Center for Hormonforstyrrende Stoffer

Litteraturgennemgang for perioden januar – marts 2013

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Humane studier ved Afd. for Vækst og Reproduktion, Rigshospitalet

Søgning er udført på PubMed og dækker perioden 15. december 2012 – 16. marts 2013
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.

Denne gang handler de udvalgte artikler om BPA, om phthalater i lægemidler, om hvordan parabener associeres med ændringer i thyroideamarkører, om og PFOA og PFOS – bl.a. en fysiologisk baseret model til simulering af pharmakokinetik. God læselyst!

Udvalgte artikler

Environ Res. 2013 Jan 8. [Epub ahead of print]

Urinary concentrations of bisphenol A in an urban minority birth cohort in New York City, prenatal through age 7 years.

Hoepner LA, Whyatt RM, Just AC, Calafat AM, Perera FP, Rundle AG.
Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, 722W. 168th St, New York, NY 10032, USA; Columbia Center for Children's Environmental Health, Mailman School of Public Health, Columbia University, 722W. 168th St, New York, NY 10032, USA.

BACKGROUND: Despite growing concern over potential health effects associated with exposures to the endocrine disruptor, bisphenol A (BPA), insufficient information is available on determinants of BPA concentrations among minority populations in the US. OBJECTIVES: To describe concentrations and predictors of BPA in an inner-city longitudinal birth cohort. METHODS: We analyzed spot urines for total BPA collected during pregnancy and child ages 3, 5, and 7 years from African Americans and Dominicans (n=568) enrolled in the Columbia Center for Children's Environmental Health birth cohort and residing in Northern Manhattan and the South Bronx. Adjusting for specific gravity, generalized estimating equations were used to compare BPA concentrations across paired samples and linear regression analyses were used to determine relationships between BPA, season of sample collection, socio-demographic variables and urinary concentrations of phthalate metabolites. RESULTS: BPA was detected in ≥94% of samples. Prenatal concentrations were significantly lower than postnatal concentrations. Geometric means were higher among African Americans compared to Dominicans in prenatal (p=0.008), 5 year (p<0.001) and 7 year (p=0.017) samples. Geometric means at 5 and 7 years were higher (p=0.021, p=0.041 respectively) for children of mothers never married compared to mothers ever married at enrollment. BPA concentrations were correlated with phthalate metabolite concentrations at prenatal, 3, 5 and 7 years (p-values <0.05). Postnatal BPA concentrations were higher in samples collected during the summer. CONCLUSIONS: This study shows widespread BPA exposure in an inner-city minority population. BPA concentration variations were associated with socio-demographic characteristics and other xenobiotics.

Reprod Toxicol. 2013 Jan 18;37C:1-5. Epub ahead of print]

Medications as a potential source of exposure to phthalates among women of childbearing age.

Hernández-Díaz S, Su YC, Mitchell AA, Kelley KE, Calafat AM, Hauser R.
Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA.

OBJECTIVE: To evaluate the association between the use of medications potentially containing phthalates and urinary concentrations of specific phthalate metabolites around conception. METHODS: Women enrolled in the Environment and Reproductive Health project from 2006 to 2009 completed questionnaires about the use of medications and provided multiple urine samples before and after conception. We compared the mean urinary concentration of phthalate metabolites between users of phthalate containing medications and a matched unexposed control group. RESULTS: One woman used Asacol(®) (mesalamine), which utilizes dibutyl phthalate (DBP) as a delayed release coating material, and had a mean urinary concentration of the main DBP metabolite 200 times higher than the controls (8176µg/L vs. 37.5µg/L). The three users of stool softeners had a higher concentration of the main diethyl phthalate (DEP) metabolite (8636µg/L vs. 714.2µg/L). Neither the three additional Prilosec(®) (omeprazole) users nor one cyclobenzaprine user had higher urinary concentration than controls. CONCLUSION: Selected medications may be important sources of DBP and DEP exposures around conception.

Sci Total Environ. 2013 Feb 15;445-446:299-305. Epub 2013 Jan 20.
Relationship between urinary triclosan and paraben concentrations and serum thyroid measures in NHANES 2007-2008.
Koeppe ES, Ferguson KK, Colacino JA, Meeker JD.
Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, MI, United States.

