Center for Hormonforstyrrende Stoffer

Litteraturgennemgang for perioden oktober – december 2012

Humane studier ved Afd. for Vækst og Reproduktion, Rigshospitalet

Søgning er udført på PubMed og dækker perioden 27. september – 14. december 2012

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

Som det fremgår af bruttolisten for humane studier, er der igen ganske mange hits. For søgetermen "endocrine disrupters" har vi fjernet alle de hits, der også fremkom ved de øvrige søgninger.

De udvalgte artikler dækker bredt. Der er studier om BPA, PFCer, phthalater og POPs, et fransk studie om faldende sædkvalitet, og et canadisk studie om eksponeringer relateret til brystkræft. God læselyst.

Aylward LL, Kirman CR, Schoeny R, Portier CJ, Hays SM. Evaluation of Biomonitoring Data from the CDC National Exposure Report in a Risk Assessment Context: Perspectives across Chemicals. Environ Health Perspect. 2012 Dec 11. [Epub ahead of print] PubMed PMID: 23232556.

Udvalgte artikler

Environ Health Perspect. 2012 Oct 4. [Epub ahead of print]
Maternal Urinary Bisphenol A during Pregnancy and Maternal and Neonatal Thyroid Function in the CHAMACOS Study.
Chevrier J, Gunier RB, Bradman A, Holland NT, Calafat AM, Eskenazi B, Harley KG.
Center for Children's Environmental Health Research, School of Public Health, University of California, Berkeley, Berkeley, California, USA.

Background: Bisphenol A is widely used in the manufacture of polycarbonate plastic bottles, food and beverage cans linings, thermal receipts and dental sealants. Animal and human studies suggest that BPA may disrupt thyroid function. Although thyroid hormones play a determinant role in human growth and brain development, no studies have investigated relations between BPA exposure and thyroid function in pregnant women or neonates. Objectives: To evaluate whether exposure to BPA during pregnancy is related to thyroid hormone levels in pregnant women and neonates. Methods: We measured BPA concentration in urine samples collected during the first and second half of pregnancy in 476 women participating in the CHAMACOS study. We also measured free thyroxine (T4), total T4 and thyroid-stimulating hormone (TSH) during pregnancy, and TSH in neonates. Results: The association between the average of the two BPA measurements and maternal thyroid hormone levels was not statistically significant. Of the two BPA measurements, only the measurement taken closest in time to the TH measurement was significantly associated with a reduction in total T4 (β=-0.13 µg/dL per log2 unit; 95%CI=-0.25, 0.00). The average of the maternal BPA concentrations was associated with reduced TSH in boys (-9.9% per log2 unit; 95%CI=-15.9%, -3.5%) but not in girls. Among boys, the relation was stronger when BPA was measured in the third trimester of pregnancy and decreased with time between BPA and TH measurements. Conclusion: Results suggest that exposure to BPA during pregnancy
is related to reduced total T4 in pregnant women and decreased TSH in male neonates. Findings may have implications for fetal and neonatal development.

Environ Int. 2012 Dec 1;50:7-14. doi: 10.1016/j.envint.2012.09.002. Epub 2012 Sep 29.
The contribution of diet to total bisphenol A body burden in humans: Results of a 48hour fasting study.
Christensen KL, Lorber M, Koslitz S, Brüning T, Koch HM.
National Center for Environmental Assessment, Office of Research and Development, United States Environmental Protection Agency, Washington, DC, USA. Electronic address: Christensen.Krista@epa.gov.

Human biomonitoring studies measuring bisphenol A (BPA) in urine have shown widespread exposure in the general population. Diet is thought to be a major route of exposure. We studied urinary BPA patterns in five individuals over a
48-h period of fasting (bottled water only). Personal activity patterns were recorded with a diary to investigate non-dietary routes of exposure. All urine void events during the fast were collected, as well as events before and after
the fast. The pattern of BPA concentrations was similar for all participants: they rose near the beginning of the fast (after the pre-fast meal), declined over the next 24h, fluctuated at lower levels during the second day, and then rose
after the post-fast meal. Concentrations (~2µg/g creatine) and calculated BPA intakes (~0.03µg/kg-day) in these individuals during the first 24h were consistent with general population exposures. For the second 24h, concentrations and intakes declined by about two-thirds. One of the individuals had an extraordinary pre-fast exposure event with concentrations rising as high as 98µg/g creatine but declining to <5µg/g creatine by day 2. Given patterns found in day 1 and the subsequent decline to lower levels in day 2, we hypothesize that BPA exposures in these individuals were diet-driven. No events in the diary (use of

personal care products, e.g.) appear associated with exposures. On day 2, non-dietary sources may still be present, such as from dust. Another hypothesis is that small reservoirs of BPA from past exposures are released from storage (lipid reservoirs, e.g.) and excreted.

