

Paris, le 1er octobre 2009

Madame Roselyne Bachelot-Narquin
Ministre de la Santé et des Sports
Ministère de la Santé et des Sports
14 avenue Duquesne
75350 PARIS 07 SP

Madame la Ministre,

Faisant suite au premier bulletin de veille sur le Bisphenol A que nous vous avons adressé le 9 juillet dernier, nous vous faisons parvenir le bulletin de veille de la période Juillet-Août qui présente une analyse des dernières publications sur les risques liés au Bisphénol A.

Ces nouveaux éléments justifient la réouverture des travaux d'expertise de l'AFSSA sur le sujet et nous sommes prêts à y apporter notre concours.

Veuillez agréer, Madame la Ministre, l'expression de nos sentiments dévoués à la cause de la santé environnementale.

André Cicoella

Porte-parole du Réseau Environnement Santé

A handwritten signature in black ink, appearing to be "A. Cicoella", with a long horizontal stroke extending to the right.

RISQUES LIES AU BISPHENOL A : ARTICLES PARUS EN JUILLET-AOUT 2009 DANS LA LITTÉRATURE SCIENTIFIQUE (Source Medline)

ANALYSE GÉNÉRALE

Exposition

Plusieurs articles analysent les sources de contamination de la population, via le biberon, les ciments dentaires, les poussières domestiques et, pour la première fois, via le travail. Les dosages biologiques urinaires confirment cette exposition en population générale en Chine (50 % contre 93 % aux Etats Unis). Un article montre que l'exposition aux perturbateurs endocriniens via les emballages est plus large que celle liée au BPA, ce qui devrait avoir des conséquences réglementaires.

Effets chez l'animal

Les données expérimentales confirment des effets chez la descendance suite à des expositions pendant la gestation à des niveaux d'exposition inférieurs à la DJA de l'AFSSA et de l'Agence sanitaire européenne AESA (DJA de 50 µg/kg/j).

- Une étude chez le rat confirme des effets transgénérationnels, sur la 4ème génération, à des doses 20 et 40 fois inférieures à la DJA européenne. Une diminution du développement de l'endomètre à l'âge adulte est observé chez des rats exposés à la naissance à une dose correspondant à la DJA européenne (schéma de l'exposition au biberon ou pendant la lactation), dont la conséquence peut donc être une atteinte de la fertilité de la femme. Par ailleurs une atteinte génotoxique est décrite, dans les tissus mammaires et hépatiques, mais à dose supérieure à la DJA.

- Une étude chez le singe montre un trouble du comportement chez les mâles exposés via la gestation à une dose égale au cinquième de la DJA européenne.

Effets chez l'homme

Chez l'homme, un effet de stress oxydant et d'inflammation est suggéré chez les femmes ménopausées (mécanismes impliqués dans la cancérogénèse).

Aspects réglementaires

Une étude répond à l'argument de la différence de métabolisation entre le rat et l'homme évoqué par l'AFSSA et l'AESA, en montrant que la conjugaison du BPA dans l'organisme est une succession de phases de conjugaison et de déconjugaison notamment dans le placenta, ce qui se traduit par une exposition du fœtus.

Dans le même esprit, un autre article critique le modèle expérimental utilisé pour construire la DJA européenne du BPA et plaide pour une remise en cause du paradigme traditionnel de la toxicologie « C'est la dose qui fait le poison ».

ANALYSE DE CHAQUE ARTICLE

Exposition

1/

Bisphenol A levels in blood and urine in a Chinese population and the personal factors affecting the levels.

He Y, Miao M, Herrinton LJ, Wu C, Yuan W, Zhou Z, Li DK.

Environ Res. 2009 Jul;109(5):629-33.