Triclosan and parabens are broad spectrum antimicrobials used in a range of consumer products. In vitro and animal studies have suggested the potential for these compounds to disrupt thyroid function, though studies in humans have been limited. The objective of the study was to assess the relationship of urinary concentrations of triclosan and parabens with serum thyroid measures in a large, representative sample of the US population. We conducted an exploratory, cross-sectional analysis of data on urinary biomarkers of triclosan and paraben exposure and serum thyroid measures obtained from 1831 subjects (ages≥12years) as part of the 2007-2008 National Health and Nutrition Examination Survey (NHANES). We found evidence of some inverse associations between parabens and circulating thyroid hormone levels in adults, with the strongest and most consistent associations among females. We also observed a positive association between triclosan and total triiodothyonine (T3) concentrations in adolescents. These results, in accordance with the in vitro and animal literature, suggest that paraben, and potentially triclosan, exposures may be associated with altered thyroid hormone levels in humans. Further research is needed for confirmation and to determine the potential clinical and public health significance of these findings.

Environ Health Perspect. 2013 Jan 28. [Epub ahead of print]
Associations of in Utero Exposure to Perfluorinated Alkyl Acids with Human Semen Quality and Reproductive Hormones in Adult Men.
Vested A, Ramlau-Hansen CH, Olsen SF, Bonde JP, Kristensen SL, Halldorsson TI, Becher G, Haug LS, Ernst EH, Toft G.
Danish Ramazzini Center, Department of Occupational Medicine, Aarhus University Hospital, Aarhus, Denmark.

BACKGROUND: Perfluorinated alkyl acids (PFAAs) are persistent chemicals with unique water-, dirt-, and oil-repellent properties, and suspected endocrine disrupting activity. The PFAA compounds perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) are found globally in humans, and since they readily cross the placental barrier, in utero exposure may be a cause of concern. OBJECTIVES: To investigate whether in utero exposure to PFOA and PFOS affects semen quality, testicular volume, and reproductive hormone profile. METHODS: We recruited 169 male offspring (19-21 years old) of a pregnancy cohort established in Aarhus, Denmark in 1988-89, corresponding to 37.6% of the eligible sons. Each provided a semen sample that was analysed for sperm concentration, total count, motility, and morphology, and a blood sample that was used to measure reproductive hormones. As a proxy of in utero exposure, PFOA and PFOS were measured in maternal blood samples from pregnancy week 30. RESULTS: Multivariable linear regression analysis suggested that in utero exposure to PFOA was associated with lower adjusted sperm concentration (p trend=0.01) and total sperm count (p trend=0.001), and with higher adjusted levels of luteinizing hormone (LH) (p trend=0.03) and follicle stimulating hormone (FSH) (p trend=0.01). PFOS did not appear to be associated with any of the outcomes assessed, before or after adjustment. CONCLUSIONS: The results suggest that in utero exposure to PFOA may affect adult human male semen quality and reproductive hormone levels.

J Toxicol Environ Health A. 2013;76(1):25-57.
Development of PBPK models for PFOA and PFOS for human pregnancy and lactation life stages.

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Perfluoroalkyl acid carboxylates and sulfonates (PFAA) have many consumer and industrial applications. Developmental toxicity studies in animals have raised concern about potential reproductive/developmental effects of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS); however, in humans conflicting results have been reported for associations between maternal PFAA levels and these outcomes. Risk assessments and interpretation of available human data during gestation and lactation are hindered due to lack of a framework for understanding and estimating maternal, fetal, and neonatal pharmacokinetics (PK). Physiologically based pharmacokinetic (PBPK) models were developed for PFOA and PFOS for the gestation and lactation life stages in humans to understand how the physiological changes associated with development affect pharmacokinetics of these compounds in the mother, fetus, and infant. These models were derived from PBPK models for PFOA/PFOS that were previously developed for adult humans and rats during gestation and lactation and from existing human pregnancy and lactation models developed for other chemicals. The models simulated PFOA and PFOS concentrations in fetal, infant, and maternal plasma and milk, were compared to available data in humans, and also were used to estimate maternal exposure. The models reported here identified several research needs, which include (1) the identification of transporters involved in renal resorption to explain the multiyear half-lives of these compounds in humans, (2) factors affecting clearance of PFOA/PFOS during gestation and lactation, and (3) data to estimate clearance of PFOA/PFOS in infants. These models may help address concerns regarding possible adverse health effects due to PFOA/PFOS exposure in the fetus and infant and may be useful in comparing pharmacokinetics across life stages.

