Committed *since 2002*
to ensuring that Europe's food is safe

Status of Activities on BPA at International Level

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Meeting with National Experts
Parma, 29-30 October 2012

International activities on BPA: Overview

- WHO
- US
- Canada
- Australia – New Zealand
- Japan

Activities on BPA: **FAO-WHO, 2010-'11**

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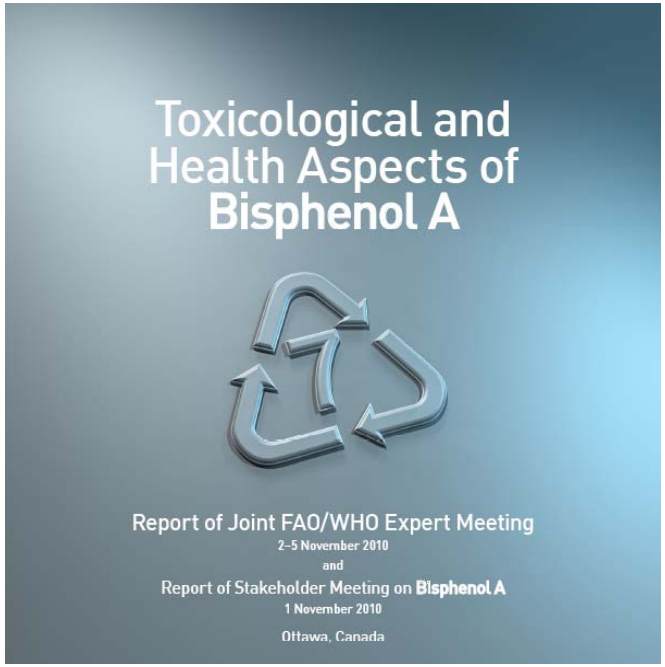
BPA exposure assessment (in µg/kg bw/day)

- Sub-population with the **highest dietary intake** is that of **infants of 0-6 months** being fed liquid formula out of PC bottles:
  - 2.4 (mean) and 4.5 (95th percentile).

- Exposure did not exceed:
  - 0.7 (mean) and 1.9 (max) for **children >3 yrs**
  - 0.4-1.4 (mean) and 1,0-4.2 (max) for **adults**.

- For most subgroups exposure to BPA from non-food sources was at least one order of magnitude lower than that from food (limited data) .



Activities on BPA: **FAO-WHO, 2010-'11**

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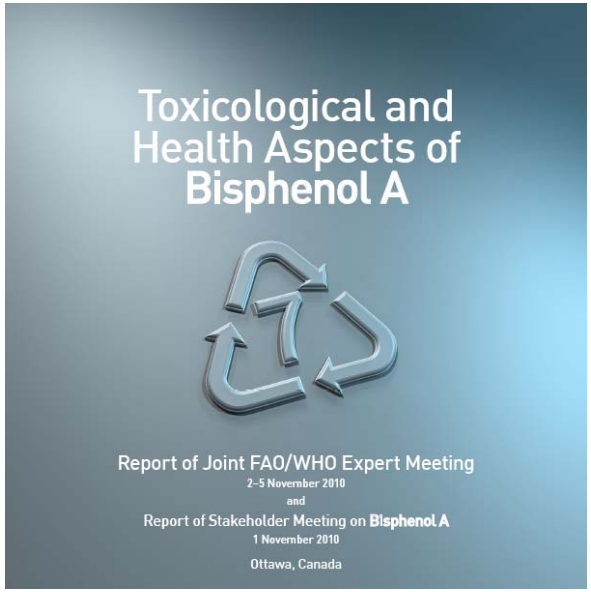
BPA Hazard & risk characterization

- For many end-points, points of departure (PODs) are much higher than human exposure.
  NO health concern.

- Some emerging new end-points (sex-specific neurodevelopment, anxiety, preneoplastic changes in mammary glands and prostate in rats, impaired sperm parameters) in a few studies show PODs close to the estimated human exposure.

- **Difficult interpretation** of these findings **& high uncertainty on the validity and relevance** of these data: it is premature to realistically estimate human risk.