Commentaire : Analyse des urines de 952 personnes recrutées en milieu de travail en Chine. Le BPA est détecté dans 50 % des échantillons urinaires. La moyenne géométrique était de 0,38 µg/g créatinine. A titre de comparaison, la moyenne géométrique dans un échantillon de population coréenne est de 8,91 µg/g créatinine (Yang 2003) et, aux Etats-Unis, le pourcentage observé en population générale était de 93 %, les niveaux mesurés étant en moyenne géométrique de 2,6 µg/g créatinine (Calafat, 2008) et de 30,3 µg/L chez les prématurés (Calafat, 2009). La population chinoise est donc moins exposée que la population américaine ou coréenne, mais le taux de 50 % montre que, même dans un pays au mode de vie différent de ceux de pays plus industrialisés, une fraction importante de la population est imprégnée de façon significative.

Abstract

The objective of the study was to describe the background bisphenol A (BPA) levels in urine and serum of a Chinese population without occupational exposure and to examine the personal characteristics influencing these levels. Workers from 10 factories and their family members were recruited and their peripheral blood and spot urine samples were collected. The conjugated and free BPA of the samples was assayed with high-performance liquid chromatography. The exposure levels were checked with 2-independent-samples test, and the potential personal factors influencing exposure levels were analyzed using nonlinear correlation. Of the total of 952 subjects participating in the study, urine and blood samples were taken from 97% and 93% of them, respectively. The detectable rates were 50% for urine samples and 17% for serum samples, given the detection limit of 0.31 microg/L for urine and 0.39 microg/L for serum. The arithmetic mean (AM) and geometric mean (GM) of non-creatinine-adjusted urinary BPA level were 10.45 and 0.87 microg/L, which became 24.93 and 0.38 microg/g Cr after the creatinine level was adjusted; serum BPA levels were 2.84 microg/L (AM) and 0.18 microg/L (GM). Males and those with smoking habit had higher biological burden of BPA. The results indicated that half of the study subjects had detectable BPA in their urine samples. BPA levels were influenced by gender and smoking status. The sources of non-occupational BPA exposures should be explored.

2/

Occupational Exposure Levels of Bisphenol A among Chinese Workers.

[He Y, Miao M, Wu C, Yuan W, Gao E, Zhou Z, Li DK.](#)

[J Occup Health. 2009 Aug 25.](#)

Commentaires : Cet article est un des premiers à traiter de la question de l'exposition professionnelle au BPA. L'usine chinoise concernée fabriquait des résines polyépoxy. Les niveaux d'imprégnation apparaissent nettement plus élevés que dans la population générale publiés par ailleurs, qu'il s'agisse d'une population chinoise (0,38 µg/g créatinine Ye, 2009) coréenne (8,91 µg/g créatinine, Yang, 2003) ou américaine (2,3 µg/g créatinine dans la population américaine (Calafat, 2008), contre 4630 ou 5400 µg/g. Les femmes enceintes dans cette usine doivent donc contaminer leurs enfants à proportion. Avec quelles conséquences ? Les auteurs demandent à juste titre que des mesures de protection des travailleurs soient prises, notamment via la définition d'une valeur limite professionnelle. Une étude du même genre serait nécessaire dans une usine de fabrication du polycarbonate. En France, le site de l'INRS ne fournit que le nombre de salariés exposés (entre 1500 et 5000 sur la base CMR). Aucune indication sur les autres bases de l'INRS METROPOL (Métrologie de Polluants), et Fiches toxicologiques.

Abstract

Objectives: The purpose of this study was to assess ambient Bisphenol A (BPA) levels in workplaces and urine BPA levels of workers.

Methods: Workers in epoxy resin and BPA manufacturing factories were recruited. Personal samples for airborne BPA were taken in the workshops and spot urine samples were collected from workers before and after their shifts. The samples were assayed with high-performance liquid chromatography with a fluorescence detector. TWA(8) of airborne BPA in the workplaces and biological BPA burden of the workers were calculated. Correlations between the external and the internal exposure levels were sought.

