Center for Hormonforstyrrende Stoffer

Litteraturgennemgang for perioden juli – september 2013

Indhold

Humane studier ved Afd. for Vækst og Reproduktion, Rigshospitalet

Søgning er udført på PubMed og dækker perioden 14. juni 2013 – 18. september 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, hvorvidt rapporterede BPA-niveauer i plasma er realistiske, om hvordan phthalater påvirker adrenale androgener og pubertetsudvikling hos drenge og piger og om hormonforstyrrende stoffers effekt på mandlig pubertetsudvikling generelt. God læselyst!

Udvalgte artikler

Are typical human serum BPA concentrations measureable and sufficient to be estrogenic in the general population? Teeguarden J, Hanson-Drury S, Fisher JW, Doerge DR. Pacific Norwest National Laboratory, Richland, WA 99352, United States. Electronic address: jt@pnl.gov. Food Chem Toxicol. 2013 Aug 17. pii: S0278-6915(13)00536-X. doi: 10.1016/j.fct.2013.08.001. [Epub ahead of print]

Mammalian estrogen receptors modulate many physiological processes. Chemicals with structural features similar to estrogens can interact with estrogen receptors to produce biological effects similar to those caused by endogenous estrogens in the body. Bisphenol A (BPA) is a structural analogue of estrogen that binds to estrogen receptors. Exposure to BPA in humans is virtually ubiquitous in industrialized societies, but BPA is rapidly detoxified by metabolism and does not accumulate in the body. Whether or not serum concentrations of BPA in humans are sufficiently high to disrupt normal estrogen-related biology is the subject of intense political and scientific debate. Here we show a convergence of robust methods for measuring or calculating serum concentrations of BPA in humans from 93 published studies of more than 30,000 individuals in 19 countries across all life stages. Typical serum BPA concentrations are orders of magnitude lower than levels measurable by modern analytical methods and below concentrations required to occupy more than 0.0009% of Type II Estrogen Binding Sites, GPR30, ERα or ERβ receptors. Occupancies would be higher, but ≤0.04%, for the highest affinity receptor, ERRγ. Our results show limited or no potential for estrogenicity in humans, and question reports of measurable BPA in human serum.

Urinary phthalates from 168 girls and boys measured twice a year during a 5-year period: associations with adrenal androgen levels and puberty. Mouritsen A, Frederiksen H, Sørensen K, Aksglaede L, Hagen C, Skakkebaek NE, Main KM, Andersson AM, Juul A. cand med, Rigshospitalet, Growth and Reproduction, Blegdamsvej 9, 2100 Copenhagen, Denmark. annette.mouritsen@rh.regionh.dk. J Clin Endocrinol Metab. 2013 Sep;98(9):3755-64. doi: 10.1210/jc.2013-1284. Epub 2013 Jul 3.

Background: Little is known about the possible deleterious effects of phthalate exposure on endogenous sex steroid levels in children. Objective: Our objective was to investigate whether urinary phthalate metabolite levels are associated with circulating adrenal androgen levels and age at puberty. Methods: This was a longitudinal study of 168 healthy children (84 girls) examined every 6 months for 5 years. Serum levels of dehydroepiandrostenedione sulfate (DHEAS), Δ4-androstenedione, testosterone, and urinary morning excretion of 14 phthalate metabolites, corresponding to 7 different phthalate diesters were determined. A variation in urinary excretion of phthalates was evident in each child, which made a mean of repetitive samples more representative for long-term excretion than a single determination. Results: We found that girls with excretion of monobutyl phthalate isomers (MBP) and di(2-ethylhexyl) phthalate metabolites above the geometric group mean (795 and 730 ng/kg, respectively) had lower levels of DHEAS and Δ4-androstenedione, although statistically significant only at 13 years of age. In boys, we found that excretion of monobenzylphthalate above the geometric group mean (346 ng/kg) was associated with lower levels of DHEAS at 11 years of age but higher levels of testosterone at 13 years of age. The same trend was observed for MBP excretion, albeit not statistically significant. A lower age at pubarche was observed in boys with excretion of MBP above the geometric group mean (11.0 vs 12.3 years, P = 0.005). Conclusion: Our data indicate that exposure to dibutyl phthalate isomers (DBP) (in girls) and butylbenzyl phthalate (in boys) are negatively associated with adrenal androgen levels and in boys positively associated with testosterone level at 13 years of age. Highexposure to DBP was associated with earlier age at pubarche in boys. In girls, no associations between phthalate exposure and age at pubertal milestones were observed.

Serum concentrations of perfluorinated alkyl acids and their associations with diet and personal characteristics among Swedish adults. Bjermo, H., Darnerud, P.O., Pearson, M., Barbieri, H.E., Lindroos, A.K., Nälsén, C., Lindh, C.H., Jönsson, B.A.G., Glynn, A. Department of Risk and Benefit Assessment, National Food Agency, Uppsala, Sweden and Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden. Mol. Nutr. Food Res. 2013, 00, 1–10. DOI 10.1002/mnfr.201200845.

Scope: In this study, food is suggested as a major source of human exposure to perfluorinated alkyl acids (PFAA). We investigated relations between serum levels of PFAA in adults and diet/lifestyle factors nationwide in Sweden. Methods and results: In 2010–2011, adults (18–80 years, N = 270) recorded their diet for 4 days and answered a food frequency questionnaire. PFAA were measured in blood serum as well as v-3 fatty acids in plasma phospholipids as a biomarker for fish consumption. Higher levels of PFAA were associated with male sex, increased age, and higher education. Women reporting full breastfeeding for ≥12 months had 32–44% lower levels of perfluorooctane sulfonate, perfluorooctanoic acid, and perfluorohexane sulfonate than women who never nursed their infants full-time. Serum perfluorooctane sulfonate, perfluorononanoic acid, perfluorodecanoic acid, and perfluoroundecanoic acid were positively related to n-3 fatty acids in plasma (partial $r = 0.19–0.34$, $p \leq 0.05$). Conclusion: The relatively strong correlations between biomarkers of fish consumption and certain PFAA suggest that PFAA exposure should be taken into account in health risk and benefit assessment of fish consumption. Breastfeeding appears to be a major source of elimination of certain PFAA among women, and consequently PFAA exposure of nursed infants could be significant.

Male pubertal development: are endocrine-disrupting compounds shifting the norms? Zawatski W, Lee MM. Department of Pediatrics, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, Massachusetts 01655, USA. J Endocrinol. 2013 Jul 11;218(2):R1-12. doi: 10.1530/JOE-12-0449. Print 2013.

Endocrine-disrupting compounds (EDCs) are synthetic or natural compounds that interfere with endogenous endocrine action. The frequent use of chemicals with endocrine active properties in household products and contamination of soil, water, and food sources by persistent chemical pollutants result in ubiquitous exposures. Wildlife observations and animal toxicological studies reveal adverse effects of EDCs on reproductive health. In humans, a growing number of epidemiological studies report an association with altered pubertal timing and progression. While these data are primarily reported in females, this review will focus on the small number of studies performed in males that report an association of polychlorinated biphenyls with earlier sexual maturity rating and confirm subtle effects of lead, dioxins, and endosulfan on delaying pubertal onset and progression in boys. Recent studies have also demonstrated that EDC exposure may affect pubertal testosterone production without having a noticeable effect on sexual maturity rating. A limitation to understand the effects of EDCs in humans is the potential for confounding due to the long temporal lag from early-life exposures to adult outcomes. The complex interplay of multiple environmental exposures over time also complicates the interpretation ofhuman studies. These studies have identified critical windows of vulnerability during development when exposures to EDCs alter critical pathways and affect postnatal reproductive health. Contemporaneous exposures can also disrupt the hypothalamic-pituitary-gonadal axis. This paper will review the normal process of puberty in males and summarize human data that suggest potential perturbations in pubertal onset and tempo with early-lifeexposures to EDCs.