Environ Health Perspect. 2012 Oct;120(10):1475-80. doi: 10.1289/ehp.1104544. Epub 2012 Jun 13.
Prenatal exposure to butylbenzyl phthalate and early eczema in an urban cohort.
Just AC, Whyatt RM, Perzanowski MS, Calafat AM, Perera FP, Goldstein IF, Chen Q, Rundle AG, Miller RL.
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BACKGROUND: Recent cross-sectional studies suggest a link between butylbenzyl phthalate (BBzP) in house dust and childhood eczema. OBJECTIVES: We aimed to evaluate whether concentrations of monobenzyl phthalate (MBzP), the main BBzP metabolite in urine, during pregnancy are associated prospectively with eczema in young children, and whether this association varies by the child's sensitization to indoor allergens or serological evidence of any allergies.
METHODS: MBzP was measured in spot urine samples during the third trimester of pregnancy from 407 African-American and Dominican women residing in New York City in 1999-2006. Repeated questionnaires asked mothers whether their doctor ever said their child had eczema. Child blood samples at 24, 36, and 60 months of age were analyzed for total, anti-cockroach, dust mite, and mouse IgE. Relative risks (RR) were estimated with multivariable modified Poisson regression. Analyses included a multinomial logistic regression model for early- and late-onset eczema versus no eczema through 60 months of age.
RESULTS: MBzP was detected in > 99% of samples (geometric mean = 13.6; interquartile range: 5.7-31.1 ng/mL). By 24 months, 30% of children developed eczema, with the proportion higher among African Americans (48%) than among Dominicans (21%) ($p < 0.001$). An interquartile range increase in log MBzP concentration was associated positively with early-onset eczema (RR = 1.52 for eczema by 24 months; 95% confidence interval: 1.21, 1.91, $p = 0.0003$, n = 113 reporting eczema/376 total sample), adjusting for urine specific gravity, sex, and race/ethnicity. MBzP was not associated with allergic sensitization, nor did seroatopy modify consistently the MBzP and eczema association.
CONCLUSIONS: Prenatal exposure to BBzP may influence the risk of developing eczema in early childhood.

Environ Health Perspect. 2012 Nov 14. [Epub ahead of print]
Persistent Environmental Pollutants and Couple Fecundity: The LIFE Study.
Buck Louis GM, Sundaram R, Schisterman EF, Sweeney AM, Lynch CD, Gore-Langton RE, Maisog J, Kim S, Chen Z, Barr DB.
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BACKGROUND: Evidence suggesting that persistent environmental pollutants may be reproductive toxicants underscores the need for prospective studies of couples for whom exposures are measured.
OBJECTIVES: To determine the relation between selected persistent pollutants and couple fecundity as measured by time-to-pregnancy. METHODS: A cohort comprising 501 couples discontinuing contraception

to become pregnant was prospectively followed for 12 months of trying to conceive or until a human chorionic gonadotrophin test confirmed pregnancy. Couples completed daily journals on lifestyle and provided biospecimens for the quantification of 9 organochlorine pesticides, 1 polybrominated biphenyl, 10 polybrominated diphenyl ethers, 36 polychlorinated biphenyls (PCBs), and 7 perfluorochemicals (PFCs) in serum. Using Cox models for discrete time, fecundability odds ratios (FORs) and 95% confidence intervals (CIs) were estimated separately for each partner's concentrations adjusting for age, body mass index, serum cotinine, serum lipids (except for PFCs), and study site (Michigan or Texas); sensitivity models further adjusted for left truncation or time off contraception (≤2 months) before enrollment. RESULTS: The adjusted reduction in fecundability associated with standard deviation increases in log-transformed serum concentrations ranged between 18%-21% for PCB congeners 118, 167, 209, and perfluorooctane sulfonamide in females, and 17%-29% for p,p'-DDE and PCB congeners 138, 156, 157, 167, 170, 172, and 209 in males. The strongest associations were observed for PCB 167 (FOR 0.79; 95% CI 0.64, 0.97) in females and PCB 138 (FOR=0.71; 95% CI 0.52, 0.98) in males. CONCLUSIONS: In a couple-based prospective cohort study with preconception enrollment and quantification of exposures in both female and male partners, a subset of persistent environmental chemicals were associated with reduced fecundity.

