Center for Hormonforstyrrende Stoffer

Litteraturgennemgang for perioden 12. december 2013 – 14. maj 2014

Indhold

Humane studier ved Afd. for Vækst og Reproduktion, Rigshospitalet

Søgning er udført på PubMed og dækker perioden 12. december 2013 – 15. maj 2014

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
For søgetermen "endocrine disrupters" har vi fjernet alle de hits, der også fremkom ved de øvrige søgninger.

Der er vældig mange spændende artikler i denne omgang, blandt andet fordi søgeperioden er ca. det dobbelte af hvad den har været hidtil. Desuden er Proceedings fra COW 2013 også udkommet i denne periode (fremstår som Reproduction 2014 Mar 2;147(4))

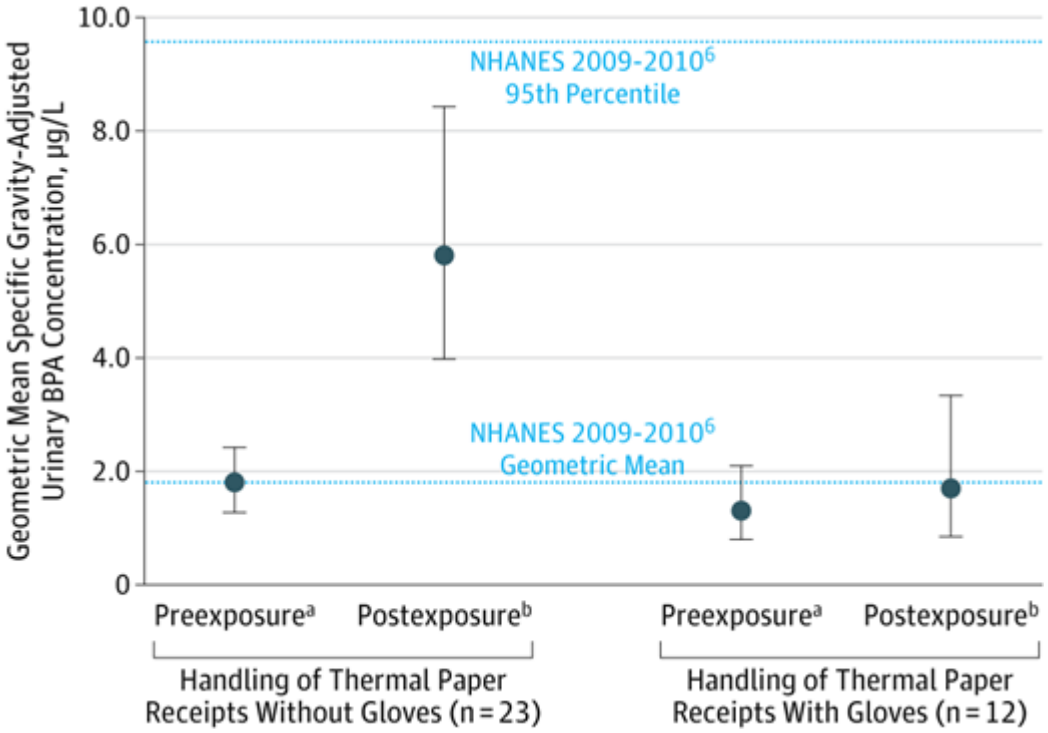
God læselyst!

Udvalgte publikationer

Ehrlich S, Calafat AM, Humblet O, Smith T, Hauser R.
Handling of thermal receipts as a source of exposure to bisphenol A
JAMA. 2014 Feb 26;311(8):859-60.doi: 10.1001/jama.2013.283735.

Intet abstract

Kommentarer
I alt 23 studerende på Harvard deltog i dette lille pilotstudie. De studerende håndterede termopapir (kasseboner) i 2 timer og fik målt BPA i urinen før og 4 timer efter papirhåndteringen. 12 af de studerende gentog øvelsen iført handsker. Resultaterne fremgår af figuren. Forskellen er signifikant. Stigningen i urin BPA som følge af termopapirhåndteringen er ikke så markant som efter indtag af tomatsuppe fra BPA coatede dåser (5,8 µg/L vs. 20,8 µg/L, studie fra 2011 også udført på Harvard). Studiet er begrænset af sin lille størrelse, men har et stærkt cross-over design. Desuden svarer de målte baseline BPA urinkoncentrationer til baggrundpopulationens. Den fulde artikel (kun 1½ side) kan læses her: http://jama.jamanetwork.com/article.aspx?articleid=1832525



Watkins DJ, Wellenius GA, Butler RA, Bartell SM, Fletcher T, Kelsey KT.
Associations between serum perfluoroalkyl acids and LINE-1 DNA methylation
Environ Int. 2014 Feb;63:71-6. doi: 10.1016/j.envint.2013.10.018. Epub 2013 Nov 18.

Abstract

Perfluoroalkyl acids (PFAAs) are persistent, synthetic compounds that are used in a number of consumer products. Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) have been associated with cardiovascular risk factors, and changes in gene expression and DNA methylation in animals and cellular systems. However, whether PFAA exposure is associated with LINE-1 DNA methylation, a potential marker of cardiovascular risk, in humans remains unknown. We sought to evaluate the cross-sectional associations between serum PFAAs and LINE-1 DNA methylation in a population highly exposed to PFOA. We measured serum PFAAs twice four to five years apart in 685 adult participants (47% male, mean age±SD=42±11years). We measured percent LINE-1 DNA methylation in peripheral blood leukocytes at the second time point (follow-up), and estimated absolute differences in LINE-1 methylation associated with an interquartile (IQR) shift in mean PFAA serum levels. IQR increases in mean serum PFOA, PFOS, perfluorononanoic acid (PFNA), and perfluorohexane sulfonate (PFHxS) were associated with differences of -0.04 (p=0.16), 0.20 (p=0.001), 0.06 (p=0.19), and 0.02 (p=0.57), respectively, in % LINE-1 methylation at follow-up after adjustment for potential confounders. We observed a monotonic increase in LINE-1 DNA methylation across tertiles of PFOS and PFNA (ptrend=0.02 for both associations), but not across tertiles of PFOA or PFHxS (ptrend=0.71 and 0.44, respectively). In summary, serum PFOS was associated with LINE-1 methylation, while serum PFOA, PFHxS, and PFNA were not. Additional research is needed to more precisely determine whether these compounds are epigenetically active.

Miao M, Zhou X, Li Y, Zhang O, Zhou Z, Li T, Yuan W, Li R, Li DK.
LINE-1 hypomethylation in spermatozoa is associated with Bisphenol A exposure.
Andrology. 2014 Jan;2(1):138-44. doi: 10.1111/j.2047-2927.2013.00166.x. Epub 2013 Dec 1.

Abstract
Bisphenol A (BPA) is an endocrine disruptor with potentially harmful effects on humans. However, epigenetic mechanisms that modulate the effects of BPA remain unclear. Methylation of long interspersed nucleotide elements (LINE-1) is a marker of genome-wide methylation status. This study aims to examine whether BPA exposure was associated with LINE-1 methylation changes in men. Male factory workers in Hunan, China (N = 149) were studied, 77 with BPA exposure in workplace (BPA-exposed group) and 72 without BPA exposure in workplace (control group). Pre-shift and post-shift urine samples were collected from the BPA-exposed group and spot urine samples were collected from the control group. Urine samples were assessed for BPA. In addition, blood and semen samples were collected from both groups for LINE-1 methylation analysis. In multivariate analysis adjusted for age, education, smoking habits and alcohol consumption, sperm LINE-1 methylation level was significantly lower in BPA exposed workers ($p < 0.001$) compared to that in the unexposed workers. Linear regression analysis also showed that log-transformed urine BPA levels were inversely associated with sperm LINE-1 methylation ($p < 0.0001$), but not peripheral blood cell LINE-1 methylation. Moreover, the association between urine BPA level and semen quality was not attenuated after adjustments for LINE-1 level. In summary, the observed independent relationship between BPA exposure and LINE-1 methylation may have public health implications on reproductive health in men because of ubiquitous exposure to BPA.

Hart R, Doherty DA, Frederiksen H, Keelan JA, Hickey M, Sloboda D, Pennell CE, Newnham JP, Skakkebaek NE, Main KM

The influence of antenatal exposure to phthalates on subsequent female reproductive development in adolescence: a pilot study.

Reproduction 2014; 147: 379-390

Abstract

We hypothesised that antenatal exposure to ubiquitous phthalates may lead to an earlier menarche and a lower prevalence of polycystic ovarian syndrome (PCOS) and polycystic ovarian morphology (PCO) in adolescence. The Western Australian Pregnancy Cohort (Raine) Study recruited 3000 women at 18 weeks of gestation in 1989-1991, 1377 had antenatal serum stored without thawing at -80 °C. An unselected subset was evaluated in the early follicular phase for PCO and PCOS by ultrasound and serum evaluation in adolescence. Serum was analysed for anti-Müllerian hormone (AMH), inhibin B, sex hormone binding globulin (SHBG), testosterone, androstenedione and DHEAS. Four hundred microlitres of the frozen maternal serum underwent isotope-diluted liquid chromatography-tandem mass spectrometry, with preceding enzymatic deconjugation followed by solid-phase extraction to determine phthalate exposure. Two hundred and forty four girls attended assessment and most common phthalate metabolites were detectable in the majority of the 123 samples available. Several phthalates were negatively associated with maternal SHBG, and associations with maternal androgens were less consistent. The sum of the metabolites of di-(2-ethylhexyl) phthalate was associated with a non-significant tendency towards an earlier age at menarche (P=0.069). Uterine volume was positively associated with mono-(carboxy-iso-octyl) phthalate (P=0.018). Exposure to monoethyl phthalate (MEP) and the sum of all phthalate metabolites (Σall phth.m) were protective against PCOS in adolescence (P=0.001 and P=0.005 respectively). There were negative associations of MEP with PCO (P=0.022) and of MEP with serum AMH (P=0.031). Consequently, our data suggest that antenatal exposure to environmental phthalates may be associated with oestrogenic and/or anti-androgenic reproductive effects in adolescent girls.