Results: Workers from the factories were occupationally exposed to BPA at median personal airborne levels of 6.67 µg/m(3) (or at the mean of 450 µg/m(3)). More than 90% of the workers who were occupationally exposed to BPA had detectable BPA levels in their blood samples. The medians of creatinine-adjusted urinary BPA levels were 84.6 µg/g Cr and 111 µg/g Cr pre- and post-shift (means of 4,630 µg/g Cr and 5,400 µg/g Cr), respectively. The urinary BPA concentration post-shift was significantly associated with the urinary BPA level pre-shift and personal airborne BPA levels. Conclusions: It was indicated that workers in epoxy resin and BPA manufacturing factories are occupationally exposed to BPA at high levels. There is an urgent need to create occupational standards and take effective preventive measures to protect workers from the potential adverse effects of BPA.

3/

Water sorption and diffusion coefficient through an experimental dental resin.

[Costella AM, Trochmann JL, Oliveira WS.](#)

[J Mater Sci Mater Med. 2009 Aug 20.](#)

Commentaire : Cette étude montre que les résines à base de BPA utilisées dans les ciments dentaires relarguent du BPA dans la salive. Un calcul de risque reste à faire pour évaluer l'importance de cette source par rapport aux sources liées à l'alimentation.

Abstract

Polymeric composites have been widely used as dental restorative materials. A fundamental knowledge and understanding of the behavior of these materials in the oral cavity is essential to improve their properties and performance. In this paper we computed the data set of water absorption through an experimental dental resin blend using specimen discs of different thicknesses to estimate the diffusion coefficient. The resins were produced using Bisphenol A glycol dimethacrylate, Bisphenol A ethoxylated dimethacrylate and Triethylene glycol dimethacrylate monomers. The water sorption test method was based on International Standard ISO 4049 "Dentistry-Polymer-based filling materials".

Results show a diffusion coefficient around 6.38×10^{-8} cm²/s, within a variance of 0.01%, which is in good agreement with the values reported in the literature and represents a very suitable value.

4/

Migration of bisphenol A from plastic baby bottles, baby bottle liners and reusable polycarbonate drinking bottles.

[Kubwabo C](#), [Kosarac I](#), [Stewart B](#), [Gauthier BR](#), [Lalonde K](#), [Lalonde PJ](#).

[Food Addit Contam Part A Chem Anal Control Expo Risk Assess.](#) **2009 Jun;26(6):928-37**

Commentaire : Cette étude évalue la migration du BPA dans les biberons au BPA à 40 degrés celsius de 0,11 µg/l dans l'eau pendant 8h à 2,39 µg/l dans l'éthanol à 50% incubé pendant 240h (simulation du lait). La concentration de BPA augmente avec la température et le temps d'incubation. Les biberons sans BPA montrent seulement des traces. Les tests ont été conduits pour le plomb et le cadmium dans les biberons en verre. Aucune trace de ces métaux n'a été détectée. L'exposition du nourrisson déduite de ces données pour une consommation de 0,5l pour 9kg est de 0,11/2/9 soit 6 ng/kg pour la migration via l'eau, 132 ng/kg pour la migration simulant l'exposition via le lait. Ces expositions sont inférieures à la DJA européenne (50 µg/kg/j), mais si la norme était calculée selon les règles de bonne pratique soit à partir des effets sur le développement, celle-ci serait de 10 ng/kg et serait donc largement dépassée lors de l'exposition via le lait à température modérée.

Abstract

Human exposure to bisphenol A (BPA) has recently received special attention. It has been shown that exposure to BPA may occur through the consumption of beverages or foods that have been in contact with polycarbonate (PC) plastic containers or epoxy resins in food packaging. A BPA migration study was conducted using a variety of plastic containers, including polycarbonate baby bottles, non-PC baby bottles, baby bottle liners, and reusable PC drinking bottles. Water was used to simulate migration into aqueous and acidic foods; 10% ethanol solution to simulate migration to low- and high-alcoholic foods; and 50% ethanol solution to simulate migration to fatty foods. By combining solid-phase extraction, BPA derivatization and analysis by GC-EI/MS/MS, a very low detection limit at the ng l(-1) level was obtained. Migration of BPA at 40 degrees C ranged from 0.11 microg l(-1) in water incubated for 8 h to 2.39 microg l(-1) in 50% ethanol incubated for 240 h. Residual BPA leaching from PC bottles increased with temperature and incubation time. In comparison with the migration observed from PC bottles, non-PC baby bottles and baby bottle liners showed only trace levels of BPA. Tests for leachable lead and cadmium were also conducted on glass baby bottles since these represent a potential alternative to plastic bottles. No

detectable lead or cadmium was found to leach from the glass.

