BPA-RELATED RISKS

- BPA scientific monitoring since May 2009: An overall assessment
- Key Findings from January to March 2012
A/ BPA scientific monitoring since May 2009: An overall assessment

Number of studies on humans and animals

Showing effects: 256 (94 %)
- On animals: 163 (45 of which are in vivo studies that used a BPA dose < ADI (EFSA))
- On humans: 93 (Health effects: 43 ; in vitro effects: 50)

Showing no effect: 15
- On animals: 8
- On humans: 7

B/ BPA scientific monitoring from January to March 2012: A comprehensive overview

EFFECTS ON HUMANS

Adverse pathophysiological effects:
- Associations between higher BPA exposure and incident coronary artery disease CAD during >10 years of follow-up in UK showed trends similar to previously reported cross-sectional findings in the more highly exposed NHANES respondents.
- Based on the examination of 1 380 subjects from the National Health and Nutritional Examination Survey 2003-2004, urinary BPA levels are associated with hypertension, independent of traditional risk factors.
- Altered DNA methylation at various CpG sites in women undergoing in vitro fertilization was associated with exposure to mercury, lead or BPA. Further studies are needed to confirm these associations.
- The presence of unconjugated BPA (uBPA) in 152 cord blood samples suggests placental transfer and fetal exposure but similar uBPA levels in control and cryptorchid groups make the participation of fetal exposure to uBPA in the physiopathology of undescended testes unlikely.
- Low doses of bisphenol-A induce rapid reduction in the K(ATP) channel activity and insulinotropic effect in pancreatic β-cells and islets of Langerhans in humans and rodents, with stronger actions in human islets. The results suggest that BPA behaves as a strong estrogen via nuclear ERβ and indicate that results obtained with BPA in mouse β-cells (insulin release) may be extrapolated to humans

In vitro effects:
- BPA can potentiate leptin action (cell proliferation) in human ovarian cancer cells by creating more binding sites for leptin and extending the time of leptin-induced Stat3, ERK1/2 and Akt phosphorylation.
- Low doses of bisphenol-A induce rapid reduction in the K(ATP) channel activity and insulinotropic effect in pancreatic β-cells and islets of Langerhans in humans and rodents, with stronger actions in human islets. The results suggest that BPA behaves as a strong estrogen via nuclear ERβ and indicate that results obtained with BPA in mouse β-cells (insulin release) may be extrapolated to humans

EFFECTS ON ANIMALS
### Rats:

- A nanomolar dose of bisphenol A (10nM) has rapid effects on the spinogenesis of adult rat hippocampal neurons.
- Developmental exposure of male rats to environmental doses of BPA impacts androgen secretion which, in turn, is alleviated by an increase in Leydig cell numbers. BPA causes biological effects at environmentally relevant exposure levels and its presence in consumer products potentially has implication for public health.
- Perinatal exposure to low doses of BPA or DES resulted in long-lasting effects in female rats, including delayed mammary gland differentiation, altered milk yield and modified milk composition.
- Perinatal exposure to BPA affects offspring phenotype and epigenetic regulation across multiple doses, indicating the need to evaluate dose effects in human clinical and population studies.
- Fetal exposure to plastic mixture (bisphenol A and phthalates), dioxin (TCDD) or jet fuel induce transgenerational negative effects on reproduction. The authors have identified exposure-specific epigenetic biomarkers that may allow for the assessment of ancestral environmental exposures associated with adult onset disease.

### Mice:

- Prenatal exposures to BPA, followed by postnatal allergic sensitization and challenges, promote the development of experimental allergic asthma in mice.
- Environmental estrogen contaminants, such as bisphenol A, can have a detrimental effect on the developmental lumbar bone growth and mineralization in mice.

### ENVIRONMENTAL EXPOSURE

#### Human impregnation studies:

- People with lower incomes have higher body burdens of BPA; the reverse was true for PFCs.

#### Environmental contamination:

- Migration tests performed on 277 baby bottles found that bottles made of PP and silicones showed a greater number of substances in the migration solutions and in greater quantity. Some substances found were not included in the Community positive list. Phthalates were also detected in silicone bottles (DiBP, DBP ans DEHP). The presence of components potentially coming from inks was also detected (potentially coming from instructions leaflets in the bottles) as well as BPA which was quantified in baby bottles made of PA, but limited to one brand (although labeled BPA free).

