Center for Hormonforstyrrende Stoffer

Litteraturgennemgang for perioden 1/7 2011 - 30/9 2011

Indholdsfortegnelse Side

Humane studier ved Afd for Vækst og Reproduktion, Rigshospitalet

Søgning er udført på PubMed og dækker perioden 1/7/2011 - 30/9/2011

Følgende søgeprofil er benyttet: (endocrine disrupt*) AND expos* AND (human OR men OR women OR child* OR adult* OR adolescen* OR infan*)

(Bemærkning: * i slutningen af et ord betyder at man søger på alle tænkelige endelser for det givne ord. For child* betyder det for eksempel at man søger på childhood, children og child)

Limits: title/abstract, English language

Brutto resultat: der blev fundet 45 artikler via denne søgning. Det var dog de allerfærreste der blev fundet relevante, hvorfor der blev foretaget mere specifikke søgninger, hvor ”endocrine disrupt*” i ovenstående søgeprofil blev erstattet med eksempelvis ”phthalat*” eller ”perfluor*”. Ialt er 12 artikler, hvoraf 5 omhandler phthalater, og 5 PFCer inkluderet og kommenteret på.

De udvalgte studier har blandt andet fokus på metabolisme, kinetik, påvirkning af thyroidea og neurologiske aspekter.

Environ Health. 2011 Sep 20;10(1):79. [Epub ahead of print]
Lower birth weight and increased body fat at school age in children prenatally exposed to modern pesticides: A prospective study.
Wohlfahrt-Veje C, Main KM, Schmidt IM, Boas M, Jensen TK, Grandjean P, Skakkebaek NE, Andersen HR.

ABSTRACT: BACKGROUND: Endocrine disrupting chemicals have been hypothesized to play a role in the obesity epidemic. Long-term effects of prenatal exposure to non-persistent pesticides on body composition have so far not been investigated. The purpose of this study was to assess possible effects of prenatal exposure to currently used pesticides on children's growth, endocrine and reproductive function. METHOD: In a prospective study of 247 children born by women working in greenhouses in early pregnancy, 168 were categorized as prenatally exposed to pesticides. At three months (n=203) and at 6 to11 years of age (n=177) the children underwent a clinical examination and blood sampling for analysis of IGF-I, IGFBP3 and thyroid hormones. Body fat percentage at age 6 to11 years was calculated from skin fold measurements. Pesticide related associations were tested by linear multiple regression analysis, adjusting for relevant confounders. RESULTS: Compared to unexposed children birth weight and weight for gestational age were lower in the highly exposed children: -173g (-322; -23), -4.8% (-9.0; -0.7) and medium exposed children: -139g (-272; -6), -3.6% (-7.2; -0.0). Exposed (medium and highly together) children had significantly larger increase in BMI Z-score (0.55 SD (95% CI: 0.1; 1.0) from birth to school age) and highly exposed children had 15.8% (0.2; 34.6) larger skin folds and higher body fat percentage compared to unexposed. If prenatally exposed to both pesticides and maternal smoking (any amount), the sum of four skin folds was 46.9% (95% CI: 8.1; 99.5) and body fat percentage 29.1% (95% CI: 3.0; 61.4) higher. There were subtle associations between exposure and TSH Z-score -0.66(-1.287; -0.022) and IGF-I Z-score (girls: -0.62(-1.0; -0.22), boys: 0.38(-0.03; 0.79)), but not IGFBP3. CONCLUSIONS: Occupational exposure to currently used pesticides may have adverse effects in spite of the added protection offered to pregnant women. Maternal exposure to combinations of modern, non-persistent pesticides during early pregnancy was associated with affected growth, both prenatally and postnatally. We found a biphasic association with lower weight at birth followed by increased body fat accumulation from birth to school age. We cannot rule out some residual confounding due to differences in social class, although this was adjusted for. Associations were stronger in highly exposed than in medium exposed children, and effects on body fat content at school age was potentiated by maternal smoking in pregnancy.

Food Chem Toxicol. 2011 Sep;49(9):2022-9. Epub 2011 May15.
A twenty-volunteer studyusing deuterium labelling to determine the kinetics and fractional excretion of primary and secondary urinary metabolites of di-2-ethylhexylphthalate anddi-iso-nonylphthalate.
Anderson WA, Castle L, Hird S, Jeffery J, Scotter MJ.

This study has obtained estimates of the kinetics and fractional excretion factors of metabolism of DEHP and DINP to their main primary and secondary metabolites. Samples were obtained from an open-label, fixed sequence, single oral dose study in 10 male and 10 female subjects. The dosed substances were deuterated di-2-ethylhexylphthalate (D(4)-DEHP) and di-isononylphthalate (D(4)-DINP) at two dose levels. Urine samples were collected at intervals up to 48h post-dose. LC-MS/MS was used to measure metabolite concentrations. Excreted amounts were then calculated using urine volumes. Metabolite half-lives were estimated to be 4-8h with more than 90% of metabolites in the first 24h of urine collections and the remainder in the 24-48h period. The four metabolites of DEHP amounted to 47.1+/-8.5% fractional excretion on a molar basis. For DINP the identified metabolites totalled 32.9+/-6.4%. For both DEHP and DINP the metabolites were in the abundance order -monoester<-oxo<-carboxy<-hydroxy. These robust fractional excretion values for the main primary and secondary phthalate metabolites along with estimates of their uncertainty can be used in future surveys of human exposure to DEHP and DINP

Int J Androl. 2011 Jun 22. doi: 10.1111/j.1365-2605.2011.01190.x. [Epub ahead of print]
Foetal exposure to phthalate esters and anogenital distance in male newborns.
Suzuki Y, Yoshinaga J, Mizumoto Y, Serizawa S, Shiraishi H.