This study indicated that non-PC plastic baby bottles, baby bottle liners and glass baby bottles might be good alternatives for polycarbonate bottles.

5/

Assessment of human exposure to Bisphenol-A, Triclosan and Tetrabromobisphenol-A through indoor dust intake in Belgium.

[Geens T](#), [Roosens L](#), [Neels H](#), [Covaci A](#)

Chemosphere. 2009 Aug;76(6):755-60.

Commentaire : Le BPA est retrouvé dans les poussières domestiques, une source à mieux identifier, notamment par rapport à l'exposition de l'enfant.

Abstract

Bisphenol-A (BPA), Triclosan (TCS) and Tetrabromobisphenol-A (TBBPA) are phenolic organic contaminants used in a variety of household applications. Through manufacture and usage, these contaminants can leach into the environment and can be detected in indoor dust. In this study, we determined the concentrations of BPA, TCS and TBBPA in indoor dust samples from 18 houses and 2 offices in Flanders, Belgium.

The analysis was performed using solid-liquid extraction, clean-up and measurement by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Median concentrations of the 18 domestic dust samples were 1460, 220 and 10 ng g(-1) dust for BPA, TCS and TBBPA, respectively. Concentrations in offices were almost 5-10 times higher for BPA and TBBPA, while TCS concentrations were comparable at both locations. An assessment of the daily intake of these contaminants through dust was made and the contribution of dust to the total human exposure was calculated.

For all three contaminants, dust seems to be a minor contributor (<10% of total exposure) to the total daily exposure. Food intake appears to be the major source of human exposure to BPA and TBBPA as dermal uptake through personal care products seems to be the major contributor for TCS.

6/

Exposure to endocrine disrupting compounds via the food chain: Is packaging a relevant source?

[Muncke J](#).

Sci Total Environ. 2009 Aug 1;407(16):4549-59.

Commentaire : Cette étude analyse les sources de contamination de la nourriture par les emballages. 50 perturbateurs endocriniens ont été identifiés dont le BPA. Les auteurs demandent que la réglementation européenne ne considère plus les polluants séparément, étant donné les effets de synergie possibles.

Abstract

Contamination of foodstuffs by environmental pollutants (e.g. dioxins, metals) receives much attention. Until recently, food packaging as a source of xenobiotics, especially those with endocrine disrupting properties, has received little awareness despite its ubiquitous use. This article reviews the regulations and use of endocrine disrupting compounds (EDCs) in food packaging and discusses their presence within the context of new toxicology paradigms. I

focused on substances known to be legally used in food packaging that have been shown to exhibit endocrine disruptive effects in biological systems. I compiled a list of 50 known or potential EDCs used in food contact materials and examined data of EDCs leaching from packaging into food, with a focus on nonylphenol. I included recent advances in toxicology: mixture effects, the developmental origins of adult disease hypothesis, low-dose effects, and epigenetics. I especially considered the case of bisphenol A.

The core hypothesis of this review is that chemicals leaching from packaging into food contribute to human EDCs exposure and might lead to chronic disease in light of the current knowledge. Food contact materials are a major source of food contaminants. Many migrating compounds, possibly with endocrine disruptive properties, remain unidentified. There is a need for information on identity/quantity of chemicals leaching into food, human exposure, and long-term impact on health. Especially EDCs in food packaging are of concern.

Even at low concentrations, chronic exposure to EDCs is toxicologically relevant. Concerns increase when humans are exposed to mixtures of similar acting EDCs and/or during sensitive windows of development. In particular, non-intentionally added substances (NIAS) migrating from food contact materials need toxicological characterization; the overall migrate of the finished packaging could be evaluated for biological effects using bioassays.

