CENTER FOR HORMONFORSTYRRENDE STOFFER

Litteraturgennemgang for perioden oktober 2016 – december 2016

Indhold

Humane studier ved Afd. for Vækst og Reproduktion, Rigshospitalet

Søgning er udført på PubMed og dækker perioden 26. september 2016 – 12. november 2016

Følgende søgeprofil er benyttet:

Bisphenol A
Phthalat*
Paraben*
(perfluor* OR polyfluor*)
Triclocarban
Triclosan
(Flame retardant)
tributyltin
endocrine disrupters

kombineret med nedenstående tekst:

AND expos* AND (human OR men OR women OR child* OR adult* OR adolescen* OR infan*)

Limits: title/abstract, English language

I den listede bruttoliste er dobbeltgængere fjernet, ligesom hits der hører under kategorierne in vivo studier, in vitro studier eller wildlife er frasorteret.

Seks artikler er udvalgte til medtaget abstract. Disse artikler omhandler primært perfluorerede stoffer: (niveauer hos danske kvinder og hvilke faktorer, der påvirker disse samt sammenhæng mellem niveauer og adfærd hos færøske børn, og niveauer og føtal vækst hos svenske og norske børn). Vi har også udvalgt en artikel, der belyser en eventuel sammenhæng mellem HPA-aksen og Bisphenol A niveauer hos gravide kvinder og endelig vises også abstract for et stort fransk biomonitoreringsstudie, vi finder værd at nævne.

God læselyst

Udvalgte artikler

Determinants of serum levels of perfluorinated alkyl acids in Danish pregnant women

Bjerregaard-Olesen C, Bach CC, Long M, Ghisari M, Bech BH, Nohr EA, Henriksen TB, Olsen J, Bonefeld-Jørgensen EC

Int J Hyg Environ Health. 2016 Nov;219(8):867-875. doi: 10.1016/j.ijheh.2016.07.008. Epub 2016 Jul 14.

Abstract

Humans are exposed to perfluorinated alkyl acids (PFAAs) from food, drinking water, air, dust, and consumer products. PFAAs are persistent and bio-accumulative. In the present study, we aimed to establish how the serum levels of PFAAs differ according to age, pre-pregnancy body mass index (BMI), previous miscarriages, educational level, country of birth, smoking, and alcohol intake. We included 1438 Danish pregnant nulliparous women from the Aarhus Birth Cohort. The women gave a blood serum sample between week 11 and 13 of pregnancy.

Sixteen PFAAs were extracted from serum using solid phase extraction and analyzed by liquid chromatography/tandem mass spectrometry. Multivariable linear regression analysis was used to determine the associations between individual characteristics of the women and their levels of seven PFAAs that were detected in at least 50% of the samples. The total concentration of the PFAAs (∑PFAA) was higher in older women. On average, normal weight women had a higher ∑PFAA level than underweight, overweight, and obese women. Higher levels were also observed for women without previous miscarriages, women with a high educational level, women born in Denmark (as opposed to women born elsewhere but currently living in Denmark), non-smokers, and women who consumed alcohol before or during pregnancy. These associations were similar for all the studied PFAAs, although the levels of perfluoroundecanoic acid varied more across the categories of age, BMI, education, smoking, and alcohol consumption than any other PFAAs measured.

Time trends of perfluorinated alkyl acids in serum from Danish pregnant women 2008-2013

Bjerregaard-Olesen C, Bach CC, Long M, Ghisari M, Bossi R, Bech BH, Nohr EA, Henriksen TB, Olsen J, Bonefeld-Jørgensen EC.

Environ Int. 2016 May;91:14-21. doi: 10.1016/j.envint.2016.02.010. Epub 2016 Feb 16.

Abstract

We aimed to estimate the levels and time trends of perfluorinated alkyl acids (PFAAs) in serum of 1533 Danish pregnant nulliparous women between 2008 and 2013. The selection criterion of only including nulliparous women was chosen to avoid confounding from parity. The serum samples were analyzed for sixteen PFAAs using solid phase extraction and liquid chromatography tandem mass spectrometry (LC-MS/MS). We investigated the time trends for seven PFAAs, which were detected in more than 50% of the samples: perfluorohexane sulfonate (PFHxS), perfluoroheptane sulfonate (PFHpS), perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnA). We found that the serum levels of all seven PFAAs decreased during the period from 2008 to 2013; on average PFHxS decreased with 7.0% per year, PFHpS

with 14.8%, PFOS with 9.3%, PFOA with 9.1%, PFNA with 6.2%, PFDA with 6.3%, and PFUnA with 7.1% per year. Adjustment for maternal age, body mass index (BMI), educational level and gestational age at blood sampling did not change the time trends much. To our knowledge, we are the first to report decreasing trends of PFNA, PFDA and PFUnA since year 2000, thereby indicating that the phase-out of these compounds are beginning to show an effect on human serum levels.