Bruttoliste

Bisphenol A

1: Predictors of urinary bisphenol A and phthalate metabolite concentrations in Mexican children. Lewis RC, Meeker JD, Peterson KE, Lee JM, Pace GG, Cantoral A, Téllez-Rojo MM. Chemosphere. 2013 Sep 13. doi:pii: S0045-6535(13)01154-5. 10.1016/j.chemosphere.2013.08.038. [Epub ahead of print] PubMed PMID: 24041567.

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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: Prenatal Exposure to Environmental Phenols: Concentrations in Amniotic Fluid and Variability in Urinary Concentrations during Pregnancy. Philippat C, Wolff MS, Calafat AM, Ye X, Bausell R, Meadows M, Stone J, Slama R, Engel SM. Environ Health Perspect. 2013 Aug 13. [Epub ahead of print] PubMed PMID: 23942273.

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Endocrine disrupters

1: Human infertility: are endocrine disruptors to blame? Pinto AM, Carvalho D. Endocr Connect. 2013 Aug 28. [Epub ahead of print] PubMed PMID: 23985363.

2: Relationship between blood cadmium, lead, and serum thyroid measures in US adults - the National Health and Nutrition Examination Survey (NHANES) 2007-2010. Luo J, Hendryx M. Int J Environ Health Res. 2013 Jun 19. [Epub ahead of print] PubMed PMID: 23782348.

3: Male pubertal development: are endocrine-disrupting compounds shifting the norms? Zawatski W, Lee MM. J Endocrinol. 2013 Jul 11;218(2):R1-12. doi: 10.1530/JOE-12-0449. Print 2013. Review. PubMed PMID: 23709001.

CEHOS Litteratur update *in vitro* og *in vivo,* DTU Fødevareinstituttet

In vitro studier

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 2013/06/01 to 2013/12/31 (Juni 2013 og fremefter)
Efter at have fjernet gengangere fra forrige litteraturopdateringslister gav litteratursøgningen, med de angivne søgekriterier, tilsammen en liste med i alt 47 artikler, plus 3 artikler, der ikke blev fanget af de valgte søgekriterier. De i alt 50 artikler 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 publikationer:

2 artikler er blevet udvalgt til nærmere beskrivelse baseret på, at de bidrager til ny eller yderligere viden om hormonforstyrrende stoffer.

Den første artikel omhandler *in vitro* studier, der viser både østrogen og anti-androgen aktivitet af et udvalg af perfluorerede stoffer (Kjeldsen et al 2013).
Den anden artikel omhandler et studie, der ved brug af udvalgte *in vitro* data, har undersøgt forskellige fordele og ulemper ved nogle af de modeller, der anvendes til at teste for eller forudsige om, der er såkaldte cocktaileffekter (Hadrup et al 2013).

Perfluorinated compounds affect the function of sex hormone receptors.
Kjeldsen LS, Bonefeld-Jørgensen EC.
Abstract
Perfluorinated compounds (PFCs) are a large group of chemicals used in different industrial and commercial applications. Studies have suggested the potential of some PFCs to disrupt endocrine homeostasis, increasing the risk of adverse health effects. This study aimed to elucidate mechanisms behind PFC interference with steroid hormone receptor functions. Seven PFCs [perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorononanoate (PFNA), perfluorodecanoate (PFDA), perfluoroundecanoate (PFUnA), and perfluorododecanoate (PFDoA)] were analyzed in vitro for their potential to affect estrogen receptor (ER) and androgen receptor (AR) transactivity as well as aromatase enzyme activity. The PFCs were assessed as single compounds and in an equimolar mixture. PFHxS, PFOS and PFOA significantly induced the ER transactivity, whereas PFHxS, PFOS, PFOA, PFNA and PFDA significantly antagonized the AR activity in a concentration-dependent manner. Moreover, PFDA weakly decreased the aromatase activity at a high test concentration. A mixture effect, more than additive was observed on AR function. We conclude that five of the seven PFCs possess the potential in vitro to interfere with the function of the ER and/or the AR. The observed mixture effect emphasizes the importance of considering the combined action of PFCs in future studies to assess related health risks.

Concentration addition, independent action and generalized concentration addition models for mixture effect prediction of sex hormone synthesis in vitro.
Hadrup N, Taxvig C, Pedersen M, Nellemann C, Hass U, Vinggaard AM.
Abstract

Humans are concomitantly exposed to numerous chemicals. An infinite number of combinations and doses thereof can be imagined. For toxicological risk assessment the mathematical prediction of mixture effects, using knowledge on single chemicals, is therefore desirable. We investigated pros and cons of the concentration addition (CA), independent action (IA) and generalized concentration addition (GCA) models. First we measured effects of single chemicals and mixtures thereof on steroid synthesis in H295R cells. Then single chemical data were applied to the models; predictions of mixture effects were calculated and compared to the experimental mixture data. Mixture 1 contained environmental chemicals adjusted in ratio according to human exposure levels. Mixture 2 was a potency-adjusted mixture containing five pesticides. Prediction of testosterone effects coincided with the experimental Mixture 1 data. In contrast, antagonism was observed for effects of Mixture 2 on this hormone. The mixtures contained chemicals exerting only limited maximal effects. This hampered prediction by the CA and IA models, whereas the GCA model could be used to predict a full dose response curve. Regarding effects on progesterone and estradiol, some chemicals were having stimulatory effects whereas others had inhibitory effects. The three models were not applicable in this situation and no predictions could be performed. Finally, the expected contributions of single chemicals to the mixture effects were calculated. Prochloraz was the predominant but not sole driver of the mixtures, suggesting that one chemical alone was not responsible for the mixture effects. In conclusion, the GCA model seemed to be superior to the CA and IA models for the prediction of testosterone effects. A situation with chemicals exerting opposing effects, for which the models could not be applied, was identified. In addition, the data indicate that in non-potency adjusted mixtures the effects cannot always be accounted for by single chemicals.

Bruttoliste *in vitro*

Parabens

1.Dermal absorption and hydrolysis of methylparaben in different vehicles through intact and damaged skin: Using a pig-ear model **in vitro**.
Pažoureková S, Hojerová J, Klimová Z, Lucová M.
Food Chem Toxicol. 2013 Sep;59:754-65. doi: 10.1016/j.fct.2013.07.025. Epub 2013 Jul 17.

