor of 3 to account for the sparse neurobehavioral and immunologic data and because none of the available studies meet current regulatory testing guidelines (US EPA 1998a; 1998b; 2005).

DIETARY BISPHENOL A EXPOSURE

As more than 99% of a person's exposure to bisphenol A is due to that in the diet (Wilson et al., 2007), there are several studies that have quantified bisphenol A exposure; some were conducted in the United States and others were completed in Europe, Japan, the United Kingdom and New Zealand. Depending upon which study one chooses to use, the results vary up to 1000-fold. This is because some laboratories use an aggregate method (e.g., measuring bisphenol A in representative foods and making estimates about the quantities of each food consumed) and others use biomonitoring (e.g., measuring total bisphenol A metabolites in urine). Each has its advantages and disadvantages. Unfortunately, the overall exposure estimates vary widely and some depend on whether consumption of wine stored in epoxy-lined vats is included or excluded.

For purposes of illustration, only margin of exposure comparisons using data from the United States are given here:

- US FDA (Bailey, 1996) Based on the bisphenol A found in infant formula stored in reusable polycarbonate infant bottles and using the highest bisphenol A concentrations measured in prepared formula from 5 leading U.S. manufacturers marketed in epoxy-lined cans, the U.S. FDA calculated total cumulative infant exposure at not more than 7 $\mu\text{g}/\text{child}$ per day to 1 year of age. Based on a 10 kg child, the daily exposure would be 0.7 $\mu\text{g}/\text{kg}\text{-day}$. Compared to the European Commission TDI, the margin of exposure is 71x and using the NSF oral RfD, the margin of exposure is 23x.

- The European Commission (2006) tabulated daily dietary exposures to bisphenol A for residents of the United States. In particular, this aggregate analysis found the infant dose depended on the bisphenol A concentration in the particular formula (10 or 50 $\mu\text{g/L}$) and whether the formula was given in polycarbonate or glass bottles. At the lower concentration in formula, the daily dose for a 3 month infant given formula in a polycarbonate bottle was twice (4 $\mu\text{g/kg-day}$) that for an infant given the same formula in a glass bottle (2 $\mu\text{g/kg-day}$). The highest aggregate exposure estimate (13 $\mu\text{g/kg-day}$) was that for a 6-month-old fed 50 $\mu\text{g/L}$ bisphenol A formula in a polycarbonate bottle. Based on the European Commission TDI, the margins of aggregate exposure are 12, 25 and 4, respectively. Using the oral RfD calculated by NSF International, the margins of aggregate exposure are 4, 8 and 1.2, respectively. However, using results from biomonitoring studies of total bisphenol A metabolites in urine, the European Commission (2006) found daily bisphenol A exposure from all sources was not more than 0.16 $\mu\text{g/kg-day}$ and the margin of exposure is 312x. Using the NSF International oral RfD, the daily margin of exposure is 100x. The discrepancies between the aggregate and the biomonitoring exposure estimates are due to assumptions about the quantity and types of food consumed (European Commission, 2006) and this is reflected in the different margins of exposure.
- Wilson et al. (2003; 2007) studied children living in Durham and Raleigh, North Carolina. These authors accounted for the child's total (aggregate) bisphenol A exposure from all liquids and from all solid foods at home and at daycare (including that from house dust and soil). Average total daily ingested bisphenol

A was 0.043 $\mu\text{g}/\text{kg}\text{-day}$ (16 times less than the US FDA result). Compared to the European Commission TDI, the margin of exposure for North Carolina children ages 1.5-5 years is 1,162x and compared to the NSF oral RfD, the margin of exposure is 372x.

DRINKING WATER AND BISPHENOL A

The numbers of reports of bisphenol A concentrations in drinking water are far fewer than those reporting bisphenol A levels in food. Three studies were identified: one from Germany (Kuch and Ballschmiter, 2001), one from Japan (Miyamoto and Kotake, 2006) and one in the US (Stackelberg et al., 2004). The drinking water bisphenol A concentrations range from 0.0003 $\mu\text{g}/\text{liter}$ to 0.42 $\mu\text{g}/\text{liter}$. Compared to the NSF International Total Allowable Concentration of 100 $\mu\text{g}/\text{liter}$ for bisphenol A in drinking water, the margin of exposure ranges from 240x (Stackelberg et al., 2004), to 588x (Miyamoto and Kotake, 2006) to 50,000 to 300,000x (Kuch and Ballschmiter, 2001).

IF NOT A BAN ON BISPHENOL A, THEN WHAT?

Regulatory agencies in North America (US EPA, 2002) and Europe use standard human health risk assessment methods combined with risk management tools to control exposures to a wide range of synthetic and naturally-occurring chemicals. The European Commission and the NSF International human health risk assessments for bisphenol A are based on the same government-audited multi-generation reproduction studies in

rodents. In each assessment, the authors concluded that the results of feeding bisphenol A to mice supported the results of feeding bisphenol A to rats. Differences in the application of a “database uncertainty factor” reduced the reference dose in the NSF analysis compared to reference dose derived by the European Commission.

Margin of exposure values vary depending upon which bisphenol A exposure data are selected for comparison. Some of the smallest margins of exposure (23-71x) are associated with assumptions that: A) an infant consumes one exclusive type (or brand) of infant formula B) all formula contains the highest bisphenol A concentration (6.6 µg/L) measured and C) the formula is given in reusable polycarbonate infant bottles that leach the highest concentration (1.7 µg/L) (Bailey, 1996). The margin of exposure based on the European Commission (2006) ranges from 1 to 312x and the margin for North Carolina children (Wilson et al., 2003; 2007) ranges from 372-1162 x. The drinking water margin of exposure ranges from 240 to 300,000x.

Historically, bisphenol A has been an indirect food additive where it was present in bisphenol A epoxy-lined cans but this has been largely replaced by polyterephthalate films (Miyamoto and Kotake, 2006). Thus, the older U.S. FDA (1996) and the European Commission (2006) aggregate exposure evaluations may overestimate current exposures. If so, current margins of exposure would be greater than those shown above. Given the remarkably broad range in exposure results between the aggregate and the biomonitoring methods, it is obvious that we need accurate quantitative measurements of daily human exposure. Only then can a regulatory agency determine the level of health risk posed by exposure to bisphenol A.

Adoption of an absolute prohibition of bisphenol A-related materials in toys or beverage and food containers uses only on the first step (Hazard Identification) of the National Academy's Principles of Toxicity Assessment. Rather than legislation of an outright ban on polycarbonate plastics in consumer products and bisphenol A-epoxy resins in food and beverage containers, the United States is fortunate to have the US FDA, the US EPA and the US Consumer Product Safety Commission. These agencies all follow the five steps of the process adopted by the National Research Council (1994) and by the Presidential/Congressional Commission (1997): Hazard Identification, Dose-Response, Risk Characterization (which includes Exposure Assessment), Uncertainty Description and Risk Communication. The results of the health risk assessment are used along with risk management factors (e.g., analytical and technical capabilities) in regulatory decision-making.

To address the on-going debate surrounding bisphenol A and public health, we need clear maximum tolerated concentration limits for foods, beverages and - depending upon the results of bisphenol A bioavailability studies - for polycarbonate consumer products. To increase the accuracy of the bisphenol A reference dose, audited GLP studies that meet current regulatory testing requirements (US EPA, 1998a; 1998b; 2005) are needed to address the data gaps. Each of these aspects can be addressed by the respective regulatory Agency using its current rule-making authority.

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Attachments (2)