Environ Int. 2012 Nov 5;51C:8-12. doi: 10.1016/j.envint.2012.09.001. [Epub ahead of print]
Biotransformation of fluorotelomer compound to perfluorocarboxylates in humans.
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Levels of perfluorocarboxylates (PFCAs) in biological compartments have been known for some time but their transport routes and distribution patterns are not properly elucidated. The opinions diverge whether the exposure of the general population occurs indirect through precursors or direct via PFCAs. Previous results showed that ski wax technicians are exposed to levels up to 92 000ng/m(3) of 8:2 fluorotelomer alcohol (FTOH) via air and have elevated blood levels of PFCAs. Blood samples were collected in 2007-2011 and analyzed for C(4)-C(18) PFCAs, 6:2, 8:2 and 10:2 unsaturated fluorotelomer acids (FTUCAs) and 3:3, 5:3 and 7:3 fluorotelomer acids (FTCAs) using UPLC-MS/MS. Perfluorooctanoic acid (PFOA) was detected in levels ranging from 1.90 to 628ng/mL whole blood (wb). Metabolic intermediates 5:3 and 7:3 FTCA were detected in all samples at levels up to 6.1 and 3.9ng/mL wb. 6:2, 8:2 and 10:2 FTUCAs showed maximum levels of 0.07, 0.64 and 0.11ng/mL wb. Also, for the first time levels of PFHxDA and PFOcDA were detected in the human blood at mean concentrations up to 4.22ng/mL wb and 4.25ng/mL wb respectively. The aim of this study was to determine concentrations of PFCAs and FTOH metabolites in blood from ski wax technicians.

Neuroepidemiology. 2012 Oct 24;40(2):125-132. [Epub ahead of print]
Cross-Sectional Association between Polyfluoroalkyl Chemicals and Cognitive Limitation in the National Health and Nutrition Examination Survey.
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Background/Aims: Our limited understanding of how polyfluoroalkyl chemicals (PFCs) may impact on human health suggests the potential for a protective impact on brain health. This study was designed to explore the association between PFCs and cognitive ability in older adults. Methods: We assessed the association between four PFCs, perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS),

perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS), and self-reported limitation due to difficulty remembering or periods of confusion using data from participants aged 60-85 years from the 1999-2000 and 2003-2008 National Health and Nutrition Examination Surveys. We also considered whether diabetic status or diabetic medication use modifies this association in light of in vitro evidence that PFCs may act on the same receptors as some diabetic medications. Results: In multivariable adjusted models, point estimates suggest a protective association between PFCs and self-reported cognitive limitation (odds ratio, OR; 95% confidence interval, CI) for a doubling in PFC concentration: PFOS (OR, 0.90; 95% CI, 0.78, 1.03), PFOA (OR, 0.92; 95% CI, 0.78, 1.09), PFNA (OR, 0.91; 95% CI, 0.79, 1.04) and PFHxS (OR, 0.93; 95% CI, 0.82, 1.06). The protective association was concentrated in diabetics, with strong, significant protective associations in nonmedicated diabetics. Conclusions: This cross-sectional study suggests that there may be a protective association between exposure to PFCs and cognition in older adults, particularly diabetics.

Am J Epidemiol. 2012 Nov 15;176(10):909-17. doi: 10.1093/aje/kws171. Epub 2012 Oct 18.
Cohort mortality study of workers exposed to perfluorooctanoic Acid.
Steenland K, Woskie S.

Perfluorooctanoic acid (PFOA) is persistent in the human body; the general population has serum levels of approximately 4 ng/mL. It causes tumors of the liver, pancreas, and testicles in rodents. The authors studied the mortality of 5,791 workers exposed to PFOA at a DuPont chemical plant in West Virginia, using a newly developed job exposure matrix based on serum data for 1,308 workers from 1979-2004. The estimated average serum PFOA level was 350 ng/mL. The authors used 2 referent groups: other DuPont workers in the region and the US population. In comparison with other DuPont workers, cause-specific mortality was elevated for mesothelioma (standardized mortality ratio (SMR) = 2.85, 95% confidence interval (CI): 1.05, 6.20), diabetes mellitus (SMR = 1.90, 95% CI: 1.35, 2.61), and chronic renal disease (SMR = 3.11, 95% CI: 1.66, 5.32). Significant positive exposure-response trends occurred for both malignant and nonmalignant renal disease (12 and 13 deaths, respectively). PFOA is concentrated in the kidneys of rodents, and there are prior findings of elevated kidney cancer in this cohort. Multiple-cause mortality analyses tended to support the results of underlying-cause analyses. No exposure-response trend was seen for diabetes or heart disease mortality. In conclusion, the authors found evidence of positive exposure-response trends for malignant and nonmalignant renal disease. These results were limited by small numbers and restriction to mortality data, which are of limited relevance for several nonfatal outcomes of a priori interest.