Bruttoliste

Bisphenol A

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Endocrine disrupters

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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 2012/12/31 to 2013/04/31 (januar 2013 og fremefter)
Efter at have fjernet genganger fra forrige litteraturopdateringslister gav litteratursøgningen, med de angivne søgekriterier, tilsammen en liste med i alt 48 artikler (Bruttolisten):

Udvalgte publikationer:

2 artikler er blevet udvalgt til nærmere beskrivelse baseret på, at de beskriver resultater, der bidrager til ny viden om hormonforstyrrende stoffer eller metoder til testning af hormonforstyrrende stoffer.
Den første artikel beskriver resultater, der bidrager med ny viden i forhold til de molekylærer signaleringsveje, der kan ligge til grund for de biologiske effekter af bisphenol A (BPA), samt udvikling af et *in vitro* system til testning af effekter på Thyreoidea hormon systemet.
Den anden artikel omhandler effekten af en blanding af 5 parabener på proliferationen af humane MCF-7 brystcancer celler ved koncentrationer fundet i humant brystvæv.

Bisphenol A interferes with thyroid specific gene expression.
Gentilcore D, Porreca I, Rizzo F, Ganbaatar E, Carchia E, Mallardo M, De Felice M, Ambrosino C.
Abstract:
Bisphenol A (BPA) is an endocrine-disrupting chemical that leads to low-dose human exposure due to its ability to leach from chemically derived products, as polycarbonate plastics and epoxy resin. In addition to its known xeno-endocrine action, BPA exerts a wide range of metabolic effects. Despite the documented BPA exposure outcomes on synthesis of thyroid hormones, there are not any data available on its actions on the thyroid follicular cells, site of synthesis of the thyroid hormones. Recently, it has been shown that several environmental pollutants, as BPA, can exert a thyroid disrupting activity. In this study, we employed in vitro and in vivo (zebrafish) models to examine the effects of BPA in regulating the expression of genes involved in the thyroid hormone synthesis and of their transcriptional regulators at BPA doses as low as 10(-9)M, a dose that is environmentally pertinent and far below the one detected in infants plasma. In both systems we could detect an altered expression of the genes involved in thyroid hormones synthesis and of thyroid specific transcriptional factors in BPA dose and time dependent manner. Our results suggest that BPA exerts a direct effect on thyroid follicular cell. We show that these cells can "sense" very low amount of BPA. Thus they, potentially, represent an ideal in vitro system to develop assays to detect BPA and other pollutants with thyroid disrupting activity at level far below the ones considered to be environmental relevant. Moreover, this report may provide new insight into the mode of BPA-induced deregulation of physiological processes as well as on the extensively debated molecular pathways underlying its biological activities.

Combinations of **parabens** at concentrations measured in human breast tissue can increase proliferation of MCF-7 human breast cancer cells.
Charles AK, Darbre PD.
Abstract:
The alkyl esters of p-hydroxybenzoic acid (parabens), which are used as preservatives in consumer products, possess oestrogenic activity and have been measured in human breast tissue. This has raised concerns for a potential involvement in the development of human breast cancer. In this paper, we have investigated the extent to which proliferation of MCF-7 human breast cancer cells can be increased by exposure to the five parabens either alone or in combination at concentrations as recently measured in 160

human breast tissue samples. Determination of no-observed-effect concentrations (NOEC), lowest-observed-effect concentrations (LOEC), EC(50) and EC(100) values for stimulation of proliferation of MCF-7 cells by five parabens revealed that 43/160 (27%) of the human breast tissue samples contained at least one paraben at a concentration ≥ LOEC and 64/160 (40%) > NOEC. Proliferation of MCF-7 cells could be increased by combining all five parabens at concentrations down to the 50(th) percentile (median) values measured in the tissues. For the 22 tissue samples taken at the site of ER + PR + primary cancers, 12 contained a sufficient concentration of one or more paraben to stimulate proliferation of MCF-7 cells. This demonstrates that parabens, either alone or in combination, are present in human breast tissue at concentrations sufficient to stimulate the proliferation of MCF-7 cells in vitro, and that functional consequences of the presence of paraben in human breast tissue should be assessed on the basis of all five parabens and not single parabens individually.

