Center for Hormonforstyrrende Stoffer

**Litteraturgennemgang for perioden april – juni 2013**

## Indhold

## Humane studier ved Afd. for Vækst og Reproduktion, Rigshospitalet

Søgning er udført på PubMed og dækker perioden 17. marts 2013 – 13. juni 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
For søgetermen "endocrine disrupters" har vi fjernet alle de hits, der også fremkom ved de øvrige søgninger. En ekstra artikel, der ikke fremkom ved nogle af søgningerne specificeret ovenfor, er kommet på listen under overskriften "Ekstra".

Denne gang handler de udvalgte artikler bl.a. om meget høj biotilgængelighed af BPA i hunde efter sublingual administration, om phthalater i danske børn og korrelation med phthalat-niveauet i deres omgivelser, og om prenatal eksponering for DDT og forhøjet blodtryk senere i livet. God læselyst!

## Udvalgte artikler

Environ Health Perspect. 2013 Jun 12. [Epub ahead of print]

**High Bioavailability of Bisphenol A from Sublingual Exposure.**

Gayrard V, Lacroix MZ, Collet SH, Viguié C, Bousquet-Melou A, Toutain PL, Picard-Hagen N.
INRA, UMR1331, TOXALIM, Research Center in Food Toxicology; and Université de Toulouse, INPT, ENVT, EIP, UPS, Toulouse, France.

BACKGROUND: Bisphenol A (BPA) risk assessment is currently hindered by the rejection of reported higher than expected BPA plasma concentrations in humans after oral ingestion. These are deemed incompatible with the almost complete hepatic first-pass metabolism of BPA into its inactive glucurono-conjugated form, BPA glucuronide (BPAG). OBJECTIVES: Using dogs as a valid model, plasma concentrations of BPA were compared over a 24-h period after intravenous, orogastric and sublingual administrations, in order to establish the absolute bioavailability of BPA administered sublingually and to compare it with oral bioavailability. METHODS: Six dogs were sublingually administered with BPA at 0.05 mg/kg and 5mg/kg. The time course of plasma BPA concentrations was compared with that obtained in the same dogs after intravenous administration of the same BPA doses and after a 20mg/kg BPA dose administrated by orogastric gavage. RESULTS: The data indicated that the systemic bioavailability of BPA deposited sublingually was high (70-90%) and that BPA transmucosal absorption from the oral cavity led to much higher BPA internal exposure than obtained for BPA absorption from the gastro-intestinal tract. The concentration ratio of BPAG to BPA in plasma was approximately 100-fold lower following sublingual administration than after oral dosing enabling the two pathways of absorption to be easily distinguished. CONCLUSIONS: These findings demonstrate that BPA can be efficiently and very rapidly absorbed through the oral mucosa by the sublingual route. This efficient systemic entry route of BPA may lead to far higher BPA internal exposures than known for BPA absorption from the gastro-intestinal tract.

Int J Hyg Environ Health. 2013 Mar 11. [Epub ahead of print]

**Bisphenol A and other phenols in urine from Danish children and adolescents analyzed by isotope diluted TurboFlow-LC-MS/MS.**

*Frederiksen H, Aksglaede L, Sorensen K, Nielsen O, Main KM, Skakkebaek NE, Juul A, Andersson AM.*
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Bisphenol A (BPA), triclosan (TCS), benzophenone-3 (BP-3), dichoro- and phenyl phenols are industrial chemicals present in numerous consumer products such as polycarbonate plastics, preservatives in personal care products, sun screens, pesticides and fungicides, respectively, and they are all suspected endocrine disrupters. In this study the urinary excretion of eight phenols in Danish children recruited from the general population were investigated. One 24h urine and two consecutive first morning samples were collected from each of 129 healthy Danish children and adolescents (6-21 years). The concentrations of urinary phenols were analyzed by a new on-line TurboFlow-liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Most of the analyzed phenols were detectable in more than 80% of the 24h urine samples and the median concentration of BPA, TCS, BP-3, 2,4-dichorophenol and 2,5-dichorophenol (analyzed as ∑DCP), 2-phenylphenol and 4-phenylphenol were 1.37, 1.45, 1.41, 0.65, 0.36 and 0.53ng/mL, respectively. The ranges of the excreted TCS and BP-3 were wide; from below limit of detection to maximum levels of 955ng/mL and 162ng/mL, respectively, while the other phenols were excreted in a more narrow range with maximum levels below 25ng/mL. Concentrations in first morning urine were in general higher than in 24h urine and comprised 30-47% of the absolute amount excreted during 24h. The youngest children aged 6-10 years had a significantly higher urinary BPA concentration

(ng/mL) and also a relatively higher daily BPA excretion (ng/kg bw/24h) than the older children and adolescents. The opposite pattern was observed for TCS, BP-3 and ∑DCP for which urinary levels increased significantly with age. No gender difference or associations to pubertal development were observed. In conclusion, our study showed that Danish children were exposed to multiple phenols simultaneously. Small children were relatively more exposed to BPA than older children, while higher exposures to TCS, BP-3 and ∑DCP were seen among adolescents.

PLoS One. 2013 May 7;8(5):e62526. doi: 10.1371/journal.pone.0062526. Print 2013.
Exposure levels of environmental endocrine disruptors in mother-newborn pairs in china and their placental transfer characteristics.
Li LX, Chen L, Meng XZ, Chen BH, Chen SQ, Zhao Y, Zhao LF, Liang Y, Zhang YH.
Source
Key Laboratory of Public Health Safety, Ministry of Education, School of Public Health, Fudan University, Shanghai, China.

There is a growing concern about the potential health effects of exposure to various environmental chemicals during pregnancy and infancy. The placenta is expected to be an effective barrier protecting the developing embryo against some endocrine disruptors (EDs) circulating in maternal blood. The current study was designed to assess in utero exposure levels of non-persistent organic pollutants (non-POPs) and persistent organic pollutants (POPs) in Chinese newborns and potential role of placenta barrier against fetal exposure to these commonly-used environmental endocrine disruptors. A total of 230 newborn-mother pairs were enrolled during 2010-2011, 201 pairs of which were recruited from Shanghai, and the other 29 pairs came from Wenzhou. Maternal blood, cord blood, and meconium specimens were collected in the subject population from Shanghai and analyzed for non-POPs, including mono-2-ethylhexyl phthalate (MEHP), octylphenol (OP) and 4-nonylphenol (4-NP). A total of 19 polybrominated diphenyl ethers (PBDEs) congeners, which belong to POPs, were detected in maternal and cord blood specimens from the other 29 pairs. Fetal-maternal ratios (F-M ratios) and regression coefficients were presented to assess potential function of placenta on barricading the mother/fetal transfer of these EDs. Concentrations of the detected non-POPs in cord blood samples were approximately 20% lower than those in maternal blood, and regression coefficients of which were all over 0.80. In contrast, PBDEs levels in cord blood samples were significantly higher than those in maternal blood. MEHP levels in meconium were much higher than those in cord blood samples, and highly correlated. Therefore, observations demonstrated that the placental barrier slightly decreased the fetal exposure to most non-POPs, while PBDEs seemed to be totally transferred across the placenta and finally reached the fetus. For in utero exposure assessment of Di-2-ethylhexyl phthalate (DEHP), MEHP level in meconium may be a useful biomarker.