Christensen KL, Makris SL, Lorber M.

Generation of Hazard Indices for Cumulative Exposure to Phthalates for Use in Cumulative Risk Assessment.

Regul Toxicol Pharmacol. 2014 May 8. pii: S0273-2300(14)00082-8. doi:10.1016/j.yrtph.2014.04.019. [Epub ahead of print]

Abstract

Exposures to multiple chemicals may contribute to increased risk of similar adverse effects. Cumulative risk may be estimated using a hazard index (HI), the sum of individual hazard quotients (HQ, ratio of exposure to the reference value). We demonstrate the HI approach for five phthalates: di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DBP), diisobutyl phthalate (DiBP), diisononyl phthalate (DiNP), and butyl benzyl phthalate (BBP). Phthalate exposure for the US general population is estimated using urine metabolite levels from NHANES, extrapolating to ingested 'dose' using the creatinine correction approach. We used two sets of reference values: European Union Tolerable Daily Intakes and Denmark Environmental Protection Agency Derived No Effect Levels. We also investigated the use of an alternate reference value for DEHP, derived from a recent study on male reproductive system development. HQs and HIs were calculated for the total population ages 6 years and older, as well as for men and women of approximate reproductive age (18 to 39 years), and children (6 to 11 years). Median HQs ranged from <0.01 for BBP, to ~0.1 (using established values) or ~2 (using an alternate value) for DEHP. Median HIs were <0.30 (95th percentiles just >1.0), and were driven by DEHP and DBP exposures

Environ Health Perspect. 2014 May;122(5):478-84. doi: 10.1289/ehp.1307309. Epub 2014 Feb 12.
Urinary bisphenol a levels in young men: association with reproductive hormones and semen quality.
Lassen TH, Frederiksen H, Jensen TK, Petersen JH, Joensen UN, Main KM, Skakkebaek NE, Juul A, Jørgensen N, Andersson AM.

Background: Few human studies have examined bisphenol A (BPA) exposure in relation to semen quality and reproductive hormones in men, and results are divergent.Objectives: We examined associations between urinary BPA concentration and reproductive hormones, as well as semen quality, in young men from the general population.Methods: Our study population consisted of 308 young men from the general population. Urinary BPA concentration was measured by isotope dilution TurboFlow-liquid chromatography-tandem mass spectrometry. We used multiple linear regression analysis to estimate associations between BPA concentration and reproductive hormones and semen quality, adjusting for confounding factors.Results: We found that 98% of the men had detectable urinary levels of BPA. Median (5th-95th percentiles) BPA concentration was 3.25 ng/mL (0.59-14.89 ng/mL). Men with BPA concentrations above the lowest quartile had higher concentrations of serum testosterone, luteinizing hormone (LH), estradiol, and free testosterone compared with the lowest quartile (ptrend ≤ 0.02). Men in the highest quartile of BPA excretion had on average 18% higher total testosterone (95% CI: 8, 28%), 22% higher LH (95% CI: 6, 39%), and 13% higher estradiol (95% CI: 4, 24%) compared with lowest quartile. Men in the highest quartile of BPA also had significantly lower percentage progressive motile spermatozoa compared with men in the lowest quartile (-6.7 percentage points, 95% CI: -11.76, -1.63). BPA was not associated with other semen parameters. Adjusting for dietary patterns did not influence the results.Conclusions: The pattern of associations between BPA and reproductive hormones could indicate an antiandrogenic or antiestrogenic effect, or both, of BPA on the hypothalamic-pituitary-gonadal hormone feedback system, possibly through a competitive inhibition at the receptor level. However, additional research is needed to confirm our findings and to further test the suggested potential mechanisms.Citation: Lassen TH, Frederiksen H, Jensen TK, Petersen JH, Joensen UN, Main KM, Skakkebaek NE, Juul A, Jørgensen N, Andersson AM. 2014. Urinary bisphenol A levels in young men: association with reproductive hormones and semen quality.

Int J Obes (Lond). 2014 Apr 11. doi: 10.1038/ijo.2014.63. [Epub ahead of print]
Urinary concentrations of bisphenol A and phthalate metabolites and weight change: a prospective investigation in US women.
Song Y, Hauser R, Hu FB, Franke AA, Liu S, Sun Q.

Objective:Both bisphenol A (BPA) and phthalates are known endocrine-disrupting chemicals for which there is widespread general population exposure. Human exposure occurs through dietary and non-dietary routes. Although animal studies have suggested a potential role of these chemicals in obesity, evidence from human studies is sparse and inconsistent, and prospective evidence is lacking. This study evaluated urinary concentrations of BPA and major phthalate metabolites in relation to prospective weight change.Methods:The study population was from the controls in a prospective case-control study of type 2 diabetes in the Nurses' Health Study (NHS) and NHSII. A total of 977 participants provided first-morning-void urine samples in 1996-2002. Urinary concentrations of BPA and nine phthalate metabolites were measured using liquid chromatography-mass spectrometry. Body weights were self-reported at baseline and updated biennially thereafter for 10 years.Results:On average, the women gained 2.09 kg (95% confidence interval (CI), -2.27 to 6.80 kg) during the 10-year follow-up. In

multivariate analysis with adjustment of lifestyle and dietary factors, in comparison with women in the lowest quartile of BPA concentration, those in the highest quartile had 0.23 kg per year (95% CI, 0.07-0.38 kg per year) greater weight gain during the 10-year follow-up (P-trend=0.02). Several phthalate metabolites, including phthalic acid, MBzP and monobutyl phthalate, were also associated with faster prospective weight gain in a dose-response fashion (P-trend<0.01), whereas other phthalates metabolites, including MEP and monoethylhexyl phthalate, were not monotonically associated with body weight change.Conclusions:These data suggest urinary concentrations of BPA and certain individual phthalate metabolites that were associated with modestly greater weight gain in a dose-response fashion. These data are consistent with a potential role of BPA and phthalates in obesity, although more prospective data are needed to corroborate these observations.

Environ Health Perspect. 2014 Mar 14. [Epub ahead of print]
Association of Urinary Concentrations of Bisphenol A and Phthalate Metabolites with Risk of Type 2 Diabetes: A Prospective Investigation in the Nurses' Health Study (NHS) and NHSII Cohorts.
Sun Q, Cornelis MC, Townsend MK, Tobias DK, Eliassen AH, Franke AA, Hauser R, Hu FB.

BACKGROUND: Prospective evidence regarding associations for exposures to bisphenol A (BPA) and phthalates with type 2 diabetes (T2D) is lacking.
OBJECTIVE: To prospectively examine urinary concentrations of BPA and phthalate metabolites with T2D risk.
METHODS: BPA and eight major phthalate metabolites were measured among 971 incident T2D case-control pairs from the Nurses' Health Study (NHS; mean age 65.6) and NHSII (mean age 45.6).
RESULTS: In the NHSII, BPA levels were not associated with incident T2D in multivariate-adjusted analysis until body mass index was adjusted: odds ratio (OR) comparing extreme BPA quartiles increased from 1.40 (95% CI: 0.91, 2.15) to 2.08 (95% CI: 1.17, 3.69; Ptrend = 0.02) with such an adjustment. In contrast, BPA concentrations were not associated with T2D in the NHS (OR 0.81; 95% CI 0.48, 1.38; Ptrend = 0.45). Likewise, urinary concentrations of total phthalate metabolites were associated with T2D in the NHSII (OR comparing extreme quartiles 2.14; 95% CI 1.19, 3.85; Ptrend = 0.02), but not in the NHS (OR 0.87; 95% CI 0.49, 1.53; Ptrend = 0.29). Summed metabolites of butyl phthalates or di-(2-ethylhexyl) phthalates were significantly associated with T2D in the NHSII only; ORs comparing extreme quartiles were 3.16 (95% CI: 1.68, 5.95; Ptrend = 0.0002) and 1.91 (95% CI: 1.04, 3.49; Ptrend = 0.20), respectively.
CONCLUSIONS: These results suggest that BPA and phthalate exposures may be associated with the risk of T2D among middle-aged women, but not older women. The divergent findings between the two cohorts might be explained by menopausal status or simply by chance. Clearly, these results need to be interpreted with caution and should be replicated in future studies, ideally with multiple urine samples collected prospectively to improve the measurement of these exposures with short half-lives.

Environ Health Perspect. 2014 May;122(5):513-20. doi: 10.1289/ehp.1307261. Epub 2014 Feb 20.
Gestational Exposure to Endocrine-Disrupting Chemicals and Reciprocal Social, Repetitive, and Stereotypic Behaviors in 4- and 5-Year-Old Children: The HOME Study.
Braun JM, Kalkbrenner AE, Just AC, Yolton K, Calafat AM, Sjödin A, Hauser R, Webster GM, Chen A, Lanphear BP.