Environ Health. 2012 Nov 19;11(1):87. [Epub ahead of print]
Breast cancer risk in relation to occupations with exposure to carcinogens and endocrine disruptors: a Canadian case--control study.
Brophy JT, Keith MM, Watterson A, Park R, Gilbertson M, Maticka-Tyndale E, Beck M, Abu-Zahra H, Schneider K, Reinhartz A, Dematteo R, Luginaah I.

ABSTRACT: BACKGROUND: Endocrine disrupting chemicals and carcinogens, some of which may not yet have been classified as such, are present in many occupational environments and could increase breast cancer risk. Prior research has identified associations with breast cancer and work in agricultural and industrial settings. The purpose of this study was to further characterize possible links between breast cancer risk and occupation, particularly in farming and manufacturing, as well as to examine the impacts of early agricultural exposures, and exposure effects that are specific to the endocrine receptor status of tumours. METHODS: 1006 breast cancer cases referred by a regional cancer center and 1146 randomly-

selected community controls provided detailed data including occupational and reproductive histories. All reported jobs were industry- and occupation-coded for the construction of cumulative exposure metrics representing likely exposure to carcinogens and endocrine disruptors. In a frequency-matched case-control design, exposure effects were estimated using conditional logistic regression. RESULTS: Across all sectors, women in jobs with potentially high exposures to carcinogens and endocrine disruptors had elevated breast cancer risk (OR = 1.42; 95% CI, 1.18-1.73, for 10 years exposure duration). Specific sectors with elevated risk included: agriculture (OR = 1.36; 95% CI, 1.01-1.82); bars-gambling (OR = 2.28; 95% CI, 0.94-5.53); automotive plastics manufacturing (OR = 2.68; 95% CI, 1.47-4.88), food canning (OR = 2.35; 95% CI, 1.00-5.53), and metalworking (OR = 1.73; 95% CI, 1.02-2.92). Estrogen receptor status of tumors with elevated risk differed by occupational grouping. Premenopausal breast cancer risk was highest for automotive plastics (OR = 4.76; 95% CI, 1.58-14.4) and food canning (OR = 5.70; 95% CI, 1.03-31.5). CONCLUSIONS: These observations support hypotheses linking breast cancer risk and exposures likely to include carcinogens and endocrine disruptors, and demonstrate the value of detailed work histories in environmental and occupational epidemiology.

Hum Reprod. 2012 Dec 4. [Epub ahead of print]

Decline in semen concentration and morphology in a sample of 26 609 men close to general population between 1989 and 2005 in France.

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STUDY QUESTION: Are temporal trends and values of semen quality parameters in France identifiable in partners of totally infertile women? SUMMARY ANSWER: Among a sample of 26 609 partners of totally infertile women undergoing an assisted reproductive technology (ART) procedures in the whole of France over a 17-year period, there was a continuous decrease in semen concentration of about 1.9% per year and a significant decrease in the percentage with morphologically normal forms but no global trend for motility.
WHAT IS KNOWN ALREADY: A global decrease in human sperm quality is still debated as geographical differences have been shown, and many criticisms have risen concerning studies with small and biased study populations or inappropriate statistical methodology. However, growing biological, toxicological, experimental and human exposure data support the endocrine disruptors' hypothesis assuming that fetal exposure to endocrine disruptors could impair reproductive outcomes.
STUDY DESIGN, SIZE, DURATION: This was a retrospective and descriptive study using data registered by Fivnat, the professional association in charge of statistics for ART in France during the 1989-2005 study period. Data were provided by 126 main ART centres over the whole metropolitan territory. The source population included 154 712 men, aged 18-70, who were partners of couples undergoing their first ART cycle and for whom semen quality indicators (concentration, total motility and percentage of morphologically normal forms), measured on fresh ejaculated semen, were available.
PARTICIPANTS/MATERIALS, SETTING, METHODS: The study population was 26,609 partners of women who had both tubes either absent or blocked. The temporal trends for each indicator of semen quality were modelled using a generalized additive model that allowed for nonlinear relationships between variables and were adjusted for season and age. In-depth sensitivity analyses included the reiteration of the analysis on data from a second spermiogram available for each man and on another subsample of men diagnosed as fertile. Variables such as centre, technique (standard in vitro fertilization or intra-cytoplasmic sperm injection) and an interaction factor between technique and time were also included in the model.
MAIN RESULTS AND THE ROLE OF CHANCE: There was a significant and continuous decrease in sperm concentration of 32.2% [26.3-36.3] during the study period. Projections indicate that concentration for a 35-year-old man went from an average of 73.6 million/ml [69.0-78.4] in 1989 to 49.9 million/ml [43.5-54.7] in 2005. A significant, but not quantifiable, decrease in the percentage of sperm with morphologically normal forms along the 17-year period was