### BPA: A GENERAL REVIEW

- Review that focuses on the developmental effects of estrogenic endocrine disrupting chemicals (EDCs), and more specifically on effects of exposure to the estrogenic EDC bisphenol A (BPA) (obesity, reproductive capacity, fetal growth).
- The report of a working group from the National Toxicology Program (NTP) concluded that type 2 diabetes and obesity could be linked to exposures to environmental chemicals.
- The available data from biomonitoring studies clearly indicate that the general population is at risk from internal exposure to unconjugated BPA and that the two toxicokinetic studies which suggested human BPA exposure is negligible have significant deficiencies and are not reliable for risk assessment.
BPA-RELATED RISKS

PEER-REVIEWED PAPERS (JANUARY-MARCH 2012)
SOURCE: PubMed
PAPER ANALYSES

A. EFFECTS ON HUMANS

1. ADVERSE PATHOPHYSIOLOGICAL EFFECTS:

- **Asthma**

  

  *This prospective birth cohort study of 398 mother-infant pairs found that there is an association between wheeze from six months to three years and log-transformed BPA concentration at 16 weeks gestation only.*

- **Breast cancer**

  

  *This study suggests that higher serum BPA levels in postmenopausal women ages 55-70 years are associated with a clinically-relevant 5% greater breast density. Further investigation into the potential influence of BPA on breast cancer risk using human populations is warranted.*

- **Coronary disease**

  

  *Associations between higher BPA exposure and incident coronary artery disease CAD during >10 years of follow-up in UK showed trends similar to previously reported cross-sectional findings in the more highly exposed NHANES respondents.*

- **Hypertension**

Based on the examination of 1 380 subjects from the National Health and Nutritional Examination Survey 2003-2004, urinary BPA levels are associated with hypertension, independent of traditional risk factors.

Reproduction


The authors found that altered DNA methylation at various CpG sites in women undergoing in vitro fertilization was associated with exposure to mercury, lead or BPA. Further studies are needed to confirm these associations.

Reproduction (cryptorchidism)


The presence of unconjugated BPA (uBPA) in 152 cord blood samples suggests placental transfer and fetal exposure but similar uBPA levels in the control and cryptorchid groups make the participation of fetal exposure to uBPA in the physiopathology of undescended testes unlikely.

Cardiovascular disease


There is a significant association between some phthalate metabolites, but not BPA, and some risk factors for coronary heart disease in subjects aged 70 years.

2. IN VITRO EFFECTS:

Cancer

The study suggests that the genetic and epigenetic alterations by BPA might damage human mammary epithelial cells function and result in complex activities related to cell proliferation and senescence, playing a role in mammary carcinogenesis.


This study confirms the carcinogenicity of bisphenol A (BPA) and methoxychlor in vitro.


This study shows that BPA creates more binding sites for leptin (cell proliferation) and extends the time of leptin-induced Stat3, ERK1/2 and Akt phosphorylation, which may potentiate leptin action in cancer cells. Confirmation required by in vivo study.

- Structural biology


The authors demonstrated that human estrogen-related receptor γ (ERRγ) residues are essential structural elements for the strong binding of BPA to ERRγ.

- Hormone metabolism

Bisphenol A (BPA) suppresses aromatase (CYP19) activity in a dose-dependent fashion in human osteoblastic (SV-HFO) and ovarian granulosa-like (KGN) cell lines.

**Genotoxicity**

Blasiak J, Synowiec E, Tarnawska J, Czarny P, Poplawski T, Reiter RJ. *Dental methacrylates may exert genotoxic effects via the oxidative induction of DNA double strand breaks and the inhibition of their repair*. Mol Biol Rep. 2012 Feb 12. [Epub ahead of print] Department of Molecular Genetics, University of Lodz, Pomorska 141/143, 90-236, Lodz, Poland


Dental adhesive consisting of 45% 2-hydroxyethyl methacrylate (HEMA) and 55% bisphenol A-diglycidyl dimethacrylate (Bis-GMA) induces DNA double strand breaks in cultured primary human gingival fibroblasts through oxidative mechanisms. Vitamin C or melatonin may reduce the detrimental effects induced by methacrylates applied in dentistry.