Background: Endocrine-disrupting chemicals (EDCs) may be involved in the etiology of autism spectrum disorders, but identifying relevant chemicals within mixtures of EDCs is difficult.Objective: Our goal was to identify gestational EDC exposures associated with autistic behaviors.Methods: We measured the

concentrations of 8 phthalate metabolites, bisphenol A, 25 polychlorinated biphenyls (PCBs), 6 organochlorine pesticides, 8 brominated flame retardants, and 4 perfluoroalkyl substances in blood or urine samples from 175 pregnant women in the HOME (Health Outcomes and Measures of the Environment) Study (Cincinnati, OH). When children were 4 and 5 years old, mothers completed the Social Responsiveness Scale (SRS), a measure of autistic behaviors. We examined confounder-adjusted associations between 52 EDCs and SRS scores using a two-stage hierarchical analysis to account for repeated measures and confounding by correlated EDCs.Results: Most of the EDCs were associated with negligible absolute differences in SRS scores (≤ 1.5). Each 2-SD increase in serum concentrations of polybrominated diphenyl ether-28 (PBDE-28) (β = 2.5; 95% CI: -0.6, 5.6) or trans-nonachlor (β = 4.1; 95% CI: 0.8-7.3) was associated with more autistic behaviors. In contrast, fewer autistic behaviors were observed among children born to women with detectable versus nondetectable concentrations of PCB-178 (β = -3.0; 95% CI: -6.3, 0.2), β-hexachlorocyclohexane (β = -3.3; 95% CI: -6.1, -0.5), or PBDE-85 (β = -3.2; 95% CI: -5.9, -0.5). Increasing perfluorooctanoate (PFOA) concentrations were also associated with fewer autistic behaviors (β = -2.0; 95% CI: -4.4, 0.4).Conclusions: Some EDCs were associated with autistic behaviors in this cohort, but our modest sample size precludes us from dismissing chemicals with null associations. PFOA, β-hexachlorocyclohexane, PCB-178, PBDE-28, PBDE-85, and trans-nonachlor deserve additional scrutiny as factors that may be associated with childhood autistic behaviors.

PLoS One. 2014 Feb 25;9(2):e89096. doi: 10.1371/journal.pone.0089096. eCollection 2014.
Maternal bisphenol a exposure impacts the fetal heart transcriptome.
Chapalamadugu KC, Vandevoort CA, Settles ML, Robison BD, Murdoch GK.

Conditions during fetal development influence health and disease in adulthood, especially during critical windows of organogenesis. Fetal exposure to the endocrine disrupting chemical, bisphenol A (BPA) affects the development of multiple organ systems in rodents and monkeys. However, effects of BPA exposure on cardiac development have not been assessed. With evidence that maternal BPA is transplacentally delivered to the developing fetus, it becomes imperative to examine the physiological consequences of gestational exposure during primate development. Herein, we evaluate the effects of daily, oral BPA exposure of pregnant rhesus monkeys (Macaca mulatta) on the fetal heart transcriptome. Pregnant monkeys were given daily oral doses (400 μg/kg body weight) of BPA during early (50-100 ± 2 days post conception, dpc) or late (100 ± 2 dpc--term), gestation. At the end of treatment, fetal heart tissues were collected and chamber specific transcriptome expression was assessed using genome-wide microarray. Quantitative real-time PCR was conducted on select genes and ventricular tissue glycogen content was quantified. Our results show that BPA exposure alters transcription of genes that are recognized for their role in cardiac pathophysiologies. Importantly, myosin heavy chain, cardiac isoform alpha (Myh6) was down-regulated in the left ventricle, and 'A Disintegrin and Metalloprotease 12', long isoform (Adam12-l) was up-regulated in both ventricles, and the right atrium of the heart in BPA exposed fetuses. BPA induced alteration of these genes supports the hypothesis that exposure to BPA during fetal development may impact cardiovascular fitness. Our results intensify concerns about the role of BPA in the genesis of human metabolic and cardiovascular diseases.

PLoS One. 2014 Jan 23;9(1):e85894. doi: 10.1371/journal.pone.0085894. eCollection 2014.
Bisphenol a exposure alters developmental gene expression in the fetal rhesus macaque uterus.
Calhoun KC, Padilla-Banks E, Jefferson WN, Liu L, Gerrish KE, Young SL, Wood CE, Hunt PA, Vandevoort CA, Williams CJ.

Bisphenol A (BPA) exposure results in numerous developmental and functional abnormalities in reproductive organs in rodent models, but limited data are available regarding BPA effects in the primate uterus. To determine if maternal oral BPA exposure affects fetal uterine development in a non-human primate model, pregnant rhesus macaques carrying female fetuses were exposed orally to 400 µg/kg BPA or vehicle control daily from gestation day (GD) 50-100 or GD100-165. Fetal uteri were collected at the completion of treatment (GD100 or GD165); tissue histology, cell proliferation, and expression of estrogen receptor alpha (ERα) and progesterone receptor (PR) were compared to that of controls. Gene expression analysis was conducted using rhesus macaque microarrays. There were no significant differences in histology or in the percentage of cells expressing the proliferation marker Ki-67, ERα, or PR in BPA-exposed uteri compared to controls at GD100 or GD165. Minimal differences in gene expression were observed between BPA-exposed and control GD100 uteri. However, at GD165, BPA-exposed uteri had significant differences in gene expression compared to controls. Several of the altered genes, including HOXA13, WNT4, and WNT5A, are critical for reproductive organ development and/or adult function. We conclude that second or third trimester BPA exposure does not significantly affect fetal uterus development based on morphological, proliferation, and steroid hormone receptor assessments. However, differences in expression of key developmental genes after third trimester exposure suggest that BPA could alter transcriptional signals influencing uterine function later in life.

Reproduction. 2014 Mar 2;147(4):443-53. doi: 10.1530/REP-13-0461. Print 2014.
Current exposure of 200 pregnant Danish women to phthalates, parabens and phenols.
Tefre de Renzy-Martin K, Frederiksen H, Christensen JS, Boye Kyhl H, Andersson AM, Husby S, Barington T, Main KM, Jensen TK.

Many phthalates, parabens and phenols are suspected to have endocrine-disrupting properties in humans. They are found in consumer products, including food wrapping, cosmetics and building materials. The foetus is particularly vulnerable and exposure to these chemicals therefore is of concern for pregnant women. We investigated current exposure to several commonly used phthalates, parabens and phenols in healthy, pregnant Danish women. A total of 200 spot urine samples were collected between 8 and 30 weeks of gestation and analysed for metabolites of ten phenols, seven parabens and 16 phthalate by liquid chromatography-tandem mass spectrometry representing 26 non-persistent compounds. The majority of analytes were present in the urine sample collected from most women who participated. Thus, in 174 of the 200 women, metabolites of more than 13 (>50%) of 26 compounds were detected simultaneously. The number of compounds detected per woman (either as the parent compound or its metabolite(s)) ranged from 7 to 21 with a median of 16. The majority of compounds correlated positively with each other within and between chemical groups, suggesting combined exposure sources. Estimated daily intakes (DIs) of phthalates and bisphenol A (BPA) were below their individual tolerable DI (TDI) and with hazard quotients below 1. In conclusion, we found detectable levels of phthalate metabolites, parabens and phenols in almost all pregnant women, suggesting combined multiple exposures. Although the estimated DI of phthalates and BPA for an individual was below TDI, our results still raise concern, as current toxicological risk assessments in humans do not take into account simultaneous exposure. The true cumulative risk for the foetus may therefore be underestimated.

8. Environ Health Perspect. 2014 May;122(5):521-8. doi: 10.1289/ehp.1307063. Epub 2014 Feb 20.
Prenatal phthalate exposures and neurobehavioral development scores in boys and girls at 6-10 years of age.
Kobrosly RW, Evans S, Miodovnik A, Barrett ES, Thurston SW, Calafat AM, Swan SH.

Background: There is concern over potential neurobehavioral effects of prenatal phthalate exposures, but available data are inconsistent.Objectives: We examined associations between prenatal urinary concentrations of phthalate metabolites and neurobehavioral scores among children.Methods: We measured phthalate metabolite concentrations in urine samples from 153 pregnant participants in the Study for Future Families, a multicenter cohort study. Mothers completed the Child Behavior Checklist when the children were 6-10 years of age. We estimated overall and sex-specific associations between phthalate concentrations and behavior using adjusted multiple regression interaction models.Results: In boys, concentrations of monoisobutyl phthalate were associated with higher scores for inattention (β = 0.27; 95% CI: 0.04, 0.50), rule-breaking behavior (β = 0.20; 95% CI: 0.01, 0.38), aggression (β = 0.34; 95% CI: 0.09, 0.59), and conduct problems (β = 0.39; 95% CI: 0.20, 0.58), whereas the molar sum of di(2-ethylhexyl) phthalate metabolites was associated with higher scores for somatic problems (β = 0.15; 95% CI: 0.03, 0.28). Higher monobenzyl phthalate concentrations were associated with higher scores for oppositional behavior (β = 0.16; 95% CI: 0.01, 0.32) and conduct problems (β = 0.21; 95% CI: 0.06, 0.37) in boys, but with reduced anxiety scores in girls (β = -0.20; 95% CI: -0.39, -0.01). In general, the associations reported above were close to the null among girls. Model coefficients represent the difference in the square root-transformed outcome score associated with a 1-unit increase in log-transformed metabolites.Conclusions: Our results suggest associations between exposure to certain phthalates in late pregnancy and behavioral problems in boys. Given the few studies on this topic and methodological and population differences among studies, additional research is warranted.

PLoS One. 2014 Feb 4;9(2):e87430. doi: 10.1371/journal.pone.0087430. eCollection 2014.
Phthalate levels in cord blood are associated with preterm delivery and fetal growth parameters in Chinese women.
Huang Y, Li J, Garcia JM, Lin H, Wang Y, Yan P, Wang L, Tan Y, Luo J, Qiu Z, Chen JA, Shu W.

Data concerning the effects of phthalate exposure on preterm delivery and fetal growth are limited in humans. In this paper, we assessed the relationship between 15 phthalate levels in cord blood and preterm delivery and fetal growth parameters in 207 Chinese women going into labor. Exposure to phthalates except DCHP was associated with gestational age reduction and preterm delivery ($p<0.05$). There were associations between phthalates and fetal growth parameters, many of which disappeared when analyses were adjusted for gestational age, especially in male infants (Only DEEP was associated with birth weight; DEP, DNHP, BBP, DNP with abdominal circumference; DEP, DBP, DCHP, DEHP with femur length in female infants. And DPP, DBEP was associated with birth length in male infants. $p<0.05$). This study indicates that prenatal exposure to phthalates is associated with younger gestational age and preterm delivery. Also, phthalate exposure may adversely affect fetal growth parameters via gestational age reduction and preterm delivery with a significant gender effect.