also observed. There was no global trend but a slight, significant increase in total motility between 1994 and 1998 was observed. The results were robust after sensitivity analysis.
LIMITATIONS, REASONS FOR CAUTION: Socioeconomic status could not be controlled for. Despite universal access to medical services in France, couples undergoing ART are expected to have a higher educational level on average compared with those of the general population. Therefore, the real values in the general population could be slightly lower than those presented and the decrease possibly stronger, as the population study is less likely to smoke or be overweight, two factors known to impair semen quality.
WIDER IMPLICATIONS OF THE FINDINGS: As the men were selected without a priori knowledge regarding their semen quality characteristics, the results are expected to be close to the values in the general French population. The very large sample size and the robustness of the results confer great statistical power and credibility to the results. To our knowledge, it is the first study concluding a severe and general decrease in sperm concentration and morphology at the scale of a whole country over a substantial period. This constitutes a serious public health warning. The link with the environment particularly needs to be determined.
STUDY FUNDING/COMPETING INTEREST(S): No specific funding was sought for this study. The authors have no conflict of interest to declare.The study has been authorized by the Commission Nationale de l'Informatique et des Libertés (CNIL), the national authority for the protection of personal data collected on individuals (authorization no DE-2010-063 dated 08/09/2010).

Bruttoliste

Bisphenol A

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In vitro studier ved DTU-FOOD

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 2012/09/01 to 2012/12/31 (september 2012 og fremefter)

Efter at have fjernet genganger fra forrige litteraturopdateringslister, gav litteratursøgningen, med de angivne søgekriterier, tilsammen en liste med i alt 29 artikler (Bruttolisten):

Udvalgte artikler

To artikler er blevet udvalgt til nærmere beskrivelse (1 fra DTU Fødevareinstituttet). Begge artikler beskriver studier, der har til formål at undersøge de hormonforstyrrende egenskaber af flourstoffer og deres nedbrydnings produkter. Disse stoffer bruges til coating af fødevareemballage og man ved at mennesker bliver udsat for disse stoffer via fødevarer, men viden om deres toksikologisk dvs. potential skadelige effekter er stadigvæk begrænset.

Fluorochemicals used in food packaging inhibit male sex hormone synthesis.
Rosenmai AK, Nielsen FK, Pedersen M, Hadrup N, Trier X, Christensen JH, Vinggaard AM.
Abstract:

Polyfluoroalkyl phosphate surfactants (PAPS) are widely used in food contact materials (FCMs) of paper and board and have recently been detected in 57% of investigated materials. Human exposure occurs as PAPS have been measured in blood; however knowledge is lacking on the toxicology of PAPS. The aim of this study was to elucidate the effects of six fluorochemicals on sex hormone synthesis and androgen receptor (AR) activation in vitro. Four PAPS and two metabolites, perfluorooctanoic acid (PFOA) and 8:2 fluorotelomer alcohol (8:2 FTOH) were tested. Hormone profiles, including eight steroid hormones, generally showed that 8:2 diPAPS, 8:2 monoPAPS and 8:2 FTOH led to decreases in androgens (testosterone, dehydroepiandrosterone, and androstenedione) in the H295R steroidogenesis assay. Decreases were observed for progesterone and 17-OH-progesterone as well. These observations indicated that a step prior to progestagen and androgen synthesis had been affected. Gene expression analysis of StAR, Bzrp, CYP11A, CYP17, CYP21 and CYP19 mRNA showed a decrease in Bzrp mRNA levels for 8:2 monoPAPS and 8:2 FTOH indicating interference with cholesterol transport to the inner mitochondria. Cortisol, estrone and 17β-estradiol levels were in several cases increased with exposure. In accordance with these data CYP19 gene expression increased with 8:2 diPAPS, 8:2 monoPAPS and 8:2 FTOH exposures indicating that this is a contributing factor to the decreased androgen and the increased estrogen levels. Overall, these results demonstrate that fluorochemicals present in food packaging materials and their

metabolites can affect steroidogenesis through decreased Bzrp and increased CYP19 gene expression leading to lower androgen and higher estrogen levels.

