BPA-RELATED RISKS

- BPA scientific monitoring since May 2009: An overall assessment
- Key Findings from July to September 2012

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A/ BPA scientific monitoring since May 2009: An overall assessment

Number of studies on humans and animals

Showing effects: 319 (94 %)
- On animals: 200 (49 of which are in vivo studies that used a BPA dose < ADI (EFSA))
- On humans: 119 (Health effects: 56 ; in vitro effects : 63)

Showing no effect: 21
- On animals: 11
- On humans: 10

B/ BPA scientific monitoring from July to September 2012: A comprehensive overview

EFFECTS ON HUMANS

Adverse pathophysiological effects:
- Exposure to BPA is associated with increased blood pressure and decreased heart rate variability, which are risk factors of cardiovascular disorders.
- BPA exposure is higher in patients with severe coronary artery stenoses compared to those with no vessel disease.
- There is positive association between increasing levels of urinary BPA and measures of obesity (NHANES 2003-2008), which is consistently present across gender and race-ethnic groups.
- Urinary BPA concentration was significantly associated with obesity in a cross-sectional study of 2838 children and adolescents based on the 2003-2008 National Health and Nutrition Examination Surveys.
- BPA may alter reproductive function in susceptible women undergoing IVF.
- High body BPA burden may not be associated with an increased prevalence of type 2 diabetes in Korean adults.

In vitro effects:
- By comparing the effects of BPA and the local anesthetic mexiletine on wild type hNav1.5 the authors have demonstrated that BPA blocks the human heart sodium channel via the local anesthetic receptor.

EFFECTS ON ANIMALS

Rats:
- Prenatal exposure of rats to BPA (0.5 and 50µg/kg/day BPA) affects pituitary gonadotroph development in
females.

**Mice:**

- The study suggests that BPAF, a chemical structurally related to bisphenol A and used as a substitute for BPA, also has neurotoxic properties.

**Monkey:**

- Exposure to doses of BPA that yield circulating levels of BPA analogous to those reported in humans alters early oogenesis and follicle formation in the fetal ovary of the rhesus monkey.

**Fish:**

- There is strong and direct evidence for ascribing an antiandrogenic mechanisms of action to BPA in vertebrates.

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**ENVIRONMENTAL EXPOSURE**

- Bisphenol A and nonylphenols were detected in drinking water samples from 35 major Italian cities and five popular Italian brands of bottled mineral water.

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**INNOVATION - METHODOLOGY**

- A study which provides a wealth of tools and information that could be used for the development of BPA substitutes devoid of hormonal activity and more generally for environmental risk assessment.
BPA-RELATED RISKS

PEER-REVIEWED PAPERS (JULY-SEPTEMBER 2012)
SOURCE: PubMed

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A. EFFECTS ON HUMANS

1. ADVERSE PATHOPHYSIOLOGICAL EFFECTS:

- **Cardiovascular disease**


  The present study showed that exposure to BPA is associated with increased blood pressure and decreased heart rate variability, which are risk factors of cardiovascular disorders. The risk of hypertension also increased with increasing concentrations of BPA in participants who had not reported previous history of hypertension.


  BPA exposure is higher in patients with severe coronary artery stenoses compared to those with no vessel disease.

- **Obesity**


  The results of this study based on the National Health and Nutritional Examination Survey (NHANES) 2003-2008 found a positive association between increasing levels of urinary BPA and measures of obesity, which is consistently present across gender and race-ethnic groups.

Urinary BPA concentration was significantly associated with obesity in a cross-sectional study of 2838 children and adolescents based on the 2003-2008 National Health and Nutrition Examination Surveys. Obesity was not associated with exposure to other environmental phenols commonly used in other consumer products.

- **Psychosocial behaviour**


  The results show that greater exposure to bisGMA-based dental composite restorations was associated with impaired psychosocial function in children.

- **Reproduction / Hepatotoxicity**


  Increased serum bisphenol A levels contribute to low-grade chronic inflammation, hepatic steatosis, and hyperandrogenism in women with PCOS.