Behavioral difficulties in 7-year old children in relation to developmental exposure to perfluorinated alkyl substances

Oulhote Y, Steuerwald U, Debes F, Weihe P, Grandjean P.
Environ Int. 2016 Sep. 10.1016/j.envint.2016.09.015. [Epub ahead of print]

Abstract

BACKGROUND: Perfluorinated alkyl substances (PFAS) are suspected endocrine disruptors that are highly persistent and neurotoxic in animals. Human epidemiological studies of exposure-related deviations of children's behaviors are sparse. We assessed the associations between prenatal, 5- and 7-year PFAS exposures and behavioral problem scores in 7-year Faroese children.

METHODS: Concentrations of perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA), perfluorooctane sulfonate (PFOS), and perfluorohexane sulfonic acid (PFHxS) were measured in maternal serum and in serum from children at ages 5 and 7years (n=539, 508, and 491, respectively). We used multivariable regressions and structural equations models to estimate the covariate-adjusted associations between serum-PFAS concentrations and behavioral difficulties, as assessed by the strengths and difficulties questionnaire (SDQ) at age 7.

RESULTS: Serum-PFOS and PFHxS concentrations declined over time, whereas PFOA, PFNA, and PFDA tended to increase. No associations were observed between prenatal PFAS concentrations and SDQ scores. However, a two-fold increase in 5-year serum-PFOA, PFNA, and PFDA concentrations was associated with increases in total SDQ scores by 1.03 (95% CI: 0.11, 1.95), 0.72 (95% CI: 0.07, 1.38) and 0.78 points (95% CI: 0.01, 1.55), respectively. For SDQ subscales, significant associations were found in regard to hyperactivity, peer relationship, and conduct problems, as well as internalizing and externalizing problems and autism screening composite scores. Cross-sectional analyses at age 7years showed possible sex-dimorphic associations between PFAS concentrations and SDQ scores, where girls had consistently positive associations with SDQ scores whereas boys exhibited a pattern of negative or null associations.

CONCLUSIONS: Higher serum PFAS concentrations at ages 5- and 7-years, but not prenatally, were associated with parent-reported behavioral problems at age 7.

Maternal serum levels of perfluoroalkyl substances and organochlorines and indices of fetal growth: a Scandinavian case-cohort study

Lauritzen HB, Larose TL, Øien T, Sandanger TM, Odland JØ, van de Bor M, Jacobsen GW.
Pediatr Res. 2016 Oct 26. doi: 10.1038/pr.2016.187. [Epub ahead of print]

Abstract

BACKGROUND: The associations between prenatal exposure to endocrine disruptive chemicals (EDCs) and fetal growth are inconsistent, and few studies have considered small-for-gestational-age (SGA) birth as an outcome. Our current study of Scandinavian parous women aimed to address these inconsistencies and gaps in the literature.

METHODS: This case-cohort study included 424 mother-child pairs who participated in a prospective, multi-center study of parous women in Norway (Trondheim and Bergen) and Sweden (Uppsala). We used linear and logistic regression with 95% confidence intervals (CIs) to analyze the associations between two perfluoroalkyl substances (PFASs) and five organochlorines (OCs) from early second trimester and indices of fetal growth.

RESULTS: Among Swedish women, prenatal exposure to perfluorooctanoate (PFOA), polychlorinated biphenyl (PCB) 153 and hexachlorobenzene (HCB) were associated with higher odds for SGA birth. We found stronger associations among Swedish male offspring. In the Norwegian cohort, we found no significant associations between EDC exposure and indices of fetal growth.

CONCLUSIONS: Some populations may be more vulnerable to EDCs, possibly due to differences in exposure levels, exposure sources and/or modifiable lifestyle factors. Male offspring may be more vulnerable to endocrine disruption.

Urinary bisphenol A is associated with dysregulation of HPA-axis function in pregnant women: Findings from the APrON cohort study

Giesbrecht GF, Liu J, Ejaredar M, Dewey D, Letourneau N, Campbell T, Martin JW; APrON Study Team.
Environ Res. 2016 Nov;151:689-697. doi: 10.1016/j.envres.2016.09.007. Epub 2016 Sep 16.

Abstract

BACKGROUND: Bisphenol A (BPA) is associated with dysregulation of hypothalamic-pituitary-adrenal (HPA) axis activity in rodents, but evidence in humans is lacking.

OBJECTIVE: To determine whether BPA exposure during pregnancy is associated with dysregulation of the HPA-axis, we examined the association between urinary BPA concentrations and diurnal salivary cortisol in pregnant women. Secondary analyses investigated whether the association between BPA and cortisol was dependent on fetal sex.