- Data gaps and recommendations for future research



Activities on BPA: **USA**

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FDA Consumer Health Information
www.fda.gov/consumer

FDA Continues to Study BPA

BPA It stands for Bisphenol A. It is a chemical used in the production of plastics and resi as some water bottles and the coatin some food cans. It is also used in some consumer goo as compact discs and thermal cash register tapes. Ar generated controversy about its impact on human hea development.

Dennis M. Keefe, Ph.D., director of FDA's Office of Food Additive Safety, and other officials at FDA say the agency takes all concerns about BPA seriously and is evaluating them as part of the agency's ongoing oversight of food safety.

Because of some studies in young animals that raised potential concerns about the safety of BPA, there has been particular concern about

FDA Consumer Health Information
www.fda.gov/consumer

"We make public health decisions based on a careful review of well performed studies, not based on claims or beliefs."

exposed to BPA because small amounts can migrate into the food and beverages from their containers. Reports from some animal studies have raised potential concerns that BPA exposure may cause multiple health problems, including reproductive disorders, diabetes and cardiovascular disease.

There have also been studies that contend that BPA is a hazard to people too. But FDA—as well as the European Food Safety Agency (EFSA)—has carefully assessed these studies

Activities on BPA: **USA**

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2008 NTP monograph

NTP conclusions regarding the possibilities that human development or reproduction might be adversely affected by exposure to bisphenol A. The NTP uses a five-level scale of concern:

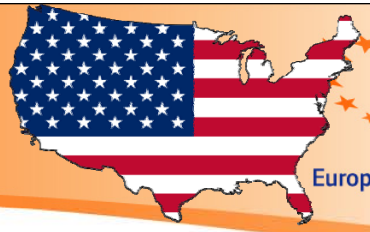
	SERIOUS Concern *for adverse effects*
	CONCERN *for adverse effects*
Developmental toxicity for fetuses, infants, and children (effects on the brain, behavior, and prostate gland)	**SOME Concern** *for adverse effects*
Developmental toxicity for fetuses, infants, and children (effects on the mammary gland and early puberty in females), and reproductive toxicity in workers	**MINIMAL Concern** *for adverse effects*
Reproductive toxicity in adult men and women and malformations in newborns	**NEGLIGIBLE Concern** *for adverse effects*

Activities on BPA: **USA**

Figure 1. Elements of the NIEHS BPA Research Program

From Birnbaum et al., EHP 2012

Activities on BPA: **USA**



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NCTR-FDA's Research Findings (support from NIEHS & NTP)

- **The level of BPA from food that could be passed from pregnant mothers to the fetus is so low that it could not be measured.**

Pregnant rodents fed 100-1,000 times more BPA than people are exposed to through food: no detection of the active form of BPA in the fetus 8 hrs after the mother's exposure.

- **Exposure to BPA in human infants is 84-92% less than previously estimated.**

Mathematical models were built to predict the fate of BPA in human body. They showed that BPA is rapidly metabolized and eliminated through feces and urine, without bio-accumulating.

- **The NCTR research has not found evidence of BPA toxicity at low doses in rodent studies, including doses that are still above human exposure levels.**

Activities on BPA: **Canada**

Health Canada

- **BPA surveillance activities**
- **Updated BPA exposure assessment from food sources**
- **Research activities**

http://www.hc-sc.gc.ca/fn-an/securit/packag-emball/bpa/index-eng.php

Activities on BPA: **Canada**

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Surveys (since 2008)

Concentrations of BPA were measured in:

General population Food	Infant Food
canned drink products	canned liquid infant formula
canned food products	canned powdered infant formula
bottled water products	baby food pre-packaged glass jars with metal lids
soft drink and beer products	85 samples of infant formula from HC Total Diet samples
HC Total Diet samples	

Based on these surveys:
probabilistic assessment of dietary exposure to BPA, both for the general population and for infants of different ages.

Probabilistic dietary exposure to BPA for infants of different age groups

- A probabilistic exposure assessment was conducted by randomly applying the BPA concentrations measured through the surveys of canned and bottled foods, as well as all food composites from the Total Diet Study, to the relevant food consumption rates reported by each individual.