Phthalate esters, commonly used as plasticizers, show anti-androgenic activity and cause male reproductive malformation in experimental animals. However, the effects of prenatal exposure to phthalate esters in humans have not been extensively studied. The purpose of this study was to examine the relationship between prenatal exposure to phthalate esters and the anogenital distance (AGD) as a reproductive endpoint in human male newborns. Spot urine samples were collected from 111 Japanese pregnant women after obtaining their informed consent. Seven urinary phthalate ester metabolites were determined by high performance liquid chromatography-tandem mass spectrometry. Urinary isoflavones concentrations were measured as possible covariates because their oestrogenicities and high exposure levels among Japanese have the potential to affect male genital development. Birth outcomes and AGD, the distance from the centre of the anus to external genitalia, were measured for their male newborns. In a multiple regression model, the log-transformed mono-2-ethylhexyl phthalate concentration (specific gravity-corrected) was negatively significant, and maternal smoking status was positively significant, in explaining anogenital index (AGI) when potential covariates were controlled for. Urinary isoflavones did not significantly contribute to AGI in any models. Our results suggest that prenatal exposure to di(2-ethylhexyl) phthalate affects reproductive development in human males.

Environ Health Perspect. 2011 Jul 11. [Epub ahead of print]
Relationship between Urinary Phthalate and Bisphenol A Concentrations and Serum Thyroid Measures in U.S. Adults and Adolescents from NHANES 2007-08.
Meeker JD, Ferguson KK.

Background: Limited animal, in vitro, and human studies have reported that exposure to phthalates or bisphenol a (BPA) may impact thyroid signaling. Objective: Explore the cross-sectional relationship between urinary concentrations of metabolites of di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), and BPA with a panel of serum thyroid measures among a representative sample of U.S. adults and adolescents. Methods: Data on urinary biomarkers of exposure to phthalates and BPA, serum thyroid measures, and important covariates from 1346 adults (ages >= 20 years) and 329 adolescents (ages 12-19) from NHANES 2007-08 were analyzed using multivariable linear regression. Results: Among adults, there were significant inverse relationships between urinary DEHP metabolites and total T4, free T4, total T3, and thyroglobulin, and positive relationships with TSH. The strongest and most consistent relationships involved total T4, where adjusted regression coefficients for quintiles of oxidative DEHP metabolites displayed monotonic dose-dependent decreases in total T4 (p-value for trend < 0.0001). Suggestive inverse relationships between urinary BPA and total T4 and TSH were also observed. Conversely, among adolescents, there were significant positive relationships between DEHP metabolites and total T3. Mono(3-carboxypropyl) phthalate (MCCP), a secondary metabolite of both DBP and di-n-octyl phthalate (DOP) was associated with several thyroid measures in both age groups, while other DBP metabolites were not associated with thyroid measures. Conclusions: These results support previous reports of associations between phthalates, and possibly BPA, and altered thyroid hormones. More detailed studies are needed to determine the temporal relationships and potential clinical and public health implications of these associations.

Environ Health Perspect. 2011 Sep 6. [Epub ahead of print]
Maternal Prenatal Urinary Phthalate Metabolite Concentrations and Child Mental, Psychomotor and Behavioral Development at Age Three Years.
Whyatt RM, Liu X, Rauh VA, Calafat AM, Just AC, Hoepner L, Diaz D, Quinn J, Adibi J, Perera FP, Factor-Litvak P.

Background: Research suggests prenatal phthalate exposures affect child executive function and behavior. Objectives: To evaluate associations between phthalate metabolite concentrations in maternal prenatal urine and mental, motor and behavioral development in children at age 3 years. Methods: Mono-n-butyl phthalate (MnBP), mono-benzyl phthalate (MBzP), mono-isobutyl phthalate (MiBP) and 4 di-2-ethylhexyl phthalate metabolites were measured in a spot urine sample collected from 319 women during the 3rd trimester. At child age 3 years, the Mental Development Index (MDI) and Psychomotor Development Index (PDI) were measured using the Bayley Scales of Infant Development II, and behavior problems were assessed by maternal report on the Child Behavior Checklist. Results: Child PDI scores decreased with increasing logeMnBP (estimated adjusted coefficient [β] = -2.81 [95% confidence interval (CI) -4.63, -1.0]) and logeMiBP (β = -2.28 [95% CI -3.90, -0.67]); odds of motor delay increased significantly (estimated adjusted odds ratios (OR) =1.64 [95%CI 1.10, 2.44] and 1.82 [95% CI 1.24, 2.66 per logeMnBP and logeMiBP). In

girls, MDI scores decreased with increasing logeMnBP (β = -2.67 [95% CI -4.70, -0.65]); the child sex difference in odds of mental delay was significant (p=0.037). The OR for clinically withdrawn behavior were 2.23 (95% CI 1.27, 3.92) and 1.57 (95% CI 1.07, 2.31) per loge unit increase in MnBP and MBzP, respectively; for clinically internalizing behaviors, the OR was 1.43 (95% 1.01, 1.90) per loge unit increase in MBzP. Significant child sex differences were seen in associations between MnBP and MBzP and behaviors in internalizing domains (p<0.05). Conclusion: Certain prenatal phthalate exposures may decrease child mental and motor development and increase internalizing behaviors.

Environ Health Perspect. 2011 Jul 7. [Epub ahead of print]
Prenatal Exposure to Phthalates and Infant Development at Six Months: Prospective Mothers and Children's Environmental Health (MOCEH) Study.
Kim Y, Ha EH, Kim EJ, Park H, Ha M, Kim JH, Hong YC, Chang N, Kim BN.

Background: There are increasing concerns over adverse effects of prenatal phthalate exposure on the neurodevelopment of infants. Objectives: Our goal was to explore the association between prenatal di (2-ethylhexyl) phthalate and dibutyl phthalate exposure and the mental (MDI) and psychomotor (PDI) developmental indices of the Bayley Scales of Infant Development at six months, as part of the Mothers and Children's Environmental Health Study. Methods: Between 2006 and 2009, 460 mother/infant pairs from Seoul, Cheonan and Ulsan participated. Prenatal mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono (2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-n-butyl phthalate (MBP) were measured in one urine sample acquired from each mother during the third trimester of pregnancy. Associations with log-transformed creatinine-corrected phthalate concentrations were estimated using linear regression models adjusted for potential confounders. Results: MDI was inversely associated with the natural log concentrations (μg/g creatinine) of MEHHP (B = -0.97, CI = -1.85 to -0.08) and MEOHP (B = -0.95, CI = -1.87 to -0.03), and PDI was inversely associated with MEHHP (B = -1.20, CI = -2.33 to -0.08). In males, MDI was inversely associated with MEHHP (B = -1.46, CI = -2.70 to -0.22), MEOHP (B = -1.57, CI = -2.87 to -0.28), and MBP (B = -0.93, CI = -1.82 to -0.05); and PDI was inversely associated with MEHHP (B = -2.36, CI = -3.94 to -0.79), MEOHP (B = -2.05, CI = -3.71 to -0.39), and MBP (B = -1.25, CI = -2.40 to -0.11). No significant linear associations were observed for females. Conclusions: The results suggest that prenatal exposure to phthalates may be inversely associated with the MDI and PDI of infants, particularly males, at six months.

