

Bisphenol A in plastics: danger or drama?

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Bisphenol A

- 4,4'-dihydroxy-2,2-diphenylpropane (IUPAC name)
- One of the highest production-volume chemicals in the world- 7 billion lbs a year w/ demand increasing almost 10% a year
- A monomer used in manufacture of hard polycarbonate plastics and epoxy resins
- Products containing BPA have been in production for more than 50 years.

Bisphenol A

- Polycarbonate plastic is clear and nearly shatter-proof
 - Water bottles
 - Baby bottles
 - other common household items- polycarbonate tableware and food storage containers, CD/DVDs, impact-resistant safety equipment, medical devices
- Epoxy resins
 - Lining of food storage and water containers
 - Lining of metal food cans
 - Dental sealants
 - Water supply pipes

Bisphenol A

Why are consumers concerned?

- Ubiquitous chemical with detectable levels in urine in >90% of most populations in developed world.
- Small amounts BPA can leach into food and water from epoxy resin lining of canned foods, food storage containers and polycarbonate water or baby bottles (*NTP report 2008*). This leaching may increase if liquid or container is heated (*Hugo 2008*)
- Numerous animal studies document a variety of adverse effects, esp. in fetuses and newborns.
- Emerging human studies of adverse effects

Bisphenol A

- BPA has well-documented estrogenic activity
- “Endocrine disruptor”- an exogenous agent that interferes w/ production, release, transport, metabolism, binding, action or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes (USEPA definition).
 - These actions occur often at extremely low doses. (*Wetherill 2007*)
 - “Activational” effects- describe adult exposures, usually reversible in nature.
 - “Organizational” effects- include exposure during organ development (prenatal through puberty). Exposure esp. important during “Critical windows” of development. These may result in persistent alterations of affected systems, even in absence of subsequent exposure. Some effects may be measured immediately, others become apparent only in adulthood. (*Richter 2007*)

Bisphenol A

- In humans, BPA undergoes “first-pass” metabolism in liver and is conjugated and rapidly excreted in the urine as metabolites BPA-glucuronide or BPA-sulfate
- Major metabolite, BPA-glucuronide does not have estrogenic activity
- NHANES 2003-04
 - Widespread exposure to BPA in US population
 - 92% of urine samples in 2517 participants had detectable levels BPA

Animal studies

Rodents

- Prior to 1997 inconsistent study results thought related to relatively high doses of BPA used for risk assessment- greater than 50 ug/kg/d (the FDA established accepted daily intake)
- Newer studies (>150) use lower doses BPA exposure, more c/w true exposure levels and mechanisms of endocrine disruptors
- Varying doses and exposure routes- oral, subcutaneous, intramuscular, intracisternal, intraperitoneal

(Richter 2007)

Animal studies

Adverse effects noted in rodent studies

- Brain
 - Physiology- upregulation of estrogen receptors, alterations in hypothalamus-pituitary-thyroid axis
 - Structure- reversal in normal sex differences in number of neurons in locus coeruleus
 - Behavior- increased defensive aggression, hyperactivity
- Males
 - reduced testosterone levels
 - lower sperm production
 - Increased prostate size and androgen responsiveness

Animal studies

Adverse effects noted in rodent studies

- Females
 - disrupted and prolonged estrous cycles
 - accelerated puberty
 - stimulation of mammary gland development
 - chromosomal abnl in oocytes and increased embryo mortality
 - alterations in maternal behavior toward young
- Metabolic
 - hypersecretion of insulin, *B*-cell dysfunction
 - obesity

Animal studies

- Criticisms of rodent studies
 - Varying doses and routes of administration of BPA make results difficult to generalize to humans. Critics dismiss studies using injection of BPA as valid route of exposure
 - Metabolism in rodents different than humans- may increase BPA toxicity in rodents

Human Studies

Exposure data

BPA levels detectable in human tissues/fluids

- Blood
- Placental tissue
- Amniotic fluid
- Umbilical cord blood
- Breast milk
- Urine (conjugated BPA)
- Ovarian follicular fluid

(Vandenberg 2007)

Human Studies

Exposure data

Proven sources of human exposure to BPA

- Food-
 - BPA detectable in food and drink after leaching from polycarbonate storage containers
 - Baby bottles
 - Plastic food storage such as Tupperware
 - Levels of BPA increase after containers cleaned w/ brushes, exposure to cleaning detergents (including dishwasher) or heating
 - Plastic wrap also implicated
 - Levels also detectable in food packaged in paper and cardboard storage (esp. recycled paper)
 - Metallic food cans- BPA epoxy resin coating protects from rust and corrosion.