METHODS: Diurnal salivary cortisol and urinary BPA were collected during pregnancy from 174 women in a longitudinal cohort study, the Alberta Pregnancy Outcomes and Nutrition (APrON) study. Associations between BPA and daytime cortisol and the cortisol awakening response (CAR) were estimated using mixed models after adjusting for covariates.

RESULTS: Higher concentrations of total BPA uncorrected for urinary creatinine were associated with dysregulation of the daytime cortisol pattern, including reduced cortisol at waking, β=-.055, 95% CI (-.100, -

.010) and a flatter daytime pattern, β=.014, 95% CI (.006, .022) and β=-.0007 95% CI (-.001, -.0002) for the linear and quadratic slopes, respectively. Effect sizes in creatinine corrected BPA models were slightly smaller. None of the interactions between fetal sex and BPA were significant (all 95% CI's include zero). CONCLUSIONS: These findings provide the first human evidence suggesting that BPA exposure is associated with dysregulation of HPA-axis function during pregnancy.

Biomarkers of exposure to environmental contaminants in French pregnant women from the Elfe cohort in 2011

Dereumeaux C, Saoudi A, Pecheux M, Berat B, de Crouy-Chanel P, Zaros C, Brunel S, Delamaire C, le Tertre A, Lefranc A, Vandentorren S, Guldner L.

Environ Int. 2016 Oct 24;97:56-67. doi: 10.1016/j.envint.2016.10.013. [Epub ahead of print]

Abstract

BACKGROUND: As part of the perinatal component of the French Human Biomonitoring (HBM) program, biomarkers levels of various chemicals have been described among pregnant women having given birth in continental France in 2011 and who have been enrolled in the Elfe cohort (French Longitudinal Study since Childhood). This paper describes the design of the study and provides main descriptive results regarding exposure biomarkers levels.
METHODS: Exposure biomarkers were measured in biological samples collected at delivery from pregnant women randomly selected among the participants in the clinical and biological component of the Elfe cohort (n=4145). The geometric mean and percentiles of the levels distribution were estimated for each biomarker. The sampling design was taken into account in order to obtain estimates representative of the French pregnant women in 2011.
RESULTS: Results provide a nation-wide representative description of biomarker levels for important environmental contaminants among pregnant women who gave birth in France in 2011. Bisphenol A (BPA), and some metabolites of phthalates, pesticides (mainly pyrethroids), dioxins, furans, polychlorobiphenyls (PCBs), brominated flame retardants (BFRs), perfluorinated compounds (PFCs) and metals (except uranium) were quantified in almost 100% of the pregnant women. Some compounds showed a downward trend compared to previous studies (lead, mercury), but others did not (pyrethroids) and should be further monitored.
CONCLUSION AND PERSPECTIVES: The present results show that French pregnant women are exposed to a wide variety of pollutants, including some that have been banned or restricted in France.

Bruttoliste

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In vitro studier ved DTU Fødevareinstituttet

Søgt i Pubmed med følgende kriterier:

" Endocrine disrupt* AND in vitro*" samt "Endocrine disrupt* AND expose* AND in vitro*",

"Paraben* AND in vitro*,"perfluor* OR polyfluor* AND in vitro*" og "Phthalat* AND in vitro*".

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Efter at have fjernet genganger fra forrige litteraturopdateringslister, samt artikler der ikke hørte til under kategorien "*in vitro*" gav litteratursøgningen, med de angivne søgekriterier, tilsammen en liste med i alt 30 artikler.

Udvalgte publikationer

2 artikler er blevet udvalgt til medtagelse af abstract baseret på, at de beskriver resultater der bidrager til ny eller yderligere viden om grupper af hormonforstyrrende stoffer.

Den første artikel omhandler et *in vitro* studie af syv plastikblødgørere, med det formål at undersøge celle toksiciteten af de syv stoffer og deres evne til at påvirke syntesen af steroidhormoner via påvirkning af aromatase aktivitet, samt dannelsen af reaktive oxygen species. Ydereligere har man også ønsket at bestemme biotilgængeligheden af stoffer i de pågældende asssays.
Den anden artikel omhandler undersøgelse af den brommerede flammehæmmer tetrabromobisphenol A (TBBPA) for at teste stoffets hormonforstyrrende egenskaber, med specifik fokus på glukokortikoid receptoren (GR), samt AR antagonisme.

Comparative toxicity, oxidative stress and endocrine disruption potential of plasticizers in JEG-3 human placental cells.
Pérez-Albaladejo E, Fernandes D, Lacorte S, Porte C.
Toxicol In Vitro. 2017 Feb;38:41-48. doi: 10.1016/j.tiv.2016.11.003.