Reproduction. 2014 Mar 4;147(4):555-65. doi: 10.1530/REP-13-0522. Print 2014.
Human urinary excretion of non-persistent environmental chemicals: an overview of Danish data collected between 2006 and 2012.
Frederiksen H, Jensen TK, Jørgensen N, Kyhl HB, Husby S, Skakkebæk NE, Main KM, Juul A, Andersson AM.

Several non-persistent industrial chemicals have shown endocrine disrupting effects in animal studies and are suspected to be involved in human reproductive disorders. Among the non-persistent chemicals that have been discussed intensively during the past years are phthalates, bisphenol A (BPA), triclosan (TCS), and parabens because of their anti-androgenic and/or estrogenic effects. Phthalates are plasticizers used in numerous industrial products. Bisphenol A is the main component of polycarbonate plastics and epoxy resins. Parabens and TCS are antimicrobial preservatives and other phenols such as benzophenone-3 (BP-3) act as a UV-screener, while chlorophenols and phenyl phenols are used as pesticides and fungicides in agriculture. In spite of the widespread use of industrial chemicals, knowledge of exposure sources and human biomonitoring studies among different segments of the population is very limited. In Denmark, we have no survey programs for non-persistent environmental chemicals, unlike some countries such as the USA (NHANES) and Germany (GerES). However, we have analyzed the excretion of seven parabens, nine phenols, and the metabolites of eight different phthalates in urine samples collected over the past 6 years from four Danish cohorts. Here, we present biomonitoring data on more than 3600 Danish children, adolescents, young men, and pregnant women from the general population. Our study shows that nearly all Danes were exposed to the six most common phthalates, to BPA, TCS, and BP-3, and to at least two of the parabens. The exposure to other non-persistent chemicals was also widespread. Our data indicate decreasing excretion of two common phthalates (di-n-butyl phthalate and di-(2-ethylhexyl) phthalate) over time.

Environ Health Perspect. 2014 Apr;122(4):345-50. doi: 10.1289/ehp.1306720. Epub 2013 Dec 23.
Associations of filaggrin gene loss-of-function variants with urinary phthalate metabolites and testicular function in young Danish Men.
Joensen UN, Jørgensen N, Meldgaard M, Frederiksen H, Andersson AM, Menné T, Johansen JD, Carlsen BC, Stender S, Szecsi PB, Skakkebæk NE, De Meyts ER, Thyssen JP.

BACKGROUND: Filaggrin is an epidermal protein that is crucial for skin barrier function. Up to 10% of Europeans and 5% of Asians carry at least one null allele in the filaggrin gene (FLG). Reduced expression of filaggrin in carriers of the null allele is associated with facilitated transfer of allergens across the epidermis. We hypothesized that these individuals may have increased transdermal uptake of endocrine disruptors, including phthalates.Objectives: We investigated urinary excretion of phthalate metabolites and testicular function in young men with and without FLG loss-of-function variants in a cross-sectional study of 861 young men from the general Danish population. METHODS: All men were genotyped for FLG R501X, 2282del4, and R2447X loss-of-function variants. We measured urinary concentrations of 14 phthalate metabolites and serum levels of reproductive hormones. We also evaluated semen quality.
RESULTS: Sixty-five men (7.5%) carried at least one FLG-null allele. FLG-null carriers had significantly higher urinary concentrations of several phthalate metabolites, including a 33% higher concentration of MnBP (mono-n-butyl phthalate; 95% CI: 16, 51%). FLG-null variants were not significantly associated with reproductive hormones or semen quality parameters.
CONCLUSION: This study provides evidence that carriers of FLG loss-of-function alleles may have higher internal exposure to phthalates, possibly due to
increased transepidermal absorption. FLG loss-of-function variants may indicate

susceptible populations for which special attention to transepidermal absorption of chemicals and medication may be warranted.

JAMA Pediatr. 2014 Jan;168(1):61-7. doi: 10.1001/jamapediatrics.2013.3699.
Environmental phthalate exposure and preterm birth.
Ferguson KK, McElrath TF, Meeker JD.

IMPORTANCE: Preterm birth is a leading cause of neonatal mortality, with a variety of contributing causes and risk factors. Environmental exposures represent a group of understudied, but potentially important, factors. Phthalate diesters are used extensively in a variety of consumer products worldwide. Consequently, exposure in pregnant women is highly prevalent.
OBJECTIVE: To assess the relationship between phthalate exposure during pregnancy and preterm birth.
DESIGN, SETTING, AND PARTICIPANTS: This nested case-control study was conducted at Brigham and Women's Hospital, Boston, Massachusetts. Women were recruited for a prospective observational cohort study from 2006-2008. Each provided demographic data, biological samples, and information about birth outcomes. From within this group, we selected 130 cases of preterm birth and 352 randomly assigned control participants, and we analyzed urine samples from up to 3 time points during pregnancy for levels of phthalate metabolites.
EXPOSURE: Phthalate exposure during pregnancy.
MAIN OUTCOMES AND MEASURES: We examined associations between average levels of phthalate exposure during pregnancy and preterm birth, defined as fewer than 37 weeks of completed gestation, as well as spontaneous preterm birth, defined as preterm preceded by spontaneous preterm labor or preterm premature rupture of the membranes (n = 57).
RESULTS: Geometric means of the di-2-ethylhexyl phthalate (DEHP) metabolites mono-(2-ethyl)-hexyl phthalate (MEHP) and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), as well as mono-n-butyl phthalate (MBP), were significantly higher in cases compared with control participants. In adjusted models, MEHP, MECPP, and Σ DEHP metabolites were associated with significantly increased odds of preterm birth. When spontaneous preterm births were examined alone, MEHP, mono-(2-ethyl-5-oxohexyl) phthalate, MECPP, Σ DEHP, MBP, and mono-(3-carboxypropyl) phthalate metabolite levels were all associated with significantly elevated odds of prematurity.
CONCLUSIONS AND RELEVANCE: Women exposed to phthalates during pregnancy have significantly increased odds of delivering preterm. Steps should be taken to decrease maternal exposure to phthalates during pregnancy.

Environ Sci Technol. 2014 Jan 7;48(1):706-12. doi: 10.1021/es402569k. Epub 2013 Dec 10.
Estimated daily intake and hazard quotients and indices of phthtalate diesters for young danish men.
Kranich SK, Frederiksen H, Andersson AM, Jørgensen N.

Because of wide exposure to phthalates, we investigated whether simultaneous exposure to several phthalates reached levels that might cause adverse antiandrogenic effects. Thirty three healthy young Danish men each delivered three 24-h urine samples during a three months period. The daily intakes of the sum of di-n-butyl and di-iso-butyl phthalate, di(2-ethylhexyl) phthalate, di-iso-nonyl phthalate, and butylbenzyl phthalate were estimated based on urinary excretion of the metabolites. Based on a hazard quotient (HQ) of the individual phthalate (i.e., the ratio between the daily intake and an acceptable level of exposure), a hazard index (HI) for each man was calculated as the sum of HQs for the individual phthalates. All men were exposed to all phthalates during the

urine collection periods. Median HIs were all below 1 (i.e., below an acceptable cumulative threshold) ranging from 0.11 to 0.17 over the three different sample collections. Of the 33 men, 2 men had HIs above 1 in one of their three samples, indicating that occasionally the combined exposure to the investigated phthalates reached a level that may not be considered safe. Besides the phthalates investigated here, humans are exposed to numerous other chemicals that also may contribute to a cumulative antiandrogenic exposure.

Int J Hyg Environ Health. 2014 Jan;217(1):78-87. doi:10.1016/j.ijheh.2013.03.014. Epub 2013 Apr 6.
Phthalate metabolites in urine samples from Danish children and correlations with phthalates in dust samples from their homes and daycare centers.
Langer S, Bekö G, Weschler CJ, Brive LM, Toftum J, Callesen M, Clausen G.

Around the world humans use products that contain phthalates, and human exposure to certain of these phthalates has been associated with various adverse health effects. The aim of the present study has been to determine the concentrations of the metabolites of diethyl phthalate (DEP), di(n-butyl) phthalate (DnBP), di(iso-butyl) phthalate (DiBP), butyl benzyl phthalate (BBzP) and di(2-ethylhexyl) phthalate (DEHP) in urine samples from 441 Danish children (3-6 years old). These children were subjects in the Danish Indoor Environment and Children's Health study. As part of each child's medical examination, a sample from his or her first morning urination was collected. These samples were subsequently analyzed for metabolites of the targeted phthalates. The measured concentrations of each metabolite were approximately log-normally distributed, and the metabolite concentrations significantly correlated with one another. Additionally, the mass fractions of DEP, DnBP, DiBP and BBzP in dust collected from the children's bedrooms and daycare centers significantly correlated with the concentrations of these phthalates' metabolites (monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP) and monobenzyl phthalate (MBzP), respectively) in the children's urine. Such correlations indicate that indoor exposures meaningfully contributed to the Danish children's intake of DEP, DnBP, DiBP and BBzP. This was not the case for DEHP. The urine concentrations of the phthalate metabolites measured in the present study were remarkably similar to those measured in urine samples from children living in countries distributed over four continents. These similarities reflect the globalization of children's exposure to phthalate containing products.

MBio. 2014 Apr 8;5(2). pii: e01015-13. doi: 10.1128/mBio.01015-13.
Triclosan Promotes Staphylococcus aureus Nasal Colonization.
Syed AK, Ghosh S, Love NG, Boles BR.