Int J Hyg Environ Health. 2013 Apr 6. pii: S1438-4639(13)00052-7. doi: 10.1016/j.ijheh.2013.03.014. [Epub ahead of print]
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.
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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.

Environ Health Perspect. 2013 May;121(5):594-9. doi: 10.1289/ehp.1205921. Epub 2013 Mar 7.

**Prenatal Exposure to the Pesticide DDT and Hypertension Diagnosed in Women before Age 50: A Longitudinal Birth Cohort Study.**

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Background: Elevated levels of the pesticide DDT (dichlorodiphenyltrichloroethane) have been positively associated with blood pressure and hypertension in studies among adults. Accumulating epidemiologic and toxicologic evidence suggests that hypertension during adulthood may also be affected by earlier life and possibly the prenatal environment.Objectives: We assessed whether prenatal exposure to the pesticide DDT increases risk of adult hypertension.Methods: We examined concentrations of DDT (p,p′- and o,p′-) and its metabolite p,p′-DDE (dichlorodiphenyldichloroethylene) in prenatal serum samples from a subset of women (n = 527) who had participated in the prospective Child Health and Development Studies birth cohort in the San Francisco Bay area while they were pregnant between 1959 and 1967. We surveyed daughters 39-47 years of age by telephone interview from 2005 to 2008 to obtain information on self-reported physician-diagnosed hypertension and use of hypertensive medication. We used multivariable regression analysis of time to hypertension based on the Cox proportional hazards model to estimate relative rates for the association between prenatal DDT exposures and hypertension treated with medication in adulthood, with adjustment for potential confounding by maternal, early-life, and adult exposures.Results: Prenatal p,p′-DDT exposure was associated with hypertension [adjusted hazard ratio (aHR) = 3.6; 95% CI: 1.8, 7.2 and aHR = 2.5; 95% CI: 1.2, 5.3 for middle and high tertiles of p,p′-DDT relative to the lowest tertile, respectively]. These associations between p,p′-DDT and hypertension were robust to adjustment for independent hypertension risk factors as well as sensitivity analyses.Conclusions: These findings suggest that the association between DDT exposure and hypertension may have its origins early in development.

## Bruttoliste

**Bisphenol A**

**1: High Bioavailability of Bisphenol A from Sublingual Exposure. Gayrard V, Lacroix MZ, Collet SH, Viguié C, Bousquet-Melou A, Toutain PL, Picard-Hagen N. Environ Health Perspect. 2013 Jun 12. [Epub ahead of print]**

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**23: Bisphenol A and other phenols in urine from Danish children and adolescents analyzed by isotope diluted TurboFlow-LC-MS/MS. Frederiksen H, Aksglaede L, Sorensen K, Nielsen O, Main KM, Skakkebaek NE, Juul A, Andersson AM. Int J Hyg Environ Health. 2013 Mar 11. doi:pii: S1438-4639(13)00016-3. 10.1016/j.ijheh.2013.01.007. [Epub ahead of print] PubMed PMID: 23491025.**

**Phthalates**

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**Parabens**

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**Per- and polyfluorinated compounds**

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**Flame retardants**

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**Tributyltin / Triclosan / Triclocarban**

1: Effects of triclocarban on the transcription of estrogen, androgen and aryl hydrocarbon receptor responsive genes in human breast cancer cells. Tarnow P, Tralau T, Hunecke D, Luch A. Toxicol In Vitro. 2013 Aug;27(5):1467-75. doi: 10.1016/j.tiv.2013.03.003. Epub 2013 Mar 21.

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**Endocrine disrupters**

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**Ekstra**

**1: Prenatal Exposure to the Pesticide DDT and Hypertension Diagnosed in Women before Age 50: A Longitudinal Birth Cohort Study. La Merrill M, Cirillo PM, Terry MB, Krigbaum NY, Flom JD, Cohn BA. Environ Health Perspect. 2013 May;121(5):594-9. doi: 10.1289/ehp.1205921. Epub 2013 Mar 7.**

## DTU Fødevareinstituttet
## 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 2013/04/01 to 2013/12/31 (April 2013 og fremefter)
Efter at have fjernet genganger fra forrige litteraturopdateringslister gav litteratursøgningen, med de angivne søgekriterier, tilsammen en liste med i alt 46 artikler (bruttolisten), som er blevet fordelt i 5 grupper: "Parabens", "Perflourinated and Polyflourinated compounds", Plastic derivatives" (BPA, Phthalates and others), "Pesticides/fungicides" og " Various EDCs, Mixtures and Other endpoints".

### Udvalgte artikler

2 artikler er blevet udvalgt til nærmere beskrivelse baseret på, at de beskriver resultater, der bidrager til ny eller yderligere viden om hormonforstyrrende stoffer. Den første artikel omhandler *in vitro* studier, der viser østrogen såvel som anti-østrogen aktivitet af triclosan og de to perfluorerede stoffer PFOS og PFOA, testet ved miljørelevante koncentrationer. Den anden artikel omhandler studier i MCF-7 celler med tributyl tin (TBTCL), der viser at TBTCL i koncentrationer under human-fysiologiske niveauer virker som en ER-α agonist og øger syntesen af aromatasen.

Comparison of **in vitro** cytotoxicity, estrogenicity and anti-estrogenicity of triclosan, **perfluorooctane** sulfonate and **perfluorooctanoic** acid.
Henry ND, Fair PA.
**Abstract**
Concern with increasing levels of emerging contaminants exists on a global scale. Three commonly observed emerging environmental contaminants: triclosan (2,4,4-trichloro-2'-hydroxydiphenyl ether), a synthetic, broad-spectrum antibacterial agent, and perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), used in stain- and water-resistant treatments, have become distributed ubiquitously across ecosystems and have been detected in wildlife and humans. MCF-7 BOS human breast cancer cells were used to investigate the potential for cytotoxicity, estrogenicity and anti-estrogenicity of these three compounds at environmentally relevant concentrations using the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt assay (MTS) and the E-SCREEN bioassay. The doses used were 0.002-200 µg ml(-1) for triclosan and 0.03-30 µg ml(-1) for PFOS and PFOA. Quantitative results from the MTS assay revealed no significant cytotoxicity at lower concentrations for any of the test compounds; however, both triclosan and PFOA were cytotoxic at the highest concentrations examined (100-200 and 30 µg ml(-1), respectively), while PFOS showed no significant cytotoxicity at any of the concentrations tested. Positive estrogenic responses ($P < 0.05$) were elicited from the E-SCREEN at all concentrations examined for triclosan and PFOA and at 30 µg ml(-1) for PFOS. Further, significant anti-estrogenic activity ($P < 0.05$) was detected for all compounds tested at all concentrations when cells were co-exposed with 10(-9) m 17-β estradiol (E(2)). The overall results demonstrated that triclosan, PFOS and PFOA have estrogenic activities and that co-exposure to contaminants and E(2) produced anti-estrogenic effects. Each of these compounds could provide a source of xenoestrogens to humans and wildlife in the environment. This article is a US Government work and is in the public domain in the USA.