(Vandenberg 2007)

Human Studies

Exposure data

- Dental products- BPA detectable in saliva in short term after placement of sealants
- Water-
 - BPA measured in landfill leachates (among other estrogenic chemicals). This may be related to degradation of plastic waste in landfill
 - BPA detected in sewage treatment works effluents, rivers, creeks and drinking water reservoirs, salt water.
- Air and dust- BPA detected in environment and household air/dust and in much higher levels in air of plastic manufacturing plants

(Vandenberg 2007)

Human Studies

Exposure data

Metabolic elimination pathways are important for BPA risk assessment

- Existing metabolic studies are based on a single exposure, rather than multiple daily exposures
- Attempts to estimate oral exposure levels by using urinary measurements and rodent models of metabolism.
 - Estimates range from under 1 ug/kg/d to 5 ug/kg/d.
 - This pharmacokinetic modeling may be inherently flawed bcs of species-specific metabolism differences, but several estimates exceed EPA accepted daily intake of 50 ug/kg/d.

Human Studies

Exposure data

- Estimating exposure levels of fetuses and neonates particularly difficult because they are known to have limited ability to perform first pass metabolism
- Complicating matters is the fact that humans are exposed to dozens of other chemicals that show estrogenic activity. There may be additive effects unaccounted for in present estimates.

Human Studies

in vitro human studies

Effect of BPA exposure on adipose tissue:

- Goal: to compare the effects of low dose estradiol and BPA on adiponectin secretion from human breast, subcutaneous and visceral adipose explants and mature adipocytes.
- Adiponectin- an adipocyte-specific hormone that increases insulin sensitivity and reduces tissue inflammation.
- BPA at 0.1 and 1 nM doses suppressed adiponectin release from all adipose tissue examined. BPA was as or more effective than equimolar concentrations of E2.
- Conclusions- environmentally relevant doses of BPA inhibit the release of a key adipokine that protects humans from the metabolic syndrome.

(Hugo 2008)

Human Studies

Epidemiologic studies

A very limited number to date

- Cross-sectional studies
 - Women w/ PCOS had higher serum levels BPA
 - Women carrying fetuses w/ abnl karyotype had higher serum BPA
 - Assoc b/w serum BPA levels and recurrent miscarriage
- Limitations-
 - Small numbers
 - Poor control of confounders
 - unable to establish causation

(Vandenberg 2007)

Human Studies

Epidemiologic studies

Lang 2008- Assoc. of urinary BPA concentration w/ medical disorders and laboratory abnormalities in adults

- Design: cross-sectional analysis of urinary BPA concentrations and health status in general US adult population using data from NHANES 2003-04
- Participants: 1455 adults aged 18-74 years (694 men, 761 women)
- Analysis: regression models adjusted for age, sex, race/ethnicity, education, income, smoking, BMI, waist circumference, urinary creat.

Human Studies

Lang study- Measures

Has a health professional ever told you that you have:

- Emphysema/chronic bronchitis
- Angina/coronary heart disease/heart attack
- Diabetes/borderline diabetes
- Arthritis
- Liver disease
- Asthma
- Thyroid disease
- Cancer

Lab evaluation:

- GGT
- Alk phos
- LDH
- TGs
- LDL
- Fasting glucose
- Fasting insulin
- B-cell function
- Insulin resistance

(Lang 2008)

Human Studies

Lang study- Results

Odd Ratios of diseases/conditions assoc w/ 1-SD increase in urinary BPA concentration