Int J Mol Epidemiol Genet. 2011 Aug 30;2(3):207-16. Epub 2011 Jun 3.
Using blood gene signatures for assessing effects of exposure to perfluoroalkyl acids (PFAAs) in humans: the NOWAC postgenome study.
Rylander C, Dumeaux V, Olsen KS, Waaseth M, Sandanger TM, Lund E.

Perfluoroalkyl acids (PFAAs) are ubiquitously present in human blood samples and the effects of these compounds on human health are not fully characterized. This study was conducted in order to investigate the applicability of peripheral blood gene expressions for exploring the impact of perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA) and perfluorohexane sulfonate (PFHxS) exposure on the general population. PFOS, PFOA and PFHxS were analyzed in blood samples from a representative group of 270 healthy, postmenopausal Norwegian women (48-62 years). Gene expression was measured in the same samples using the Applied Biosystems microarray platform. Forty-eight different gene sets, all previously linked to PFAA exposure were explored in relation to the selected PFAAs. Two gene sets, both related to the citric acid cycle, were differentially expressed between the "PFOS high" (>30ng/ml, n=42) and the "PFOS low" (<30ng/ml, n=228) group. Based on the results of this study we believe that blood gene signatures have a large potential for elucidating which biological pathways are being affected by environmental pollutants. To the best of our knowledge, this study is the first assessment of the impact of PFAAs on blood gene expressions in humans from the general population.

Am J Epidemiol. 2011 Aug 26. [Epub ahead of print]
Perfluoroalkyl Chemicals and Chronic Kidney Disease in US Adults.
Shankar A, Xiao J, Ducatman A.

Chronic kidney disease (CKD) is a major public health problem. Identifying novel risk factors for CKD, including widely prevalent environmental exposures, is therefore important. Perfluoroalkyl chemicals (PFCs), including perfluorooctanoic acid and perfluorooctane sulfonate, are manmade chemicals that have been detected in the blood of more than 98% of the US population. Results from experimental animal studies have suggested that an association between PFCs and CKD is plausible. However, in humans, the relation between serum PFCs and CKD has not been examined. The authors examined the relation of serum PFCs and CKD in 4,587 adult participants (51.1% women) from the combined 1999-2000 and 2003-2008 cycles of the National Health and Nutritional Examination Survey for whom PFC measurements were available. The main outcome was CKD, defined as a glomerular filtration rate of less than 60 mL/minute/1.73 m(2). The authors found that serum levels of PFCs, including perfluorooctanoic acid and perfluorooctane sulfonate, were positively associated with CKD. This association was independent of confounders such as age, sex, race/ethnicity, body mass index, diabetes, hypertension, and serum cholesterol level. Compared with subjects in quartile 1(referent), the multivariable odds ratio for CKD among subjects in quartile 4 was 1.73 (95% confidence interval: 1.04, 2.88; P for trend = 0.015) for perfluorooctanoic acid and 1.82 (95% confidence interval: 1.01, 3.27; P for trend = 0.019) for perfluorooctane sulfonate. The present results suggest that elevated PFC levels are associated with CKD.

Int J Hyg Environ Health. 2011 Sep 19. [Epub ahead of print]

Placental transfer of perfluorinated compounds is selective - A Norwegian Mother and Child sub-cohort study.

Gützkow KB, Haug LS, Thomsen C, Sabaredzovic A, Becher G, Brunborg G.

Perfluorinated compounds (PFCs) comprise a large group of man-made fluorinated chemicals used in a number of consumer products and industrial applications. PFCs have shown to be persistent, bio-accumulative and widespread in the environment. Animal studies have demonstrated hepatotoxicity, immunotoxicity, developmental toxicity as well as hormonal effects. We investigated prenatal exposure to several PFCs and detected up to seven different PFCs in 123 paired samples of human maternal and cord blood, from a subcohort of the Norwegian Mother and Child Cohort Study (MoBa). The maternal and foetal levels were significantly correlated for all PFCs tested with median PFC concentrations in cord blood ranging between 30 and 79% of the maternal concentrations, demonstrating placental passage. The composition of the different PFCs varied between cord and maternal blood, with a higher proportion of shorter chained PFCs together with a higher amount of the branched isomers of perfluorooctane sulfonate (PFOS) in cord blood. Additionally, the sulfonate group seems to impede transfer efficiency. This indicates a selective placental passage of the different PFCs and hence a specific foetal exposure.

Environ Sci Technol. 2011 Sep 1;45(17):7465-72. Epub 2011 Aug 12.

Trans-placental transfer of thirteen perfluorinated compounds and relations with fetal thyroid hormones.

Kim S, Choi K, Ji K, Seo J, Kho Y, Park J, Kim S, Park S, Hwang I, Jeon J, Yang H, Giesy JP.

While the results of animal studies have shown that perfluorinated compounds (PFCs) can modulate concentrations of thyroid hormones in blood, limited information is available on relationships between concentrations of PFCs in human blood serum and fetal thyroid hormones. The relationship between concentrations of PFCs in blood and fetal thyroid hormone concentrations or birth weight, and ratios of major PFCs between maternal and fetal serum were determined. Concentrations of PFCs were measured in blood serum of pregnant women (n = 44), fetal cord blood serum (n = 43) and breast milk (n = 35). Total concentrations of thyroxin (T4), triiodothyronin (T3) and thyroid stimulating hormone (TSH) in blood serum were also quantified. The ratios of major PFCs in maternal versus fetal serum were 1:1.93, 1.02, 0.72, and 0.48 for perfluorotridecanoic acid (PFTrDA), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorooctane sulfonate (PFOS), respectively. Fetal PFOS, PFOA, PFTrDA and maternal PFTrDA were correlated with fetal total T4 concentrations, but after adjusting for major covariates, most of the relationships were no longer statistically significant. However, the significant negative correlations between maternal PFOS and fetal T3, and maternal PFTrDA and fetal T4 and T3 remained. Since thyroid hormones are crucial in the early development of the fetus, its clinical implication should be evaluated. Given the observed trans-placental transfer of PFCs, efforts should be also made to elucidate the exposure sources among pregnant women.