**Metabolic disorders**


Low doses of bisphenol-A induce rapid reduction in the K(ATP) channel activity and insulinotropic effect in pancreatic B-cells and islets of Langerhans in humans and rodents, with stronger actions in human islets. The results suggest that BPA behaves as a strong estrogen via nuclear ERβ and indicate that results obtained with BPA in mouse B-cells (insulin release) may be extrapolated to humans.

**Effects on genes**

Hwang KA, Hyun SH, Jeung EB, Choi KC. *Bisphenol a and 17-Beta-oestradiol resulted in the gene alterations in oestrogen-receptor positive bg-1 ovarian cancer cells*. Reprod Fertil Dev. 2011 Dec;24(1):188. Laboratory of Veterinary Biochemistry and Immunology, College of Veterinary Medicine, Chungbuk National University, Cheongju, Chungbuk 361-763 Republic of Korea.


The results indicate that BPA may have an oestrogenic effect by regulating E2-responsive genes in ER-positive BG-1 ovarian cancer cells and that BG-1 cells would be the best in vitro model to detect these oestrogenic endocrine disrupting chemicals.
B. EFFECTS ON ANIMALS

a) RATS:

- **Cancer: signalisation**


This study shows that Xenoestrogens, like physiologic estrogens, can evoke downstream kinase signaling involving selective interactions of ERα with G(αi) and caveolin I, which could explain their disruptive actions.

- **Genotoxicity**


In this study, adult male and female rats were orally administered with various doses of BPA (2.4μg, 10μg, 5mg and 50mg/kgbw) once a day for six consecutive days. Then, in-vivo and in-vitro assays were performed to determine genotoxic and mutagenic effects of BPA. The data obtained clearly documents that BPA is not mutagenic but exhibits genotoxic activity and oxidative stress could be one of the mechanisms leading to genetic toxicity.

- **Nervous system**

This study demonstrates that a nanomolar dose of bisphenol A (10nM) has rapid effects on the spinogenesis of adult rat hippocampal neurons.

- **Hormone disruption mechanism**


This study shows that atrazine, vinclozolin, methoxychlor, and bisphenol A have different aromatase regulation profiles between animals with similar estrogen-to-androgen ratios but with different chemical treatments. The measurement of many endpoints is necessary for good risk assessment.

- **Reproduction**


Developmental exposure of male rats to environmental doses of BPA impacts androgen secretion which, in turn, is alleviated by an increase in Leydig cell numbers. BPA causes biological effects at environmentally relevant exposure levels and its presence in consumer products potentially has implication for public health.

- **Effects on mammary gland**


This study found that perinatal exposure to low doses of BPA or DES resulted in long-lasting effects in female rats, including delayed mammary gland differentiation, altered milk yield and modified milk composition.

- **Développement**


Perinatal BPA exposure interferes with the normal development of affective behaviors in a non-linear, dose-dependent manner, which corresponds to behavioral demasculinization of adult males.

- **Transgenerational effects**

Perinatal exposure to BPA affects offspring phenotype and epigenetic regulation across multiple doses, indicating the need to evaluate dose effects in human clinical and population studies.

- Transgenerational effects (reproduction)


Fetal exposure to plastic mixture (bisphenol A and phthalates), dioxin (TCDD) or jet fuel induce transgenerational negative effects on reproduction. The authors have identified exposure-specific epigenetic biomarkers that may allow for the assessment of ancestral environmental exposures associated with adult onset disease.

- Modelisation /cocktail effect on human


This study suggests that women of reproductive age may not be protected sufficiently against the combined effects of chemicals that affect the hormonal milieu required for normal male sexual differentiation.

b) MICE :

- Cytotoxicity and genotoxicity (in vitro)

BisGMA demonstrated a cytotoxic and genotoxic effects on murine macrophage cell line RAW264.7 which are mediated by DNA damage and caspase activation.