Bruttoliste in vitro

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Lukac N, Lukacova J, Pinto B, Knazicka Z, Tvrda E, Massanyi P.
J Environ Sci Health A Tox Hazard Subst Environ Eng. 2013;48(8):973-9. doi: 10.1080/10934529.2013.762744.

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Woo CS, Wan ML, Ahokas J, El-Nezami H.
Reprod Toxicol. 2013 Mar 2. doi:pii: S0890-6238(13)00052-X. 10.1016/j.reprotox.2013.02.034. [Epub ahead of print]

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Shappell NW.
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Guibert E, Prieur B, Cariou R, Courant F, Antignac JP, Pain B, Brillard JP, Froment P.
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Maletz S, Floehr T, Beier S, Klümper C, Brouwer A, Behnisch P, Higley E, Giesy JP, Hecker M, Gebhardt W, Linnemann V, Pinnekamp J, Hollert H.
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Wang H, Machtaler S, Bettinger T, Lutz AM, Luong R, Bussat P, Gambhir SS, Tranquart F, Tian L, Willmann JK.

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Aquat Toxicol. 2013 Mar 15;128-129:43-52. doi: 10.1016/j.aquatox.2012.10.016. Epub 2012 Nov 23.

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Wilson B, Babubhai PP, Sajeev MS, Jenita JL, Priyadarshini SR.
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Reven S, Homar M, Peternel L, Kristl J, Žagar E.
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In Vivo studier ved DTU - FOOD

Søgning er udført på PubMed og dækker perioden 1/1-15/3 2013
(1. januar- marts 2013)
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 49 artikler (Bruttolisten)

Fire artikler er blevet udvalgt til nærmere beskrivelse. Disse 4 er valgt fordi vi mener de bidrager til ny viden om Bisphenol A og Adfærd (Beronius et al 2013, der har undersøgt 44 DNT studier med BPA); screening af Hormonforstyrrende stoffer - Fisk vs. pattedyr (Ankley & Gray 2013). Derudover er medtaget et studie hvor der er se på phthalat eksponering og adfærd (carbone et al 2013) samt et studie om kostindtag af pesticider (Jensen BH et al 2013).

Ud fra bruttolisten (se længere nede i dokumentet) er udvalgt følgende 4 artikler til engelsk abstrakt:

Udvalgte publikationer:

The influence of study design and sex-differences on results from developmental neurotoxicity studies of **bisphenol A**, implications for toxicity testing.
Beronius A, Johansson N, Rudén C, Hanberg A.
Toxicology. 2013 Feb 25. doi:pii: S0300-483X(13)00056-5. 10.1016/j.tox.2013.02.012. [Epub ahead of print]
valgt (kun Abstract)

Abstract
Developmental neurotoxicity (DNT) of bisphenol A (BPA) has been investigated in a large number of studies. However, there are discrepancies in the results reported between the studies. The aim of this study was to identify and analyze factors that may contribute to these differences and to assess whether there are sex-differences in the sensitivity of certain endpoints or tests used in DNT-studies.
Forty-four DNT studies of BPA were identified from the open literature. Details about study design and results from each study, as well as the criteria for DNT testing according to the standardized OECD test guideline (TG) 426, were collected in a database. This enabled systematic and detailed comparisons between studies as well as to the criteria and recommendations stated in TG 426. Multivariate analyses were also used to investigate how different factors of the study design contributed to differences in study results.
The analyses showed behavioral effects were often observed for endpoints that are not required according to OECD TG 426, such as anxiety-related, social and sexual behaviors, especially at very low doses and in female offspring. On the other hand relatively few studies observed any effects on motor activity, which is commonly used in screening for neurotoxic effects in regulatory testing. However, varied and to some extent seemingly contradictory results have been reported in these studies, especially for endpoints related to motor activity and anxiety and exploration. Many studies were also poorly reported, limiting these analyses. No strong conclusions could be drawn from the multivariate analyses. A few factors of study design, such as the size of the dose and number of dose levels used and the use of litter or individual pup as statistical unit seemed to have some influence on study results. In conclusion, this analysis suggests that

DNT-studies conducted according to the standardized OECD TG 426 may overlook sensitive effects of BPA, and possibly other potential endocrine disruptors, especially in female offspring.