Abstract
Plasticizers are suspected to be toxic and/or to modulate or disrupt the endocrine system of humans and to cross the placental barrier, being embryonic and fetal development a particularly vulnerable period. This work investigates the comparative toxicity and ability to interfere with the synthesis of steroids and to generate reactive oxygen species (ROS) of a selected number of plasticizers, including bisphenol A (BPA), nonyl- (NP) and octylphenol (OP), benzyl butyl phthalate (BBP), dibutyl phthalate (DBP), di(2-ethylhexyl)phthalate (DEHP) and dimethyl phthalate (DMP), in the human placenta JEG-3 cells. Moreover, the bioavailability of chemicals in culture medium has been investigated. After 24h exposure, OP and NP showed the highest cytotoxicity (EC_{50}: 36-40μM) followed by BPA (138-219μM), whereas no significant toxicity was observed for phthalates. Notwithstanding, BBP and DBP significantly decreased P450 aromatase activity (experimental IC_{50}: 14-15μM), while NP and OP (20μM) increased the activity. Overall, this study evidences the differential toxicity and ability to modulate placental aromatase activity of some of the compounds nowadays used as plasticizers, and highlights the need of an accurate determination of the bioavailability of chemicals to improve the sensitivity of in-vitro tests.

Evaluation of tetrabromobisphenol A effects on human glucocorticoid and androgen receptors: A comparison of results from human- with yeast-based in vitro assays.
Beck KR, Sommer TJ, Schuster D, Odermatt A.
Toxicology. 2016 Aug 31;370:70-77. doi: 10.1016/j.tox.2016.09.014.

Abstract
The incidence of immune-related diseases increased over the last years in industrialized countries, suggesting a contribution of environmental factors. Impaired glucocorticoid action has been associated with immune disorders. Thus, there is an increasing interest to identify chemicals disrupting glucocorticoid action. The widely used flame retardant tetrabromobisphenol A (TBBPA) was reported earlier to potently inhibit glucocorticoid receptor (GR) and moderately androgen receptor (AR) activity in yeast-basedreporter gene assays. To further characterize possible GR disrupting effects of TBBPA, transactivation experiments using a humanHEK-293 cell-based reporter gene assay and cell-free receptor binding experiments were performed in the present study. Both, transactivation and GR binding experiments failed to detect any activity of TBBPA on GR function. Molecular docking calculations supported this observation. Additionally, the current study could confirm the antiandrogenic activity of TBBPA seen in the yeast assay, although the effect was an order of magnitude less pronounced in the HEK-293 cell-based system. In conclusion, TBBPA does not directly affect GR function and, considering its rapid metabolism and low concentrations found in humans, it is unlikely to cause adverse effects by acting through AR. This study emphasizes the use of cell-free assays in combination with cell-based assays for the in vitro evaluation of endocrine disrupting chemicals.

Bruttoliste

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Perego MC, Schutz LF, Caloni F, Cortinovis C, Albonico M, Spicer LJ. J Appl Toxicol. 2016 Dec 5. doi: 10.1002/jat.3417. [Epub ahead of print]

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Shannon M, Green B, Willars G, Wilson J, Matthews N, Lamb J, Gillespie A, Connolly L. Toxicol Lett. 2016 Nov 24;265:97-105. doi: 10.1016/j.toxlet.2016.11.015. [Epub ahead of print]

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König M, Escher BI, Neale PA, Krauss M, Hilscherová K, Novák J, Teodorović I, Schulze T, Seidensticker S, Kamal Hashmi MA, Ahlheim J, Brack W. Environ Pollut. 2017 Jan;220(Pt B):1220-1230. doi: 10.1016/j.envpol.2016.11.011.

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Huang W, Quan C, Duan P, Tang S, Chen W, Yang K. Toxicology. 2016 Dec 12;373:41-53. doi: 10.1016/j.tox.2016.11.006.

9. Comparative toxicity, oxidative stress and endocrine disruption potential of plasticizers in JEG-3 human placental cells.
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10. The influence of phthalates and bisphenol A on the obesity development and glucose metabolism disorders.
Stojanoska MM, Milosevic N, Milic N, Abenavoli L. Endocrine. 2016 Nov 7. [Epub ahead of print] Review.