ABSTRACT The biocide triclosan is used in many personal care products, including toothpastes, soaps, clothing, and medical equipment. Consequently, it is present as a contaminant in the environment and has been detected in some human fluids, including serum, urine, and milk. Staphylococcus aureus is an opportunistic pathogen that colonizes the noses and throats of approximately 30% of the population. Colonization with S. aureus is known to be a risk factor for several types of infection. Here we demonstrate that triclosan is commonly found in the nasal secretions of healthy adults and the presence of triclosan trends positively with nasal colonization by S. aureus. We demonstrate that triclosan can promote the binding of S. aureus to host proteins such as collagen, fibronectin, and keratin, as well as inanimate surfaces such as plastic and glass. Lastly, triclosan-exposed rats are more susceptible to nasal colonization

with S. aureus. These data reveal a novel factor that influences the ability of S. aureus to bind surfaces and alters S. aureus nasal colonization. IMPORTANCE Triclosan has been used as a biocide for over 40 years, but the broader effects that it has on the human microbiome have not been investigated. We demonstrate that triclosan is present in nasal secretions of a large portion of a test population and its presence correlates with Staphylococcus aureus nasal colonization. Triclosan also promotes the binding of S. aureus to human proteins and increases the susceptibility of rats to nasal colonization by S. aureus. These findings are significant because S. aureus colonization is a known risk factor for the development of several types of infections. Our data demonstrate the unintended consequences of unregulated triclosan use and contribute to the growing body of research demonstrating inadvertent effects of triclosan on the environment and human health.

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Flame retardants

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Tributyltin / Triclosan / Triclocarban

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Endocrine disrupters

Porta M, Pumarega J, Gasull M, Lopez T. Contamination from endocrine disrupters of the general population at low and high concentrations. Vitam Horm. 2014;94:167-92. doi: 10.1016/B978-0-12-800095-3.00006-7.

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*".

Publiceret fra i perioden 2013/12/01 to 2014/04/30 (December 2013 og fremefter)

Efter at have fjernet genganger fra forrige litteraturopdateringslister gav litteratursøgningen, med de angivne søgekriterier, tilsammen en liste med i alt 81 artikler plus 1 artikel, der ikke blev fundet af de valgte søgekriterier. De i alt 82 artikler er blevet fordelt i 6 grupper:"Parabens","Various Nano-materials/compounds","Perflourinated and Polyflourinated compounds", Plastic derivatives" (BPA, Phthalates and others), "Pesticides/Fungicides/Insecticides/Biocides" og "Various EDCs, Mixtures and Other endpoints".

Ud fra bruttolisten (se længere nede i dokumentet) er 2 artikler er blevet udvalgt til nærmere beskrivelse baseret på, at de beskriver resultater, der bidrager til ny eller yderligere viden om hormonforstyrrende stoffer og metoder til at undersøge hormonforstyrrende stoffer.

Den første artikel omhandler in vitro studier, der har til formål at udvikle en bedre in vitro model til at undersøge miljøkemikalier effekt på produktionen af steroidhormoner under foster perioden/ graviditeten og det samspil der er mellem fostre og placenta.

Den anden artikel omhandler et studie, hvor man har undersøgt bisphenol A (BPA) og 5 mulige alternativer til BPA i forskellige in vitro assays for hormonforstyrrende effekter, med det formål at undersøge, om de mulige alternativer har nogle af de samme hormonforstyrrende egenskaber, som er kendt for BPA.

Udvalgte publikationer

A Unique Co-culture Model for Fundamental and Applied Studies of Human Fetoplacental Steroidogenesis and Interference by Environmental Chemicals.

Thibeault AA, Deroy K, Vaillancourt C, Sanderson JT.

Abstract

Background: Experimental tools for studying the complex steroidogenic interactions that occur between placenta and fetus during human pregnancy are extremely limited. Objectives: We aimed to develop a co-culture model to study steroidogenesis by the human fetoplacental unit and its disruption by exposure to environmental contaminants. Methods: We cultured BeWo human choriocarcinoma cells, representing the villous cytotrophoblast, and H295R human adrenocortical carcinoma cells, representing the fetal unit, in a carefully adapted co-culture medium. We placed H295R cells in 24-well plates and BeWo cells on transwell inserts with or without pesticide treatment (atrazine or prochloraz) and assessed CYP19 activity and hormonal production after 24 hr of co-culture. Results: The co-culture exhibited the steroidogenic profile of the fetoplacental unit, allowing a synergistic production of estradiol and estriol (but not of estrone) of 133.3 ± 11.3 pg/mL and 440.8 ± 44.0 pg/mL, respectively. Atrazine and prochloraz had cell-type specific effects on CYP19 activity and estrogen production in co-culture. Atrazine induced CYP19 activity and estrogen production in H295R cells only, but did not affect overall estrogen production in co-culture, whereas prochloraz inhibited CYP19 activity exclusively in BeWo cells and reduced estrogen production in co-culture by almost 90%. In contrast, prochloraz did not affect estradiol or estrone production in BeWo cells in monoculture. These differential effects underline the relevance of our co-culture approach to model fetoplacental steroidogenesis. Conclusions: The co-culture of H295R and BeWo cells creates a unique in vitro model to reproduce the steroidogenic cooperation between fetus and placenta during pregnancy and can be used to study the endocrine-disrupting effects of environmental chemicals.

Are structural analogues to bisphenol a safe alternatives?

Rosenmai AK, Dybdahl M, Pedersen M, Alice van Vugt-Lussenburg BM, Wedebye EB, **Taxvig** C, Vinggaard AM.

Abstract

Background: Bisphenol A (BPA) is a chemical with widespread human exposure suspected of causing low-dose effects. Thus, a need for developing alternatives to BPA exists. Structural analogues of BPA have already been detected in foods and humans. Due to the structural analogy of the alternatives, there is a risk of effects similar to BPA. Objectives: The aim was to elucidate and compare the hazards of bisphenol B (BPB), bisphenol E (BPE), bisphenol F (BPF), bisphenol S (BPS) and 4-cumylphenol (HPP) to BPA. Methods: In vitro studies on steroidogenesis, receptor activity, and biomarkers of effect, as well as Quantitative Structure-Activity Relationship (QSAR) modeling. Results: All test compounds caused the same qualitative effects on estrogen receptor and androgen receptor activities, and most of the alternatives exhibited potencies within the same range as BPA. Hormone profiles for the compounds indicated a specific mechanism of action on steroidogenesis which generally lead to decreased androgen, and increased estrogen and progestagen levels. Differential effects on corticosteroid synthesis were observed suggesting a compound-specific mechanism. Overall, BPS was less estrogenic and antiandrogenic than BPA, but BPS showed the largest efficacy on 17α-hydroxyprogesterone (17α-OH progesterone). Finally, there were indications of DNA damage, carcinogenicity, oxidative stress, effects on metabolism, and skin sensitization of one or more of the test compounds. Conclusions: Interference with the endocrine system was the predominant effect of the test compounds. A substitution of BPA with these structural analogues should be carried out with caution.

Bruttolisten *in vitro*

Parabens

1.Assessment of combined antiandrogenic effects of binary parabens mixtures in a yeast-based reporter assay.

Ma D, Chen L, Zhu X, Li F, Liu C, Liu R.

Environ Sci Pollut Res Int. 2014 Jan 28. [Epub ahead of print]

2.Exposure to **parabens** at the concentration of maximal proliferative response increases migratory and invasive activity of human breast cancer cells **in vitro**.

Khanna S, Dash PR, Darbre PD.

J Appl Toxicol. 2014 Mar 20. doi: 10.1002/jat.3003. [Epub ahead of print]

3.A proposed study on the transplacental transport of **parabens** in the human placental perfusion model.

Mathiesen L, Zuri G, Andersen MH, Knudsen LE.

Altern Lab Anim. 2013 Dec;41(6):473-82.

4.Disruption of Sertoli cell vimentin filaments in prepubertal rats: An acute effect of butylparaben in vivo and **in vitro**.

Alam MS, Kurohmaru M.

Acta Histochem. 2014 Jan 17. pii: S0065-1281(13)00239-0. doi: 10.1016/j.acthis.2013.12.006. [Epub ahead of print]

5.Transesterification of a series of 12 **parabens** by liver and small-intestinal microsomes of rats and humans.

Fujino C, Watanabe Y, Uramaru N, Kitamura S.

Food Chem Toxicol. 2014 Feb;64:361-8. doi: 10.1016/j.fct.2013.12.013. Epub 2013 Dec 17.

6.Hydrolytic enzymes production by Aspergillus section Nigri in presence of butylated hydroxyanisole and propyl **paraben** on peanut meal extract agar.

Barberis CL, Landa MF, Barberis MG, Giaj-Merlera G, Dalcero AM, Magnoli CE.

Rev Iberoam Micol. 2014 Apr-Jun;31(2):131-6. doi: 10.1016/j.riam.2013.02.005. Epub 2013 Apr 11.

Various Nano-materials/compounds

1.Nanoparticle incorporation of melittin reduces sperm and vaginal epithelium cytotoxicity.

Jallouk AP, Moley KH, Omurtag K, Hu G, Lanza GM, Wickline SA, Hood JL.

PLoS One. 2014 Apr 18;9(4):e95411. doi: 10.1371/journal.pone.0095411. eCollection 2014.

2.Anti-Angiogenesis Therapy in the Vx2 Rabbit Cancer Model with a Lipase-cleavable Sn 2 Taxane Phospholipid Prodrug using αvβ3-Targeted Theranostic Nanoparticles.

Pan D, Schmieder AH, Wang K, Yang X, Senpan A, Cui G, Killgore K, Kim B, Allen JS, Zhang H, Caruthers SD, Shen B, Wickline SA, Lanza GM.
Theranostics. 2014 Mar 11;4(6):565-78. doi: 10.7150/thno.7581. eCollection 2014.