- **Protective Effects of Ginsenosides**


Ginsenosides have protective effects against BPA-induced cell damage.

- **Mutagenic, genotoxic and reproductive effects**


Both X-rays and BPA administered alone to male mice decreased sperm count and quality. X-rays induced DNA strand breaks in spleen cells, whereas BPA induced DNA strand breaks in lymphocytes and in cells from spleen, kidneys, and lung and in germ cells. Results confirmed the mutagenic ability of BPA which is genotoxic and reprotoxic.

- **Diabetes**


Short-term treatment with low doses of BPA slows down whole body energy metabolism and disrupts insulin signaling in peripheral tissues in mice. These findings support the notion that BPA can be considered a risk factor for the development of type 2 diabetes.

- **Cytotoxicity of dental materials (BisGMA)**

  Kuan YH, Li YC, Huang FM, Chang YC. **The upregulation of tumour necrosis factor-α and surface antigens expression on macrophages by bisphenol A-glycidyl-methacrylate.** Int Endod J. 2012 Jan 23. doi: 10.1111/j.1365-2591.2012.02017.x. [Epub ahead of print] Department of Pharmacology, Chung Shan Medical University, Taichung Department Dentistry, Chung Shan Medical University Hospital, Taichung School of Dentistry, Chung Shan Medical University, Taichung, Taiwan.  
BisGMA is cytotoxic to murine macrophage cell line RAW264.7. When exposed to BisGMA, the ability of macrophages to induce an appropriate immune response has the potential to upregulate tumour necrosis factor-a production and expression of surface antigens.

- **Asthma**


> Prenatal exposures to BPA, followed by postnatal allergic sensitization and challenges, promote the development of experimental allergic asthma in mice.

- **Reproduction**


> Early prepubertal exposure to BPA accelerated the onset of puberty but decreased reproductive parameters in female mice.

- **Effects on the musculoskeletal system**


> This study suggests that environmental estrogen contaminants can have a detrimental effect on the developmental lumbar bone growth and mineralization in mice. Further studies measuring the impact of environmental estrogen mimics, such as bisphenol A, are then warranted.

- **Nervous system**

Komada M, Asai Y, Morii M, Matsuki M, Sato M, Nagao T. *Maternal bisphenol A oral dosing relates to the acceleration of neurogenesis in the developing neocortex of mouse fetuses.* Toxicology. 2012 May...
Maternal oral exposure to BPA related to the disruption of the cell cycle in fetal intermediate progenitor cells (IPCs) and the effects of neurogenesis in the developing neocortex.

**Uterine infection**


Exposure to low doses of 17α-éthinyl oestradiol (EE) or BPA induces pyometra (uterine infection) in C57BL/6 mice but not in CD1 mice.

**Calcic absorption**


This study shows that BPA administration at 20mg/kg body weight/day during pregnancy decreases serum calcium (Ca) in pre-delivery mice, which may be partly due to decreased paracellular Ca absorption.

**MONKEY**

**Effects on thyroid hormone (In vitro)**


The results of this study indicate that low concentrations of BPA suppress the thyroid hormone receptor (TR) transcription by disrupting physiologic concentrations of T3/T4-mediated β3 integrin/c-Src/MAPK/TR-B1 pathways, followed by recruiting N-CoR/SMRT to TR-B1, providing a novel insight regarding the TH disruption effects of low concentration BPA.
Feminization


Injection of BPA or nonylphenol into the eggs of Japanese quail just before incubation revealed that both substances have a dose-independent potential of ovotestis induction (feminization of the male gonad) in the Japanese quail embryo.

E) FISH AND AMPHIBIANS

Thyroid metabolism


The results suggest that BPA disrupts thyroid function by potentiating the effect of endogenous T3 in early development.

Ecotoxicology

Chow WS, Chan WK, Chan KM. Toxicity assessment and vitellogenin expression in zebrafish (Danio rerio) embryos and larvae acutely exposed to bisphenol A, endosulfan, heptachlor, methoxychlor and tetrabromobisphenol A. J Appl Toxicol. 2012 Feb 21. doi: 10.1002/jat.2723. [Epub ahead of print] Biochemistry Program, School of Life Sciences, Faculty of Science, The Chinese University of Hong Kong, Sha Tin, N.T., Hong Kong, SAR, China.