Perflourinated and Polyflourinated compounds

1.**Perfluorooctanoate** Suppresses Spheroid Attachment on Endometrial Epithelial Cells Through Peroxisome Proliferator-Activated Receptor Alpha and Down-Regulation of Wnt Signaling.
Tsang H, Cheung TY, Kodithuwakku SP, Chai J, Yeung WS, Wong CK, Lee KF.
Reprod Toxicol. 2013 Aug 23. doi:pii: S0890-6238(13)00338-9. 10.1016/j.reprotox.2013.08.001. [Epub ahead of print]

2.Structure-activity relationships for **perfluoroalkane**-induced **in vitro** interference with rat liver mitochondrial respiration.
Wallace KB, Kissling GE, Melnick RL, Blystone CR.
Toxicol Lett. 2013 Aug 14;222(3):257-264. doi: 10.1016/j.toxlet.2013.07.025. [Epub ahead of print]

3.**Perfluorocarbon** emulsion improves oxygen transport of normal and sickle cell human blood **in vitro**.
Torres Filho IP, Pedro JR, Narayanan SV, Nguyen NM, Roseff SD, Spiess BD.
J Biomed Mater Res A. 2013 Jul 27. doi: 10.1002/jbm.a.34885. [Epub ahead of print]

4.Indocyanine green-loaded **perfluorocarbon** nanoemulsions for bimodal (19)F-magnetic resonance/nearinfrared fluorescence imaging and subsequent phototherapy.
Wang YG, Kim H, Mun S, Kim D, Choi Y.
Quant Imaging Med Surg. 2013 Jun;3(3):132-40. doi: 10.3978/j.issn.2223-4292.2013.06.03.

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Shi Z, Hou J, Guo X, Zhang H, Yang F, Dai J.
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6. Microbubbles from Gas-Generating **Perfluorohexane** Nanoemulsions for Targeted Temperature-Sensitive Ultrasonography and Synergistic HIFU Ablation of Tumors.
Zhou Y, Wang Z, Chen Y, Shen H, Luo Z, Li A, Wang Q, Ran H, Li P, Song W, Yang Z, Chen H, Wang Z, Lu G, Zheng Y.
Adv Mater. 2013 Aug 14;25(30):4123-30. doi: 10.1002/adma.201301655. Epub 2013 Jun 21.

7.Thrombus-targeted **perfluorocarbon**-containing liposomal bubbles for enhancement of ultrasonic thrombolysis: in vitro and in vivo study.
Hagisawa K, Nishioka T, Suzuki R, Maruyama K, Takase B, Ishihara M, Kurita A, Yoshimoto N, Nishida Y, Iida K, Luo H, Siegel RJ.
J Thromb Haemost. 2013 Aug;11(8):1565-73. doi: 10.1111/jth.12321.

8.**Perfluorinated** compounds affect the function of sex hormone receptors.
Kjeldsen LS, Bonefeld-Jørgensen EC.
Environ Sci Pollut Res Int. 2013 Jun 14. [Epub ahead of print]

9.Sertoli cell is a potential target for **perfluorooctane** sulfonate-induced reproductive dysfunction in male mice.
Qiu L, Zhang X, Zhang X, Zhang Y, Gu J, Chen M, Zhang Z, Wang X, Wang SL.
Toxicol Sci. 2013 Sep;135(1):229-40. doi: 10.1093/toxsci/kft129. Epub 2013 Jun 12.

Plastic derivatives (BPA, Phthalates and others)

1.Canine toys and training devices as sources of exposure to phthalates and bisphenol A: Quantitation of chemicals in leachate and **in vitro** screening for endocrine activity.
Wooten KJ, Smith PN.
Chemosphere. 2013 Sep 2. doi:pii: S0045-6535(13)01059-X. 10.1016/j.chemosphere.2013.07.075. [Epub ahead of print]

2.Bisphenol A and Human Health: A review of the literature.
Rochester JR.
Reprod Toxicol. 2013 Aug 29. doi:pii: S0890-6238(13)00345-6. 10.1016/j.reprotox.2013.08.008. [Epub ahead of print]

3. Association between urinary levels of bisphenol-A and estrogen metabolism in Korean adults.
Kim EJ, Lee D, Chung BC, Pyo H, Lee J.
Sci Total Environ. 2013 Aug 15. doi:pii: S0048-9697(13)00808-5. 10.1016/j.scitotenv.2013.07.040. [Epub ahead of print]

4. New insights for the risk of bisphenol A: Inhibition of UDP-glucuronosyltransferases (UGTs).
Jiang HM, Fang ZZ, Cao YF, Hu CM, Sun XY, Hong M, Yang L, Ge GB, Liu Y, Zhang YY, Dong Q, Liu RJ.
Chemosphere. 2013 Aug 12. doi:pii: S0045-6535(13)00927-2. 10.1016/j.chemosphere.2013.06.070. [Epub ahead of print]

5. Individual and combined developmental toxicity assessment of bisphenol A and genistein using the embryonic stem cell test **in vitro**.
Kong D, Xing L, Liu R, Jiang J, Wang W, Shang L, Wei X, Hao W.
Food Chem Toxicol. 2013 Oct;60:497-505. doi: 10.1016/j.fct.2013.08.006. Epub 2013 Aug 12.

6. Bisphenol A reduces differentiation and stimulates apoptosis of osteoclasts and osteoblasts.

Hwang JK, Min KH, Choi KH, Hwang YC, Jeong IK, Ahn KJ, Chung HY, Chang JS.
Life Sci. 2013 Sep 17;93(9-11):367-72. doi: 10.1016/j.lfs.2013.07.020. Epub 2013 Jul 27.

7. Phthalates efficiently bind to human peroxisome proliferator activated receptor and retinoid X receptor α, β, γ subtypes: an in silico approach.
Sarath Josh MK, Pradeep S, Vijayalekshmi Amma KS, Balachandran S, Abdul Jaleel UC, Doble M, Spener F, Benjamin S.
J Appl Toxicol. 2013 Jul 11. doi: 10.1002/jat.2902. [Epub ahead of print]

8.[Di-(2-ethylhexyl) **phthalate** activates the apoptosis Caspase pathway in rat Leydig cells **in vitro**].
Wu WG, Tang YJ, Sun ZL.
Zhonghua Nan Ke Xue. 2013 Aug;19(8):683-8. Chinese.

9. Low-dose monobutyl **phthalate** stimulates steroidogenesis through steroidogenic acute regulatory protein regulated by SF-1, GATA-4 and C/EBP-beta in mouse Leydig tumor cells.
Hu Y, Dong C, Chen M, Lu J, Han X, Qiu L, Chen Y, Qin J, Li X, Gu A, Xia Y, Sun H, Li Z, Wang Y.
Reprod Biol Endocrinol. 2013 Jul 26;11:72. doi: 10.1186/1477-7827-11-72.

10. Assessment of estrogenic potential of di-n-butyl **phthalate** and butyl benzyl **phthalate** in vivo.
Ahmad R, Verma Y, Gautam A, Kumar S.
Toxicol Ind Health. 2013 Jul 5. [Epub ahead of print]

11. **In-vitro** metabolites of di-2-ethylhexyl adipate (DEHA) as biomarkers of exposure in human biomonitoring applications.
Silva MJ, Samandar E, Ye X, Calafat AM.
Chem Res Toxicol. 2013 Sep 9. [Epub ahead of print]

12. Migration of plasticisers from Tritan™ and polycarbonate bottles and toxicological evaluation.
Guart A, Wagner M, Mezquida A, Lacorte S, Oehlmann J, Borrell A.
Food Chem. 2013 Nov 1;141(1):373-80. doi: 10.1016/j.foodchem.2013.02.129. Epub 2013 Mar 14.