<u>Condition</u>	<u>OR</u>	<u>p-value</u>
Arthritis	0.97 (0.78-1.21)	.75
Cancer	1.14 (0.86-1.52)	.33
CVDz	1.39 (1.18-1.63)	.001
Diabetes	1.39 (1.21-1.60)	<.001
Liver dz	0.74 (0.37-1.44)	.35
Asthma	0.98 (0.84-1.14)	.80
Emphysema	0.98 (0.74-1.29)	.87
Stroke	0.97 (0.74-1.27)	.82
Thyroid dz	1.09 (0.88-1.37)	.40

Human Studies

Lang study- Results

Linear regression coefficients of logged analytes assoc w/ 1-SD increase in urinary BPA concentration

<u>Analyte</u>	<u>B (95% CI)</u>	<u>p-value</u>
C-reactive protein	0.02 (-0.02-0.06)	.24
Insulin	0.07 (0.00-0.15)	.06
Glucose	0.01 (-0.01-0.04)	.37
B-cell fxn	0.03 (-0.01-0.07)	.09
Insulin resistance	0.07 (-0.01-0.15)	.07
LDL	-0.01 (-0.06-0.03)	.58
TGs	0.01 (-0.04-0.05)	.79
Alk phos	0.02 (0.01-0.04)	.01
GGT	0.06 (0.03-0.10)	.001
LDH	0.01 (0.00-0.03)	.04

Human Studies

Lang study- Conclusions

- Higher urinary BPA levels are associated w/ increased prevalence of CVDz (angina, coronary heart disease, heart attack) diabetes and liver enzyme abnl
- Limitations
 - Cross-sectional study so unable to establish causality. Longitudinal data would be much more compelling
 - Single urine sample reflects only recent exposure and these results may not reflect effects of repeated exposures over time
 - Very broad hypothesis and extremely complex analysis w/ numerous independent and dependent variables- may produce false-positive results

Regulatory Agencies- Canada

- 2006 Canadian regulators selected BPA as one of 200 substances deserving a thorough safety assessment bcs preliminary studies had found it to be “inherently toxic”.
- April 2008 - Health Canada released a draft assessment of BPA which concluded the chemical may pose some risk to infants and proposed classifying BPA as “toxic to human health and the environment”.

(Environment Canada website 2008)

- October 2008 Canada intensified its language to declare BPA a “hazardous substance” and is seeking to restrict imports, sales and advertising of polycarbonate baby bottles containing BPA” .

Regulatory Agencies- Canada

- Wal-mart announced it was immediately ceasing sales in Canada of food containers, water and baby bottles, sippy cups and pacifiers containing BPA and it would phase out baby bottles w/ BPA in US stores by early 2009.

(Washington Post, April 2008)

- Nalgene announced it will stop using the chemical in its products.
- Toys-R-Us will cease selling baby bottles made w/ BPA.

(CBS news April 2008)

Regulatory Agencies- Europe

- 2006 German regulators announced polycarbonate baby bottles are safe and stated that published research on health effects BPA is “difficult to interpret and occasionally contradictory”.
- 2006 European Union’s Food Safety Authority (EFSA) reached similar conclusions, expressing “considerable reservations” about the biologic significance and robustness of low-dose exposure studies on rodents.
- 2007 Japan also concluded that “the current exposure levels of BPA will not pose any unacceptable risk to human health and that a ban is not needed”.

Regulatory Agencies- Europe

- 2007 EFSA comprehensive safety assessment established the Tolerable Daily Intake (TDI) as 50 ug/kg/day and reported human exposure is “well below the TDI” and that BPA is “safe”.
- 2008 ESFA updated assessment focusing specifically on the capabilities of fetuses and infants to metabolize BPA concluded that the established TDI “provides a sufficient margin of safety for the protection of the consumer, including foetuses and newborns”.

Regulatory Agencies- US

National Toxicology Program

- National Toxicology Program (NTP) is an inter-agency program w/ the mission to coordinate, conduct and communicate toxicological research across the US gvmt. Functions under NIH/NIEHS.
- NTP Center for the evaluation of risks to human reproduction (CERHR)
 - Convened an expert panel on BPA in 2007 “Chapel Hill Expert Panel”
 - Received public comments throughout the process
 - Final monograph underwent peer review and released in Sept 2008.