The widespread legal use of EDCs in food packaging requires dedicated assessment and should be updated according to contemporary scientific knowledge.

Effets chez l'animal

7/

Impairment in protein expression profile of testicular steroid receptor coregulators in male rat offspring perinatally exposed to Bisphenol A.

Salian S, Doshi T, Vanage G.

Life Sci. 2009 Jul 3;85(1-2):11-8.

Commentaire : Cette étude menée chez le rat montre qu'une exposition de la génération F0 (du 12^{ème} jour de la gestation au 21^{ème} jour post-natal) a un impact sur les récepteurs stéroïdiens testiculaires chez les mâles en génération F3 (ce qui correspond au Rapport d'arrière-grand-mère à arrière-petit-fils). Les niveaux d'exposition sont 20 et 40 fois plus faibles que la norme européenne, ce qui démontre que celle-ci n'est pas protectrice.

Abstract

AIMS: Steroid hormones and steroid receptors (SRs) play a crucial role in spermatogenesis. Steroid receptor coregulators are the major determinants of SR functioning, and any alteration in their expression is known to be associated with impaired spermatogenesis. Since Bisphenol A (BPA) exposure leads to an impairment of spermatogenesis, we hypothesized that this effect could be associated with the altered expression of steroid receptors and their coregulators in the testes. The present study describes the effect of perinatal exposure of rats to BPA on the expression profile of testicular steroid receptor coregulators in the F(1) generation. These effects were further studied in the F(2) and F(3) generations to determine vertical transmission.

MAIN METHODS: Pregnant female rats (F(0)) were gavaged daily with BPA (1.2 and 2.4 microg/kg bw) (or vehicles for controls) from gestation day 12 through postnatal day (PND) 21 to obtain the F(1) and subsequent F(2) and F(3) generations. Immunohistochemical

localization of steroid receptor coactivator-1 (SRC-1), G-receptor integrating protein-1 (GRIP-1), p300/CBP/cointegrator-associated protein (p/CIP) and nuclear corepressor (NCoR) was carried out in the testes of F(1), F(2) and F(3) generation adult rats.

KEY FINDINGS: A significant reduction in the expression of SRC-1 and NCoR, with a parallel increase in the expression of p/CIP and GRIP-1, was observed in the testes of rats exposed perinatally to BPA. Surprisingly, a similar pattern was observed in the testes of F(2) and F(3) rats.

SIGNIFICANCE: Perinatal exposure of male rats to BPA leads to transgenerational perturbations in the expression profile of testicular steroid receptor coregulators

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Effects of Neonatal Exposure to Bisphenol A on Steroid Regulation of Vascular Endothelial Growth Factor Expression and Endothelial Cell Proliferation in the Adult Rat Uterus.

[Bosquiazzo VL](#), [Varayoud J](#), [Muñoz-de-Toro M](#), [Luque EH](#), [Ramos JG](#).
[Biol Reprod.](#) 2009 Aug 19.

Commentaire : Cette étude chez le rat a analysé l'impact d'une exposition néonatale au BPA et au Distilbène sur le développement, chez l'animal adulte, de l'endomètre (paroi intérieure de l'utérus) relatif au processus d'implantation de l'embryon. La 1^{ère} dose utilisée pour le BPA correspond à la norme européenne 50 µg/kg/j. On observe une diminution du développement de l'endomètre. Les auteurs concluent : « nos données suggèrent que l'exposition néonatale au BPA peut avoir des conséquences négatives sur la fertilité de la femme ». Ce modèle expérimental correspond à l'enfant nourri au biberon en polycarbonate. Cette étude démontre, là encore, la non-validité de la DJA de l'Agence européenne de sécurité alimentaire.

Abstract

Hormonally controlled vascular changes play a key role in endometrial development and in the differentiation process necessary for implantation. Vascular endothelial growth factor (VEGF) has emerged as one of the central regulators of the uterine vasculature. Hormonal perturbations during neonatal development may alter sex-steroid-dependent regulation of VEGF and may ultimately affect fertility later in life.