3.Methotrexate-loaded PLGA nanobubbles for ultrasound imaging and Synergistic Targeted therapy of residual tumor during HIFU ablation.

Zhang X, Zheng Y, Wang Z, Huang S, Chen Y, Jiang W, Zhang H, Ding M, Li Q, Xiao X, Luo X, Wang Z, Qi H.
Biomaterials. 2014 Jun;35(19):5148-61. doi: 10.1016/j.biomaterials.2014.02.036. Epub 2014 Mar 28.

Perflourinated and Polyflourinated compounds

1.**Perfluorocarbon** nanoemulsions with fluorescent, colloidal and magnetic properties.

Janjic JM, Shao P, Zhang S, Yang X, Patel SK, Bai M.

Biomaterials. 2014 Jun;35(18):4958-68. doi: 10.1016/j.biomaterials.2014.03.006. Epub 2014 Mar 25.

2.Identification of **perfluorooctane** sulfonate binding protein in the plasma of tiger pufferfish Takifugu rubripes.

Honda M, Muta A, Akasaka T, Inoue Y, Shimasaki Y, Kannan K, Okino N, Oshima Y.

Ecotoxicol Environ Saf. 2014 Mar 10. pii: S0147-6513(13)00505-8. doi: 10.1016/j.ecoenv.2013.11.010. [Epub ahead of print]

3.**Endocrine disruption** effects of long-term exposure to perfluorodecanoic acid (PFDA) and perfluorotridecanoic acid (PFTrDA) in zebrafish (Danio rerio) and related mechanisms.

Jo A, Ji K, Choi K.
Chemosphere. 2014 Feb 26. pii: S0045-6535(14)00171-4. doi: 10.1016/j.chemosphere.2014.01.080. [Epub ahead of print]

4.An **in-vitro** investigation of the effect of **perfluorooctane** sulphonate on cell lines of embryonic origin.
Karakas-Celik S, Aras N.

Mol Biol Rep. 2014 Feb 18. [Epub ahead of print]

5.**Polyfluorinated** Alkyl Phosphate Ester Surfactants - Current Knowledge and Knowledge Gaps.

Taxvig C, Rosenmai AK, Vinggaard AM.

Basic Clin Pharmacol Toxicol. 2014 Feb 8. doi: 10.1111/bcpt.12208. [Epub ahead of print]

6.Gold Nanoshelled Liquid **Perfluorocarbon** Nanocapsules for Combined Dual Modal Ultrasound/CT Imaging and Photothermal Therapy of Cancer.

Ke H, Yue X, Wang J, Xing S, Zhang Q, Dai Z, Tian J, Wang S, Jin Y.

Small. 2014 Mar;10(6):1220-7. doi: 10.1002/smll.201302252. Epub 2014 Feb 5.

7.Evaluating the additivity of **perfluoroalkyl** acids in binary combinations on peroxisome proliferator-activated receptor-α activation.
Wolf CJ, Rider CV, Lau C, Abbott BD.
Toxicology. 2014 Feb 28;316:43-54. doi: 10.1016/j.tox.2013.12.002. Epub 2013 Dec 26.

Plastic derivatives (BPA, Phthalates and others)

1.Bisphenol A affects human endometrial endothelial cell angiogenic activity **in vitro**.

Helmestam M, Davey E, Stavreus-Evers A, Olovsson M.
Reprod Toxicol. 2014 Mar 14;46C:69-76. doi: 10.1016/j.reprotox.2014.03.002. [Epub ahead of print]

2.Bisphenol-A and diethylstilbestrol exposure induces the expression of breast cancer associated long noncoding RNA HOTAIR **in vitro** and in vivo.

Bhan A, Hussain I, Ansari KI, Bobzean SA, Perrotti LI, Mandal SS.

J Steroid Biochem Mol Biol. 2014 May;141:160-70. doi: 10.1016/j.jsbmb.2014.02.002. Epub 2014 Feb 14.

3.Bisphenol A induces differentiation of human preadipocytes in the absence of glucocorticoid and is inhibited by an estrogen-receptor antagonist.

Boucher JG, Boudreau A, Atlas E.

Nutr Diabetes. 2014 Jan 13;4:e102. doi: 10.1038/nutd.2013.43.

4.Antagonistic effects of a mixture of low-dose nonylphenol and di-N-butyl phthalate (monobutyl phthalate) on the sertoli cells and serum reproductive hormones in prepubertal male rats **in vitro** and in vivo.
Hu Y, Wang R, Xiang Z, Qian W, Han X, Li D.
PLoS One. 2014 Mar 27;9(3):e93425. doi: 10.1371/journal.pone.0093425. eCollection 2014.

5.Classification of phthalates based on an **in vitro** neurosphere assay using rat mesencephalic neural stem cells.

Ishido M, Suzuki J.

J Toxicol Sci. 2014;39(1):25-32.

6.In vivo chronic and **in vitro** acute effects of di(2-ethylhexyl) phthalate on pseudopregnant rabbit corpora lutea: possible involvement of peroxisome proliferator-activated receptor gamma.

Parillo F, Maranesi M, Brecchia G, Gobbetti A, Boiti C, Zerani M.

Biol Reprod. 2014 Feb 27;90(2):41. doi: 10.1095/biolreprod.113.109223. Print 2014 Feb.

7.Mono(2-ethylhexyl) **phthalate** induces apoptosis in p53-silenced L02 cells via activation of both mitochondrial and death receptor pathways.

Yang G, Zhang W, Qin Q, Wang J, Zheng H, Xiong W, Yuan J.
Environ Toxicol. 2014 Apr 5. doi: 10.1002/tox.21990. [Epub ahead of print]

8.Butylbenzyl **phthalate** hydrolysis in liver microsomes of humans, monkeys, dogs, rats and mice.

Takahara Y, Kinashi Y, Takahara Y, Hichiya H, Okada K, Murata M, Shigeyama M, Hanioka N.
Biol Pharm Bull. 2014;37(4):703-6.

9.Associations between serum **phthalates** and biomarkers of reproductive function in 589 adult men.

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Environ Mol Mutagen. 2014 May;55(4):343-53. doi: 10.1002/em.21847. Epub 2014 Jan 24.

11.Role of Ca/CaN/NFAT signaling in IL-4 expression by splenic lymphocytes exposed to **phthalate** (2-ethylhexyl) ester in spleen lymphocytes.

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Chen X, Liu YN, Zhou QH, Leng L, Chang Y, Tang NJ.

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13.A critical assessment of the endocrine susceptibility of the human testis to phthalates from fetal life to adulthood.
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Herudover er der yderligere 1 artikel, som ikke blev fanget af de valgte søgekriterier:

Are structural analogues to bisphenol a safe alternatives?

Rosenmai AK, Dybdahl M, Pedersen M, Alice van Vugt-Lussenburg BM, Wedebye EB, **Taxvig** C, Vinggaard AM.

Toxicol Sci. 2014 May;139(1):35-47. doi: 10.1093/toxsci/kfu030. Epub 2014 Feb 22.

Pesticides/Fungicides/Insecticides/Biocides

1.Consequences of tributyltin chloride induced stress in Leydig cells: An ex-vivo approach.
Mitra S, Srivastava A, Khanna S, Khandelwal S.
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Biemann R, Fischer B, Blüher M, Navarrete Santos A.

Chem Biol Interact. 2014 May 5;214:1-9. doi: 10.1016/j.cbi.2014.01.021. Epub 2014 Feb 8.

3.Effects of prochloraz on DNA damage, lipid peroxidation and antioxidant system **in vitro**.

Alpertunga B, Kara M, Abudayyak M, Oztas E, Ozden S, Ozhan G.

Toxicol Mech Methods. 2014 Jan 27. [Epub ahead of print]

4.Vinclozolin: a case study on the identification of endocrine active substances in the past and a future perspective.

van Ravenzwaay B, Kolle SN, Ramirez T, Kamp HG.
Toxicol Lett. 2013 Dec 16;223(3):271-9. doi: 10.1016/j.toxlet.2013.03.029. Epub 2013 Apr 1.

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Karaca H, Pérez-Gago MB, Taberner V, Palou L.

Int J Food Microbiol. 2014 Mar 31;179C:72-79. doi: 10.1016/j.ijfoodmicro.2014.03.027. [Epub ahead of print]

Various EDCs, Mixtures and Other endpoints

1.Exposure to the Three Structurally Different PCB Congeners (PCB 118, 153, and 126) Results in Decreased Protein Expression and Altered Steroidogenesis in the Human Adrenocortical Carcinoma Cell Line H295R.

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Stoner MA, Yang CZ, Bittner GD.
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3.The **in Vitro** estrogenic activities of triclosan and triclocarban.

Huang H, Du G, Zhang W, Hu J, Wu D, Song L, Xia Y, Wang X.
J Appl Toxicol. 2014 Apr 16. doi: 10.1002/jat.3012. [Epub ahead of print]

4.Methodology for profiling anti-androgen mixtures in river water using multiple passive samplers and bioassay-directed analyses.

Liscio C, Abdul-Sada A, Al-Salhi R, Ramsey MH, Hill EM.
Water Res. 2014 Mar 27;57C:258-269. doi: 10.1016/j.watres.2014.03.039. [Epub ahead of print]

5.Coactivation of the PI3K/Akt and ERK signaling pathways in PCB153-induced NF-κB activation and caspase inhibition.

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Toxicol Appl Pharmacol. 2014 Apr 11. pii: S0041-008X(14)00131-8. doi: 10.1016/j.taap.2014.03.027. [Epub ahead of print]

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Chem Res Toxicol. 2014 Apr 8. [Epub ahead of print]

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Li J, Ren S, Han S, Li N.
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In Vivo studier ved DTU Fødevareinstituttet

Søgning er udført på PubMed og dækker perioden midt dec. 2013-28/4 2014

(December 2013-April 2014)

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 ((perfluor* OR polyfluor*)AND in vivo).