Effects of low dose treatment of tributyltin on the regulation of estrogen receptor functions in MCF-7 cells.
Sharan S, Nikhil K, Roy P.
**Abstract**

Endocrine disrupting chemicals are the natural/synthetic compounds which mimic or inhibit the actions of endogenous hormones. Organotin compounds, such as tributyltin (TBT) are typical environmental contaminants and suspected endocrine-disrupting chemical. The present study evaluates the estrogenic potential of this compound in vitro in ER (+) breast adenocarcinoma, MCF-7 cell line. Our data showed that tributyltin chloride (TBTCl) had agonistic activities for estrogen receptor-α (ER-α). Its estrogenic potential was checked using cell proliferation assay, aromatase assay, transactivation assay, and protein expression analysis. Low dose treatment of TBTCl had a proliferative effect on MCF-7 cells and resulted in up-regulation of aromatase enzyme activity and enhanced estradiol production in MCF-7 cells. Immunofluorescence staining showed translocation of ER-α from cytoplasm to nucleus and increased expression of ER-α, 3β-HSD and aromatase on treatment with increasing doses of TBTCl. Further, to decipher the probable signaling pathways involved in its action, the MCF-7 cells were transfected with different pathway dependent luciferase reporter plasmids (CRE, SRE, NF-κB and AP1). A significant increase in CRE and SRE and decrease in NF-κB regulated pathway were observed ($p<0.05$). Our results thus showed that the activation of SRE by TBTCl may be due to ligand dependent ER-α activation of the MAPK pathway and increased phosphorylation of ERK. In summary, the present data suggests that low dose of tributyltin genomically and non-genomically augmented estrogen dependent signaling by targeting various pathways.

### Bruttolisten *in vitro*

**Parabens**

1. Inverse antagonist activities of **parabens** on human oestrogen-related receptor γ (ERRγ): **In vitro** and in silico studies. Zhang Z, Sun L, Hu Y, Jiao J, Hu J. Toxicol Appl Pharmacol. 2013 Jul 1;270(1):16-22. doi: 10.1016/j.taap.2013.03.030. Epub 2013 Apr 11.

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Barberis CL, Landa MF, Barberis MG, Giaj-Merlera G, Dalcero AM, Magnoli CE.
Rev Iberoam Micol. 2013 Apr 11. doi:pii: S1130-1406(13)00027-2. 10.1016/j.riam.2013.02.005. [Epub ahead of print]

3. **Parabens** enable suspension growth of MCF-10A immortalized, non-transformed human breast epithelial cells. Khanna S, Darbre PD. J Appl Toxicol. 2013 May;33(5):378-82. doi: 10.1002/jat.2753. Epub 2012 Jun 29.

**Perflourinated and Polyflourinated compounds**

1. **In vitro** PFOS exposure on immune endpoints in bottlenose dolphins (Tursiops truncatus) and mice.
Wirth JR, Peden-Adams MM, White ND, Bossart GD, Fair PA.
J Appl Toxicol. 2013 May 30. doi: 10.1002/jat.2891. [Epub ahead of print]

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Mrózek L, Coufalová L, Rárová L, Plaček L, Opatřilová R, Dohnal J, Kráľová K, Paleta O, Král V, Drašar P, Jampílek J. Steroids. 2013 May 23. doi:pii: S0039-128X(13)00122-0. 10.1016/j.steroids.2013.05.012. [Epub ahead of print]

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Contrast Media Mol Imaging. 2013 Jul-Aug;8(4):366-74. doi: 10.1002/cmmi.1532.

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O'Brien JM, Williams A, Yauk CL, Crump D, Kennedy SW. Toxicol In Vitro. 2013 Apr 16;27(6):1649-1658. doi: 10.1016/j.tiv.2013.04.003. [Epub ahead of print]

7. Genetically encoded multispectral labeling of proteins with **polyfluorophores** on a DNA backbone.
Singh V, Wang S, Kool ET. J Am Chem Soc. 2013 Apr 24;135(16):6184-91. doi: 10.1021/ja4004393. Epub 2013 Apr 16.

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Dewitte H, Geers B, Liang S, Himmelreich U, Demeester J, De Smedt SC, Lentacker I. J Control Release. 2013 Apr 6;169(1-2):141-149. doi: 10.1016/j.jconrel.2013.03.022. [Epub ahead of print]

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Wan Ibrahim WN, Tofighi R, Onishchenko N, Rebellato P, Bose R, Uhlén P, Ceccatelli S.
Toxicol Appl Pharmacol. 2013 May 15;269(1):51-60. doi: 10.1016/j.taap.2013.03.003. Epub 2013 Mar 14.

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Xu S, Wang P, Wei K, Liu F, Liang Z, Zhao X, Li A, Chen L.
Inflammation. 2013 Apr;36(2):512-20. doi: 10.1007/s10753-012-9572-0.

**12. Comparison of in vitro cytotoxicity, estrogenicity and anti-estrogenicity of triclosan, perfluorooctane sulfonate and perfluorooctanoic acid.**
**Henry ND, Fair PA. J Appl Toxicol. 2013 Apr;33(4):265-72. doi: 10.1002/jat.1736. Epub 2011 Sep 21. (Valgt)**

**Plastic derivatives (BPA, Phthalates and others)**
1. **In vitro** study on the agonistic and antagonistic activities of bisphenol-S and other bisphenol-A congeners and derivatives via nuclear receptors.
Molina-Molina JM, Amaya E, Grimaldi M, Sáenz JM, Real M, Fernández MF, Balaguer P, Olea N.
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Hulak M, Gazo I, Shaliutina A, Linhartova P.

Comp Biochem Physiol C Toxicol Pharmacol. 2013 May 13;158(2):64-71. doi: 10.1016/j.cbpc.2013.05.002. [Epub ahead of print]

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Zhang XF, Zhang LJ, Li L, Feng YN, Chen B, Ma JM, Huynh E, Shi QH, De Felici M, Shen W.
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Morton WJ, Muller CT, Goodwin N, Wilkes AR, Hall JE.
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6. Effects of di(n-butyl) and monobutyl **phthalate** on steroidogenesis pathways in the murine Leydig tumor cell line MLTC-1.
Chen X, Zhou QH, Leng L, Chen X, Sun ZR, Tang NJ.
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Cheng Z, Nie XP, Wang HS, Wong MH.
Environ Int. 2013 Jul;57-58:75-80. doi: 10.1016/j.envint.2013.04.005.

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Balbuena P, Campbell J Jr, Clewell HJ 3rd, Clewell RA.
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Choi K, Joo H, Campbell JL Jr, Andersen ME, Clewell HJ 3rd.
Toxicol In Vitro. 2013 Aug;27(5):1451-7. doi: 10.1016/j.tiv.2013.03.012. Epub 2013 Mar 29.

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Li L, Li HS, Song NN, Chen HM.
Immunopharmacol Immunotoxicol. 2013 Apr;35(2):272-81. doi: 10.3109/08923973.2013.768267.

11. Effect of temperature on the release of intentionally and non-intentionally added substances from polyethylene terephthalate (PET) bottles into water: chemical analysis and potential toxicity.
Bach C, Dauchy X, Severin I, Munoz JF, Etienne S, Chagnon MC.
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Pesticides/fungicides
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Various EDCs, Mixtures and Other endpoints
1. Paracetamol, aspirin and indomethacin display endocrine disrupting properties in the adult human testis in vitro.
Albert O, Desdoits-Lethimonier C, Lesné L, Legrand A, Guillé F, Bensalah K, Dejucq-Rainsford N, Jégou B.
Hum Reprod. 2013 May 12. [Epub ahead of print]

2. Assessment and molecular actions of endocrine-disrupting chemicals that interfere with estrogen receptor pathways.
Kerdivel G, Habauzit D, Pakdel F.
Int J Endocrinol. 2013;2013:501851. doi: 10.1155/2013/501851. Epub 2013 May 2.