The aim of this study was to determine whether neonatal exposure to the environmental estrogenic chemical, bisphenol A (BPA), affects the adult rat uterine response to hormonal stimuli. Newborn female rats were given s.c. injections of vehicle, BPA (0.05 mg/kg/day or 20 mg/kg/day) or diethylstilbestrol (0.2 microg/kg/d) on Postnatal Days (PND) 1, 3, 5, and 7. To evaluate the long-term effects, rats were ovariectomized at PND80 and submitted to hormonal replacement. Rats neonatally exposed to xenoestrogens, showed a decreased induction of uterine endothelial proliferation and a decreased Vegf mRNA expression, in response to ovarian steroid treatment. Besides that, while the estrogen receptor alpha (ESR1) expression was lower in subepithelial cells than in controls, a higher expression of silencing mediator of retinoic acid and thyroid hormone receptor (NCOR1, also known as SMRT) co-repressor was evidenced in the same compartment.

The results indicate that disturbed Vegf expression in BPA rats could be the result of changes in endocrine pathways, such as an altered induction of ESR1 and/or

NCOR1 expression. Because of the importance of VEGF in the implantation process, our data suggest that neonatal BPA exposure might have negative consequences on female fertility.

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Formation of adducts by bisphenol A, an endocrine disruptor, in DNA in vitro and in liver and mammary tissue of mice.

Izzotti A, Kanitz S, D'Agostini F, Camoirano A, De Flora S.
Mutat Res. 2009 Aug 3.

Commentaires : Le bisphénol A se lie chimiquement à l'ADN. Les effets génotoxiques et carcinogéniques d'une exposition pré- et périnatale au bisphénol A, en particulier sur le développement de tumeurs mammaires, ont été décrits dans des modèles animaux évoquant un risque probable chez la femme exposée à ce perturbateur endocrinien tout au long de sa vie. Cependant les mécanismes d'action du BPA sont encore peu connus. Dans ce travail, les auteurs émettent l'hypothèse que le BPA pourrait former des adduits (complexes chimiques) avec l'ADN, ce qui pourrait altérer l'expression de certains gènes. Dans des modèles in vitro acellulaires et in vivo chez la souris soumises à des doses de 200mg/kg pendant 8 jours de BPA, les auteurs montrent l'existence d'adduits BPA/ADN. Certains des adduits détectés in vitro sont aussi observés in vivo dans le foie et dans la glande mammaire (4,7 fois supérieur au contrôle). Les adduits chimiques sur l'ADN, s'ils ne sont pas excisés par la machinerie cellulaire, peuvent favoriser le processus de prolifération cellulaire et pourraient rendre compte du risque carcinogénique mammaire qui est supposé associé au BPA. La limite de l'étude est qu'elle a utilisé une dose nettement plus élevée que celle à laquelle est exposée la population humaine (100 000 fois).

Abstract

Endocrine disruptors (ED) represent a major toxicological and public health issue, and the xenoestrogen bisphenol A (BPA) has received much attention due to its high production volume and widespread human exposure. Also, due to its similarity to diethylstilbestrol, a known human carcinogen, BPA has been investigated for its genotoxic and carcinogenic properties, but the results have been either inconclusive or controversial. Metabolically activated BPA has previously been shown to form DNA adducts both in vitro and in rat liver. The present study was designed (a) to assess the sensitivity threshold of DNA-adduct detection by (32)P-postlabelling in an a-cellular system and (b) to evaluate formation of DNA adducts in both liver and mammary cells of female CD-1 mice receiving BPA in their drinking-water (200mg/kg body weight) for eight consecutive days. The reaction of BPA with calf-thymus DNA, in the presence of S9 mix, resulted in a dose-dependent formation of multiple DNA adducts, with a detection limit of approximately 10ng of this ED under our experimental conditions. Administration of BPA to mice confirmed that DNA adducts are formed in liver (3.4-fold higher levels than in controls). In addition, new evidence is provided that DNA adducts are formed in target mammary cells (4.7-fold higher than in controls). Although DNA adducts do not necessarily evolve into tumours or other chronic degenerative diseases, the formation of these molecular lesions in target mammary cells may bear relevance for the potential involvement of BPA in breast carcinogenesis.