Cross-species conservation of endocrine pathways: A critical analysis of tier 1 fish and rat screening assays with 12 model chemicals.
Ankley GT, Gray LE.
Environ Toxicol Chem. 2013 Feb 7. doi: 10.1002/etc.2151. [Epub ahead of print]

Abstract
Many structural and functional aspects of the vertebrate hypothalamic-pituitary-gonadal (HPG) axis are known to be highly conserved, but the relative significance of this from a toxicological perspective has received comparatively little attention. High-quality data generated through development and validation of Tier 1 tests for the U.S. Environmental Protection Agency Endocrine Disruptor Screening Program (EDSP) offer a unique opportunity to compare responses of mammals versus fish to chemicals that may affect shared pathways within the HPG axis. The present study focuses on data generated with model chemicals that act (primarily) as estrogen receptor agonists (17α-ethynylestradiol, methoxychlor, bisphenol A), androgen receptor agonists (methyltestosterone, 17β-trenbolone), androgen receptor antagonists (flutamide, vinclozolin, p,p'-DDE) or inhibitors of different steroidogenic enzymes (ketoconazole, fadrozole, fenarimol, prochloraz). All 12 chemicals had been tested in the EDSP fish short-term (21-d) reproduction assay and in one or more of the four in vivo Tier 1 screens with rats (uterotrophic, Hershberger, male and female pubertal assays). There was a high concordance between the fish and rat assays with respect to identifying chemicals that impacted specific endocrine pathways of concern. Although most chemicals were detected as positive in both rat and fish assays, eliminating data from one class of vertebrate or the other would weaken the battery. For example, the effects of competitive inhibitors of steroid hormone synthesis were far more obvious in the fish assay, whereas the activity of androgen receptor antagonists was clearer in mammalian assays. The observations are significant both to the cross-species extrapolation of toxicity of HPG-active substances and the optimization of screening and testing frameworks for endocrine-disrupting chemicals.

Antiandrogenic effect of perinatal exposure to the endocrine disruptor di-(2-ethylhexyl) phthalate increases anxiety-like behavior in male rats during sexual maturation.
Carbone S, Ponzo OJ, Gobetto N, Samaniego YA, Reynoso R, Scacchi P, Moguilevsky JA, Cutrera R.
Horm Behav. 2013 Feb 8. doi:pii: S0018-506X(13)00022-6. 10.1016/j.yhbeh.2013.01.006. [Epub ahead of print]

Abstract
Di-2-ethylhexyl phthalate (DEHP) is the most widely used phthalate to convey flexibility and transparency to plastic products made of polyvinyl chloride. It has been recognized as endocrine disruptor and associated with reproductive toxic effects. We examined the effects of perinatal exposure to DEHP on anxiety-like behavior, using the Elevated Plus Maze (EPM) test, in male and female rats at different stages of sexual development. Anxiety-like behavior was expressed as a) frequency of open arm entries over the total arm entries (% FEO); b) time spent in them compared with total time the animal stayed in the EPM (% TSO) and c) time spent in closed arms (TSC). Because DEHP has anti-androgenic action we also tested control and exposed immature male rats pretreated with testosterone. We found sex differences in behavior induced by DEHP; while male rats of 45 and 60days of age showed a significant decrease in FEO and TSO percentages, as well as an increase in TSC, no changes were observed in anxiety-like behavior in perinatal DEHP exposed females at these ages of sexual maturation. In 60-day-old male rats, DEHP exposure produced a significant decrease in serum testosterone levels. Testosterone replacement was able to antagonize the adverse effects of DEHP exposure on LH, activating the negative feed-back mechanism of

this steroid on reproductive axis, as well as increasing FEO and TSO percentages to similar values observed in the control group. These findings suggest that the anti-androgenic action of this chemical could be one possible mechanism underlie anxiogenic-like behavior produced by perinatal DEHP exposure in 60-day-old male rats.