3. The ovarian follicular reserve in cattle: what regulates its formation and size?
Fortune JE, Yang MY, Allen JJ, Herrick SL.
J Anim Sci. 2013 Jun 4. [Epub ahead of print]

4. Development of an in vitro thin-film solid-phase microextraction method to determine the bioavailability of xenoestrogens in soil.
Engler KN, Lemley AT.
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6. Identification of putative estrogen receptor-mediated endocrine disrupting chemicals using QSAR- and structure-based virtual screening approaches.
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Toxicol Appl Pharmacol. 2013 May 23. doi:pii: S0041-008X(13)00216-0. 10.1016/j.taap.2013.04.032. [Epub ahead of print]

7. In silico methods in the discovery of endocrine disrupting chemicals.
Vuorinen A, Odermatt A, Schuster D.
J Steroid Biochem Mol Biol. 2013 May 17. doi:pii: S0960-0760(13)00073-3. 10.1016/j.jsbmb.2013.04.009. [Epub ahead of print]

8. In vitro effects of pollutants from particulate and volatile fractions of air samples-day and night variability.
Novák J, Giesy JP, Klánová J, Hilscherová K.
Environ Sci Pollut Res Int. 2013 Apr 24. [Epub ahead of print]

9. Solution by dilution?-A review on the pollution status of the Yangtze River.

Floehr T, Xiao H, Scholz-Starke B, Wu L, Hou J, Yin D, Zhang X, Ji R, Yuan X, Ottermanns R, Roß-Nickoll M, Schäffer A, Hollert H.
Environ Sci Pollut Res Int. 2013 Apr 23. [Epub ahead of print]

10. Effects of 17α-ethinylestradiol (EE2) on reproductive endocrine status in mummichog (Fundulus heteroclitus) under differing salinity and temperature conditions.
Meina EG, Lister A, Bosker T, Servos M, Munkittrick K, Maclatchy D.
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11. Effects of endocrine disrupting chemicals on in vitro global DNA methylation and adipocyte differentiation.
Bastos Sales L, Kamstra JH, Cenijn PH, van Rijt LS, Hamers T, Legler J.
Toxicol In Vitro. 2013 Apr 18;27(6):1634-1643. doi: 10.1016/j.tiv.2013.04.005. [Epub ahead of print]

12. A multi-assay screening approach for assessment of endocrine-active contaminants in wastewater effluent samples.
Metcalfe CD, Kleywegt S, Letcher RJ, Topp E, Wagh P, Trudeau VL, Moon TW.
Sci Total Environ. 2013 Jun 1;454-455:132-40. doi: 10.1016/j.scitotenv.2013.02.074. Epub 2013 Mar 27.

**13. Effects of low dose treatment of tributyltin on the regulation of estrogen receptor functions in MCF-7 cells.**
**Sharan S, Nikhil K, Roy P.**
**Toxicol Appl Pharmacol. 2013 Jun 1;269(2):176-86. doi: 10.1016/j.taap.2013.03.009. Epub 2013 Mar 21. (Valgt)**

14. An interaction model for estimating **in vitro** estrogenic and androgenic activity of chemical mixtures.
Johnson CM, Achary M, Suri RP. Environ Sci Technol. 2013 May 7;47(9):4661-9. doi: 10.1021/es304939c. Epub 2013 Apr 8.

15. A Screen for Disruptors of the Retinol (Vitamin A) Signaling Pathway.
Chen Y, Reese DH.
Birth Defects Res B Dev Reprod Toxicol. 2013 May 21. doi: 10.1002/bdrb.21062.

16. An in vitro investigation of endocrine disrupting effects of the mycotoxin alternariol.
Frizzell C, Ndossi D, Kalayou S, Eriksen GS, Verhaegen S, Sørlie M, Elliott CT, Ropstad E, Connolly L.
Toxicol Appl Pharmacol. 2013 May 9. doi:pii: S0041-008X(13)00191-9. 10.1016/j.taap.2013.05.002.

17. Transgenic (cyp19a1b-GFP) zebrafish embryos as a tool for assessing combined effects of oestrogenic chemicals.
Petersen K, Fetter E, Kah O, Brion F, Scholz S, Tollefsen KE. Aquat Toxicol. 2013 May 9;138-139C:88-97. doi: 10.1016/j.aquatox.2013.05.001. [Epub ahead of print]

18. Cyclopenta[c]phenanthrenes - Chemistry and biological activity. Brzuzan P, Góra M, Luczyński MK, Woźny M. Chem Biol Interact. 2013 Jun 25;204(1):58-65. doi: 10.1016/j.cbi.2013.04.009. Epub 2013 Apr 27.

## In Vivo studier ved DTU - FOOD

**Søgning er udført på PubMed og dækker perioden 1/4-20/6 2013**
**(April - Juni 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) Disse er efter Miljøstyrelsens ønske blevet fordelt i grupper efter stofnavne "Parabens", "phytooestrogens", Plastic derivatives" (BPA, Phthalates and others), "Pesticides/fungicides" og " Various EDCs, Mixtures and Other endpoints".

To artikler er blevet udvalgt til nærmere beskrivelse. Disse 2 er valgt fordi vi mener de bidrager til ny viden om pubertet (KISS peptin) efter eksponering for EE2 eller en blanding af pesticider (Overgaard et al. 2013) og om blandinger af phytoøstrogener (Boberg et al 2013).

Ud fra bruttolisten (se længere nede i dokumentet) er udvalgt følgende 2 artikler til engelsk abstrakt og dansk resume og kommentarer:

### Udvalgte artikler

Title: Endocrine disrupting effects in rats perinatally exposed to a dietary relevant mixture of phytoestrogens.
Boberg J, Mandrup KR, Jacobsen PR, Isling LK, Hadrup N, Berthelsen L, Elleby A, Kiersgaard M, Vinggaard AM, Hass U, Nellemann C.
Reprod Toxicol. 2013 Jun 12. doi:pii: S0890-6238(13)00134-2. 10.1016/j.reprotox.2013.05.014.

**Abstract**
Dietary phytoestrogens may prevent certain human diseases, but endocrine activity has been reported in animal studies. Sprague-Dawley rats were exposed perinatally to a 1-, 10- or 100-fold "high human dietary intake" mixture of 12 phytoestrogens consisting of mainly the lignan secoisolarici resinol and the isoflavones genistein and daidzein. This mixture induced persistent adverse effects, as adult male mammary glands showed hypertrophic growth. A reduced anogenital distance in newborn males indicated an anti-androgenic mode of action. Testosterone levels, testis and prostate weights, and expression of selected genes in testis and prostate were unaffected. Decreased serum estradiol was seen in genistein-exposed dams. This study indicated adverse effects at high intake levels in rats, but does not provide evidence for risk of phytoestrogen-mediated endocrine disruption at normal human dietary consumption levels. Further studies are warranted to increase the knowledge upon which risk assessment on dietary phytoestrogen exposure during pregnancy and infancy is based.