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Alterations in male infant behaviors towards its mother by prenatal exposure to bisphenol A in cynomolgus monkeys (*Macaca fascicularis*) during early suckling period.

[Nakagami A, Negishi T, Kawasaki K, Imai N, Nishida Y, Ihara T, Kuroda Y, Yoshikawa Y, Koyama T.](#)
[Psychoneuroendocrinology. 2009 Sep;34\(8\):1189-97.](#)

Commentaire : Cette étude montre chez le singe exposé pendant la gestation à la dose de 10µg/kg/j (soit le cinquième de la DJA européenne) des modifications du comportement chez les mâles.

Abstract

Bisphenol A (BPA) is an environmental chemical with physiological potencies that cause adverse effects, even at environmentally relevant exposures, on the basis of a number of studies in experimental rodents. Thus, there is an increasing concern about environmental exposure of humans to BPA. In the present study, we used experimentally controlled cynomolgus monkeys (Macaca fascicularis) to assess the influence of prenatal exposure to BPA (10 microg/(kg day)) via subcutaneously implanted pumps and examined social behaviors between infants and their mothers during the suckling period. Mother-infant interactions in cynomolgus monkeys had behavioral sexual dimorphism associated with sex of infant from early suckling period. Prenatal exposure to BPA altered the behaviors of male infants significantly; BPA-exposed male infants behaved as female infants. And it also affected some of female infant behaviors. Consequently, gestational BPA exposure altered some behaviors of their mothers, mainly in male-nursing mothers. These results suggest that BPA exposure affects behavioral sexual differentiation in male monkeys, which promotes the understanding of risk of BPA exposure in human.

Effets chez l'homme

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[Bisphenol A exposure is associated with oxidative stress and inflammation in postmenopausal women.](#)

[Yang YJ, Hong YC, Oh SY, Park MS, Kim H, Leem JH, Ha EH.](#)

[Environ Res. 2009 Aug;109\(6\):797-801.](#)

Commentaire : L'étude a été conduite auprès de 485 adultes pour déterminer le lien entre exposition au BPA et un impact de type inflammation et stress oxydatif. Les résultats suggèrent que cette exposition pourrait promouvoir un tel effet, principalement chez les femmes postménopausées.

Abstract

Bisphenol A (BPA) is widely used in the production of polycarbonate plastics and epoxy resins. There is increasing health concerns regarding low-level exposure to BPA among the general population. The aim of this study was to determine the association between BPA exposure with oxidative stress and inflammation in adult populations. A cross-sectional study was conducted. This study included 485 adults (259 men, 92 premenopausal women, and 134 postmenopausal women) living in general communities within large cities. Urinary concentrations of BPA, malondialdehyde (MDA), and 8-hydroxydeoxyguanosine (8-OHdG), white blood cell (WBC) count, and C-reactive protein (CRP) were measured. Multivariate analyses were applied to determine the associations of BPA exposure with oxidative stress and inflammation. The geometric means of urinary BPA for men, premenopausal women,

and postmenopausal women were 0.53, 0.61, and 0.58 microg/g cr, respectively. The urinary BPA concentrations were positively associated with MDA, 8-OHdG, and CRP levels in the postmenopausal women; however, such associations did not exist in men and premenopausal women.

The findings of this study suggest that BPA exposure would promote oxidative stress and inflammation, in which postmenopausal women are likely to be more susceptible to BPA-induced health effects.

Aspects réglementaires

12/

Does Rapid Metabolism Ensure Negligible Risk from Bisphenol A?

Gary Ginsberg and Deborah C. Rice.

<http://www.ehponline.org/members/2009/0901010/0901010.pdf>

Commentaire : L'étude porte sur l'impact de la vitesse de métabolisation du BPA, argument évoqué par l'agence européenne (AESA) pour justifier de ne pas considérer les composés conjugués du BPA dans l'urine. L'avis de l'AESA repose sur le fait que l'homme détoxifierait le BPA mieux que le rat en le conjuguant. Cette étude montre qu'il y a déconjugaison du BPA dans le placenta et chez le nouveau-né. Cela remet en cause la norme de l'AESA.