Pesticides/fungicides

1. Currently used pesticides and their mixtures affect the function of sex hormone receptors and aromatase enzyme activity.
Kjeldsen LS, Ghisari M, Bonefeld-Jørgensen EC.
Toxicol Appl Pharmacol. 2013 Jul 16;272(2):453-464. doi: 10.1016/j.taap.2013.06.028. [Epub ahead of print]**(valgt)**

2. Cancer-related genes transcriptionally induced by the fungicide penconazole.
Perdichizzi S, Mascolo MG, Silingardi P, Morandi E, Rotondo F, Guerrini A, Prete L, Vaccari M, Colacci A.
Toxicol **In Vitro**. 2013 Jun 27. doi:pii: S0887-2333(13)00157-4. 10.1016/j.tiv.2013.06.006. [Epub ahead of print]

3. The E-screen test and the MELN gene-reporter assay used for determination of estrogenic activity in fruits and vegetables in relation to pesticide residues.
Schilirò T, Porfido A, Longo A, Coluccia S, Gilli G.
Food Chem Toxicol. 2013 Aug 7;62C:82-90. doi: 10.1016/j.fct.2013.07.067. [Epub ahead of print]

Herudover er der yderligere 2 artikler, som ikke blev fanget af de valgte søgekriterier:

In vitro - in vivo correlations for endocrine activity of a mixture of currently used **pesticides**.
Taxvig C, Hadrup N, Boberg J, Axelstad M, Bossi R, Bonefeld-Jørgensen EC, Vinggaard AM.

Toxicol Appl Pharmacol. 2013 Aug 13. doi:pii: S0041-008X(13)00338-4. 10.1016/j.taap.2013.07.028. [Epub ahead of print]

Predictive value of cell assays for developmental toxicity and embryotoxicity of conazole fungicides.
Dreisig K, Taxvig C, Birkhøj Kjærstad M, Nellemann C, Hass U, Vinggaard AM.
ALTEX. 2013;30(3):319-30.

Various EDCs, Mixtures and Other endpoints

1. Assessment of Cellular Estrogenic Activity Based on Estrogen Receptor-Mediated Reduction of Soluble-Form Catechol-O-Methyltransferase (COMT) Expression in an ELISA-Based System.
Ho PW, Tse ZH, Liu HF, Lu S, Ho JW, Kung MH, Ramsden DB, Ho SL.
PLoS One. 2013 Sep 6;8(9):e74065. doi: 10.1371/journal.pone.0074065.

2.Environmental alkylphenols modulate cytokine expression in plasmacytoid dendritic cells.
Hung CH, Yang SN, Wang YF, Liao WT, Kuo PL, Tsai EM, Lee CL, Chao YS, Yu HS, Huang SK, Suen JL.
PLoS One. 2013 Sep 11;8(9):e73534. doi: 10.1371/journal.pone.0073534.

3.In vivo endocrine effects of naphthenic acids in fish.
Knag AC, Sebire M, Mayer I, Meier S, Renner P, Katsiadaki I.
Chemosphere. 2013 Sep 11. doi:pii: S0045-6535(13)01149-1. 10.1016/j.chemosphere.2013.08.033. [Epub ahead of print]

4.Early neuroendocrine disruption in hypothalamus and hippocampus: developmental effects including female sexual maturation and implications for **endocrine disrupting** chemical screening.
Bourguignon JP, Franssen D, Gérard A, Janssen S, Pinson A, Naveau E, Parent AS.
J Neuroendocrinol. 2013 Sep 12. doi: 10.1111/jne.12107. [Epub ahead of print]

5.**In vitro** and in vivo toxicities of sediment and surface water in an area near a major steel industry of Korea: **Endocrine disruption**, reproduction, or survival effects combined with instrumental analysis.
Kim S, Lee S, Kim C, Liu X, Seo J, Jung H, Ji K, Hong S, Park J, Khim JS, Yoon S, Lee W, Park J, Choi K.
Sci Total Environ. 2013 Sep 7. doi:pii: S0048-9697(13)00924-8. 10.1016/j.scitotenv.2013.08.010. [Epub ahead of print]

6.**Endocrine Disruptors** Differentially Target ATP-binding Cassette Transporters in the Blood-Testis Barrier and Affect Leydig Cell Testosterone Secretion **in vitro**.
Dankers AC, Roelofs MJ, Piersma AH, Sweep FC, Russel FG, van den Berg M, van Duursen MB, Masereeuw R.
Toxicol Sci. 2013 Sep 6. [Epub ahead of print]

7.Simultaneous determination of the UV-filters benzyl salicylate, phenyl salicylate, octyl salicylate, homosalate, 3-(4-methylbenzylidene) camphor and 3-benzylidene camphor in human placental tissue by LC-MS/MS. Assessment of their **in vitro** endocrine activity.
Jiménez-Díaz I, Molina-Molina JM, Zafra-Gómez A, Ballesteros O, Navalón A, Real M, Sáenz JM, Fernández MF, Olea N.
J Chromatogr B Analyt Technol Biomed Life Sci. 2013 Oct 1;936:80-7. doi: 10.1016/j.jchromb.2013.08.006. Epub 2013 Aug 8.

8.Thyroid endocrine system disruption by pentachlorophenol: An **in vitro** and in vivo assay.
Guo Y, Zhou B.
Aquat Toxicol. 2013 Aug 21;142-143C:138-145. doi: 10.1016/j.aquatox.2013.08.005. [Epub ahead of print]

9. The brominated flame retardant TBECH activates the zebrafish (Danio rerio) androgen receptor, alters gene transcription and causes developmental disturbances.
Pradhan A, Kharlyngdoh JB, Asnake S, Olsson PE.
Aquat Toxicol. 2013 Aug 6;142-143C:63-72. doi: 10.1016/j.aquatox.2013.07.018. [Epub ahead of print]

10. Effects of non-steroidal estrogen diethylstilbestrol on pH and ion transport in the mantle epithelium of a bivalve Anodonta cygnea.
Alves MG, Oliveira PF.
Ecotoxicol Environ Saf. 2013 Aug 13. doi:pii: S0147-6513(13)00322-9. 10.1016/j.ecoenv.2013.07.024. [Epub ahead of print]

11. The effects of nanomaterials as **endocrine disruptors**.
Iavicoli I, Fontana L, Leso V, Bergamaschi A.
Int J Mol Sci. 2013 Aug 14;14(8):16732-801. doi: 10.3390/ijms140816732.

12. Development of a solid phase extraction method for the simultaneous determination of steroid hormones in H295R cell line using liquid chromatography-tandem mass spectrometry.
Abdel-Khalik J, Björklund E, Hansen M.
J Chromatogr B Analyt Technol Biomed Life Sci. 2013 Sep 15;935:61-9. doi: 10.1016/j.jchromb.2013.07.013. Epub 2013 Jul 25.

13. Estrogen-, androgen- and aryl hydrocarbon receptor mediated activities in passive and composite samples from municipal waste and surface waters.
Jálová V, Jarošová B, Bláha L, Giesy JP, Ocelka T, Grabic R, Jurčíková J, Vrana B, Hilscherová K.
Environ Int. 2013 Sep;59:372-83. doi: 10.1016/j.envint.2013.06.024. Epub 2013 Aug 1.