The effect of perinatal exposure to ethinyl oestradiol or a mixture of endocrine disrupting pesticides on kisspeptin neurons in the rat hypothalamus.
Overgaard A, Holst K, Mandrup KR, Boberg J, Christiansen S, Jacobsen PR, Hass U, Mikkelsen JD.
Neurotoxicology. 2013 May 6;37C:154-162. doi: 10.1016/j.neuro.2013.04.012. [Epub ahead of print]

**Abstract**

Early life exposure to endocrine disruptors is considered to disturb normal development of hormone sensitive parameters and contribute to advanced puberty and reduced fecundity in humans. Kisspeptin is a positive regulator of the hypothalamic–pituitary–gonadal axis, and plays a key role in the initiation of puberty. In the adult, Kiss1 gene expression occurs in two hypothalamic nuclei, namely the anteroventral periventricular nucleus (AVPV) and the arcuate nucleus (ARC), which are differentially regulated by peripheral sex steroid hormones. In this study we determined the effects on puberty onset and Kiss1 mRNA levels in each of the two nuclei after long-term perinatal exposure of rats to ethinyl oestradiol (EE2) or to five different pesticides, individually and in a mixture. Rat dams were per orally administered with three doses of EE2 (5, 15 or 50 mg/kg/day) or with the pesticides epoxiconazole, mancozeb, prochloraz, tebuconazole, and procymidone, alone or in a mixture of the five pesticides at three different doses. Kiss1 mRNA expression was determined in the AVPV and in the ARC of the adult male and female pups in the EE2 experiment, and in the adult female pups in the pesticide experiment. We find that perinatal EE2 exposure did not affect Kiss1 mRNA expression in this study designed to model human exposure to estrogenic compounds, and we find only minor effects on puberty onset. Further, the Kiss1 system does not exhibit persistent changes and puberty onset is not affected after perinatal exposure to a pesticide mixture in this experimental setting. However, we find that the pesticide mancozeb tends to increase Kiss1 expression in the ARC, presumably through neurotoxic mechanisms rather than via classical endocrine disruption, calling for increased awareness that Kiss1 expression can be affected by environmental pollutants through multiple mechanisms.

**Bruttolisten *in vivo*** (delt ind i emner):
**Phytooestrogens**

**Title: Endocrine disrupting effects in rats perinatally exposed to a dietary relevant mixture of phytoestrogens.**
**Boberg J, Mandrup KR, Jacobsen PR, Isling LK, Hadrup N, Berthelsen L, Elleby A, Kiersgaard M, Vinggaard AM, Hass U, Nellemann C.**
**Reprod Toxicol. 2013 Jun 12. doi:pii: S0890-6238(13)00134-2. 10.1016/j.reprotox.2013.05.014. [Epub ahead of print] (valgt)**

**Plastic derivatives (BPA, Phthalates and others):**

**BPA**

Long-term bisphenol A exposure accelerates insulitis development in diabetes-prone NOD mice.
Bodin J, Bølling AK, Samuelsen M, Becher R, Løvik M, Nygaard UC.
Immunopharmacol Immunotoxicol. 2013 Jun;35(3):349-58. doi: 10.3109/08923973.2013.772195. Epub 2013 Mar 18.

Organizational effects of perinatal exposure to bisphenol-A and diethylstilbestrol on arcuate nucleus circuitry controlling food intake and energy expenditure in male and female CD-1 mice.
Mackay H, Patterson ZR, Khazall R, Patel S, Tsirlin D, Abizaid A.
Endocrinology. 2013 Apr;154(4):1465-75. doi: 10.1210/en.2012-2044. Epub 2013 Mar 14.

Perinatal exposure to bisphenol-A inhibits synaptogenesis and affects the synaptic morphological development in offspring male mice.
Xu X, Xie L, Hong X, Ruan Q, Lu H, Zhang Q, Zhang G, Liu X.
Chemosphere. 2013 May;91(8):1073-81. doi: 10.1016/j.chemosphere.2012.12.065. Epub 2013 Mar 13.

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 Apr;63(4):598-605. doi: 10.1016/j.yhbeh.2013.02.016. Epub 2013 Mar 5.

Low-dose bisphenol A and estrogen increase ventricular arrhythmias following ischemia-reperfusion in female rat hearts.
Yan S, Song W, Chen Y, Hong K, Rubinstein J, Wang HS.
Food Chem Toxicol. 2013 Jun;56:75-80. doi: 10.1016/j.fct.2013.02.011. Epub 2013 Feb 18.

Effects of low doses of bisphenol A on the metabolome of perinatally exposed CD-1 mice.
Cabaton NJ, Canlet C, Wadia PR, Tremblay-Franco M, Gautier R, Molina J, Sonnenschein C, Cravedi JP, Rubin BS, Soto AM, Zalko D.
Environ Health Perspect. 2013 May;121(5):586-93. doi: 10.1289/ehp.1205588. Epub 2013 Feb 4.

Melatonin ameliorates bisphenol A-induced DNA damage in the germ cells of adult male rats.
Wu HJ, Liu C, Duan WX, Xu SC, He MD, Chen CH, Wang Y, Zhou Z, Yu ZP, Zhang L, Chen Y.
Mutat Res. 2013 Apr 15;752(1-2):57-67. doi: 10.1016/j.mrgentox.2013.01.005. Epub 2013 Feb 9.

[Bisphenol A and hormone-dependent cancers: potential risk and mechanism].
Rochefort H.
Med Sci (Paris). 2013 May;29(5):539-44. doi: 10.1051/medsci/2013295019. Epub 2013 May 28. **French.**

Sex-specific epigenetic disruption and behavioral changes following low-dose in utero bisphenol A exposure.
Kundakovic M, Gudsnuk K, Franks B, Madrid J, Miller RL, Perera FP, Champagne FA.
Proc Natl Acad Sci U S A. 2013 Jun 11;110(24):9956-61. doi: 10.1073/pnas.1214056110. Epub 2013 May 28.

Low-Dose BPA Exposure Alters the Mesenchymal and Epithelial Transcriptomes of the Mouse Fetal Mammary Gland.
Wadia PR, Cabaton NJ, Borrero MD, Rubin BS, Sonnenschein C, Shioda T, Soto AM.
PLoS One. 2013 May 21;8(5):e63902. doi: 10.1371/journal.pone.0063902. Print 2013.

High Bioavailability of Bisphenol A from Sublingual Exposure.
Gayrard V, Lacroix MZ, Collet SH, Viguié C, Bousquet-Melou A, Toutain PL, Picard-Hagen N.
Environ Health Perspect. 2013 Jun 12. [Epub ahead of print]

Urine bisphenol-a level in relation to obesity and overweight in school-age children.
Li DK, Miao M, Zhou Z, Wu C, Shi H, Liu X, Wang S, Yuan W.
PLoS One. 2013 Jun 12;8(6):e65399. doi: 10.1371/journal.pone.0065399. Print 2013.

Hepatic DNA methylation modifications in early development of rats resulting from perinatal BPA exposure contribute to insulin resistance in adulthood.
Ma Y, Xia W, Wang DQ, Wan YJ, Xu B, Chen X, Li YY, Xu SQ.
Diabetologia. 2013 Jun 8. [Epub ahead of print]

Bisphenol a: a model endocrine disrupting chemical with a new potential mechanism of action.
Nagel SC, Bromfield JJ.
Endocrinology. 2013 Jun;154(6):1962-4. doi: 10.1210/en.2013-1370. No abstract available.