- For each survey respondent, BPA exposure from all foods was summed to give an estimate of the distribution for total dietary BPA exposure within a population.

- 500 different exposure scenarios were generated for each individual, from which mean exposure estimates were calculated for each age-sex group.

Activities on BPA: **Canada**

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Health Canada: 2012 BPA dietary exposure

Age group	Mean (µg/kg bw/day)	95 th (95% CI)
0-1 month	**0.083**	0.814 (0.772, 1.142)
2-3 months	0.143	1.159 (1.004, 2696)
4-7 months	**0.164**	0.737 (0.713. 0.982)
8-12 months	0.092	0.373 (0.360, 0.408)
1-3 years	0.106	0.557 (0.536, 0.620)
4-8 years	0.078	0.415
Adults	**0.055**	0.259

These figures align with exposure estimates from population-based biomonitoring studies.

Activities on BPA: **Canada**

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- **2012** dietary exposure assessment: **on average 3 fold lower than that of 2008**. Due to the use of some low dose animal studies, the Government of Canada recommends the application of the **ALARA principle** (as low as reasonably achievable) to limit BPA exposure of infants and newborns from FCM, specifically from pre-packaged infant formula (only food source for babies).
- Based on the overall weight of evidence, HC continues to conclude that current dietary exposure to BPA through food packaging uses is not expected to pose a health risk to the general population, including newborns and young children.

- This conclusion is **consistent with** those of food regulatory bodies in the **US, EU and Japan**.

Activities on BPA: **Australia-New Zealand**

Food Standards FSANZ

- **FSANZ recently undertook a survey of BPA in food and drinks in Australia** to determine exposure to BPA from packaging materials.

- No detectable levels of BPA in infant formula, including infant formula made in BPA containing bottles.
- Very low levels of BPA (parts per billion range) in a small number of samples, mainly canned foods.

- **Dietary exposure estimate to BPA**
- Australians of all ages are exposed to extremely low levels (in the range of parts per billion to parts per trillion).
- Liver enzymes are very efficient at combining with BPA, making 99.9% of it non-toxic, and it's excreted in the urine.

Activities on BPA: **Australia-New Zealand**

Food Standards FSANZ

- FSANZ has carefully considered the toxicological database for BPA and concurs with the hazard assessment and **TDI of 0.05 mg/kg bw/day**.

- FSANZ considered the possible risks of BPA and they remain convinced that the weight of evidence, obtained from an extensive range of safety studies, indicates that **BPA is safe for the whole population at the very low levels of current exposure.**

- FSANZ acknowledges **unresolved uncertainties in the data on BPA**, and notes that further studies are currently being conducted in the US to address these uncertainties.

Activities on BPA: **Japan**

Institute of Advanced Industrial Science & Technology (AIST)

- July 2011: **Updated Hazard Assessment of BPA**
  - Critical endpoints: Hepatotoxicity and nephrotoxicity (NTP,1985; Tyl et al, 2008)
  - Lowest BMDL10 were found for centrilobular hepatocyte hypertrophy (15 mg/kg/d) and nephropathy (90 mg/kg/d) in mice from the 2 generation reproductive study of Tyl
  - A factor of 5 was further applied to BMDLs to extrapolate data from short to long term exposure → NOAELs.
- **NOAEL: 3 mg/kg bw/day** for centrilobular hepatocyte hypertrophy
- **UF: 25**
  - **2.5 for inter-species differences (1 for TK and 2.5 for dynamics)**
  - **10 for intra-species differences**

Activities on BPA: **Japan**

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Institute of Advanced Industrial Science & Technology (AIST)

- **Exposure assessment** (95th percentile, in µg/kg bw/d)
  - max in 1-6 yr old children: 3.9 (males) - 4.1 (females)
  - Adults: 0.037-0.064 (men) & 0.043-0.075 (women)

- **MOE** (using data at the 95th percentile)
  - **730-770 for 1-6 yr old children**
  - **40,000-81,000 for adults**

The AIST concluded: *"These values were much larger than the MOE (25) that was presumed to cause health effects in humans or the conventional and conservative MOE (100)…, and thus the risk of BPA with regard to human health was believed to be very small."*