Perfluorooctane sulfonate (PFOS) affects hormone receptor activity, steroidogenesis, and expression of endocrine-related genes **in vitro** and in vivo.
Du G, Hu J, Huang H, Qin Y, Han X, Wu D, Song L, Xia Y, Wang X.
Abstract:

Perfluorooctane sulfonate (PFOS) is a widespread and persistent chemical in the environment. We investigated the endocrine-disrupting effects of PFOS using a combination of in vitro and in vivo assays. Reporter gene assays were used to detect receptor-mediated (anti-)estrogenic, (anti-)androgenic, and (anti-) thyroid hormone activities. The effect of PFOS on steroidogenesis was assessed both at hormone levels in the supernatant, and at expression levels of hormone-induced genes in the H295R cell. A zebrafish-based short-term screening method was developed to detect the effect of PFOS on endocrine function in vivo. The results indicate that PFOS can act as an estrogen receptor agonist and thyroid hormone receptor antagonist. Exposure to PFOS decreased supernatant testosterone (T), increased estradiol (E2) concentrations in H295R cell medium, and altered the expression of several genes involved in steroidogenesis. In addition, PFOS increased early thyroid development gene (hhex and pax8) expression in a concentration-dependent manner, decreased steroidogenic enzyme gene (CYP17, CYP19a, CYP19b) expression, and changed the expression pattern of estrogen receptor production genes (esr1, esr2b) after 500-μg/L PFOS treatment in zebrafish embryos. These results indicate that PFOS has the ability to act as an endocrine disruptor both in vitro and in vivo by disrupting the function of nuclear hormone receptors, interfering with steroidogenesis, and altering the expression of endocrine-related genes in zebrafish embryo

Bruttoliste in vitro

1.Decline in semen concentration and morphology in a sample of 26 609 men close to general population between 1989 and 2005 in France.
Rolland M, Le Moal J, Wagner V, Royère D, De Mouzon J.
Hum Reprod. 2012 Dec 4. [Epub ahead of print]

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In Vivo studier ved DTU - FOOD

Søgning er udført på PubMed og dækker perioden 24/9-31/12 2012

(slut. september- December 2012)

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)).

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 45 artikler (Bruttolisten)

Tre artikler er blevet udvalgt til nærmere beskrivelse. Disse 3 er valgt fordi vi mener de bidrager til ny viden om Bisphenol A og Adfærd (Ferguson et al samt Jašarević et al 2012) samt effekter hos rotter efter eksponering for en type flammehæmmer (Firemaster ® - FM 550) (Patisaul et al 2012).

Ud fra bruttolisten (se længere nede i dokumentet) er udvalgt følgende 3 artikler:

Udvalgte artikler

Accumulation and Endocrine Disrupting Effects of the Flame Retardant Mixture Firemaster(®) 550 in Rats: An Exploratory Assessment.
Patisaul HB, Roberts SC, Mabrey N, McCaffrey KA, Gear RB, Braun J, Belcher SM, Stapleton HM.
J Biochem Mol Toxicol. 2012 Nov 8. doi: 10.1002/jbt.21439. [Epub ahead of print] **valgt**

Abstract
Firemaster® 550 (FM 550), a fire-retardant mixture used in foam-based products, was recently identified as a common contaminant in household dust. The chemical structures of its principle components suggest they have endocrine disrupting activity, but nothing is known about their physiological effects at environmentally relevant exposure levels. The goal of this exploratory study was to evaluate accumulation, metabolism and endocrine disrupting effects of FM 550 in rats exposed to 100 or 1000 µg/day across gestation and lactation. FM 550 components accumulated in tissues of exposed dams and offspring and induced phenotypic hallmarks associated with metabolic syndrome in the offspring. Effects included increased serum thyroxine levels and reduced hepatic carboxylesterease activity in dams, and advanced female puberty, weight gain, male cardiac hypertrophy, and altered exploratory behaviors in offspring. Results of this study are the first to implicate FM 550 as an endocrine disruptor and an obesogen at environmentally relevant levels.

Sex and dose-dependent effects of developmental exposure to bisphenol A on anxiety and spatial learning in deer mice (Peromyscus maniculatus bairdii) offspring.

Jašarević E, Williams SA, Vandas GM, Ellersieck MR, Liao C, Kannan K, Roberts RM, Geary DC, Rosenfeld CS.