Environ Health Perspect. 2011 Jul 14. [Epub ahead of print]
Isomer Profiles of Perfluorochemicals in Matched Maternal, Cord and House Dust Samples: Manufacturing Sources and Transplacental Transfer.
Beesoon S, Webster GM, Shoeib M, Harner T, Benskin JP, Martin JW.

BACKGROUND: Perfluorochemicals are detectable in the general population and in the human environment, including house dust. Sources are not well-characterized, but isomer patterns should enable differentiation of historical and contemporary manufacturing sources. Isomer-specific maternal-fetal transfer of perfluorochemicals has not been examined despite known rodent developmental toxicity of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA). OBJECTIVES: To elucidate relative contributions of electrochemical (phased out in 2001) and telomer (contemporary) perfluorochemicals in dust, and to measure how transplacental transfer efficiency (TTE, based on a comparison of maternal and cord sera concentrations) is affected by perfluorinated chain-length and isomer branching pattern. METHODS: Matching samples of house dust (n=18), maternal sera (n=20) and umbilical cord-sera (n=20) were analyzed by isomer specific HPLC-MS/MS. RESULTS: PFOA isomer signatures revealed that telomer sources accounted for 0 to 95% of total PFOA in house dust (median = 31 %). This may partly explain why serum PFOA concentrations are not declining in some countries despite the phase-out of electrochemical PFOA. TTE data indicate that total branched isomers crossed the placenta more efficiently than linear isomers for both PFOS ($p<0.01$) and PFOA ($p=0.02$), and that placental transfer of branched isomers of PFOS increased as the branching point moved closer to the sulfonate (SO3-) end of the molecule. CONCLUSIONS: Results suggest that humans are exposed to telomer PFOA, but larger studies that also account for dietary sources should be conducted. The exposure profile of PFOS and PFOA isomers can differ between the mother and fetus, an important consideration for perinatal epidemiology studies of perfluorochemicals.

J Clin Endocrinol Metab. 2011 Aug 10. [Epub ahead of print]
The Exposure of Fetuses and Children to Endocrine Disrupting Chemicals: A European Society for Paediatric Endocrinology (ESPE) and Pediatric Endocrine Society (PES) Call to Action Statement.
Skakkebaek NE, Toppari J, Söder O, Gordon CM, Divall S, Draznin M.

Objective: During recent years, evidence has accumulated that both wildlife species and humans are exposed to ubiquitous endocrine-disrupting chemicals. Some are persistent in our bodies; others are nonpersistent but are produced in large quantities. Hitherto, the bulk of research in this area has been carried out by basic and experimental scientists and wildlife researchers. Relatively few clinical scientists have been engaged in research on this topic to date. The aim of this statement is to have pediatric endocrinologists consider the issue of endocrine disrupters in their clinical work and research. Participants: Six pediatric endocrinologists who belonged to working groups on endocrine disrupters endorsed by the European Society for Paediatric Endocrinology (ESPE) and the Pediatric Endocrine Society (PES) participated, including three members from each society. Meetings were limited to the members of the working groups. No funding was associated with the work. Evidence: Important data sources were publications from the World Health Organization, the European Science Foundation, and The Endocrine Society. Several of the participants have made long-standing contributions to the field of endocrine disruption. No unpublished work was considered. Consensus Process: The statement was written by the committee members together, using e-mail and phone. A draft was submitted to the Boards of the ESPE and PES. After some changes, the draft was accepted by both Boards. Conclusions: Pediatric endocrinologists are urged to be alert to the possible significance of endocrine-disrupting chemicals when assessing both clinical problems and research data where etiologies of endocrine symptoms or diseases are unknown.

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34: Marquez EC, Traylor-Knowles N, Novillo-Villajos A, Callard IP. Cloning of estrogen receptor alpha and aromatase cDNAs and gene expression in turtles (Chrysemys picta and Pseudemys scripta) exposed to different environments. Comp Biochem Physiol C Toxicol Pharmacol. 2011 Sep;154(3):213-25. Epub 2011 Jun 1. PubMed PMID: 21664488.

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38: Ye X, Zhou X, Furr J, Ahn KC, Hammock BD, Gray EL, Calafat AM. Biomarkers of exposure to triclocarban in urine and serum. Toxicology. 2011 Aug 15;286(1-3):69-74. Epub 2011 May 23. PubMed PMID: 21635932.

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41: Xu X, Tian D, Hong X, Chen L, Xie L. Sex-specific influence of exposure to bisphenol-A between adolescence and young adulthood on mouse behaviors.Neuropharmacology. 2011 Sep;61(4):565-73. Epub 2011 May 5. PubMed PMID: 21570416.

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44: Kundakovic M, Champagne FA. Epigenetic perspective on the developmental effects of bisphenol A. Brain Behav Immun. 2011 Aug;25(6):1084-93. Epub 2011 Feb 17. PubMed PMID: 21333735.

45: Wang H, Wang SF, Ning H, Ji YL, Zhang C, Zhang Y, Yu T, Ma XH, Zhao XF, Wang Q, Liu P, Meng XH, Xu DX. Maternal cypermethrin exposure during lactation impairs testicular development and spermatogenesis in male mouse offspring. Environ Toxicol. 2011 Aug;26(4):382-94. doi: 10.1002/tox.20566. Epub 2010 Feb 3. PubMed PMID: 20131380.

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*"
Limits Activated**:** published in the last 180 days (juli-september 2011)
Efter at have fjernet genganger fra forrige litteraturopdateringslister, gav litteratursøgningen med de to søgekriterier tilsammen en liste med i alt 27 artikler.

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

Udvalgte publikationer:

Estrogen agonist/antagonist properties of dibenzyl phthalate (DBzP) based on **in vitro** and in vivo assays.

Zhang Z, Hu Y, Zhao L, Li J, Bai H, Zhu D, Hu J.