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15. Evaluation of tetrabromobisphenol A effects on human glucocorticoid and androgen receptors: A comparison of results from human- with yeast-based in vitro assays.
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22. Comparison of Perfluorodecalin and HEMOXCell as Oxygen Carriers for Islet Oxygenation in an In Vitro Model of Encapsulation.
Rodriguez-Brotons A, Bietiger W, Peronet C, Langlois A, Magisson J, Mura C, Sookhareea C, Polard V, Jeandidier N, Zal F, Pinget M, Sigrist S, Maillard E. Tissue Eng Part A. 2016 Nov 24. [Epub ahead of print]

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25. Melatonin-loaded silica coated with hydroxypropyl methylcellulose phthalate for enhanced oral bioavailability: Preparation, and in vitro-in vivo evaluation.
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26. Chemical activity-based environmental risk analysis of the plasticizer di-ethylhexyl phthalate and its main metabolite mono-ethylhexyl phthalate.
Gobas FA, Otton SV, Tupper-Ring LF, Crawford MA, Clark KE, Ikonomou MG. Environ Toxicol Chem. 2016 Nov 17. doi: 10.1002/etc.3689. [Epub ahead of print]

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Andrade MA, Azevedo CD, Motta FN, Santos ML, Silva CL, Santana JM, Bastos IM. BMC Complement Altern Med. 2016 Nov 8;16(1):444.

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Maghen L, Shlush E, Gat I, Filice M, Barretto T, Jarvi K, Lo K, Gauthier-Fisher AS, Librach CL. Reproduction. 2016 Oct 25. pii: REP-16-0220. [Epub ahead of print]

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Anand K, Tiloke C, Phulukdaree A, Ranjan B, Chuturgoon A, Singh S, Gengan RM. J Photochem Photobiol B. 2016 Dec;165:87-95. doi: 10.1016/j.jphotobiol.2016.09.039.

Herudover er der yderligere 1 artikel, som ikke blev fanget af de valgte søgekriterier:

Enniatin B and beauvericin are common in Danish cereals and show high hepatotoxicity on a high-content imaging platform.
Svingen T, Lund Hansen N, Taxvig C, Vinggaard AM, Jensen U, Have Rasmussen P. Environ Toxicol. 2016 Sep 15. doi: 10.1002/tox.22367. [Epub ahead of print]

In Vivo studier ved DTU Fødevareinstituttet

Søgning er udført på PubMed og dækker perioden September - Primo December 2016

Følgende søgeprofil er benyttet i PubMed: ((endocrine disrupt*) AND (rat OR mice OR mammal*)) OR ((endocrine disrupt*) AND (in vivo*)) OR ((endocrine disrupt*) AND (Paraben*)) OR ((endocrine disrupt*) AND (Phthalat*)) OR ((Endocrine disrupt* AND (antiandrogen)) OR ((endocrine disrupt*) AND (behaviour OR behavior*)) OR ((Endocrine disrupt*) AND (Bisphenol A or BPA) OR ((PFAS* OR Perfluor*) AND (endocrine disrupt*) AND risk assessment

Efter at have fjernet gengangere fra dem vi havde med på den forrige litteraturopdateringsliste samt *in vitro*, human eller SDU relevante artikler, gav litteratursøgningen en liste med i alt 32 artikler (Bruttolisten).

Udvalgte publikationer

Tre artikler er blevet udvalgt til medtagelse af abstract. Disse artikler er valgt, fordi vi mener, de bidrager til ny viden om hormonforstyrrende stoffer og her er der særligt fokus på vurderinger af effekter på brystvæv (Filgo et al. 2016) samt ubalance i tarmens bakteriesamfund efter eksponeringer for Bisphenol A og ethinyl estradiol (Javurek et al. 2016). Endelig er der medtaget abstract fra en artikel, der beskriver videnskabelige principper for identifikationen af ED (Solecki et al. 2016).

Rigtig god læselyst.

Mammary Gland Evaluation in Juvenile Toxicity Studies: Temporal Developmental Patterns in the Male and Female Harlan Sprague-Dawley Rat.

Filgo AJ, Foley JF, Puvanesarajah S, Borde AR, Midkiff BR, Reed CE, Chappell VA, Alexander LB, Borde PR, Troester MA, Bouknight SA, Fenton SE.
Toxicol Pathol. 2016 Oct;44(7):1034-58

Abstract

There are currently no reports describing mammary gland development in the Harlan Sprague-Dawley (HSD) rat, the current strain of choice for National Toxicology Program (NTP) testing. Our goals were to empower the NTP, contract labs, and other researchers in understanding and interpreting chemical effects in this rat strain. To delineate similarities/differences between the female and male mammary gland, data were compiled starting on embryonic day 15.5 through postnatal day 70. Mammary gland whole mounts, histology sections, and immunohistochemically stained tissues for estrogen, progesterone, and androgen receptors were evaluated in both sexes; qualitative and quantitative differences are highlighted using a comprehensive visual timeline. Research on endocrine disrupting chemicals in animal models has highlighted chemically induced mammary gland anomalies that may potentially impact human health. In order to investigate these effects within the HSD strain, 2,3,7,8-tetrachlorodibenzo-p-dioxin, diethylstilbestrol, or vehicle control was gavage dosed on gestation day 15 and 18 to demonstrate delayed, accelerated, and control mammary gland growth in offspring, respectively. We provide illustrations of normal and chemically altered mammary gland development in HSD male and female rats to help inform researchers unfamiliar with the tissue and may facilitate enhanced evaluation of both male and female mammary glands in juvenile toxicity studies.