Perinatal bisphenol a exposure and adult glucose homeostasis: identifying critical windows of exposure.
Liu J, Yu P, Qian W, Li Y, Zhao J, Huan F, Wang J, Xiao H.
PLoS One. 2013 May 10;8(5):e64143. doi: 10.1371/journal.pone.0064143. Print 2013.
Prolonged exposure to a low-dose of bisphenol A increases spontaneous motor activity in adult male rats.
Nojima K, Takata T, Masuno H.
J Physiol Sci. 2013 May 8. [Epub ahead of print]

Exposure of neonatal rats to the endocrine disrupter Bisphenol A affects ontogenic expression pattern of testicular steroid receptors and their coregulators.
Salian-Mehta S, Doshi T, Vanage G.
J Appl Toxicol. 2013 Apr 26. doi: 10.1002/jat.2882. [Epub ahead of print]

Bisphenol a exposure disrupts genomic imprinting in the mouse.
Susiarjo M, Sasson I, Mesaros C, Bartolomei MS.
PLoS Genet. 2013 Apr;9(4):e1003401. doi: 10.1371/journal.pgen.1003401. Epub 2013 Apr 4.

Bisphenol a modulates calcium currents and intracellular calcium concentration in rat dorsal root ganglion neurons.
Wang W, Wang J, Wang Q, Wu W, Huan F, Xiao H.
J Membr Biol. 2013 May;246(5):391-7. doi: 10.1007/s00232-013-9545-8. Epub 2013 Apr 11.

Perinatal exposure to bisphenol A enhances contextual fear memory and affects the serotoninergic system in juvenile female mice.
Matsuda S, Matsuzawa D, Ishii D, Tomizawa H, Sajiki J, Shimizu E.
Horm Behav. 2013 May;63(5):709-16. doi: 10.1016/j.yhbeh.2013.03.016. Epub 2013 Apr 6.

Bisphenol A affects androgen receptor function via multiple mechanisms.
Teng C, Goodwin B, Shockley K, Xia M, Huang R, Norris J, Merrick BA, Jetten AM, Austin CP, Tice RR.
Chem Biol Interact. 2013 May 25;203(3):556-64. doi: 10.1016/j.cbi.2013.03.013. Epub 2013 Apr 4.

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Veiga-Lopez A, Luense LJ, Christenson LK, Padmanabhan V.
Endocrinology. 2013 May;154(5):1873-84. doi: 10.1210/en.2012-2129. Epub 2013 Mar 22.

**Phthalates and others**

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 May;63(5):692-9. doi: 10.1016/j.yhbeh.2013.01.006. Epub 2013 Feb 8.

Evidence of reproductive disruption associated with neuroendocrine changes induced by UV-B filters, Phtalates and Nonylphenol during sexual maturation in rats of both gender.
Ponzo OJ, Silvia C.
Toxicology. 2013 Jun 15. doi:pii: S0300-483X(13)00144-3. 10.1016/j.tox.2013.05.014. [Epub ahead of print]

Phthalates suppress type I interferon in human plasmacytoid dendritic cells via epigenetic regulation.
Kuo CH, Hsieh CC, Kuo HF, Huang MY, Yang SN, Chen LC, Huang SK, Hung CH.
Allergy. 2013 Jun 5. doi: 10.1111/all.12162. [Epub ahead of print]

Diethylhexyl phthalate exposure impairs follicular development and affects oocyte maturation in the mouse.
Zhang XF, Zhang LJ, Li L, Feng YN, Chen B, Ma JM, Huynh E, Shi QH, De Felici M, Shen W.
Environ Mol Mutagen. 2013 Jun;54(5):354-61. doi: 10.1002/em.21776. Epub 2013 Apr 26.

**Pesticides/fungicides**

Reproductive toxicity and thyroid effects in Sprague Dawley rats exposed to low doses of ethylenethiourea.
Maranghi F, De Angelis S, Tassinari R, Chiarotti F, Lorenzetti S, Moracci G, Marcoccia D, Gilardi E, Di Virgilio A, Eusepi A, Mantovani A, Olivieri A.
Food Chem Toxicol. 2013 Jun 14. doi:pii: S0278-6915(13)00354-2. 10.1016/j.fct.2013.05.048. [Epub ahead of print]

**The effect of perinatal exposure to ethinyl oestradiol or a mixture of endocrine disrupting pesticides on kisspeptin neurons in the rat hypothalamus.**
**Overgaard A, Holst K, Mandrup KR, Boberg J, Christiansen S, Jacobsen PR, Hass U, Mikkelsen JD. Neurotoxicology. 2013 May 6;37C:154-162. doi: 10.1016/j.neuro.2013.04.012. [Epub ahead of print](Valgt)**

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 Apr 1. doi:pii: S0378-4274(13)00143-4. 10.1016/j.toxlet.2013.03.029. [Epub ahead of print]

Exposure to 2,4-dichlorophenoxyacetic acid alters glucose metabolism in immature rat Sertoli cells.
Alves MG, Neuhaus-Oliveira A, Moreira PI, Socorro S, Oliveira PF.
Reprod Toxicol. 2013 Jul;38:81-8. doi: 10.1016/j.reprotox.2013.03.005. Epub 2013 Mar 26.

Does thyroid disruption contribute to the developmental neurotoxicity of chlorpyrifos?
Slotkin TA, Cooper EM, Stapleton HM, Seidler FJ.
Environ Toxicol Pharmacol. 2013 Apr 21;36(2):284-287. doi: 10.1016/j.etap.2013.04.003. [Epub ahead of print]

Thermoregulatory deficits in adult Long Evans rat exposed perinatally to the antithyroidal drug, propylthiouracil.
Johnstone AF, Gilbert ME, Aydin C, Grace CE, Hasegawa M, Gordon CJ.
Neurotoxicol Teratol. 2013 May 31. doi:pii: S0892-0362(13)00153-0. 10.1016/j.ntt.2013.05.005. [Epub ahead of print]

**Various EDCs, Mixtures and Other endpoints**

Assessing Effects of Environmental Chemicals on Neuroendocrine Systems: Potential Mechanisms and Functional Outcomes.
Ottinger MA, Carro T, Bohannon M, Baltos L, Marcell AM, McKernan M, Dean KM, Lavoie E, Abdelnabi M.
Gen Comp Endocrinol. 2013 Jun 14. doi:pii: S0016-6480(13)00269-4. 10.1016/j.ygcen.2013.06.004. [Epub ahead of print]

Endocrine-Disrupting Chemicals: Some Actions of POPs on Female Reproduction.
Gregoraszczuk EL, Ptak A.

Int J Endocrinol. 2013;2013:828532. doi: 10.1155/2013/828532. Epub 2013 May 23.

Changes in Mouse Uterine Transcriptome in Estrus and Proestrus.
Stanley Yip K, Suvorov A, Connerney J, Lodato NJ, Waxman DJ.
Biol Reprod. 2013 Jun 5. [Epub ahead of print]

Assessment and molecular actions of endocrine-disrupting chemicals that interfere with estrogen receptor pathways.
Kerdivel G, Habauzit D, Pakdel F.
Int J Endocrinol. 2013;2013:501851. doi: 10.1155/2013/501851. Epub 2013 May 2.