Abstract

The most commonly used phthalates have been banned or restricted for use as plasticizers in toys in some countries because of their endocrine-disrupting properties. Dibenzyl phthalate (DBzP) has been proposed as a possible alternative for the banned/restricted phthalates. In this study, the estrogen agonist/antagonist properties of DBzP were predicted by molecular docking and confirmed by yeast estrogen screen (YES) and immature mouse uterotrophic assays. The YES assay results showed a dose-dependent increase in DBzP estrogen agonist activity from 10^{-6} to 10^{-4} M, and at concentrations from 1.95×10^{-6} M to higher, DBzP significantly inhibited the agonist activity of 10^{-9} M 17β-estradiol (E_2), inhibiting 10^{-9} M E_2 by 74.5% at its maximum effectiveness. The *in vivo* estrogen agonist/antagonist activities of DBzP were demonstrated in immature mouse uterotrophic assays. The antagonist activity of DBzP inhibited E_2-induced uterine growth promoted at 40 and 400 μg/kg bw (body weight) ($P < 0.05$). In addition, we also analyzed the estrogen agonist/antagonist potentials of benzyl butyl phthalate (BBP) by YES, and found both were weaker than those of DBzP, suggesting DBzP would be more toxic than BBP and should not be used as an alternative plasticizer.

In vitro steroidogenic effects of mixtures of persistent organic pollutants (POPs) extracted from burbot (Lota lota) caught in two Norwegian lakes.

Zimmer KE, Montaño M, Olsaker I, Dahl E, Berg V, Karlsson C, Murk AJ, Skaare JU, Ropstad E, Verhaegen S.

Abstract

This study investigated the effects of two mixtures of persistent organic pollutants (POPs) on steroidogenesis in the H295R cell line. The two mixtures were obtained from the livers of burbot (Lota lota) caught in two Norwegian lakes (Mjøsa and Losna) with different contaminant profiles. Steroid hormone levels in the cell culture medium and mRNA levels of 16 genes involved in steroidogenesis were investigated. The crude Lake Mjøsa extract had to be diluted ten times more than the Lake Losna extract in order to prevent cytotoxicity. The ten times diluted Lake Mjøsa mixture had higher levels of DDT and derivates (∑DDTs, 1.7 times) and brominated flame retardants (∑BDEs and HBCD, 15-25 times) than the Lake Losna mixture, which, on the other hand, had higher concentrations of ∑PCBs (1.5 times higher) and also of HCB, ∑HCH isomers and ∑chlordane isomers (5-20 times higher). In the cell culture media, only cortisol levels were increased at the highest exposure concentration to the Lake Mjøsa mixture, while both cortisol and estradiol levels were increased following exposure to the two highest Lake Losna mixture exposure

concentrations. Testosterone levels decreased only at the highest exposure concentration of the Lake Losna mixture. Multivariate models suggested that ∑PCBs, and to a lesser extent ∑DDTs, were responsible for the cortisol responses, while estradiol and testosterone alterations were best explained by HCB and ∑PCBs, respectively. Exposure to the mixtures generally increased mRNA levels, with smaller effects exerted by the Lake Mjøsa mixture than the Lake Losna mixture. It was concluded that both mixtures affected steroidogenesis in the H295R cells. Small differences in mixture composition, rather than the high content of brominated flame retardants in the Lake Mjøsa mixture, were suggested to be the most probable reason for the apparent differences in potencies of the two mixtures.

Does the oestrogen receptor encourage oestrogenicity in environmental pollutants? The case of **4-nonylphenol**.
Graham LA, Shaw IC.
Abstract
A computer-aided docking study was conducted to explore in detail the binding interactions between the structurally unlikely environmental oestrogen 4-nonylphenol (4NP) and three of its metabolites with the human oestrogen receptor alpha (hERα). Docking was done within the Schrodinger Suite 2008 using both a conventional rigid receptor with flexible ligand and the induced-fit docking protocol. Induced-fit docking allows side-chain and backbone movement in the receptor to accommodate the ligand. This study has revealed unconventional interactions between the ligands and the hERα binding pocket that could explain the observed oestrogen-like behaviour of 4NP and suggests some of the metabolites of 4NP may also be oestrogenic

Bruttolisten

1. Actions of estrogens and **endocrine disrupting** chemicals on human prostate stem/progenitor cells and prostate cancer risk.
Hu WY, Shi GB, Hu DP, Nelles JL, Prins GS.
Mol Cell Endocrinol. 2011 Sep 5. [Epub ahead of print]

2. **In vitro** modulation of intracellular receptor signaling and cytotoxicity induced by extracts of cyanobacteria, complex water blooms and their fractions.
Stěpánková T, Ambrožová L, Bláha L, Giesy JP, Hilscherová K.
Aquat Toxicol. 2011 Aug 9;105(3-4):497-507. [Epub ahead of print]

3. Estrogen agonist/antagonist properties of dibenzyl phthalate (DBzP) based on **in vitro** and in vivo assays.
Zhang Z, Hu Y, Zhao L, Li J, Bai H, Zhu D, Hu J.
Toxicol Lett. 2011 Aug 27. [Epub ahead of print]

4. Multivariate toxicity profiles and QSAR modeling of non-dioxin-like PCBs - An investigation of **in vitro** screening data from ultra-pure congeners.
Stenberg M, Hamers T, Machala M, Fonnum F, Stenius U, Lauy AA, van Duursen MB, Westerink RH, Fernandes EC, Andersson PL.
Chemosphere. 2011 Sep 2. [Epub ahead of print]

5. Evaluation of the fish short term reproduction assay for detecting **endocrine disrupters**.

Dang Z, Traas T, Vermeire T.
Chemosphere. 2011 Aug 30. [Epub ahead of print]

6. The feasibility of using mosquitofish (Gambusia affinis) for detecting **endocrine-disrupting** chemicals in the freshwater environment.
Kamata R, Itoh K, Nakajima D, Kageyama S, Sawabe A, Terasaki M, Shiraishi F.
Environ Toxicol Chem. 2011 Aug 31. doi: 10.1002/etc.669. [Epub ahead of print]

7. Enantioselective **endocrine-disrupting** effects of bifenthrin on hormone synthesis in rat ovarian cells.
Liu J, Yang Y, Zhuang S, Yang Y, Li F, Liu W.
Toxicology. 2011 Aug 19. [Epub ahead of print]

8. Gene alterations of ovarian cancer cells expressing estrogen receptors by estrogen and bisphenol a using microarray analysis.
Hwang KA, Park SH, Yi BR, Choi KC.
Lab Anim Res. 2011 Jun;27(2):99-107. Epub 2011 Jun 22.