14. Downregulation of cytochrome P450scc as an initial adverse effect of adult exposure to diethylstilbestrol on testicular steroidogenesis.
Maeda N, Okumura K, Tanaka E, Suzuki T, Miyasho T, Haeno S, Ueda H, Hoshi N, Yokota H.
Environ Toxicol. 2013 Jul 20. doi: 10.1002/tox.21875. [Epub ahead of print]

15. Luteinizing hormone receptor (lhcgr) as a marker gene for characterizing estrogenic **endocrine-disrupting** chemicals in zebrafish ovarian follicle cells.
Liu KC, Wu RS, Ge W.
Gen Comp Endocrinol. 2013 Jul 10. doi:pii: S0016-6480(13)00299-2. 10.1016/j.ygcen.2013.06.023. [Epub ahead of print]

16. UVB irradiation as a tool to assess ROS-induced damage in human spermatozoa.
Amaral S, Redmann K, Sanchez V, Mallidis C, Ramalho-Santos J, Schlatt S.
Andrology. 2013 Sep;1(5):707-14. doi: 10.1111/j.2047-2927.2013.00098.x. Epub 2013 Jul 9.

17. Direct photodegradation of androstenedione and testosterone in natural sunlight: inhibition by dissolved organic matter and reduction of **endocrine disrupting** potential.
Young RB, Latch DE, Mawhinney DB, Nguyen TH, Davis JC, Borch T.
Environ Sci Technol. 2013 Aug 6;47(15):8416-24. doi: 10.1021/es401689j. Epub 2013 Jul 10.

18. Toxicity of environmental contaminants to fish spermatozoa function **in vitro**-A review.
Hatef A, Alavi SM, Golshan M, Linhart O.
Aquat Toxicol. 2013 Sep 15;140-141:134-44. doi: 10.1016/j.aquatox.2013.05.016. Epub 2013 May 28.

19.**In vitro** and in vivo testing methods of epigenomic endpoints for evaluating **endocrine disruptors**.
Greally JM, Jacobs MN.

ALTEX. 2013 Jun 20. doi:pii: S1868696X1302211X. [Epub ahead of print]

20. Response to fish specific reproductive hormones and **endocrine disrupting** chemicals of a Sertoli cell line expressing endogenous receptors from an endemic cyprinid Gnathopogon caerulescens.
Higaki S, Koyama Y, Shimada M, Ono Y, Tooyama I, Fujioka Y, Sakai N, Ikeuchi T, Takada T.
Gen Comp Endocrinol. 2013 Sep 15;191:65-73. doi: 10.1016/j.ygcen.2013.06.002. Epub 2013 Jun 13.

21. Occurrence of glucocorticogenic activity in various surface waters in The Netherlands.
Schriks M, van der Linden SC, Stoks PG, van der Burg B, Puijker L, de Voogt P, Heringa MB.
Chemosphere. 2013 Sep;93(2):450-4. doi: 10.1016/j.chemosphere.2013.04.091. Epub 2013 Jun 10.

22. No substantial changes in estrogen receptor and estrogen-related receptor orthologue gene transcription in Marisa cornuarietis exposed to estrogenic chemicals.
Bannister R, Beresford N, Granger DW, Pounds NA, Rand-Weaver M, White R, Jobling S, Routledge EJ.
Aquat Toxicol. 2013 Sep 15;140-141:19-26. doi: 10.1016/j.aquatox.2013.05.002. Epub 2013 May 17.

23. Triennial Reproduction Symposium: the ovarian follicular reserve in cattle: what regulates its formation and size?
Fortune JE, Yang MY, Allen JJ, Herrick SL.
J Anim Sci. 2013 Jul;91(7):3041-50. doi: 10.2527/jas.2013-6233. Epub 2013 Jun 4.

24.An integrated approach to assess the role of chemical exposure in obesity.
Legler J.
Obesity (Silver Spring). 2013 Jun;21(6):1084-5. doi: 10.1002/oby.20478.

25.Investigation of current infection-control practices for ultrasound coupling gel: a survey, microbiological analysis, and examination of practice patterns.
Provenzano DA, Liebert MA, Steen B, Lovetro D, Somers DL.
Reg Anesth Pain Med. 2013 Sep-Oct;38(5):415-24. doi: 10.1097/AAP.0b013e3182a0e12f.

26.Phase-transition thresholds and vaporization phenomena for ultrasound phase-change nanoemulsions assessed via high-speed optical microscopy.
Sheeran PS, Matsunaga TO, Dayton PA.
Phys Med Biol. 2013 Jul 7;58(13):4513-34. doi: 10.1088/0031-9155/58/13/4513. Epub 2013 Jun 13.

27.Addressing the use of PDIF-CN2 molecules in the development of n-type organic field-effect transistors for biosensing applications.
Barra M, Viggiano D, Ambrosino P, Bloisi F, Di Girolamo FV, Soldovieri MV, Taglialatela M, Cassinese A.
Biochim Biophys Acta. 2013 Sep;1830(9):4365-73. doi: 10.1016/j.bbagen.2012.11.025. Epub 2012 Dec 6.

28.Development of bioadhesive chitosan superporous hydrogel composite particles based intestinal drug delivery system.
Chavda H, Modhia I, Mehta A, Patel R, Patel C.
Biomed Res Int. 2013;2013:563651. doi: 10.1155/2013/563651. Epub 2013 Aug 4.

29.Antagonistic effect of the inflammasome on thymic stromal lymphopoietin expression in the skin.
Schuepbach-Mallepell S, Philippe V, Brüggen MC, Watanabe H, Roques S, Baldeschi C, Gaide O.
J Allergy Clin Immunol. 2013 Aug 13. doi:pii: S0091-6749(13)01049-X. 10.1016/j.jaci.2013.06.033. [Epub ahead of print]

30. Preparation, characterization, and evaluation in vivo of Ins-SiO2-HP55 (insulin-loaded silica coating HP55) for oral delivery of insulin.
Zhao X, Shan C, Zu Y, Zhang Y, Wang W, Wang K, Sui X, Li R.
Int J Pharm. 2013 Sep 15;454(1):278-84. doi: 10.1016/j.ijpharm.2013.06.051. Epub 2013 Jul 3.

31. Obesogens and obesity-An alternative view?
Sharpe RM, Drake AJ.
Obesity (Silver Spring). 2013 Jun;21(6):1081-3. doi: 10.1002/oby.20373.

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

Concentration addition, independent action and generalized concentration addition models for mixture effect prediction of sex hormone synthesis in vitro.
Hadrup N, Taxvig C, Pedersen M, Nellemann C, Hass U, Vinggaard AM.
PLoS One. 2013 Aug 22;8(8):e70490. doi: 10.1371/journal.pone.0070490.

In vivo studier

Søgning er udført på PubMed og dækker perioden 20/6-24/9 2013

(Juli - September 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 44 artikler (Bruttolisten)
Disse er efter Miljøstyrelsens ønske blevet fordelt i grupper efter stofnavne: "Triclosan", Plastic derivatives" (BPA, Phthalates and others), "Pesticides/fungicides" og " Various EDCs, Mixtures and Other endpoints".