Horm Behav. 2012 Oct 7. doi:pii: S0018-506X(12)00232-2. 10.1016/j.yhbeh.2012.09.009. [Epub ahead of print]

Abstract

Bisphenol A (BPA) is a widely produced, endocrine disrupting compound that is pervasive in the environment. Data suggest that developmental exposure to BPA during sexual differentiation of the brain leads to later behavioral consequences in offspring. Outbred deer mice (Peromyscus maniculatus bairdii) are an excellent animal model for such studies as they exhibit well-defined sex- and steroid-dependent behaviors. Here, dams during gestation and lactation were fed with a phytoestrogen-free control diet, the same diet supplemented with either ethinyl estradiol (0.1ppb), or one of the three doses of BPA (50mg, 5mg, 50μg/kg feed weight). After weaning, the pups were maintained on control diet until they reached sexual maturity and then assessed for both spatial learning capabilities and anxiety-like and exploratory behaviors. Relative to controls, males exposed to the two upper but not the lowest dose of BPA demonstrated similar impairments in spatial learning, increased anxiety and reduced exploratory behaviors as ethinyl estradiol-exposed males, while females exposed to ethinyl estradiol, but not to BPA, consistently exhibited masculinized spatial abilities. We also determined whether dams maintained chronically on the upper dose of BPA contained environmentally relevant concentrations of BPA in their blood. While serum concentrations of unconjugated BPA in controls were below the minimum level of detection, those from dams on the BPA diet were comparable (5.48±2.07ng/ml) to concentrations that have been observed in humans. Together, these studies demonstrate that developmental exposure to environmentally relevant concentrations of BPA can disrupt adult behaviors in a dose- and sex-dependent manner.

Developmental treatment with bisphenol A causes few alterations on measures of postweaning activity and learning.

Ferguson SA, Law CD, Abshire JS. Neurotoxicol Teratol. 2012 Nov-Dec;34(6):598-606. doi: 10.1016/j.ntt.2012.09.006. Epub 2012 Oct 3.

Abstract

Widespread Bisphenol A (BPA) exposure necessitates increased knowledge of its potential effects for better risk assessment and regulatory guidance. Here, female Sprague-Dawley rats, reared in low exogenous estrogen environments and bred at adulthood, were gavaged on gestational days 6-21 with vehicle (VEH), 2.5 or 25.0μg/kg/day BPA, or 5.0 or 10.0μg/kg/day ethinyl estradiol (EE(2)). Offspring were orally treated on postnatal days (PNDs) 1-21 with the same dose their dam received. A naïve control group (NC) was not gavaged. Post-weaning, one offspring/sex/litter (n=11-12/sex/group) was assessed for the typical behaviors measured in developmental neurotoxicology studies. At PND 29, novelty preference was unaffected by treatment; however, relative to the VEH group, males and females of both EE(2) groups were more active. VEH males appeared somewhat hypoactive in open field assessments at PNDs 40-42 and, as a result, males of

the BPA and EE(2) groups were significantly more active. Latency to locate the Barnes maze escape box at PNDs 47-50 was increased in males and females of the 5.0μg/kg/day EE(2) group. Relative to other male groups, VEH males exhibited an increased startle response on the first trial block at PND 54 and thus, males of both BPA groups and the 10.0μg/kg/day EE(2) group exhibited a significantly decreased startle response. PNDs 43-44 motor coordination and PNDs 75-79 water maze performance were unaffected by treatment. These results indicate few consistent or dose-related effects resulting from developmental treatment with BPA at these doses. Few of these behaviors, however, were sexually dimorphic which may prove more sensitive.

Bruttoliste *in vivo*

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6.Effects of octylphenol and bisphenol A on the expression of calcium transport genes in the mouse duodenum and kidney during pregnancy.Kim S, An BS, Yang H, Jeung EB.
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Wildlife studier ved Biologisk Institut, Syddansk Universitet (SDU)

Søgningen er udført på Web of Science og dækker perioden 21/9 2012 – 10/12 2012.

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 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 og 2 omhandler begge det indledende arbejde med henblik på udviklingen af OECD test guidelines med mollusker. I OECD's "Detailed Review Paper on Mollusc Life-Cycle Toxicity Testing" fra 2010 foreslås tre arter af mollusker som kandidater til udvikling af tests med fokus på hormonforstyrrende stoffer og andre kemikalier. De tre arter er *Lymnaea stagnalis* (stor mosesnegl), *Potamopyrgus antipodarum* (ungefødende dyndsnegl) og *Crassostrea gigas* (Stillehavsøsters). Artikel 1 omhandler udviklingen af en embryo toksicitets-test med *L. stagnalis*. Artikel 2 omhandler identifikationen af østrogen-responsivt mRNA i *P. antipodarum*.