9. Can pharmaceuticals interfere with the synthesis of active androgens in male fish? An **in vitro** study.
Fernandes D, Schnell S, Porte C.
Mar Pollut Bull. 2011 Aug 4. [Epub ahead of print]

10. Human meiotic progression and recombination are affected by Bisphenol A exposure during **in vitro** human oocyte development.
Brieño-Enríquez MA, Robles P, Camats-Tarruella N, García-Cruz R, Roig I, Cabero L, Martínez F, Caldés MG.
Hum Reprod. 2011 Oct;26(10):2807-18. Epub 2011 Jul 26.

11. Bis(hydroxyphenyl)methane-bisphenol F-metabolism by the HepG2 human hepatoma cell line and cryopreserved human hepatocytes.
Dumont C, Perdu E, de Sousa G, Debrauwer L, Rahmani R, Cravedi JP, Chagnon MC.
Drug Chem Toxicol. 2011 Oct;34(4):445-53. Epub 2011 Jul 19.

12. Screening of multiple hormonal activities in surface water and sediment from the Pearl River system, South China, using effect-directed **in vitro** bioassays.
Zhao JL, Ying GG, Yang B, Liu S, Zhou LJ, Chen ZF, Lai HJ.
Environ Toxicol Chem. 2011 Oct;30(10):2208-15. doi: 10.1002/etc.625. Epub 2011 Aug 17.

13. Benzo[a]pyrene Reduces Testosterone Production in Rat Leydig Cells via a Direct Disturbance of Testicular Steroidogenic Machinery.
Chung JY, Kim YJ, Kim JY, Lee SG, Park JE, Kim WR, Yoon YD, Yoo KS, Yoo YH, Kim JM.
Environ Health Perspect. 2011 Jul 7. [Epub ahead of print]

14. **In vitro** profiling of **endocrine disrupting** potency of 2,2',4,4'-tetrabromodiphenyl ether (BDE47) and related hydroxylated analogs (HO-PBDEs).
Liu H, Hu W, Sun H, Shen O, Wang X, Lam MH, Giesy JP, Zhang X, Yu H.
Mar Pollut Bull. 2011;63(5-12):287-96. Epub 2011 Jul 6.

15. Persistent organic pollutants have dose and CAG repeat length dependent effects on androgen receptor activity **in vitro**.
Björk C, Nenonen H, Giwercman A, Bergman A, Rylander L, Giwercman YL.
Reprod Toxicol. 2011 Jun 25. [Epub ahead of print]

16. The anti-estrogenic activity of sediments from agriculturally intense watersheds: assessment using in vivo and **in vitro** assays.
Sellin Jeffries MK, Conoan NH, Cox MB, Sangster JL, Balsiger HA, Bridges AA, Cowman T, Knight LA, Bartelt-Hunt SL, Kolok AS.
Aquat Toxicol. 2011 Sep;105(1-2):189-98. Epub 2011 Apr 22.

17. Adverse effects in wild fish living downstream from pharmaceutical manufacture discharges.
Sanchez W, Sremski W, Piccini B, Palluel O, Maillot-Maréchal E, Betoulle S, Jaffal A, Aït-Aïssa S, Brion F, Thybaud E, Hinfray N, Porcher JM.
Environ Int. 2011 Nov;37(8):1342-8. Epub 2011 Jun 30.

18. **In vitro** exposure of Nile tilapia (Oreochromis niloticus) testis to estrogenic **endocrine disrupting** chemicals: mRNA expression of genes encoding steroidogenic enzymes.
Ribeiro C, Urbatzka R, Castro LF, Carrola J, Fontainhas-Fernandes A, Monteiro RA, Rocha E, Rocha MJ.
Toxicol Mech Methods. 2011 Jul 1. [Epub ahead of print]

19. Changed preference for sweet taste in adulthood induced by perinatal exposure to bisphenol A-A probable link to overweight and obesity.
Xu X, Tan L, Himi T, Sadamatsu M, Tsutsumi S, Akaike M, Kato N.
Neurotoxicol Teratol. 2011 Jul-Aug;33(4):458-63. Epub 2011 Jun 17.

20. Effect of brominated flame retardant BDE-47 on androgen production of adult rat Leydig cells.
Zhao Y, Ao H, Chen L, Sottas CM, Ge RS, Zhang Y.
Toxicol Lett. 2011 Aug 28;205(2):209-14. Epub 2011 Jun 16.

21. CADMIUM-INDUCED APOPTOSIS AND NECROSIS IN HUMAN OSTEOBLASTS: ROLE OF CASPASES AND MITOGEN-ACTIVATED PROTEIN KINASES PATHWAYS.
Brama M, Politi L, Santini P, Migliaccio S, Scandurra R.
J Endocrinol Invest. 2011 Jun 21. [Epub ahead of print]

22. Xenobiotic Effects on Ovarian Preantral Follicles.
Mark-Kappeler CJ, Hoyer PB, Devine PJ.
Biol Reprod. 2011 Jun 22. [Epub ahead of print]

23. Effect of ozonation on the estrogenicity and androgenicity of oil sands process-affected water.
He Y, Wiseman SB, Hecker M, Zhang X, Wang N, Perez LA, Jones PD, El-Din MG, Martin JW, Giesy JP.
Environ Sci Technol. 2011 Aug 1;45(15):6268-74. Epub 2011 Jun 29.

24. Epigenetic screening in product safety assessment: are we there yet?
Rasoulpour RJ, LeBaron MJ, Ellis-Hutchings RG, Klapacz J, Gollapudi BB.

Toxicol Mech Methods. 2011 May;21(4):298-311. Review.

25. **In vitro** steroidogenic effects of mixtures of persistent organic pollutants (POPs) extracted from burbot (Lota lota) caught in two Norwegian lakes.
Zimmer KE, Montaño M, Olsaker I, Dahl E, Berg V, Karlsson C, Murk AJ, Skaare JU, Ropstad E, Verhaegen S.
Sci Total Environ. 2011 May 1;409(11):2040-8. Epub 2011 Mar 21.