A comparative survey of chemistry-driven in silico methods to identify hazardous substances under REACH.
Nendza M, Gabbert S, Kühne R, Lombardo A, Roncaglioni A, Benfenati E, Benigni R, Bossa C, Strempel S, Scheringer M, Fernández A, Rallo R, Giralt F, Dimitrov S, Mekenyan O, Bringezu F, Schüürmann G.
Regul Toxicol Pharmacol. 2013 May 21;66(3):301-314. doi: 10.1016/j.yrtph.2013.05.007. [Epub ahead of print]

Does Cancer Start in the Womb? Altered Mammary Gland Development and Predisposition to Breast Cancer due to in Utero Exposure to Endocrine Disruptors.
Soto AM, Brisken C, Schaeberle C, Sonnenschein C.
J Mammary Gland Biol Neoplasia. 2013 May 24. [Epub ahead of print]

In silico methods in the discovery of endocrine disrupting chemicals.
Vuorinen A, Odermatt A, Schuster D.
J Steroid Biochem Mol Biol. 2013 May 17. doi:pii: S0960-0760(13)00073-3. 10.1016/j.jsbmb.2013.04.009. [Epub ahead of print]

Towards a humanized PPARγ reporter system for in vivo screening of obesogens.
Punzon I, Latapie V, Le Mével S, Hagneau A, Jolivet P, Palmier K, Fini JB, Demeneix BA.
Mol Cell Endocrinol. 2013 Jul 15;374(1-2):1-9. doi: 10.1016/j.mce.2013.04.004. Epub 2013 Apr 16.

Histologic Features of Prepubertal and Pubertal Reproductive Development in Female Sprague-Dawley Rats.
Picut CA, Remick AK, Asakawa MG, Simons ML, Parker GA.
Toxicol Pathol. 2013 Apr 18. [Epub ahead of print]

INSL3 as a Biomarker of Leydig Cell Functionality.
Ivell R, Wade JD, Anand-Ivell R.
Biol Reprod. 2013 Jun 13;88(6):147. doi: 10.1095/biolreprod.113.108969. Print 2013.

Disruption of reproductive aging in female and male rats by gestational exposure to estrogenic endocrine disruptors.
Walker DM, Kermath BA, Woller MJ, Gore AC.
Endocrinology. 2013 Jun;154(6):2129-43. doi: 10.1210/en.2012-2123. Epub 2013 Apr 16.

Sensitization of restraint-induced corticosterone secretion after chronic restraint in rats: Involvement of 5-HT7 receptors.
García-Iglesias BB, Mendoza-Garrido ME, Gutiérrez-Ospina G, Rangel-Barajas C, Noyola-Díaz M, Terrón JA.
Neuropharmacology. 2013 Aug;71:216-27. doi: 10.1016/j.neuropharm.2013.03.013. Epub 2013 Mar 28.

An interaction model for estimating in vitro estrogenic and androgenic activity of chemical mixtures.
Johnson CM, Achary M, Suri RP.
Environ Sci Technol. 2013 May 7;47(9):4661-9. doi: 10.1021/es304939c. Epub 2013 Apr 8.

Endocrine-disrupting chemicals and male reproductive health.
Knez J.
Reprod Biomed Online. 2013 May;26(5):440-8. doi: 10.1016/j.rbmo.2013.02.005. Epub 2013 Feb 18.

Mechanism-based testing strategy using in vitro approaches for identification of thyroid hormone disrupting chemicals.
Murk AJ, Rijntjes E, Blaauboer BJ, Clewell R, Crofton KM, Dingemans MM, Furlow JD, Kavlock R, Köhrle J, Opitz R, Traas T, Visser TJ, Xia M, Gutleb AC.
Toxicol In Vitro. 2013 Jun;27(4):1320-46. doi: 10.1016/j.tiv.2013.02.012. Epub 2013 Feb 27.

Nanotoxicity: a growing need for study in the endocrine system.
Lu X, Liu Y, Kong X, Lobie PE, Chen C, Zhu T.
Small. 2013 May 27;9(9-10):1654-71. doi: 10.1002/smll.201201517. Epub 2013 Feb 11.

### Wildlife studier ved Biologisk Institut, Syddansk Universitet (SDU)

Søgningen er udført på Web of Science og dækker perioden 13/3 2013 - 24/6 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 fem artikler til medtagelse af abstract og yderligere kommentarer. Artikel 4 og 5 omhandler begge gestagener og kommenteres samlet. 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:

**Triclosan interferes with the thyroid axis in the zebrafish (Danio rerio).**
Pinto, P. I. S.; Guerreiro, E. M.; and Power, D. M. 2013. Toxicology Research 2, 60-69.

Abstract: This study focuses on the effects of triclosan (TCS), a ubiquitous antimicrobial agent and aquatic contaminant, on the thyroid of adult zebrafish. The morphology of the thyroid was modified after short term (21 days) dietary exposure of zebrafish to TCS (100 µg g−1 fish per day). Hyperplasia of the thyroid tissue was observed in TCS treated zebrafish, and they had significantly ($p < 0.01$) more follicles, significantly ($p < 0.05$) bigger follicles and a significant reduction ($p < 0.001$) in thyrocyte height relative to the control fish, which is indicative of thyroid inactivation. Analysis of thyroid hormone synthesis associated transcripts in whole zebrafish heads revealed that TCS exposure caused a significant up-regulation of the sodium–iodide symporter (NIS) and thyroid-stimulating hormone (TSH), but did not modify thyroglobulin, thyroid peroxidase or cathepsin Ba. The increase in TSH and NIS transcription coupled to histology indicative of thyroid inactivation suggests that a reduction in circulating thyroid hormones probably occurred, although the exact mechanisms by which TCS reduces thyroid gland activity remains to be

established. To our knowledge this is the first study demonstrating that TCS acts on the fish thyroid axis. The importance of the thyroid in basic physiological processes such as metabolism and nervous tissue development means that interference with this axis may have profound consequences for organism health and survival, and the results of the present study highlight the need for more detailed studies of the effects of TCS, which accumulates in sediments and organisms in aquatic environments.

Artikel 2:

**Exposure of zebrafish embryos/larvae to TDCPP alters concentrations of thyroid hormones and transcriptions of genes involved in the hypothalamic-pituitary-thyroid axis.**
Wang, Q. W.; Liang, K.; Liu, J. F.; Yang, L. H.; Guo, Y. Y.; Liu, C. S.; and Zhou, B. S. 2013. Aquatic Toxicology 126, 207-213.