Effects of exposure to bisphenol A and ethinyl estradiol on the gut microbiota of parents and their offspring in a rodent model

Javurek AB, Spollen WG, Johnson SA, Bivens NJ, Bromert KH, Givan SA, Rosenfeld CS.
Gut Microbes. 2016 Nov;7(6):471-485.

Abstract

Gut dysbiosis may result in various diseases, such as metabolic and neurobehavioral disorders. Exposure to endocrine disrupting chemicals (EDCs), including bisphenol A (BPA) and ethinyl estradiol (EE), especially during development, may also increase the risk for such disorders. An unexplored possibility is that EDC-exposure might alter the gut microbial composition. Gut flora and their products may thus be mediating factors for the disease-causing effects of these chemicals. To examine the effects of EDCs on the gut microbiome, female and male monogamous and biparental California mice (Peromyscus californicus) were exposed to BPA (50 mg/kg feed weight) or EE (0.1 ppb) or control diet from periconception through weaning. 16s rRNA sequencing was performed on bacterial DNA isolated from fecal samples, and analyses

performed for P0 and F1 males and females. Both BPA and EE induced generational and sex-dependent gut microbiome changes. Many of the bacteria, e.g. Bacteroides, Mollicutes, Prevotellaceae, Erysipelotrichaceae, Akkermansia, Methanobrevibacter, Sutterella, whose proportions increase with exposure to BPA or EE in the P0 or F1 generation are associated with different disorders, such as inflammatory bowel disease (IBD), metabolic disorders, and colorectal cancer. However, the proportion of the beneficial bacterium, Bifidobacterium, was also elevated in fecal samples of BPA- and EE-exposed F1 females. Intestinal flora alterations were also linked to changes in various metabolic and other pathways. Thus, BPA and EE exposure may disrupt the normal gut flora, which may in turn result in systemic effects. Probiotic supplementation might be an effective means to mitigate disease-promoting effects of these chemicals.

Scientific principles for the identification of endocrine-disrupting chemicals: a consensus statement.

Solecki R, Kortenkamp A, Bergman Å, Chahoud I, Degen GH, Dietrich D, Greim H, Håkansson H, Hass U, Husoy T, Jacobs M, Jobling S, Mantovani A, Marx-Stoelting P, Piersma A, Ritz V, Slama R, Stahlmann R, van den Berg M, Zoeller RT, Boobis AR.

Arch Toxicol. 2016 Oct 6. [Epub ahead of print]

Abstract

Endocrine disruption is a specific form of toxicity, where natural and/or anthropogenic chemicals, known as "endocrine disruptors" (EDs), trigger adverse health effects by disrupting the endogenous hormone system. There is need to harmonize guidance on the regulation of EDs, but this has been hampered by what appeared as a lack of consensus among scientists. This publication provides summary information about a consensus reached by a group of world-leading scientists that can serve as the basis for the development of ED criteria in relevant EU legislation. Twenty-three international scientists from different disciplines discussed principles and open questions on ED identification as outlined in a draft consensus paper at an expert meeting hosted by the German Federal Institute for Risk Assessment (BfR) in Berlin, Germany on 11-12 April 2016. Participants reached a consensus regarding scientific principles for the identification of EDs. The paper discusses the consensus reached on background, definition of an ED and related concepts, sources of uncertainty, scientific principles important for ED identification, and research needs. It highlights the difficulty in retrospectively reconstructing ED exposure, insufficient range of validated test systems for EDs, and some issues impacting on the evaluation of the risk from EDs, such as non-monotonic dose-response and thresholds, modes of action, and exposure assessment. This report provides the consensus statement on EDs agreed among all participating scientists. The meeting facilitated a productive debate and reduced a number of differences in views. It is expected that the consensus reached will serve as an important basis for the development of regulatory ED criteria.

Bruttoliste

1. Perinatal exposure to glyphosate-based herbicide alters the thyrotrophic axis and causes thyroid hormone homeostasis imbalance in male rats. de Souza JS, Kizys MM, da Conceição RR, Glebocki G, Romano RM, Ortiga-Carvalho TM, Giannocco G, da Silva ID, da Silva MR, Romano MA, Chiamolera MI.
Toxicology. 2016 Dec 1. pii: S0300-483X(16)30264-5. doi: 10.1016/j.tox.2016.11.005. [Epub ahead of print]

2. Scientific principles for the identification of endocrine-disrupting chemicals: a consensus statement.
Solecki R, Kortenkamp A, Bergman Å, Chahoud I, Degen GH, Dietrich D, Greim H, Håkansson H, Hass U, Husoy T, Jacobs M, Jobling S, Mantovani A, Marx-Stoelting P, Piersma A, Ritz V, Slama R, Stahlmann R, van den Berg M, Zoeller RT, Boobis AR. Arch Toxicol. 2016 Oct 6. [Epub ahead of print] (abstract)

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Rebuli ME, Gibson P, Rhodes CL, Cushing BS, Patisaul HB.
Gen Comp Endocrinol. 2016 Nov 1;238:39-46. doi: 10.1016/j.ygcen.2016.04.018.