26. Estrogenic activity profiles and risks in surface waters and sediments of the Pearl River system in South China assessed by chemical analysis and **in vitro** bioassay.
Zhao JL, Ying GG, Chen F, Liu YS, Wang L, Yang B, Liu S, Tao R.
J Environ Monit. 2011 Apr;13(4):813-21. Epub 2010 Dec 15.

27. Effects of progesterone on sperm motility in fathead minnow (Pimephales promelas).
Murack PJ, Parrish J, Barry TP.
Aquat Toxicol. 2011 Jul;104(1-2):121-5. Epub 2011 Apr 15.

Herudover er der yderligere 3 artikeler, som ikke blev fanget af de valgte søgekriterier
Does the oestrogen receptor encourage oestrogenicity in environmental pollutants? The case of **4-nonylphenol**.
Graham LA, Shaw IC.
SAR QSAR Environ Res. 2011 Jun;22(3):329-50.

Androgen receptor binding affinity: a **QSAR** evaluation.
Todorov M, Mombelli E, Ait-Aissa S, Mekenyan O.
SAR QSAR Environ Res. 2011 Jun;22(3):265-91.

Screening for low **aquatic bioaccumulation** (2): physico-chemical constraints.
Nendza M, Herbst T.
SAR QSAR Environ Res. 2011 Jun;22(3):351-64.

In Vivo studier ved DTU - FOOD

Søgning er udført på PubMed og dækker perioden 23/6/2011-22/9 2011

(Juli – September 2011)

Følgende søgeprofil er benyttet: ”(endocrine disrupt*) AND utero* AND (rat OR mice OR mammal*)” samt ”(endocrine disrupt*) AND (rat OR mice OR mammal*)”. Derudover er der også søgt på ”Paraben* AND in vivo*”.

Efter at have fjernet genganger fra dem vi havde med på den forrige litteraturopdateringsliste, gav litteratursøgningen tilsammen en liste med i alt 25 artikler: (Bruttolisten):

De udvalgte studier har fokus på phthalater, mixture (mammary gland) og BPA.

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

Udvalgte publikationer:

Dose-response assessment of fetal testosterone production and gene expression levels in rat testes following in utero exposure to diethylhexyl phthalate, diisobutyl phthalate, diisoheptyl phthalate, and diisononyl phthalate.

Hannas BR, Lambright CS, Furr J, Howdeshell KL, Wilson VS, Gray LE Jr.
Toxicol Sci. 2011 Sep;123(1):206-16. Epub 2011 Jun 1.

Abstract Several phthalate esters have been linked to the Phthalate Syndrome, affecting male reproductive development when administered to pregnant rats during in utero sexual differentiation. The goal of the current study was to enhance understanding of this class of compounds in the Sprague Dawley (SD) fetal rat following exposure on gestational days (GDs) 14-18 by determining the relative potency factors for several phthalates on fetal testes endpoints, the effects of a nine phthalate mixture on fetal testosterone (T) production, and differences in SD and Wistar (W) strain responses of fetal T production and testicular gene expression to di(2-ethylhexyl) phthalate (DEHP). We determined that diisobutyl phthalate (DIBP) and diisoheptyl phthalate (DIHP) reduced fetal testicular T production with similar potency to DEHP, whereas diisononyl phthalate (DINP) was 2.3-fold less potent. DINP was also less potent at reducing StAR and Cyp11a gene expression levels, whereas DIBP was slightly more potent than DEHP. We observed that administration of dilutions of a mixture of nine phthalates (DEHP, DIHP, DIBP, dibutyl-, benzyl butyl-, dicyclohexyl-, diheptyl-, dihexyl-, and dipentyl phthalate) reduced fetal T production in a dose-dependent manner best predicted by dose addition. Finally, we found that the differential effects of in utero DEHP treatment on epididymal and gubernacular differentiation in male SD and W rats (0, 100, 300, 500, 625, 750, or 875 mg DEHP/kg/day) are likely due to tissue-specific strain differences in the androgen and insl3 signaling pathways rather than differential effects of DEHP on fetal testis T and insl3 production.

Abnormal peripubertal development of the rat mammary gland following exposure in utero and during lactation to a mixture of genistein and the food contaminant vinclozolin.

El Sheikh Saad H, Meduri G, Phrakonkham P, Bergès R, Vacher S, Djallali M, Auger J, Canivenc-Lavier MC, Perrot-Applanat M.
Reprod Toxicol. 2011 Jul;32(1):15-25. Epub 2011 Apr 23.

Abstract The impact of early exposure to endocrine disruptor mixtures on mammary gland development is poorly known. Here, we identify the effects of a conception to weaning exposure of rats to the phytoestrogen genistein (G) and/or the antiandrogen vinclozolin (V) at 1mg/kg-d, alone or in association. Using several approaches, we found that G- and GV-exposed rats displayed significantly greater epithelial branching and proliferation, wider terminal end buds than controls at PND35, as well as ductal hyperplasia and periductal fibrosis. Focal branching defects were present in V-exposed rats. An increased ER and AR expression was observed in G- and GV- as compared to V-exposed rats at PND35. Surprisingly, a significant number of GV- and to a lesser extent, V-exposed animals displayed abnormal hyperplasic alveolar structures at PND50. Thus, gestational and lactational exposure to low doses of genistein plus vinclozolin may seriously affect peripubertal development of the rat mammary gland.