Abstract: Tris(1,3-dichloro-2-propyl) phosphate (TDCPP) has been frequently detected in the environment and in various biota, including fish, and has been implicated in disruption of the thyroid endocrine system. In the present study, zebrafish (Danio rerio) embryos were exposed to different concentrations of TDCPP (10, 50, 100, 300 and 600 μg/L) from 2 h post-fertilization (hpf) to 144 hpf. Developmental endpoints, and whole-body concentrations of thyroid hormones and transcriptional profiles of genes involved in the hypothalamic–pituitary–thyroid (HPT) axis were examined. Exposure to TDCPP caused a dose-dependent developmental toxicity, including decreased body weight, reduced hatching, survival and heartbeat rates, and increased malformation (spinal curvature). Treatment with the positive control chemical 3,3',5-triiodo-l-thyronine (T3) significantly decreased whole-body thyroxin (T4) concentrations, increased whole-body T3 concentrations, and upregulated mRNA expression involved in the HPT axis as a compensatory mechanism. These results suggested that the HPT axis in 144-hpf zebrafish larvae was responsive to chemical exposure and could be used to evaluate the effects of chemicals on the thyroid endocrine system. TDCPP exposure significantly decreased whole-body T4 concentrations and increased whole-body T3 concentrations, indicating thyroid endocrine disruption. The upregulation of genes related to thyroid hormone metabolism (dio1 and ugt1ab) might be responsible for decreased T4
concentrations. Treatment with TDCPP also significantly increased transcription of genes involved in thyroid hormone synthesis (tshβ, slc5a5 and tg) and thyroid development (hhex, nkx2.1 and pax8) as a compensatory mechanism for decreased T4 concentrations. Taken together, these results suggest that TDCPP alters the transcription of genes involved in the HPT axis and changes whole-body concentrations of thyroid hormones in zebrafish embryos/larvae, thus causing an endocrine disruption of the thyroid system.

Artikel 3:

**Propiconazole Inhibits Steroidogenesis and Reproduction in the Fathead Minnow (Pimephales promelas).**
Skolness, S. Y.; Blanksma, C. A.; Cavallin, J. E.; Churchill, J. J.; Durhan, E. J.; Jensen, K. M.; Johnson, R. D.; Kahl, M. D.; Makynen, E. A.; Villeneuve, D. L.; and Ankley, G. T. 2013. Toxicological Sciences 132, 284-297.

Abstract: Conazoles are designed to inhibit cytochrome P450 (CYP) 14α-demethylase, an enzyme key to fungal cell wall formation. In vertebrates, conazoles may inhibit other CYPs, potentially
disrupting processes like sex steroid synthesis. Propiconazole is a current-use pesticide that is among the first chemicals being tested in the U.S. Environmental Protection Agency endocrine disruptor screening program. Fathead minnows (*Pimephales promelas*) were exposed to 0, 5, 50, 500, or 1000 μg propiconazole/l in a 21-day study that evaluated apical reproductive endpoints (fecundity, fertility, hatch); measures of endocrine function and steroid synthesis, such as cholesterol, vitellogenin (VTG), and sex

steroid (testosterone [T], 17β-estradiol [E2]) concentrations in the plasma; and changes in gonadal expression of steroidogenic genes. Plasma
E2 and VTG concentrations in females were reduced by exposure to propiconazole, and egg production was decreased in the 500 and 1000 µg/l treatment groups. These *in vivo* effects coincided with inhibition of E2 synthesis by ovary explants exposed to propiconazole *in vitro*. We also observed a compensatory response in females exposed to propiconazole, manifested as increased gonad weight and upregulation of genes coding for key steriodogenic proteins, including CYP19 (aromatase), CYP17 (hydroxylase/lyase), CYP11A (cholesterol side-chain-cleavage), and steroidogenic acute regulatory protein. Other than an increase in relative testis weight, effects on endocrine function in males were less pronounced than in females. This study provides important data relative to the potential endocrine activity of propiconazole in fish and, more generally, to the further delineation of pathways for the reproductive effects of steroid synthesis inhibitors in fish.

Artikel 4:

**Several Synthetic Progestins with Different Potencies Adversely Affect Reproduction of Fish.**
Runnalls, T. J.; Beresford, N.; Losty, E.; Scott, A. P.; and Sumpter, J. P. 2013. Environmental Science & Technology 47, 2077-2084.

Abstract: Synthetic progestins are widely used as a component in both contraceptives and in hormone replacement therapy (HRT), both on their own and in combination with EE2. Their presence in the environment is now established in wastewater effluent and river water and this has led to concerns regarding their potential effects on aquatic organisms living in these waters. We
carried out in vivo experiments to determine the potencies of four different synthetic progestins on the reproductive capabilities of the fathead minnow (Pimephales promelas). We then performed a series of in vitro assays to try and determine the reason for the effects seen in the in vivo experiments. In the first experiment, fathead minnow exposed to a single concentration of 100 ng/L of either Levonorgestrel or Gestodene stopped spawning almost completely. The same nominal concentration of Desogestrel and Drospirenone did not affect reproduction (21 d NOECs of 100 ng/L). The second experiment investigated two progestins of different potency: Gestodene at 1, 10, and 100 ng/L and Desogestrel at 100 ng/L, 1 µg/L, and 10 µg/L. Gestodene concentrations as low as 1 ng/L had significant effects on reproduction over 21 d, whereas concentrations of Desogestrel at or above 1 µg/L were required to significantly reduce egg production. The synthetic progestins also masculinized the female fish in a concentration-dependent manner. Results from yeast-based in vitro assays demonstrated that the progestins are all strongly androgenic, thereby explaining the masculinization effects. The results strongly suggest that synthetic progestins merit serious consideration as environmental pollutants.

Artikel 5:

**The Synthetic Progestin Levonorgestrel Is a Potent Androgen in the Three-Spined Stickleback (Gasterosteus aculeatus).**
Svensson, J.; Fick, J.; Brandt, I.; and Brunstrom, B. 2013. Environmental Science & Technology 47, 2043-2051.

Abstract: The use of progestins has resulted in contamination of aquatic environments and some progestins have in experimental studies been shown to impair reproduction in fish and amphibians at low ng $L^{-1}$ concentrations. The mechanisms underlying their reproductive toxicity are largely unknown. Some progestins, such as levonorgestrel (LNG), exert androgenic effects in mammals by activating the androgen receptor (AR). Male three-spined stickleback (Gasterosteus aculeatus) kidneys produce spiggin, a gluelike

glycoprotein used in nest building, and its production is directly governed by androgens. Spiggin is normally absent in females but its production in female kidneys can be induced by AR agonists. Spiggin serves as the best known biomarker for androgens in fish. We exposed adult female sticklebacks to LNG at 5.5, 40, and 358 ng $L^{-1}$ for 21 days. Androgenic effects were found at LNG concentrations ≥40 ng $L^{-1}$ including induction of spiggin transcription, kidney hypertrophy, and suppressed liver vitellogenin transcription. These are the first in vivo quantitative data showing that LNG is a potent androgen in fish supporting the contention that androgenic effects of certain progestins contribute to their reproductive toxicity.

## Bruttoliste

*Bisphenol A, alkylphenoler, parabener og PAH*

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Angioni, S. A.; Scortichini, G.; Diletti, G.; Perletta, F.; Ceci, R.; and Ferri, N. 2013. Veterinaria Italiana 49, 69-77.

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**Wang, Q. W.; Liang, K.; Liu, J. F.; Yang, L. H.; Guo, Y. Y.; Liu, C. S.; and Zhou, B. S. 2013. Aquatic Toxicology 126, 207-213.**

*Triclosan*

**Triclosan interferes with the thyroid axis in the zebrafish (Danio rerio).**
**Pinto, P. I. S.; Guerreiro, E. M.; and Power, D. M. 2013. Toxicology Research 2, 60-69.**

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*Lægemidler og syntetiske steroider*

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Runnalls, T. J.; Beresford, N.; Losty, E.; Scott, A. P.; and Sumpter, J. P. 2013. Environmental Science & Technology 47, 2077-2084.**

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*Diverse hormonforstyrrende stoffer*

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*Eksponering i naturen (ferskvand, saltvand, sediment, spildevand)*

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*Testmetoder og -organismer*

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