The use of vitellogenin mRNA induction in zebrafish embryos and larvae was found to be a sensitive biomarker of exposure to organochlorine pesticides tetrabromobisphenol A (flame retardant), and its precursor compound bisphenol A.

a) INSECTS / WATER SNAILS

Ecotoxicology

This study shows that Bisphenol A has the ability to activate non-coding sequences mainly located at telomeres and centromeres. It provides evidence that xenobiotics can induce specific responses in ncRNAs derived from repetitive sequences that could be relevant in the toxic response.

➢ Ecotoxicology


The authors developed assays on the freshwater snail Physa acuta to address correlations between embryo toxicity and genotoxicity following waterborne pollutant exposure. The results found that benzo(a)pyrene, fluoxetine and BPA are toxic to embryos. The authors conclude that the embryo toxicity test is a starting point for the development of a life cycle test with freshwater snails even for undertaking multigeneration studies.

C. ENVIRONMENTAL EXPOSURE

HUMAN IMPREGNATION STUDIES:

➢ Impregnation during pregnancy


The study found that urinary phthalate metabolites and BPA concentrations were variable before and during pregnancy, but the magnitude of variability was biomarker specific. A single spot-urine sample adequately classified MBP and MEP concentrations during pregnancy. The present results should be replicated in other pregnancy cohorts.

➢ Impregnation and social disparities


People with lower incomes had higher body burdens of BPA; the reverse was true for PFCs. For both BPA and PFCs there was smaller and less consistent associations with education and occupation.
Maternal and fetal impregnation / ethnicity


The authors found significant racial/ethnic differences in maternal/fetal BPA concentrations. African-Americans had the highest maternal serum concentrations; Hispanics had higher fetal concentrations than non-Hispanics.

Swedish population


This study found that food is a source of BPA and 4-Nonylphenol (NP) in the general Swedish population and that there is a continuous source of exposure to those pollutants that is high enough for free NP and BPA to be detected in some consumers.

Dental composite fillings

Chung SY, Kwon H, Choi YH, Karmaus W, Merchant AT, Song KB, Sakong J, Ha M, Hong YC, Kang D. Dental composite fillings and bisphenol A among children: a survey in South Korea. Int Dent J. 2012 Apr;62(2):65-69. doi: 10.1111/j.1875-595X.2011.00089.x. Department of Preventive Dentistry, School of Dentistry, Kyungpook National University, Daegu, South Korea Department of Preventive Medicine, College of Medicine, Dankook University, Choongnam, South Korea Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC, USA http://www.ncbi.nlm.nih.gov/pubmed/22420473

This study, conducted on a total of 495 children aged 8-9 years, found that having many dental composite filling surfaces on teeth may increase the urinary BPA concentration in children.

Bioaccumulation


BPA could be detected in almost all adipose tissue, liver and brain samples from 11 individuals. Its potential for bioaccumulation is low though. The reported concentrations of free BPA in the various tissues are in slight disagreement with pharmacokinetic models in humans and rats.

ENVIRONMENTAL CONTAMINATION
Baby bottles


Migration tests performed on 277 baby bottles found that bottles made of PP and silicones showed a greater number of substances in the migration solutions and in greater quantity (alkanes and benzene derivatives). Some substances found were not included in the Community positive list. Phthalates were also detected in silicone bottles (DiBP, DBP ans DEHP). The presence of components potentially coming from inks was also detected (potentially coming from instructions leaflets in the bottles) as well as BPA which was quantified in baby bottles made of PA, but limited to one brand (although labeled BPA free).

Food


This study found that food is a source of BPA and 4-Nonylphenol (NP) in the general Swedish population and that there is a continuous source of exposure to those pollutants that is high enough for free NP and BPA to be detected in some consumers.

Dentistry


Monomers from resin-based composite materials used in dentistry such as bisphenol-A diglycidyl methacrylate (Bis-GMA) are detected in the saliva of patients shortly after restorative therapy. One week after treatment, no monomers could be detected in patients' saliva samples.