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Tapella L, Sesta A, Cassarino MF, Zunino V, Catalano MG, Pecori Giraldi F.
Pituitary. 2016 Nov 16. [Epub ahead of print]

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Komsky-Elbaz A, Roth Z.
Reprod Toxicol. 2016 Nov 9;67:15-25. doi: 10.1016/j.reprotox.2016.11.001. [Epub ahead of print]

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Huang W, Quan C, Duan P, Tang S, Chen W, Yang K.
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Javurek AB, Spollen WG, Johnson SA, Bivens NJ, Bromert KH, Givan SA, Rosenfeld CS.
Gut Microbes. 2016 Nov;7(6):471-485.(valgt)

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Jedeon K, Loiodice S, Salhi K, Le Normand M, Houari S, Chaloyard J, Berdal A, Babajko S.
Endocrinology. 2016 Nov;157(11):4287-4296.

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Abolaji AO, Adedara IA, Abajingin AO, Fatunmibi OJ, Ladipo EO, Farombi EO.
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Miller MM, Alyea RA, LeSommer C, Doheny DL, Rowley SM, Childs KM, Balbuena P, Ross SM, Dong J, Sun B, Andersen MA, Clewell RA.
Toxicol Sci. 2016 Nov;154(1):162-173.

23. Mammary Gland Evaluation in Juvenile Toxicity Studies: Temporal Developmental Patterns in the Male and Female Harlan Sprague-Dawley Rat.
Filgo AJ, Foley JF, Puvanesarajah S, Borde AR, Midkiff BR, Reed CE, Chappell VA, Alexander LB, Borde PR, Troester MA, Bouknight SA, Fenton SE.
Toxicol Pathol. 2016 Oct;44(7):1034-58. (Valgt).

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Chemosphere. 2016 Nov;163:373-81. doi: 10.1016/j.chemosphere.2016.08.062.

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Wildlife studier ved Biologisk Institut, Syddansk Universitet (SDU)

Søgningen er udført på Web of Science (all databases) og dækker perioden 23/9 - 12/12 2016.

Søgeprofilen kombinerer:	”Endocrine disrupt*” and	Fish* Amphibia* Bird* OR avia* Invertebrat* Mollus* Gastropod* Insect* Crustacea* Echinoderm* Ursus Reptil* OR alligator Whal* OR seal* OR dolphin*

Fra bruttolisten (længere nede i dokumentet) er udvalgt tre artikler til medtagelse af abstract. Kriterierne for udvælgelse er at publikationerne bidrager til ny viden omkring effekter af og virkningsmekanismer for hormonforstyrrende stoffer i ’wildlife’ og/eller, at de repræsenterer vigtig viden, som vurderes at have særlig interesse for Miljøstyrelsen bl.a. i forbindelse med styrelsens fokus på udvikling af testmetoder eller at de omhandler ’nye’ stoffer, der har vist sig hormonforstyrrende; specielt hvis disse har relevans for danske forhold.

Udvalgte publikationer

Environmentally relevant concentrations of nitrate increase plasma testosterone concentrations in female American alligators (Alligator mississippiensis).
Hamlin HJ, Edwards TM, McCoy J, Cruze L, Guillette LJ.
General and Comparative Endocrinology. 238: 55-60. 2016.

Abstract
Anthropogenic nitrogen is a ubiquitous environmental contaminant that is contributing to the degradation of freshwater, estuarine, and coastal ecosystems worldwide. The effects of environmental nitrate, a principal form of nitrogen, on the health of aquatic life is of increasing concern. We exposed female American alligators to three concentrations of nitrate (0.7, 10 and 100 mg/L NO_3-N) for a duration of five weeks and five months from hatch. We assessed growth, plasma sex steroid and thyroid hormone concentrations, and transcription levels of key genes involved in steroidogenesis (StAR, 3β-HSD, and $P450_{scc}$) and hepatic clearance (Cyp1a, Cyp3a). Exposure to 100 mg/L NO3-N for both five weeks and five months resulted in significantly increased plasma testosterone (T) concentrations compared with alligators in the reference treatment. No differences in 17β-estradiol, progesterone, or thyroid hormones were observed, nor were there differences in alligator weight or the mRNA abundance of steroidogenic or hepatic genes. Plasma and urinary nitrate concentrations increased with increasing nitrate treatment levels, although relative plasma concentrations of nitrate were significantly lower in five month, versus five week old animals, possibly due to improved kidney function in older animals. These results indicate that environmentally relevant concentrations of nitrate can increase circulating concentrations of T in young female alligators.