To artikler er blevet udvalgt til nærmere beskrivelse og en til abstract. Disse 3 er valgt fordi vi mener de bidrager til ny viden om effekter af ethinyl østradiol eksponering på hunrotter (Mandrup et al. 2013) og om hormonforstyrrende effekter efter triclosan eksponering (Axelstad et al. 2013). Derudover er et abstract fra workshoppen i Berlin (om non-monoton dosis respons og low dose) taget med her (Beausoleil et al. 2013).

Ud fra bruttolisten (se længere nede i dokumentet) er udvalgt følgende 2 artikler til engelsk abstrakt og dansk resume og kommentarer, samt 1 med kun abstract:

Effects of perinatal ethinyl estradiol exposure in male and female Wistar rats.
Mandrup KR, Jacobsen PR, Isling LK, Axelstad M, Dreisig K, Hadrup N, Vinggaard AM, Hass U, Boberg J.
Reprod Toxicol. 2013 Sep 11. doi:pii: S0890-6238(13)00347-X. 10.1016/j.reprotox.2013.09.001. [Epub ahead of print]

Abstract
Perinatal exposure to endocrine disrupting chemicals with estrogenic activity can adversely affect reproductive development, but few studies evaluating estrogen-sensitive endpoints have been performed in Wistar rats. Therefore, time-mated Wistar rats (n=10) were gavaged during gestation and lactation with 0, 5, 15 or 50μg/kg bw/day of ethinyl estradiol. This potent estrogen was found to induce an increased number of nipples and reduced ovary weight in female offspring. Malformations of female genitalia were found in young as well as adult offspring, as an increased AGD was seen at birth and a deeper urethral slit length was seen in adulthood. In prepubertal male offspring, estrogen-regulated gene expression in ventral prostate was increased dose-dependently and a decreased ventral prostate weight was seen at 15μg/kg. Female external sexual characteristics and prostate development were found to be targets for exposure to estrogenic compounds and may be of interest in studies on estrogenic environmental compounds.

Triclosan exposure reduces thyroxine levels in pregnant and lactating rat dams and in directly exposed offspring.
Axelstad M, Boberg J, Vinggaard AM, Christiansen S, Hass U.
Food Chem Toxicol. 2013 Sep;59:534-40. doi: 10.1016/j.fct.2013.06.050. Epub 2013 Jul 4.

Abstract
Thyroid disrupting chemicals can potentially disrupt brain development. Two studies investigating the effect of the antibacterial compound triclosan on thyroxine (T4) levels in rats are reported. In the first, Wistar rat dams were gavaged with 75, 150 or 300mg triclosan/kg bw/day throughout gestation and lactation. Total T4 serum levels were measured in dams and offspring, and all doses of triclosan significantly lowered T4 in dams, but no significant effects on T4 levels were seen in the offspring at the end of the lactation period. Since this lack of effect could be due to minimal exposure through maternal milk, a second study using direct per oral pup exposure from postnatal day 3-16 to 50 or 150mg triclosan/kg bw/day was performed. This exposure pointed to significant T4 reductions in 16 day old offspring in both dose groups. These results corroborate previous studies showing that in rats lactational transfer of triclosan seems limited. Since an optimal study design for testing potential developmental neurotoxicants in rats, should include exposure during both the pre- and postnatal periods of brain development, we suggest that in the case of triclosan, direct dosing of pups may be the best way to obtain that goal.

Low dose effects and non-monotonic dose responses for endocrine active chemicals: Science to practice workshop: Workshop summary.
Beausoleil C, Ormsby JN, Gies A, Hass U, Heindel JJ, Holmer ML, Nielsen PJ, Munn S, Schoenfelder G.
Chemosphere. 2013 Aug 8. doi:pii: S0045-6535(13)00885-0. 10.1016/j.chemosphere.2013.06.043. [Epub ahead of print]

Abstract

A workshop was held in Berlin September 12-14th 2012 to assess the state of the science of the data supporting low dose effects and non-monotonic dose responses ("low dose hypothesis") for chemicals with endocrine activity (endocrine disrupting chemicals or EDCs). This workshop consisted of lectures to present the current state of the science of EDC action and also the risk

assessment process. These lectures were followed by breakout sessions to integrate scientists from various backgrounds to discuss in an open and unbiased manner the data supporting the "low dose hypothesis". While no consensus was reached the robust discussions were helpful to inform both basic scientists and risk assessors on all the issues. There were a number of important ideas developed to help continue the discussion and improve communication over the next few years.

Bruttoliste *in vivo*

(delt ind i emner, 44 artikler i alt)

Triclosan

1. Triclosan exposure reduces thyroxine levels in pregnant and lactating rat dams and in directly exposed offspring.
Axelstad M, Boberg J, Vinggaard AM, Christiansen S, Hass U.
Food Chem Toxicol. 2013 Sep;59:534-40. doi: 10.1016/j.fct.2013.06.050. Epub 2013 Jul 4.

2. Triclosan exhibits a tendency to accumulate in the epididymis and shows sperm toxicity in male sprague-dawley **rats**.
Lan Z, Hyung Kim T, Shun Bi K, Hui Chen X, Sik Kim H.
Environ Toxicol. 2013 Aug 9. doi: 10.1002/tox.21897. [Epub ahead of print]

Plastic derivatives (BPA Phthalates and others)

BPA
1. Mouse Strain Does Not Influence the Overall Effects of **Bisphenol A**-Induced Toxicity in Adult Antral Follicles.
Peretz J, Neese SL, Flaws JA.
Biol Reprod. 2013 Sep 11. [Epub ahead of print]

2. Does preconception paternal exposure to a physiologically relevant level of **bisphenol A** alter spatial memory in an adult **rat**?
Fan Y, Ding S, Ye X, Manyande A, He D, Zhao N, Yang H, Jin X, Liu J, Tian C, Xu S, Ying C.
Horm Behav. 2013 Sep 1. doi:pii: S0018-506X(13)00168-2. 10.1016/j.yhbeh.2013.08.014. [Epub ahead of print]

3. In ovo inhibition of steroid metabolism by **bisphenol-A** as a potential mechanism of **endocrine disruption**.
Clairardin SG, Paitz RT, Bowden RM.
Proc Biol Sci. 2013 Sep 4;280(1769):20131773. doi: 10.1098/rspb.2013.1773. Print 2013.

4. **Bisphenol A** Modifies the Regulation Exerted by Testosterone on 5 α -Reductase Isozymes in Ventral Prostate of Adult **Rats**.
Sánchez P, Castro B, Torres JM, Olmo A, Del Moral RG, Ortega E.
Biomed Res Int. 2013;2013:629235. doi: 10.1155/2013/629235. Epub 2013 Jul 25.

5. **Bisphenol A** and Human Health: A review of the literature.
Rochester JR.

Reprod Toxicol. 2013 Aug 29. doi:pii: S0890-6238(13)00345-6. 10.1016/j.reprotox.2013.08.008. [Epub ahead of print]

6. Computer-aided identification of novel protein targets of **bisphenol A**.
Montes-Grajales D, Olivero-Verbel J.
Toxicol Lett. 2013 Aug 20;222(3):312-320. doi: 10.1016/j.toxlet.2013.08.010. [Epub ahead of print]

7. Mouse leydig cells with different **androgen** production potential are resistant to estrogenic stimuli but responsive to **bisphenol a** which attenuates testosterone metabolism.
Savchuk I, Söder O, Svechnikov K.
PLoS One. 2013;8(8):e71722. doi: 10.1371/journal.pone.0071722.