Hsu WY, Wang VS, Lai CC, Tsai FJ. Simultaneous determination of components released from dental composite resins in human saliva by liquid chromatography/multiple-stage ion trap mass spectrometry. Electrophoresis. 2012 Feb;33(4):719-25. doi: 10.1002/elps.201100571. Department of Medical Research, China Medical University Hospital, Taichung, Taiwan.

This study was able to successfully quantify monomers (TEGDMA, UDMA, et Bis-GMA) and their principal biodegradation products from dental composite resins in human saliva.

- **Consumer Products**

Silent Spring Institute. 

The authors found 55 endocrine disruptors and asthma-related chemicals in a range of cosmetics, personal care products, cleaners, sunscreens, and vinyl products, many of which were not listed on labels.

- **Seawater**


A new sensitive and green analytical chemistry method was used to detect the presence of BPA (0.035 μg L⁻¹) and nonylphenol (0.14 μg L⁻¹) in seawater samples from different sites of A Coruña (Northwest of Spain).

- **Seawater and outfall discharges (Spain)**


There were no significant differences in contamination levels by EDs between the environmental mixing zone of the outfall of the Santander sanitation system and control sites except for 4-tert-octylphenol which was higher in the outfall site.

- **Source waters (Spain)**

Bisphenol a, triazine herbicides, alkylphenols, and phthalates were detected in a very low concentration in a few water sources intended for bottling in Spain. Spring water intended for consumption remains of good quality.

- **Sediments (Germany)**


A sediment sample from the river Elbe/Germany was found to be contaminated with xenoestrogens: 17β-estradiol, estrone, 4-isoo-nonylphenols, bisphenol A, stigmasterol and chlorophene.

- **Sediments (China)**


Detection of endocrine disrupting chemicals (nonylphenol (NP), octylphenol (4-t-OP) and bisphenol A (BPA)), in sediments of the Suzhou Creek (China) and its branches. The accumulation of pollutants closely related to the intensity of anthropogenic activities.

- **Surface water and sediment (China)**


Pollution of Dianchi Lake, China, with phenolic endocrine disrupting compounds including nonylphenol-di-, nonylphenol-mono-ethoxylate, 4-nonylphenol, bisphenol A, 4-cumylphenol and 4-tert-octylphenol. This pollution comes mainly from industry, agriculture and daily life.


Sediment from the Gulf of Mexico, New Orleans surface water, and the influent and effluent of a New Orleans municipal sewage treatment plant are contaminated with EDCs, including organochlorine pesticides, polychlorinated biphenyls, bisphenol A and steroid hormones.
Mortazavi S, Riyahi Bakhtiari A, Sari AE, Bahramifar N, Rahbarizade F. Phenolic endocrine disrupting chemicals (EDCs) in Anzali Wetland, Iran: Elevated concentrations of 4-nonylphenol, octylphenol and bisphenol A. Mar Pollut Bull. 2012 Mar 27. [Epub ahead of print] Environmental Forensic Laboratory, Department of Environmental Sciences, Faculty of Natural Resource and Marine Science, Tarbiat Modares University, P.O. Box 46414 356, Noor, Mazandaran, Iran. http://www.ncbi.nlm.nih.gov/pubmed/22459496

This study found that sediments from Anzali Wetland, Iran, are contaminated with 4-nonylphenol (4-NP), octylphenol (OP) and bisphenol A (BPA). High levels of alkylphenols and BPA were also found near urban areas.

- Sewage sludge (California)


High concentrations of EDCs (bisphenol A, estrone, nonylphenol and octylphenol) and personal care products (acetylsalicylic acid, carbamazepine, clofibric acid, diclofenac, gemfibrozil, ibuprofen, ketoprofen, naproxen, paracetamol and triclosan) were found in sewage sludge, from sewage treatment plants in southern California.

D. METABOLISM AND BIOMONITORING

- Excretion via sweat


The study shows that BPA can be found in human sweat, even in individuals with no BPA detected in their serum or urine samples. The authors conclude that Biomonitoring of BPA through blood and/or urine testing may underestimate the total body burden of this potential toxicant and that sweat analysis should be considered as an additional method for monitoring bioaccumulation of BPA in humans.