Probabilistic assessment of the cumulative dietary exposure of the population of Denmark to endocrine disrupting pesticides.

Jensen BH, Petersen A, Christiansen S, Boberg J, Axelstad M, Herrmann SS, Poulsen ME, Hass U.
Food Chem Toxicol. 2013 Jan 16;55C:113-120. doi: 10.1016/j.fct.2013.01.002. [Epub ahead of print]

Abstract
The four pesticides epoxiconazole, prochloraz, procymidone and tebuconazole, are commonly used pesticides, all suspected of acting as endocrine disrupters. In the present study, we assessed the acute cumulative dietary exposure to the women of child bearing age and the general population of Denmark to these pesticides from the intake of fruit and vegetables. The assessment was carried out using the probabilistic approach combined with the relative potency factor (RPF) approach. Residue data for prochloraz, procymidone, and tebuconazole were obtained from the Danish monitoring programme 2006-2009, while residue data for epoxiconazole were obtained from the Swedish monitoring programme carried out in the period 2007-2009. Food consumption data were obtained from the Danish nationwide dietary survey conducted in 2000-2002. Relative potency factors for the four pesticides were obtained from rat studies. Prochloraz was used as the index compound. All four pesticides increased nipple retention in male offspring, and epoxiconazole, prochloraz, and tebuconazole also increased the gestation period in pregnant rat dams. For women of childbearing age, the high-end cumulative exposure (99.9th percentile) was calculated to 9% of the Adjusted Reference Value (ARV) for the effect on nipple retention and to 1% of the ARV for the effect on increased gestation period.

Bruttoliste *in vivo*

1. The influence of study design and sex-differences on results from developmental neurotoxicity studies of **bisphenol A**, implications for toxicity testing.
Beronius A, Johansson N, Rudén C, Hanberg A.
Toxicology. 2013 Feb 25. doi:pii: S0300-483X(13)00056-5. 10.1016/j.tox.2013.02.012. [Epub ahead of print]
Valgt

2. The Effects of **Bisphenol A** on Emotional **Behavior** Depend upon the Timing of Exposure, Age and Gender in **Mice**.
Gioiosa L, Parmigiani S, Vom Saal FS, Palanza P.
Horm Behav. 2013 Mar 4. doi:pii: S0018-506X(13)00051-2. 10.1016/j.yhbeh.2013.02.016. [Epub ahead of print]

3. Bisphenol s disrupts estradiol-induced nongenomic signaling in a **rat** pituitary cell line: effects on cell functions.
Viñas R, Watson CS.
Environ Health Perspect. 2013 Mar;121(3):352-8. doi: 10.1289/ehp.1205826. Epub 2012 Dec 13.

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Wildlife studier ved Biologisk Institut, Syddansk Universitet (SDU)

Søgningen er udført på Web of Science og dækker perioden 10/12 2012 – 12/3 2013.

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 disse publikationer 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:

Ciocan,C.M., Cubero-Leon,E., Peck,M.R., Langston,W.J., Pope,N., Minier,C., and Rotchell,J.M. 2012. Intersex in *Scrobicularia plana*: Transcriptomic analysis reveals novel genes involved in endocrine disruption. Environmental Science & Technology 46, 12936-12942.

Abstract: Intersex, the appearance of female characteristics in male gonads, has been identified in a wide range of aquatic species worldwide, yet the underpinning molecular etiology remains uncharacterized. The presence of intersex has been shown to be a widespread phenomenon in bivalve, *S. plana*, populations from the southwest coast of the U.K., as well as inducible in an experimental exposure regime using endocrine disrupting compounds (EDCs). Herein, we use the suppressive subtractive hybridization approach to isolate differentially expressed transcripts in *S. plana* males exhibiting intersex. Transcripts involved in cell signaling, cell cycle control, energy production/metabolism, microtubule assembly, and sperm physiology are all highlighted as differentially expressed in intersex male clams. These provide both an insight into the molecular mechanisms of action involved in the development of intersex, as well as facilitating potential molecular-level "early warning" biomarkers of the condition.