8. New insights for the risk of **bisphenol A**: Inhibition of UDP-glucuronosyltransferases (UGTs).
Jiang HM, Fang ZZ, Cao YF, Hu CM, Sun XY, Hong M, Yang L, Ge GB, Liu Y, Zhang YY, Dong Q, Liu RJ.
Chemosphere. 2013 Aug 12. doi:pii: S0045-6535(13)00927-2. 10.1016/j.chemosphere.2013.06.070. [Epub ahead of print]

9. Individual and combined developmental toxicity assessment of **bisphenol A** and genistein using the embryonic stem cell test in vitro.
Kong D, Xing L, Liu R, Jiang J, Wang W, Shang L, Wei X, Hao W.
Food Chem Toxicol. 2013 Oct;60:497-505. doi: 10.1016/j.fct.2013.08.006. Epub 2013 Aug 12.

10. **Bisphenol A** inhibits cultured mouse ovarian follicle growth partially via the aryl hydrocarbon receptor signaling pathway.
Ziv-Gal A, Craig ZR, Wang W, Flaws JA.
Reprod Toxicol. 2013 Aug 6;42C:58-67. doi: 10.1016/j.reprotox.2013.07.022. [Epub ahead of print]

11. Adolescent exposure to **Bisphenol-A** increases anxiety and sucrose preference but impairs spatial memory in **rats** independent of sex.
Diaz Weinstein S, Villafane JJ, Juliano N, Bowman RE.
Brain Res. 2013 Sep 5;1529:56-65. doi: 10.1016/j.brainres.2013.07.018. Epub 2013 Jul 18.

12. A systematic review of **Bisphenol A** "Low Dose" studies in the context of human exposure: A case for establishing standards for reporting "low-dose" effects of chemicals.
Teeguarden JG, Hanson-Drury S.
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Wildlife studier ved Biologisk Institut, Syddansk Universitet (SDU)

Søgningen er udført på Web of Science og dækker perioden 24/6 2013 – 23/9 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 og yderligere kommentarer.
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: Anti-androgens act jointly in suppressing spiggin concentrations in androgen-primed female three-spined sticklebacks - Prediction of combined effects by concentration addition. Pottinger, T. G.; Katsiadaki, I.; Jolly, C.; Sanders, M.; Mayer, I.; Scott, A. P.; Morris, S.; Kortenkamp, A.; and Scholze, M. 2013. Aquatic toxicology (Amsterdam, Netherlands) 140-141, 145-156.

Abstract: Increasing attention is being directed at the role played by anti-androgenic chemicals in endocrine disruption of wildlife within the aquatic environment. The co-occurrence of multiple contaminants with anti-androgenic activity highlights a need for the predictive assessment of combined effects, but information about anti-androgen mixture effects on wildlife is lacking. This study evaluated the suitability of the androgenised female stickleback screen (AFSS), in which inhibition of androgen-induced spiggin production provides a quantitative assessment of anti-androgenic activity, for predicting the effect of a four component mixture of anti-androgens. The anti-androgenic activity of four known anti-androgens (vinclozolin, fenitrothion, flutamide, linuron)

was evaluated from individual concentration-response data and used to design a mixture containing each chemical at equipotent concentrations. Across a 100-fold concentration range, a concentration addition approach was used to predict the response of fish to the mixture. Two studies were conducted independently at each of two laboratories. By using a novel method to adjust for differences between nominal and measured concentrations, good agreement was obtained between the actual outcome of the mixture exposure and the predicted outcome. This demonstrated for the first time that androgen receptor antagonists act in concert in an additive fashion in fish and that existing mixture methodology is effective in predicting the outcome, based on concentration-response data for individual chemicals. The sensitivity range of the AFSS assay lies within the range of anti-androgenicity reported in rivers across many locations internationally. The approach taken in our study lays the foundations for understanding how androgen receptor antagonists work together in fish and is essential in informing risk assessment methods for complex anti-androgenic mixtures in the aquatic environment.

Artikel 2: Testosterone levels and fecundity in the hermaphroditic aquatic snail Lymnaea stagnalis exposed to testosterone and endocrine disruptors.
Giusti, A.; Ducrot, V.; Joaquim-Justo, C.; and Lagadic, L. 2013. Environmental Toxicology and Chemistry 32, 1740-1745.

Abstract: Endocrine disruptors are known to alter endogenous free and esterified levels of androgenic and estrogenic steroid hormones in aquatic mollusks. The origin of steroids in these animals, however, remains controversial. In the present study, free and esterified testosterone concentrations were measured in the hermaphroditic aquatic gastropod Lymnaea stagnalis exposed to molecules known for their androgenic (testosterone and tributyltin), anti-androgenic (cyproterone-acetate), and estrogenic (chlordecone) properties, by reference to their mode of action in vertebrates. In parallel, snail oviposition and fecundity were followed over a 21-d exposure period. Testosterone exposure resulted in increased esterified testosterone levels, whereas free testosterone concentrations remained stable. In contrast, cyproterone-acetate significantly increased the free form of testosterone with no changes in the esterified form, whereas chlordecone showed a tendency to reduce (though not significantly) esterified testosterone concentrations without changing free testosterone levels. Finally, tributyltin did not alter testosterone homeostasis. The production of egg clutches and eggs was significantly reduced only in the snails exposed to the highest concentrations of chlordecone (19.6 µg/L) and tributyltin (94.2 ng Sn/L). Overall, the present study demonstrates that uptake of testosterone from the exposure medium occurs in L. stagnalis. Moreover, it shows that cyproterone-acetate and, to a lesser extent, chlordecone can alter endogenous testosterone levels in this freshwater snail. However, the relationship between hormonal changes and snail reproduction has not been established.

Artikel 3: Effects of in vivo exposure to UV filters (4-MBC, OMC, BP-3, 4-HB, OC, OD-PABA) on endocrine signaling genes in the insect Chironomus riparius.
Ozaez, I.; Luis Martinez-Guitarte, J.; and Morcillo, G. 2013. Science of the Total Environment 456, 120-126.

Abstract: There is increasing evidence indicating that several UV filters might have endocrine disruptive effects. Numerous studies have evaluated hormonal effects in vertebrates, mainly reporting estrogenic and androgenic activities in mammals and fishes. There is only limited

knowledge about potential endocrine activity in invertebrate hormonal systems. In this work, the effects on endocrine signaling genes of six frequently used UV filters were investigated in Chironomus riparius, a reference organism in aquatic toxicology. The UV filters studied were: octyl-p-methoxycinnamate (OMC) also called 2-ethylhexyl-4-methoxycinnamate (EHMC); 4-methylbenzylidene camphor (4-MBC); benzophenone-3 (BP-3); 4-hidroxybenzophenone (4-HB); octocrylene (OC); and octyldimethyl-p-aminobenzoate (OD-PABA). After in vivo exposure at different dosages, expression levels of the genes coding for the ecdysone receptor (EcR), the ultraspiracle (usp, ortholog of the RXR) and the estrogen-related receptor (ERR) were quantified by Real Time PCR. The EcR gene was significantly upregulated by 4-MBC, OMC/EHMC and OD-PABA, with a dose-related response following 24 h exposure. In contrast, the benzophenones, BP-3 and 4-HB, as well as OC did not alter this gene at the same exposure conditions. The transcription profiles of the usp and ERR genes were not significantly affected, except for BP-3 that inhibited the usp gene at the highest concentration. To our knowledge, this is the first experimental evidence in invertebrates of a direct effect of UV filters on endocrine-related genes, and is consistent with the known effects on vertebrate hormonal receptor genes. The capability of 4-MBC, OMC/EHMC and OD-PABA to stimulate the expression of the ecdysone receptor, a key transcription factor for the ecdysone-genomic response in arthropods, suggests the possibility of a broad and long-term effect on this hormonal pathway. These findings strengthen the need for further research about the ecotoxicological implications of chronic exposure to these compounds in aquatic invertebrates.