Per- and polyfluoroalkyl substances (PFASs) - New endocrine disruptors in polar bears (Ursus maritimus)?
Pedersen KE, Letcher RJ, Sonne C, Dietz R, Styrishave B.
Environment International. 96: 180-189. 2016.

Abstract
Per- and polyfluoroalkyl substances (PFASs) are emerging in the Arctic and accumulate in brain tissues of East Greenland (EG) polar bears. In vitro studies have shown that PFASs might possess endocrine disrupting abilities and therefore the present study was conducted to investigate potential PFAS induced alterations in brain steroid concentrations. The concentrations of eleven steroid hormones were determined in eight brain regions from ten EG polar bears. Pregnenolone (PRE), the dominant progestagen, was found in mean concentrations of 5–47 ng/g (ww) depending on brain region. PRE showed significantly ($p < 0.01$) higher concentrations in female compared to male bears. Dehydroepiandrosterone (DHEA) found in mean concentrations 0.67–4.58 ng/g (ww) was the androgen found in highest concentrations. Among the estrogens estrone (E1) showed mean concentrations of 0.90–2.21 ng/g (ww) and was the most abundant. Remaining steroid hormones were generally present in concentrations below 2 ng/g (ww). Steroid levels in brain tissue could not be explained by steroid levels in plasma. There was however a trend towards increasing estrogen levels in plasma resulting in increasing levels of androgens in brain tissue. Correlative analyses showed positive associations between PFASs and 17α-hydroxypregnenolone (OH-PRE) (e.g.

perflouroalkyl sulfonates (ΣPFSA): $p < 0.01$, $r=0.39$; perfluoroalkyl carboxylates (ΣPFCA): $p < 0.01$, $r = 0.61$) and PFCA and testosterone (TS) (ΣPFCA: $p = 0.03$, $r = 0.30$) across brain regions. Further when investigating correlative associations in specific brain regions significant positive correlations were found betweenΣPFCA and several steroid hormones in the occipital lobe. Correlative positive associations between PFCAs and steroids were especially observed for PRE, progesterone (PRO), OH-PRE, DHEA, androstenedione (AN) and testosterone (TS) (all $p \leq 0.01$, $r \geq 0.7$). The results from the present study generally indicate that an increase in PFASs concentration seems to concur with an increase in steroid hormones of EG polar bears. It is, however, not possible to determine whether alterations in brain steroid concentrations arise from interference with de novo steroid synthesis or via disruption of peripheral steroidogenic tissues mainly in gonads and feedback mechanisms. Steroids are important for brain plasticity and gender specific behavior as well as postnatal development and sexually dimorph brain function. The present work indicates an urgent need for a better mechanistic understanding of how PFASs may affect the endocrine system of polar bears and potentially other mammal species.

Long-term exposure to triphenylphosphate alters hormone balance and HPG, HPI, and HPT gene expression in zebrafish (*Danio rerio*).

Liu X, Jung D, Jo A, Ji K, Moon HB, Choi K.

Environmental Toxicology and Chemistry. 35(9): 2288-2296. 2016.

Abstract

With the global decline in the use of polybrominated diphenyl ethers, the demand for alternative flame retardants, such as triphenylphosphate (TPP), has increased substantially. Triphenylphosphate is now detected in various environments including aquatic ecosystems worldwide. However, studies on the toxicological consequences of chronic TPP exposure on aquatic organisms are scarce. The zebrafish model was used to investigate the effects of long-term TPP exposure on the endocrine system. Zebrafish embryos were exposed to 5 μg/L, 50 μg/L, or 500 μg/L TPP for 120 d, and hormonal and transcriptional responses were measured along the hypothalamic-pituitary-gonad (HPG) axis, the hypothalamic-pituitary-interrenal (HPI) axis, and the hypothalamic-pituitary-thyroid (HPT) axis. Exposure to TPP significantly increased plasma 17β-estradiol, but decreased 11-ketotestosterone in both sexes. Gene expression data support these changes. In the HPI axis, plasma cortisol and proopiomelanocortin (pomc) and mineralocorticoid receptor transcripts increased in females, but in males cortisol decreased whereas pomc increased ($p<0.05$). Thyroxine and triiodothyronine increased, and thyrotrophin-releasing hormone receptor 2 (trhr2) and trh expression were affected only in females ($p<0.05$). In summary, long-term exposure to TPP enhanced estrogenicity in both males and females, potentially through influencing the HPG axis, but modulated the HPI, and HPT axes differently by sex, suggesting that both genomic and nongenomic responses might be involved.

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