- **Reproduction**


  The study shows that BPA may alter reproductive function in susceptible women undergoing IVF, notably because there was a significant linear dose-response association between increased urinary BPA concentrations and decreased number of oocytes, decreased number of normally fertilized oocytes and decreased E(2) levels.

- **Diabetes**


  This cross-sectional study based on a Korean human biomonitoring survey suggests that a high body BPA burden may not be associated with an increased prevalence of type 2 diabetes in Korean adults.
Allergic asthma


This study based on the data from NHANES 2005-2006 shows that urinary BPA is significantly associated with allergic asthma in females.

Development


There are no significant differences in physical development over 5 years in children treated with dental composites or amalgam.

2. IN VITRO EFFECTS:

Hormone metabolism


An in vitro test designed to determine the dermal penetration rate of BPA in human skin shows that the systemic exposure to BPA via the skin contributes in a negligible way to total systemic BPA exposure.

Cardiac function


This study investigated the interaction between BPA and hNav1.5, the predominant voltage-gated sodium channel subtype expressed in the human heart. By comparing the effects of BPA and the local anesthetic mexiletine on wild type hNav1.5 and the F1760A mutant, the authors have demonstrated that BPA blocks the human heart sodium channel via the local anesthetic receptor.

Modelling BPA interactions /Receptor ERRγ
The study shows that both BPA and its putative chlorinated and nitrated metabolites, formed by the oxidative biotransformation of BPA, have strong binding affinity for the human estrogen-related receptor-gamma (ERRγ) compared to estradiol.

B. EFFECTS ON ANIMALS

a) RATS:

➤ Hormone metabolism


Pituitary GH content and liver IGF-I concentration were increased by neonatal BPA treatment of female rats from postnatal day 1 to 10. The findings indicate that perinatal exposure to BPA may compromise the sexually dimorphic capacity of the liver to metabolize drugs and steroids.

➤ Reproduction


The study found that prenatal exposure of rats to BPA (0.5 and 50µg/kg/day BPA) affects pituitary gonadotroph development in females.

➤ Hepatotoxicity


BPA exposure generates ROS and reduces the antioxidant gene expression which causes hepatotoxicity in Rat Model.

➤ Diabetes (in vitro)
Exposure to bisphenol A (BPA), octylphenol (OP) and nonylphenol (NP) can disrupt insulin secretion, pancreatic islets morphology and B-cells function in rat in vitro.

Behavioral effects


Exposure to BPA from gestation through puberty induces behavioral effects (e.g. Anxiety) in rats which can manifest during adolescence, but wane in adulthood, and may be mitigated by diet (soy-based or soy-free).

MICE:

Lung inflammation


Maternal exposure to BPA has subtle and qualitatively different effects on allergic lung inflammation but these persistent changes in adult offspring do not lead to significant differences in overall airway responsiveness, suggesting that early life exposure to BPA does not exacerbate allergic inflammation into adulthood.

Reproduction


This study shows that exposure of pregnant mice to BPA and DEHP induce negative influence on the development and functions of the reproductive system of male pups.

Cancer


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3434201/


Prenatal exposure to BPA up- or down-regulates various proteins. Among them, SET, a putative oncogene and inhibitor of phosphatase 2A, is significantly down-regulated in a BPA dose-dependent manner. SET can therefore be applied as a new biomarker for prenatal BPA exposure. BPA new mechanism of action includes CYP17 disruption via SET.

**Immunology / Inflammatory response**


BisGMA, a BPA-based dental composite resin, induces nitric oxide, ROS, and inflammatory cytokines in murine macrophages. In addition, BisGMA may activate macrophage via NF-κB activation, IκB degradation, and p-Akt activation.

**Reproduction / development**


Exposure of 3-day-old mice to BPA (0, 20 and 40 μg kg⁻¹ day⁻¹) hampers spermatogenesis and the subsequent development of offspring.

**Brain development**


A single neonatal exposure to bisphenol A during the peak of the brain growth spurt can alter the adult levels of proteins important for normal brain development. Neonatal exposure to bisphenol A can act as a developmental neurotoxicant.