Artikel 2:

Zheng,X.M., Zhu,Y.T., Liu,C.S., Liu,H.L., Giesy,J.P., Hecker,M., Lam,M.H.W., and Yu,H.X. 2012. Accumulation and biotransformation of BDE-47 by zebrafish larvae and teratogenicity and expression of genes along the hypothalamus-pituitary-thyroid axis. Environmental Science & Technology 46, 12943-12951.

Abstract: Accumulation and effects of BDE-47 and two analogues, 6-OH-BDE-47 and 6-MeO-BDE-47, on ontogeny and profiles of transcription of genes along the hypothalamus−pituitary−thyroid (HPT) axis of zebrafish (*Danio rerio*) embryos exposed from 4 h post fertilization (hpf) to 120 hpf were investigated. The 96 h-LC50 of the most toxic compound, based on teratogenicity, was 330 μg of 6-OH-BDE-47/L. 6-OH-BDE-47 significantly down-regulated expression of mRNA of thyroid stimulating hormone receptor (TSHR), thyroid hormone receptors (TRs, including TRα and TRβ), sodium/iodide symporter (NIS), and transthyretin (TTR) while upregulating expression of thyroglobulin (TG) and thyrotropin-releasing hormone (TRH). Spontaneous movement was affected by 1 mg of 6-OH-BDE-47/L or 5 mg of 6-MeO-BDE-47/L. BDE-47 did not alter activity of larvae at any concentration tested. 6-MeO-BDE-47 significantly up-regulated expression of mRNA of TRH, TRα, TRβ and NIS. Both 6-OH-BDE-47 and 6-MeO-BDE-47 affected the thyroid hormone pathway. BDE-47 and 6-MeO-BDE-47 were accumulated more than 6-OH-BDE-47. 6-MeO-BDE-47 was transformed into 6-OH-BDE-47, but BDE-47 was not transformed into it. In summary, the synthetic brominated flame retardant, BDE-47, did not elicit the adverse effects caused by the other two analogues and appeared to have less toxicological relevance than the two natural product analogues 6-OH- and 6-MeO-BDE-47.

Artikel 3:

Qin,F., Wang,L.H., Wang,X.Q., Liu,S.Z., Xu,P., Wang,H.P., Wu,T.T., Zhang,Y.Y., Zheng,Y., Li,M., Zhang,X., Yuan,C., Hu,G.J., and Wang,Z.Z. 2013. Bisphenol A affects gene expression of gonadotropin-releasing hormones and type I GnRH receptors in brains of adult rare minnow *Gobiocypris rarus*. Comparative Biochemistry and Physiology C-Toxicology & Pharmacology 157, 192-202.

Abstract: Recent studies support the notion that endocrine disrupting chemicals (EDCs) could affect the reproductive regulations of the neuroendocrine system. The objectives of the present study were to determine whether the weak estrogenic chemical, bisphenol A (BPA), disrupts gonadotropin-releasing hormone (GnRH) system by altering the transcription of *GnRH*s and GnRH receptor (GnRHR) genes in adult rare minnow *Gobiocypris rarus*. In the present study, the histological examination of the ovary after 35-day BPA exposure at 15 μg/L demonstrated the perturbing effects of environmentally relevant BPA on the ovarian development in *G. rarus*. In addition mRNA expression of ovarian P450 aromatase in both ovaries and testes were significantly down-regulated by 15 μg/L BPA. *GnRH2*, *GnRH3*, *GnRHR1A* and *GnRHR1B* gene were identified in *G. rarus*. The expression patterns of *GnRHs* and *GnRHR1s* were analyzed in various tissues of *G. rarus* by quantitative real-time PCR. *GnRH*s and *GnRHR1*s were all predominantly expressed in the brains. Both *GnRH3* and *GnRHR1A* were significantly upregulated in the brains of female exposed to 15 μg/L BPA for 35 days. It would suggest a potential negative feedback in the GnRH system in response to the disturbance of downstream of the brain-pituitary-gonadal axis. Collectively, the present findings suggest that the transcripts of some key genes in the neuroendocrine system can be used as critical biomarkers in endocrine disruption assays of teleost fish.

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