Efter at have fjernet gengangere fra dem vi havde med på den forrige litteraturopdateringsliste (I tidligere CEHOS) samt *in vitro*, human eller SDU relevante artikler, gav litteratursøgningen en liste med i alt 66 artikler (Bruttolisten)
Disse er blevet fordelt i grupper efter stofnavne: ”Parabens, ”Plastic derivatives” (BPA, Phthalates and others), ”Pesticides/fungicides” og ” Various EDCs, Mixtures and Other endpoints”.

Tre artikler er blevet udvalgt til nærmere beskrivelse. Disse 3 artikler er valgt fordi vi mener de bidrager til ny viden om lavdosiseffekter af Bisphenol A hos gnavere. Den første er fra forskere i FDAs Nationale Center for Toksikologisk Forskning (Delclos et al. 2014). Den anden omhandler effekter på brystudviklingen (Kass et al. 2014) mens den sidste omhandler påvirkningerne på det neuroendokrine stress respons efter BPA eksponering (Panagiotidou et al. 2014).

Ud fra bruttolisten (se længere nede i dokumentet) er udvalgt følgende 3 artikler til engelsk abstrakt og dansk resume og kommentarer.

Udvalgte artikler

Toxicity evaluation of bisphenol a administered by gavage to sprague dawley rats from gestation day 6 through postnatal day 90.

Delclos KB1, Camacho L, Lewis SM, Vanlandingham MM, Latendresse JR, Olson GR, Davis KJ, Patton RE, Gamboa da Costa G, Woodling KA, Bryant MS, Chidambaram M, Trbojevich R, Juliar BE, Felton RP, Thorn BT.

Toxicol Sci. 2014 May;139(1):174-97. doi: 10.1093/toxsci/kfu022. Epub 2014 Feb 4.

Abstract

Bisphenol A (BPA) is a high production volume industrial chemical to which there is widespread human oral exposure. Guideline studies used to set regulatory limits detected adverse effects only at doses well above human exposures and established a no-observed-adverse-effect level (NOAEL) of 5 mg/kg body weight (bw)/day. However, many reported animal studies link BPA to potentially adverse effects on multiple organ systems at doses below the NOAEL. The primary goals of the subchronic study reported here were to identify adverse effects induced by orally (gavage) administered BPA below the NOAEL, to characterize the dose response for such effects and to determine doses for a subsequent chronic study. Sprague Dawley rat dams were dosed daily from gestation day 6 until the start of labor, and their pups were directly dosed from day 1 after birth to termination. The primary focus was on seven equally spaced BPA doses (2.5-2700 μg/kg bw/day). Also included were a naïve control, two doses of ethinyl estradiol (EE2) to demonstrate the estrogen responsiveness of the animal model, and two high BPA doses (100,000 and 300,000 μg/kg bw/day) expected from guideline studies to produce adverse effects. Clear adverse effects of BPA, including depressed gestational and postnatal body weight gain, effects on the ovary (increased cystic follicles, depleted corpora lutea, and antral follicles), and serum hormones (increased serum estradiol and prolactin and decreased progesterone), were observed only at the two high doses of BPA. BPA-induced effects partially overlapped those induced by EE2, consistent with the known weak estrogenic activity of BPA.

Prenatal Bisphenol A exposure delays the development of the male rat mammary gland.

Kass L, Durando M, Altamirano GA, Manfroni-Ghibaudo GE, Luque EH, Muñoz-de-Toro M.

Reprod Toxicol. 2014 Feb 22. pii: S0890-6238(14)00024-0. doi: 10.1016/j.reprotox.2014.02.001. [Epub ahead of print]

Abstract

Our aims were to evaluate whether exposure to Bisphenol A (BPA) modifies the development of the male rat mammary gland (MG) and to evaluate whether this modification is gender specific. From gestational day 9, pregnant rats were exposed either subcutaneously to 0, 25 or 250μg BPA/kg bw/day until parturition or orally to 0 and 64μg BPA/kg bw/day until weaning. MG development was analyzed on postnatal days (PND) 5, 15 and 30. On PND30, steroid hormone receptor expression and mammary growth were also evaluated. On PND30, the exposure to 64BPA and 250BPA induced a delay in male MG development, evidenced by reduced ductal growth, decreased number of terminal structures and lower expression of androgen receptor (AR). In contrast, female mammary ductal growth was altered only by 250BPA. Regardless of the administration route and length of the exposure period, BPA induced a delay in MG development and modified AR expression in prepubertal male rats.

Perinatal exposure to low-dose bisphenol A affects the neuroendocrine stress response in rats.
Panagiotidou E, Zerva S, Mitsiou DJ, Alexis MN, Kitraki E.
J Endocrinol. 2014 Jan 27;220(3):207-18. doi: 10.1530/JOE-13-0416. Print 2014 Mar.

Abstract
Bisphenol A (BPA) is an estrogen-mimicking endocrine disruptor. Early-life exposures to low doses of BPA exert long-lasting effects on animals' reproductive and brain physiology. However, little is known about the effects of BPA on the stress-response system. Given the interaction of sex and stress hormones, we examined the effect of a low perinatal BPA exposure on the function of the hypothalamic-pituitary-adrenal (HPA) axis at rest and upon application of acute stress. Throughout pregnancy and lactation rats received daily 40μg BPA/kg body weight orally via cornflakes. We studied the effect of this low but chronic exposure to BPA in the male and female offspring at puberty. BPA exposure led to abnormal adrenal histology including reduced zona reticularis especially in male offspring, hyperplasia of zona fasciculata in both sexes, and increased adrenal weight in female offspring. BPA-treated females had increased basal corticosterone and reduced hypothalamic glucocorticoid receptors (GR) levels. Stressed BPA-exposed females exhibited anxiety-like behavioral coping, a less rigorous corticosterone response, and did not downregulate GR in the hypothalamus, compared with control females. BPA-exposed males exhibited a heightened corticosterone stress response compared with females; they also displayed increased pro-opiomelanocortin mRNA levels and retained the prestress levels of pituitary corticotropin-releasing hormone-receptor 1, compared with control males. We found that perinatal chronic exposure to a low dose of BPA perturbs the basal and stress-induced activity of the HPA axis in a sexually dimorphic manner at adolescence. Exposure to BPA might contribute to increased susceptibility to stress-related disorders in later life.

Bruttolisten in vivo

Plastic derivatives (BPA, Phthalates and others)

BPA

1. Investigation of the Effects of Subchronic Low Dose Oral Exposure to Bisphenol A (**BPA**) and Ethinyl Estradiol (EE) on Estrogen Receptor Expression in the Juvenile and Adult Female Rat Hypothalamus.
Rebuli ME, Cao J, Sluzas E, **Delclos** KB, Camacho L, Lewis SM, Vanlandingham MM, Patisaul HB.
Toxicol Sci. 2014 Apr 20. [Epub ahead of print]

2. Comparison of life-stage-dependent internal dosimetry for bisphenol a, ethinyl estradiol, a reference estrogen, and endogenous estradiol to test an estrogenic mode of action in sprague dawley rats.
Churchwell MI, Camacho L, Vanlandingham MM, Twaddle NC, Sepehr E, **Delclos** KB, Fisher JW, Doerge DR.
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Various EDCs, Mixtures and Other endpoints

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Isling LK, Boberg J, Jacobsen PR, Mandrup KR, Axelstad M, Christiansen S, Vinggaard AM, Taxvig C, Kortenkamp A, Hass U.
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Wildlife studier ved Biologisk Institut, Syddansk Universitet (SDU)

Søgningen er udført på Web of Knowledge (all databases) og dækker perioden 12/12 2013 – 28/4 2014.

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 seks artikler til medtagelse af abstract.
Kriterierne for udvælgelsen af publikationer til kommentering er, at de 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. Desuden kommenteres artikler, der omhandler 'nye' stoffer og miljøfaktorer, der har vist sig hormonforstyrrende; specielt hvis disse har relevans for danske forhold. Endelig medtages efter Miljøstyrelsens ønske artikler omhandlende parabener.

Udvalgte artikler

Artikel 1: Vitellogenin as biomarker for estrogenicity in flounder Platichthys flesus in the field and exposed to 17 alpha-ethinylestradiol via food and water in the laboratory.
Madsen, L. L.; Korsgaard, B.; Pedersen, K. L.; Bjerregaard, L. B.; Aagaard, T.; and Bjerregaard, P. 2013. Marine environmental research 92, 79-86.

Abstract: The ability of 17α-ethinylestradiol (EE2) to elevate vitellogenin levels were investigated in male flounder *Platichthys flesus* and vitellogenin concentrations in flounders from the Danish coastal environment were determined. Male flounders were exposed to 17α-ethinylestradiol (EE2) via food or water. Average vitellogenin concentrations in the control fish ranged between 25 and 100 ng mL^{-1}. Exposure to 5.1, 8.1 and 16.8 ng EE2 L^{-1} in water and 500 and 5000 ng EE2 kg^{-1} body weight (bw) every second day in the food increased the plasma vitellogenin concentration in a concentration and time dependent manner, whereas exposure to 2.7 ng EE2 L^{-1} in water for 21 d and 5 and 50 ng EE2 kg^{-1} bw for 12 days in the food did not. EE2 could be detected in liver and testes (but not in muscle) after exposure to 8.1 and 16.8 ng EE2 L^{-1} in the water and 5000 ng EE2 kg^{-1} bw in the food; the highest concentration was 6 ng g^{-1} wet weight in liver. The majority of the male flounders collected from nine coastal Danish sites from 1999 to 2004 had vitellogenin concentrations below 100 ng mL^{-1}, and only at two sites moderate estrogenic inputs were indicated.