Bruttoliste

Bisphenol A og alkylphenoler

In vitro effects of bisphenol A on the quality parameters, oxidative stress, DNA integrity and adenosine triphosphate content in sterlet (Acipenser ruthenus) spermatozoa.
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Reproductive toxicity effects of 4-nonylphenol with known endocrine disrupting effects and induction of vitellogenin gene expression in silkworm, Bombyx mori.
Yuan, H. X.; Xu, X.; Sima, Y. H.; and Xu, S. Q. 2013. Chemosphere 93, 263-268.

Phthalater

Endocrine disruption by di-(2-ethylhexyl)-phthalate in Chinese rare minnow (Gobiocypris rarus).
Wang, X.; Yang, Y.; Zhang, L.; Ma, Y.; Han, J.; Yang, L.; and Zhou, B. 2013. Environmental Toxicology and Chemistry 32, 1846-1854.

Flammehæmmere

Effects of TDCPP or TPP on gene transcriptions and hormones of HPG axis, and their consequences on reproduction in adult zebrafish (Danio rerio).
Liu, X.; Ji, K.; Jo, A.; Moon, H. B.; and Choi, K. 2013. Aquatic Toxicology 134, 104-111.

UV-filtre

Effects of in vivo exposure to UV filters (4-MBC, OMC, BP-3, 4-HB, OC, OD-PABA) on endocrine signaling genes in the insect Chironomus riparius.
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Perfluorerede stoffer

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PAH

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TBT og TPT

Reproductive impacts of tributyltin (TBT) and triphenyltin (TPT) in the hermaphroditic freshwater gastropod Lymnaea stagnalis.
Giusti, A.; Barsi, A.; Dugue, M.; Collinet, M.; Thome, J. P.; Joaquim-Justo, C.; Roig, B.; Lagadic, L.; and Ducrot, V. 2013. Environmental Toxicology and Chemistry 32, 1552-1560.

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Morales, M.; Martinez-Paz, P.; Ozaez, I.; Luis Martinez-Guitarte, J.; and Morcillo, G. 2013. Comparative Biochemistry and Physiology C-Toxicology & Pharmacology 158, 57-63.

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Pesticider

Effects of the insecticide fipronil on reproductive endocrinology in the fathead minnow.
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Thyroid endocrine disruption in zebrafish larvae following exposure to hexaconazole and tebuconazole.
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Tungmetaller

To breed or not to breed: endocrine response to mercury contamination by an Arctic seabird.
Tartu, S.; Goutte, A.; Bustamante, P.; Angelier, F.; Moe, B.; Clement-Chastel, C.; Bech, C.; Gabrielsen, G. W.; Bustnes, J. O.; and Chastel, O. 2013. Biology Letters 9,

Lægemidler og syntetiske steroider

Impact of environmental oxygen, exercise, salinity, and metabolic rate on the uptake and tissue-specific distribution of 17 alpha-ethynylestradiol in the euryhaline teleost Fundulus heteroclitus.
Blewett, T. A.; Robertson, L. M.; MacLatchy, D. L.; and Wood, C. M. 2013. Aquatic Toxicology 138, 43-51.

Developing Predictive Approaches to Characterize Adaptive Responses of the Reproductive Endocrine Axis to Aromatase Inhibition: II. Computational Modeling.
Breen, M.; Villeneuve, D. L.; Ankley, G. T.; Bencic, D. C.; Breen, M. S.; Watanabe, K. H.; Lloyd, A. L.; and Conolly, R. B. 2013. Toxicological Sciences 133, 234-247.

The effects of 17-alpha-ethinylestradiol (EE2) on molecular signaling cascades in mummichog (Fundulus heteroclitus).
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Developmental disorders and altered gene expression in the tropical clawed frog (Silurana tropicalis) exposed to 17alpha-ethinylestradiol.
Hirakawa, I.; Miyagawa, S.; Mitsui, N.; Miyahara, M.; Onishi, Y.; Kagami, Y.; Kusano, T.; Takeuchi, T.; Ohta, Y.; and Iguchi, T. 2013. Journal of applied toxicology : JAT 33, 1001-1010.

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Toxicity and endocrine disruption in zebrafish (Danio rerio) and two freshwater invertebrates (Daphnia magna and Moina macrocopa) after chronic exposure to mefenamic acid.
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Effects of non-steroidal anti-inflammatory drugs on hormones and genes of the hypothalamic-pituitary-gonad axis, and reproduction of zebrafish.
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An Androgenic Agricultural Contaminant Impairs Female Reproductive Behaviour in a Freshwater Fish.
Saaristo, M.; Tomkins, P.; Allinson, M.; Allinson, G.; and Wong, B. B. 2013. Plos One 8, **Article number:** e62782.

Low concentrations, potential ecological consequences: Synthetic estrogens alter life-history and demographic structures of aquatic invertebrates.
Souza, M. S.; Hallgren, P.; Balseiro, E.; and Hansson, L. A. 2013. Environmental Pollution 178, 237-243.

Evidence of small modulation of ethinylestradiol induced effects by concurrent exposure to trenbolone in male eelpout Zoarces viviparus.
Velasco-Santamaria, Y. M.; Bjerregaard, P.; and Korsgaard, B. 2013. Environmental Pollution 178, 189-196.

Developing Predictive Approaches to Characterize Adaptive Responses of the Reproductive Endocrine Axis to Aromatase Inhibition: I. Data Generation in a Small Fish Model.
Villeneuve, D. L.; Breen, M.; Bencic, D. C.; Cavallin, J. E.; Jensen, K. M.; Makynen, E. A.; Thomas, L. M.; Wehmas, L. C.; Conolly, R. B.; and Ankley, G. T. 2013. Toxicological Sciences 133, 225-233.

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Yuan, C.; Zhang, Y.; Hu, G.; Li, M.; Zheng, Y.; Gao, J.; Yang, Y.; Zhou, Y.; and Wang, Z. 2013. Comparative Biochemistry and Physiology C-Toxicology & Pharmacology 158, 1-9.

Molecular characterization of five steroid receptors from pengze crucian carp and their expression profiles of juveniles in response to 17alpha-ethinylestradiol and 17alpha-methyltestosterone.
Zheng, Y.; Wang, L.; Li, M.; Liang, H.; Qin, F.; Liu, S.; Wang, H.; Wu, T.; Zhang, Y.; and Wang, Z. 2013. General and comparative endocrinology 191, 113-122.

Studier med flere stoffer fra flere af de ovennævnte kategorier

Testosterone levels and fecundity in the hermaphroditic aquatic snail Lymnaea stagnalis exposed to testosterone and endocrine disruptors.
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