Thank you

90-day study design (Barry Delclos, FDA)

- **Animal model**: SD rat from NCTR colony

- **Treatment groups**
- Control
- 7 BPA low doses: 2.5, 8, 25, 80, 260, 840, 2700 µg/kg/day
- 2 BPA high dose groups: 100000, 300000 µg/kg bw/day)
- 2 Ethynyl estradiol (EE_2): 0.5, 5 µg/kg bw/day

- **Exposure**: continuous - in utero & postnatal - until sacrifice
- in utero: GD 6-21 dams, gavage, 0.3%carboxymethylcellulose
- postnatal: direct oral dosing of pups (gavage): PND 1-90

- **Endpoints**: serum levels at Cmax on PND 4, 21, 80, general toxicity signs (viability, bw, organ weight, etc), clinical chemistry, organ histopathology

90-day study results (Barry Delclos, FDA)

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EE2 groups

Females (both doses): multiple dose-related effects
- weights of immature reproductive organs
-delayed puberty
-altered serum clinical chemistry
-altered estrous cycles and reproductive tract morphology.

Males
high dose: multiple adverse effects on reproductive organs and delayed puberty onset
low dose: mammary gland hyperplasia (only effect clearly observed)

90-day study results (Barry Delclos, FDA)

BPA

300,000 µg/kg/d: as for EE2, in both sexes multiple reproductive organ effects, serum chemistry changes and mild renal effects; in both sexes body weight gain depression (not seen in EE2)

≥ 100,000 µg/kg/d: changes in serum thyroid hormones (↑ T3 at PND 5), ↓ gestational weight gain, aberrant estrous cycle.

2.5-2,700 µg/kg/d: sporadic pathological effects with no consistent dose response in incidence or severity.

90-day study results (Barry Delclos, FDA)

Ovarian histopathology

- Antral follicle depletion
- Corpus luteum depletion

EE2: strong effects at 0.5 – 5 µg/kg bw/day
BPA: severe effects only at 300,000 µg/kg bw/day

Neoplasms & BPA

- None in males
-1 ductal neoplasm at 2.5 µg BPA/kg bw/day in females

Activities on BPA: **USA**

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FDA

-Report on 90 day study. Publication date?
- 2-year cancer bioassay: study to start in the summer, data available in min 3 yrs
- Biomonitoring studies in specific populations: hospitalized babies, cashiers (dermal exposure), etc

By 31 March: FDA reply to the petition of the Natural Resources Defense Council to prohibit the use of BPA in human food and food packaging

Activities on BPA: **USA**

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NCTR-FDA's Research Findings (with support from NIEHS & NTP)

- **The NCTR research has not found evidence of BPA toxicity at low doses in rodent studies, including doses that are still above human exposure levels.**
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Experiments in pregnant rodents fed 100-1,000 times more BPA than people are exposed to through food: no detection of the active form of BPA in the fetus 8 hrs after the mother's exposure

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FAO-WHO Expert Meeting

- The sub-population with the highest dietary intake of BPA is that of infants of 0-6 months being fed liquid formula out of PC bottles: this accounts for 2.4 and 4.5 µg/kg bw/day (mean & 95th percentile).
- Exposure (in µg BPA/kg bw per day) did not exceed 0.7 (mean) and 1.9 (max) for children >3 years, and 1.4 (mean) and 4.2 (max) for adults.
- For most subgroups BPA exposure from non-food sources was at least one order of magnitude lower than that from food.
- For many end-points, points of departure (POD) are much higher than human exposure. Hence, there is no health concern for these end-points.
- Some emerging new end-points (sex-specific neurodevelopment, anxiety, preneoplastic changes in mammary glands and prostate in rats, impaired sperm parameters) in a few studies show PODs close to the estimated human exposure.
- However, it is difficult to interpret these findings, taking into account all available kinetic data and current understanding of classical estrogenic activity. However, new studies indicate that BPA may also act through other mechanisms

Dietary exposure assessment – **FAO-WHO, 2011**

Highest exposure for 0-6 month infants drinking liquid formula out of PC bottles:

- 2.4 µg/kg bw/ day (mean)
- 4.5 µg/kg bw/day (95th perc).