Artikel 2: Endocrine-Disrupting Effects of Compounds in Danish Streams.
Long, M.; Strand, J.; Lassen, P.; Kruger, T.; Dahllof, I.; Bossi, R.; Larsen, M. M.; Wiberg-Larsen, P.; and Bonefeld-Jorgensen, E. C. 2014. Archives of Environmental Contamination and Toxicology 66, 1-18.

Abstract: Effluents from municipal wastewater-treatment plants and scattered dwellings, as well as runoff from agricultural fields, are sources of endocrine-disrupting compounds (EDCs) in the aquatic environment. The present study investigated the correlation between the occurrence of EDCs in nine Danish streams using passive samplers (polar organic integrative samplers and silicone membranes) and determined their possible biological effects as assessed by mammal cell cultures and the mussel (*Unio tumidus*). The passive samplers and mussels were exposed simultaneously at the study sites. The extracts from the passive samplers were used to measure the concentrations of EDCs and the biological effects on the estrogen (ER), androgen (AR), and aryl hydrocarbon (AhR)-receptor transactivation. Male mussels were investigated for biomarkers of endocrine effects, such as the levels of vitellogenin-like proteins measured as alkalilabile phosphate (ALP). EDC concentrations, hormonereceptor transactivation (ER, AR, AhR), and level of ALP were greater downstream of wastewater-treatment plants compared with upstream sites and sites supposed to be relatively nonimpacted by wastewater. Furthermore, there was a significant positive correlation between in vitro AhR transactivation and frequency of ALP of male mussels. We

conclude that wastewater effluent is an important source of endocrine-disrupting effects in the aquatic environment and that the combination of biological effect measurements and chemical analyses based on passive sampling is useful in the assessment of the ecological state of the aquatic environment.

Artikel 3: Developmental exposure of zebrafish (Danio rerio) to bisphenol-S impairs subsequent reproduction potential and hormonal balance in adults.
Naderi, M.; Wong, M. Y. L.; and Gholami, F. 2014. Aquatic toxicology (Amsterdam, Netherlands) 148, 195-203.

Abstract: In the recent years, there has been a growing concern about the production and use of bisphenol-A substitute, namely bisphenol-S (BPS). Due to its novel nature, there have been few studies addressing the ability of BPS to disrupt the endocrine system of animals. In the present study, zebrafish (Danio rerio) embryos were exposed to and reared in various concentrations of BPS (0, 0.1, 1, 10 and 100 μg/l) for 75 days. Then adult males and females were paired in spawning tanks for 7 days in clean water and the consequent effects on fish development, reproduction, plasma vitellogenin (VTG), sex steroids and thyroid hormone levels were investigated as endpoints. After 75 days of exposure, there was a skewed sex ratio in favor of females. The results also showed that body length and weight significantly decreased in males exposed to100 μg/l of BPS. Gonadosomatic index was significantly reduced in fish at ≥10 μg/l. Hepatosomatic index exhibited a significant increase in both male and female fish. At ≥1 μg/l of BPS, plasma 17β-estradiol levels were significantly increased in both males and females. However, plasma testosterone showed a significant reduction in males exposed to 10 and 100 μg/l of BPS. A significant induction in plasma VTG level was observed in both males and females at ≥10 μg/l of BPS. Plasma thyroxine and triiodothyronine levels were significantly decreased at 10 and 100 μg/l of BPS in males, and at 100 μg/l in females. Egg production and sperm count were also significantly decreased in groups received 10 and 100 μg/l of BPS. Moreover, once time to hatching and hatching rates were calculated for fertilized eggs the postponed and decreased rates of hatching were observed. Taken together, these results suggest that developmental exposure to low concentrations of BPS has adverse effects on different parts of the endocrine system in zebrafish.

Artikel 4: Environmental concentrations of an androgenic progestin disrupts the seasonal breeding cycle in male three-spined stickleback (Gasterosteus aculeatus).
Svensson, J.; Fick, J.; Brandt, I.; and Brunstrom, B. 2014. Aquatic Toxicology 147, 84-91.

Abstract: Synthetic steroid hormones from contraceptive pharmaceuticals have become global aquatic contaminants. Progestins, the synthetic analogs to progesterone, are receiving increasing attention as contaminants and have been shown to impair reproduction in fish and amphibians at low ng L^{-1} concentrations. Certain progestins, such as levonorgestrel have androgenic properties and seem to be several orders of magnitude more potent in terms of reproductive impairment in fish

than non-androgenic progestins and progestagens. We recently reported that levonorgestrel has strong androgenic effects in female three-spined sticklebacks (Gasterosteus aculeatus), including induction of the normally male-specific glue protein spiggin and suppression of vitellogenesis. In light of this we investigated if exposure to levonorgestrel could disrupt the highly androgen-dependent seasonal reproductive cycle in male sticklebacks. Male sticklebacks that were in the final stage of a breeding period were exposed to various concentrations of levonorgestrel for six weeks in winter conditions in terms of light and temperature, after which reproductive status was evaluated from gross morphology, histology and key gene transcript levels. During the experimental period the controls had transitioned from full breeding condition into the non-breeding state, including regression of secondary sex characteristics, cessation of spiggin production in the kidney, and resumption of spermatogenesis in the testes. This is ascribed to the natural drop in plasma androgen levels after breeding. However, in the groups concurrently exposed to levonorgestrel, transition to the non-breeding condition was dose-dependently inhibited. Our results show that levonorgestrel can disrupt the seasonal breeding cycle in male sticklebacks. The fitness costs of such an effect could be detrimental to natural stickleback populations. Some effects occurred at a levonorgestrel concentration of 6.5 ng L^{-1}, well within the range of levonorgestrel levels in surface waters and may therefore occur in progestin-contaminated waters. Furthermore, the effects by levonorgestrel in the present study were likely mediated mainly by its androgenic activity, and the low concentration at which they occurred makes levonorgestrel one of the most potent androgenic contaminants known.

Artikel 5: Levonorgestrel exposure to fathead minnows (Pimephales promelas) alters survival, growth, steroidogenic gene expression and hormone production.
Overturf, M. D.; Overturf, C. L.; Carty, D. R.; Hala, D.; and Huggett, D. B. 2014. Aquatic toxicology (Amsterdam, Netherlands) 148, 152-161.

Abstract: Human pharmaceuticals are commonly detected in the environment. Concern over these compounds in the environment center around the potential for pharmaceuticals to interfere with the endocrine system of aquatic organisms. The main focus of endocrine disruption research has centered on how estrogenic andandrogenic compounds interact with the endocrine system to elicit reproductive effects. Other classes of compounds, such as progestins, have been overlooked. Recently, studies have investigated the potential for synthetic progestins to impair reproduction and growth in aquatic organisms. The present study utilizes the OECD 210 Early-life Stage (ELS) study to investigate the impacts levonorgestrel (LNG), a synthetic progestin, on fathead minnow (FHM) survival and growth. After 28 days post-hatch, survival of larval FHM was impacted at 462 ng/L, while growth was significantly reduced at 86.9 ng/L. Further analysis was conducted by measuring specific endocrine related mRNA transcript profiles in FHM larvae following the 28 day ELS exposure to LNG. Transcripts of 3β-HSD, 20β-HSD, CYP17, AR, ERα, and FSH were signifi-cantly down-regulated following 28 d exposure to 16.3 ng/L LNG, while exposure to 86.9 ng/L significantly down-regulated 3β-HSD, 20β-HSD, CYP19A, and FSH. At 2392 ng/L of LNG, a significant down-regulation occurred with CYP19A and ERβ transcripts, while mPRα and mPRβ profiles were significantly induced. No significant changes occurred in 11β-HSD, CYP11A, StAR, LHβ, and VTG mRNA expression following LNG exposure. An ex vivo steroidogenesis assay was

conducted with sexually mature female FHM following a 7 day exposure 100 ng/L LNG with significant reductions observed in pregnenolone, 17α,20β-dihydroxy-4-pregnen-3-one (17,20-DHP), testosterone, and 11-ketotestosterone. Together these data suggest LNG can negatively impact FHM larval survival and growth, with significant alterations in endocrine related responses.

Artikel 6: The synthetic progestin megestrol acetate adversely affects zebrafish reproduction.
Han, J.; Wang, Q.; Wang, X.; Li, Y.; Wen, S.; Liu, S.; Ying, G.; Guo, Y.; and Zhou, B. 2014. Aquatic toxicology (Amsterdam, Netherlands) 150, 66-72.

Abstract: Synthetic progestins contaminate the aquatic ecosystem, and may cause adverse health effects on aquatic organisms. Megestrol acetate (MTA) is present in the aquatic environment, but its possible effects on fish reproduction are unknown. In the present study, we investigated the endocrine disruption and impact of MTA on fish reproduction. After a pre-exposure period of 14 days, reproductively mature zebrafish (Danio rerio) (F0) were exposed to MTA at environmental concentrations (33, 100, 333, and 666 ng/L) for 21 days. Egg production was decreased in F0 fish exposed to MTA, with a significant decrease at 666 ng/L. The exposure significantly decreased the circulating concentrations of estradiol (E2) and testosterone (T) in female fish or 11-keto testosterone (11-KT) in male fish. MTA exposure significantly downregulated the transcription of certain genes along the hypothalamic-pituitary-gonadal (HPG) axis. MTA did not affect early embryonic development or hatching success in the F1 generation. The present study showed that MTA is a potent endocrine disruptor in fish, and short-term exposure to MTA could significantly affect reproduction in fish and negatively impact the fish population.

Bruttoliste

Alkylphenoler

Effects of 4-nonylphenol on balance of steroid and thyroid hormones in sexually immature male yellowfin seabream (Acanthopagrus latus).
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Bisphenoler

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