**Neurotoxicity**


The study suggests that BPAF, a chemical structurally related to bisphenol A and used as a substitute for BPA, also has neurotoxic properties.
Contact Allergy and cytotoxicity


The allergenic effects of diglycidyl ethers of bisphenol F (DGEBF) depend on its terminal epoxide groups. In contrast, DGEBF cytotoxicity not only depends on the presence of epoxide groups, but also on other structural features.

C) MONKEY

Reproduction


Exposure to doses of BPA that yield circulating levels of BPA analogous to those reported in humans alters early oogenesis and follicle formation in the fetal ovary of the rhesus monkey.

D) CHICKEN

Immune system


Exposure of chick embryos to a very low-dose level of BPA induce toxic effect on the development of the central immune organs of specific-pathogen-free chick embryos.

E) FISH

Hormone metabolism

The results of this study carried out on fish (fathead minnows) provide strong and direct evidence for ascribing an antiandrogenic mechanisms of action to BPA in vertebrates.

C. ENVIRONMENTAL EXPOSURE

HUMAN IMPREGNATION STUDIES:

- Belgian population


This study shows that the general Belgian population is extensively exposed to BPA and triclosan. Dietary intake would be the primary route of exposure to BPA.

ENVIRONMENTAL CONTAMINATION

- Drinking water


Bisphenol A and nonylphenols were detected in drinking water samples from 35 major Italian cities and five popular Italian brands of bottled mineral water. Herbicides were found mainly in samples from cities in northern Italy.

- Water / restored stormwater pipes


Neither BPA, nor phthalates (DEHP and BBP) were detected in water in contact with stormwater pipe-repair materials used by Ultraliner and Troliner technologies.

- Thermal paper
BPA was detected in all thermal paper samples collected in Belgium. An estimation of human exposure to BPA through thermal paper results in a median intake of 445 ng BPA/day for the general population, which corresponds to an exposure of 6.4 ng/kg bw/day for a person of 70 kg. Occupational exposure can be much higher.

Food-contact recycled-paper materials


The FUSLE and UPLC-ESI-QTOF-MS method was applied to the determination of bisphenol-type endocrine disrupting compounds in food-contact recycled-paper materials. The analysis of food-contact paper and cardboard samples confirmed the presence of for BPA, BPF, BADGE and BFDGE in these packaging.

D. METABOLISM AND BIOMONITORING

European biomonitoring: Assessment and methodology


As part of the ENRIECO project, the authors evaluated existing human biomonitoring data for BFRs, PFCs, phthalates and phenols in European birth cohorts and develop recommendations for more harmonized methods that will enable combination and comparison of cohort data in the future.

E. BPA: A GENERAL REVIEW

BPA in drinking water

BPA in drinking water represents a minor component of overall human exposure. Human biomonitoring data indicate that ingestion of drinking water represents <2.8% of the total intake of BPA.

- **Exposure from food**


This review reports that food is the main source of BPA exposure and that the total exposure remains below the current tolerable daily intake of 50µg/kg/j.

- **Effects on memory**


This review documents rapid effects of estradiol on memory which enhances memory consolidation within 1h in rats. Bisphenol-A, rapidly antagonizes enhancements in memory in both sexes possibly through actions on spines. In conclusion, estradiol and related compounds exert rapid alterations in cognition through non-genomic mechanisms.

- **Epigenetic effects**


In vitro and in vivo studies show that in utero exposure to environmental toxicants such as BPA and phthalates causes epigenetic modifications that can induce alterations in gene expression that may persist throughout life and over several generations.

**F. INNOVATION - METHODOLOGY**

- **Risk assessment / BPA substitutes**

This study provides a wealth of tools and information that could be used for the development of BPA substitutes devoid of hormonal activity and more generally for environmental risk assessment.

- European biomonitoring: Assessment and methodology


As part of the ENRIECO project, the authors evaluated existing human biomonitoring data for BFRs, PFCs, phthalates and phenols in European birth cohorts and develop recommendations for more harmonized methods that will enable combination and comparison of cohort data in the future.
LIST OF UNCOMMENTED STUDIES


Rosenfeld CS. Effects of maternal diet and exposure to bisphenol A on sexually dimorphic responses in conceptuses and offspring. Reprod Domest Anim. 2012 Aug. USA. 