Artikel 1:

Bandow,C. and Weltje,L., 2012. Development of an embryo toxicity test with the pond snail *Lymnaea stagnalis* using the model substance tributyltin and common solvents. Science of the Total Environment 435, 90-95.

Abstract: The development of a chronic mollusc toxicity test is a current work item on the agenda of the OECD. The freshwater pond snail *Lymnaea stagnalis* is one of the candidate snail species for such a test. This paper presents a 21-day chronic toxicity test with *L. stagnalis*, focusing on embryonic development. Eggs were collected from freshly laid egg masses and exposed individually until hatching. The endpoints were hatching success and mean hatching time. Tributyltin (TBT), added as TBT-chloride, was chosen as model substance. The selected exposure concentrations ranged from 0.03 to 10 µg TBT/L (all as nominal values) and induced the full range of responses. The embryos were sensitive to TBT (the NOEC for mean hatching time was 0.03 µg TBT/L and the NOEC for hatching success was 0.1 µg TBT/L). In addition, data on maximum limit concentrations of seven common solvents, recommended in OECD aquatic toxicity testing guidelines, are presented. Among the results, further findings as average embryonic growth and mean hatching time of control groups are provided. In conclusion, the test presented here could easily be standardised and is considered useful as a potential trigger to judge if further studies, e.g. a (partial) life-cycle study with molluscs, should be conducted.

Artikel 2:

Stange,D. and Oehlmann,J., 2012. Identification of oestrogen-responsive transcripts in *Potamopyrgus antipodarum*. Journal of Molluscan Studies 78, 337-342.

Abstract: The freshwater caenogastropod *Potamopyrgus antipodarum* is a promising test species for partial lifecycle toxicity testing and also for studies of endocrine disruptors. However, endocrine signalling pathways and the genes/transcripts involved are barely identified and characterized in this snail. We therefore performed whole transcriptome sequencing (454 pyrosequencing), selected transcripts that are known to be hormone-responsive in vertebrates and determined their expression via quantitative real-time PCR after 24 h exposure to the oestrogens 17α-ethinyloestradiol (EE2) and 17β-oestradiol (E2). Examined mRNAs were: nuclear receptors [oestrogen receptor (ER), chicken ovalbumin upstream promoter-transcription factor (COUP-TF), ecdysone-induced protein (E75)], repressors of oestrogen-induced activity [prohibitin-2 (PHB-2), striatin (STRN)] and the egg yolk precursor vitellogenin (VTG). Significantly increased expression by EE2 and E2 treatment was detected for ER and VTG. E2 induced significant upregulation of E75, PHB-2 and STRN, while EE2 did not. COUP-TF expression was unaffected by EE2 or by E2. Variations between replicates were higher in snails exposed to EE2 than to E2. The identification of these oestrogen-responsive transcripts contributes to a better characterization of the endocrine system of *P. antipodarum* and provides possible biomarkers for the detection of endocrine disruption.

Artikel 3:

Jubeaux,G., Simon,R., Salvador,A., Lopes,C., Lacaze,E., Queau,H., Chaumot,A., and Geffard,O., 2012. Vitellogenin-like protein measurement in caged *Gammarus fossarum* males as a biomarker of endocrine disruptor exposure: Inconclusive experience. Aquatic Toxicology 122, 9-18.

Abstract: A vitellogenin (Vg) mass spectrometry-based assay was recently developed to actively biomonitor and assess the exposure of the amphipod *Gammarus fossarum* to endocrine-disrupting chemicals in freshwater hydrosystems. This paper focuses on the appropriate use of this biomarker, which requires good knowledge of its basal level in males and its natural variability related to intrinsic biotic and environmental abiotic factors. To obtain the lowest biomarker variability, we first studied some of these confounding

factors. We observed that the spermatogenesis stage did not have an impact on the Vg level, allowing flexibility in the choice of transplanted gammarids. In the second part of the study, males were transplanted in two clean stations for 21 days, with results indicating a spatial and temporal variability of Vg levels. These Vg changes could not be correlated to environmental factors (e.g., temperature, pH and hardness of waters). Vg induction was then assessed in 21 stations having various levels of contamination. Inductions were observed for only two of the impacted stations studied. Under reference and contaminated conditions, a high interindividual variability of Vg levels was observed in caged organisms, severely limiting the sensitivity of the biomarker and its ability to detect a significant endocrine-disruptor effect. This may be explained by unidentified environmental factors that should later be determined to improve the use of Vg as a biomarker in male *G. fossarum*. Moreover, as discussed in this paper, recent advancements regarding the pleiotropic functions of the Vg gene in some species may complicate the application of this biomarker in males of invertebrate species.

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