- Pharmacokinetics

The study of BPA pharmacokinetics in mice shows that less than 0.01% of the administered dose remains in adipose tissue after 24h. The authors underscore the non-persistent nature of BPA.

- **US and Canadian population exposure**


This study compares human exposure to BPA in the US and Canada using biomonitoring data from the American NHANES and Canadian CHMS. After they have examined CHMS and NHANES methodologies, the authors conclude that BPA intakes for both countries are below health-based guidance values set by the US, Canada and the European Food Safety Authority.

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**E. BPA: A GENERAL REVIEW**

- **Autism**


Perinatal exposure to EDCs such as BPA, pesticides, phthalates, PCBs etc. appears to be associated with the occurrence of autism spectrum (ASD) as well as attention deficit hyperactivity (ADHD) disorders.

- **Alternative mechanisms**


This review analyzes with substantiated scientific evidence the strong estrogenic activity of BPA at very low concentrations when it acts through alternative mechanisms of action at least in certain cell types.

- **Brain Development**

Pathology & Applied Neurobiology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan.

This review focuses on the effects of prenatal and lactational exposure to low doses of BPA on brain development in mice. Functionally, BPA exposure disturbs murine behavior accompanied with a disrupted neurotransmitter system, in the postnatal development period and in adult mice. Epigenetic alterations in promoter-associated CpG islands might underlie some of the effects on brain development.

- Inventory of the situation in Israel


This article reports on human biomonitoring studies carried out in Israel.

- Obesity - diabetes


This review focuses on the developmental effects of estrogenic endocrine disrupting chemicals (EDCs), and more specifically on effects of exposure to the estrogenic EDC bisphenol A (BPA) (obesity, reproductive capacity, fetal growth).

http://www.ncbi.nlm.nih.gov/pubmed/22296744

The report of a working group from the National Toxicology Program (NTP) concluded that type 2 diabetes and obesity could be linked to exposures to environmental chemicals.


There is evidence of the obesogenic effect of polluting chemical substances (DES, genistein, bisphenol A, organotins, and phthalates) in tissues and experimental animals, but few data are available in humans.
Human exposure

Vandenberg LN, Chahoud I, Heindel JJ, Padmanabhan V, Paumgartten FJ, Schoenfelder G. Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. Cien Saude Colet. 2012 Feb;17(2):407-34. Tufts Center for Regenerative and Developmental Biology, Department of Biology, Tufts University, Medford, MA 02155, USA.


This review concludes that available data from biomonitoring studies clearly indicate that the general population is at risk from internal exposure to unconjugated BPA and that the two toxicokinetic studies which suggested human BPA exposure is negligible have significant deficiencies and are not reliable for risk assessment.

Dermal exposure


This paper argues that human exposure to indoor pollutants through the dermal pathway is underestimated. Health consequences vary with exposure pathway. For example, an SVOC that enters the blood through the skin does not encounter the same detoxifying enzymes that an ingested SVOC.

Reproduction


The authors of this review discuss how environmental toxicants (cadmium, bisphenol A and lead) may affect reproductive function and how toxicant-induced damage may be effectively managed so that fertility can be maintained.

Cardiovascular disease


This review of the scientific literature reports that there exist associations between plastic-associated chemicals (BPA, phthalates), persistent organic pollutants, and overt cardiovascular disease.
Extra-nuclear ER signals are highly susceptible to different ligands such as BPA that, by unbalancing E2-induced cell functions, drive cells to different functional endpoints.

F. METHODOLOGY

- Reproduction: antigestagenic effects


The authors developed a flexible in vitro model based on human endometrial Ishikawa cells to study quantitatively effects of antiprogesterin-like chemicals on endometrial target genes. Assays found, inter alia, that 4-nonylphenol, bisphenol A and apigenin have antagonistic effects on progesterone.

- Potentiel de perturbation endocrinienne


According to OECD test guideline 455(TG455), the estrogenic activity of BBP, BPA and NP are weaker than 17B-estradiol whereas DEHP, DBP and DEP did not show any estrogenicity activity in a STTA assay.