Regulatory Agencies- US

National Toxicology Program

- Reported “levels of concern” for BPA exposure
 - Serious concern
 - Concern
 - Some concern
 - Minimal concern
 - Negligible concern

NTP BPA Brief Conclusions:

- “*some concern*” for effects on brain, behavior and prostate gland in fetuses, infants and children at current human exposures of BPA.
- “*minimal concern*” for effects on the mammary gland and an earlier age for puberty for females, in fetuses, infants and children at current human exposures to BPA. *(NTP Report 2008)*

Regulatory Agencies- US

National Toxicology Program

NTP BPA Brief Conclusions:

- “*negligible concern*” that exposure of pregnant women to BPA will result in fetal or neonatal mortality, birth defects, or reduced birth weight and growth in their offspring.
- “*negligible concern*” that exposure to BPA will cause reproductive effects in non-occupationally exposed adults.
- “*minimal concern*” for workers exposed to higher levels in occupational settings.

(NTP Report 2008)

Regulatory Agencies- US

- As of April 2008, several states had legislation affecting use of BPA (Ca, Md, Conn, NJ, others).
- Legislation pending in Congress to ban BPA nationally from all products for infants.
- Investigations pending of Weinberg Group, a chemical industry consulting firm, for its role in downplaying health effects of BPA and other chemicals.
- Energy and Commerce Committee in House of Rep asked for reassessment of BPA by FDA.

Regulatory Agencies- US

- Aug 2008 -FDA has maintained BPA is “safe”- concludes “that an adequate margin of safety exists for BPA at current levels of exposure from food contact uses for infants and adults”
- Established accepted daily intake dose (ADI) of 50ug/kg/d was not revised.
- Consumer Product Safety Commission agreed.
- Critics contend this level is too high and is based on studies performed in the early 1980s which used only very high doses of BPA and insensitive assays (? and funded by the chemical industry) .

Industry Response

- Human exposure levels are well below levels of toxicity and are supported by regulatory agencies such as the FDA and EFSA (50ug/kg/d).
- Rodent models are not appropriate to use in risk assessment for humans due to species differences in BPA metabolism.
- The risk to infants and fetuses is exaggerated- infants have the capacity to metabolize BPA at current estimates of exposure and fetuses have low exposure due to maternal rapid metabolism.
- Industry groups such as American Chemistry Council/ BPA Global Group and Grocery Manufacturers Assoc. support these assertions.

Bisphenol A

Conclusions

- BPA is an ubiquitous chemical found in many plastic household items.
- BPA is detectable in the overwhelming majority of persons in the developed world.
- BPA is detectable in our ecologic system- in water, air, dust.
- Exposures to BPA are likely multifactorial and chronic.

Bisphenol A

Conclusions

- Many animal studies (predominantly rodent) identify potential human risk for adverse health outcomes.
- There exist significant concerns about the use of rodent models for risk assessment in humans.
- Preliminary human studies have found associations of elevated BPA levels and adverse health outcomes including metabolic disorders, cardiovascular disease and liver damage.

Bisphenol A

Future research needs:

- Estimates of exposure in developing countries.
- Further understanding of metabolism after chronic, low-dose exposures.
- Longitudinal studies that assess relationship of BPA exposure to human disorders, esp fetuses and neonates who may have a greater risk because of their small size and limited capacity to metabolize BPA.
- Further definition of other estrogenic exposures and their independent or additive effects.

Bisphenol A

Avoiding the risk

- Don't microwave polycarbonate plastic food containers
- Don't wash polycarbonate plastic containers in dishwasher or w/ harsh detergents
- Avoid use of containers w/ #7 on bottom, some are polycarbonate and might contain BPA (also #3?)
- Reduce use of canned food (including soda?)- eat fresh or frozen foods
- Use baby bottles that are BPA free
- Use toys that are labeled BPA free
- Opt for glass, porcelain, stainless steel or safer types of plastics for hot foods or liquids
- Request BPA free dental sealants

(NTP Report 2008)

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