Abstract

Background: Bisphenol A (BPA) risks are being evaluated by many regulatory bodies since exposure is widespread and the potential exists for toxicity at low doses.

Objectives: To evaluate evidence that BPA is cleared more rapidly in humans than in rats in relation to BPA risk assessment. The European Food and Safety Authority (AESA) relied on pharmacokinetic evidence to conclude that rodent toxicity data are not directly relevant to human risk assessment. Further, AESA argues that rapid metabolism will result in negligible exposure during the perinatal period because of BPA glucuronidation in pregnant women or sulfation in newborns.

Discussion: These arguments fail to consider the deconjugation of BPA glucuronide in utero by β -glucuronidase, an enzyme that is present in high concentration in placenta and various other tissues. Further, arylsulfatase C, which reactivates endogenous sulfated estrogens, develops early in life and so may deconjugate BPA sulfate in newborns. Biomonitoring studies and laboratory experiments document free BPA in rat and human maternal, placental, and fetal tissues indicating that human BPA exposure is not negligible. The pattern of these detections is consistent with deconjugation in the placenta, resulting in fetal exposure. The tolerable daily intake (TDI) set by AESA (0.05 mg/kg/d) is well above effect levels reported in some animal studies.

Conclusion: This potential risk should not be dismissed on the basis of an uncertain pharmacokinetic argument. Rather, risk assessors need to decipher the BPA dose response and apply it to humans with comprehensive pharmacokinetic models that account for metabolite deconjugation.

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A Clash of Old and New Scientific Concepts in Toxicity, with Important Implications for Public Health

John Peterson Myers, R. Thomas Zoeller, Frederick S. vom Saal.

<http://www.ehponline.org/members/2009/0900887/0900887.pdf>

Commentaire : Démonstration sur la base de plusieurs exemples, dont le BPA, de la nécessité de remettre en cause le paradigme de Paracelse ("C'est la dose qui fait le poison") pour définir la réglementation des perturbateurs endocriniens. Un exemple connu est celui de la mise en œuvre des thérapies hormonales comme le Tamoxifen qui induit des effets contradictoires selon qu'il est utilisé à haute dose ou à faible dose. A faible dose, il y a stimulation de la réponse alors que, à haute dose, il y a inhibition. Cet article plaide pour la remise en cause des études fondées sur le protocole des GLP (Good Laboratory Practices) définies dans les années 70, avant que l'on prenne conscience de ce phénomène pour les substances de type perturbateur endocrinien.

Abstract

Background : A core assumption of current procedures used by toxicology to establish health standards for chemical exposures is that testing the safety of chemicals at high doses can be used to predict the effects of low dose exposures, such as those common in the general population. This assumption is based upon the precept that 'the dose makes the poison:' higher doses will cause greater effects.

Objectives : We challenge the validity of assuming that high dose testing can be used to predict low dose effects for contaminants that behave like hormones. We review data from endocrinology and toxicology that falsify this assumption, and summarize current mechanistic understanding of how low doses can lead to effects unpredictable from high dose experiments.

Discussion : Falsification of this assumption raises profound issues for regulatory toxicology. Many exposure standards are based upon this assumption. Rejecting the assumption will require that these standards be re-evaluated, and that procedures employed to set health standards be changed. The consequences of these changes may be significant for public health, because of the range of health conditions now plausibly linked to exposure to endocrine disrupting contaminants.

Conclusions : We recommend that procedures to establish acceptable exposure levels for endocrine disrupting compounds incorporate the inability for high dose tests to predict low dose results. Setting acceptable levels of exposure must include testing for health consequences at prevalent levels of human exposure, not extrapolations from the effects observed in high dose experiments. Scientists trained in endocrinology must be engaged systematically in standard setting for endocrine-disrupting compounds.