Changed preference for sweet taste in adulthood induced by perinatal exposure to bisphenol A-A probable link to overweight and obesity
Xu X, Tan L, Himi T, Sadamatsu M, Tsutsumi S, Akaike M, Kato N.
Neurotoxicol Teratol. 2011 Jul-Aug;33(4):458-63. Epub 2011 Jun 17.
Abstract
Background The preference of obesity has risen dramatically worldwide over the past decades. Some latest reports showed significant increase of obesity in men compared to women. Implication of environmental endocrine disruptors has been focused more and more. Numerous studies in vitro and vivo implied metabolic actions of bisphenol A (BPA), however much less consideration is given to the possibility of BPA exposure-induced change in gender-specific behaviors which result in obesity and overweight.
Objectives To examine whether perinatal exposure to BPA at relative dose to environmental levels can influence sweet preference of male and female rats and consequently lead to alteration in bodyweight.
Methods Rats perinatally exposed to BPA at doses of 0.01, 0.1 and 1.0 mg/L were tested sweet preference for 0.25%, 0.5% saccharin and 15% sucrose by two-bottle choice (water vs. saccharin/sucrose). The food intake, liquid consumption and bodyweight of each rat were monitored daily. At the end of the test, the fat percentage and tail blood pressure were measured.
Results Significant sex difference of preference for 0.25% and 0.5% saccharin was shown in control and all BPA-treated groups ($p < 0.001$, female vs. male). 0.1 and 1.0 mg/L BPA treatment induced the increase of preference for 0.25% saccharin solution in males, but not in females. 0.1 mg/L BPA treatment increased sucrose preference in males at postnatal day (PND) 70 and 140 ($p < 0.05$ and $p < 0.001$, compared to control respectively) but decreased sucrose preference in females at PND 140 ($p < 0.05$, compared to control). The males treated by BPA showed overweight ($p < 0.001$), high fat percentage ($p < 0.001$) and tail blood pressure ($p < 0.05$) than control at PND 140.
Conclusion Perinatal exposure to a low dose of BPA could increase sweet preference of male rats. Calorie intake may be programmed during early life, leading to changes of body weight depending on the gender. Although further researches concerning the mechanism are required, the results of the present study are particularly important with regards to the more significant increasing prevalence of obesity in men and the environmental endocrine disruptors.

Bruttolisten in vivo

1. Inhibition of human and rat testicular steroidogenic enzyme activities by bisphenol A.
Ye L, Zhao B, Hu G, Chu Y, Ge RS.
Toxicol Lett. 2011 Sep 8. [Epub ahead of print]

2. ERα phenotype, estrogen level, and benzo[a]pyrene exposure modulate tumor growth and metabolism of lung adenocarcinoma cells.
Lin S, Lin CJ, Hsieh DP, Li LA.
Lung Cancer. 2011 Sep 13. [Epub ahead of print]

3. Diethyl hexyl phthalate-induced changes in insulin signaling molecules and the protective role of antioxidant vitamins in gastrocnemius muscle of adult male rat.
Srinivasan C, Khan AI, Balaji V, Selvaraj J, Balasubramanian K.
Toxicol Appl Pharmacol. 2011 Sep 2. [Epub ahead of print]

4. Mechanistic mammalian target of rapamycin (MTOR) cell signaling: Effects of select nutrients and secreted phosphoprotein 1 on development of mammalian conceptuses.
Bazer FW, Song G, Kim J, Erikson DW, Johnson GA, Burghardt RC, Gao H, Carey Satterfield M, Spencer TE, Wu G.
Mol Cell Endocrinol. 2011 Sep 1. [Epub ahead of print]

5. Enantioselective endocrine-disrupting effects of bifenthrin on hormone synthesis in rat ovarian cells.
Liu J, Yang Y, Zhuang S, Yang Y, Li F, Liu W.
Toxicology. 2011 Aug 19. [Epub ahead of print]

6. Bisphenol-A suppresses neurite extension due to inhibition of phosphorylation of mitogen-activated protein kinase in PC12 cells.
Seki S, Aoki M, Hosokawa T, Saito T, Masuma R, Komori M, Kurasaki M.
Chem Biol Interact. 2011 Aug 19. [Epub ahead of print]

7. Effects of di-n-butyl phthalate on male rat reproduction following pubertal exposure.
Bao AM, Man XM, Guo XJ, Dong HB, Wang FQ, Sun H, Wang YB, Zhou ZM, Sha JH.
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Wildlife studier ved Biologisk Institut, Syddansk Universitet (SDU)

Søgningen er udført på Web of Science og dækker perioden 27/6 2011 – 23/9 2011.

Søgeprofilen kombinerer:	Endocrine disrupt*	og	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 3 artikler til medtagelse af abstract og yderligere kommentarer.

Artikel 1:

Title: Adverse effects in wild fish living downstream from pharmaceutical manufacture discharges
Author(s): Sanchez Wilfried; Sremski William; Piccini Benjamin; et al.
Source: ENVIRONMENT INTERNATIONAL Volume: 37 Issue: 8 Pages: 1342-1348

Abstract: A set of biochemical and histological responses was measured in wild gudgeon collected upstream and downstream of urban and pharmaceutical manufacture effluents. These individual end-points were associated to fish assemblage characterisation. Responses of biotransformation enzymes, neurotoxicity and endocrine disruption biomarkers revealed contamination of investigated stream by a mixture of pollutants. Fish from sampled sites downstream of the industrial effluent exhibited also strong signs of endocrine disruption including vitellogenin induction, intersex and male-biased sex-ratio. These individual effects were associated to a decrease of density and a lack of sensitive fish species. This evidence supports the hypothesis that pharmaceutical compounds discharged in stream are involved in recorded endocrine disruption effects and fish population disturbances and threaten disappearance of resident fish species. Overall, this study gives argument for the utilisation of an effect-based monitoring approach to assess impacts of pharmaceutical manufacture discharges on wild fish populations.

Artikel 2:

Title: Selective uptake and biological consequences of environmentally relevant antidepressant pharmaceutical exposures on male fathead minnows
Author(s): Schultz Melissa M.; Painter Meghan M.; Bartell Stephen E.; et al.
Source: AQUATIC TOXICOLOGY Volume: 104 Issue: 1-2 Pages: 38-47

Abstract: Antidepressant pharmaceuticals have been reported in wastewater effluent at the nanogram to low microgram-per-liter range, and include bupropion (BUP), fluoxetine (FLX), sertraline (SER), and venlafaxine (VEN). To assess the effects of antidepressants on reproductive anatomy, physiology, and behavior, adult male fathead minnows (Pimephales promelas) were exposed for 21 days either to a single concentration of the antidepressants FLX, SER, VEN, or BUP, or to an antidepressant mixture. The data demonstrated that exposure to VEN (305 ng/L and 1104 ng/L) and SER (5.2 ng/L) resulted in mortality. Anatomical alterations were noted within the testes of fish exposed to SER and FLX, both modulators of the neurotransmitter serotonin. Additionally, FLX at 28 ng/L induced vitellogenin in male fish—a common endpoint for estrogenic endocrine disruption. Significant alterations in male secondary sex characteristics

were noted with single exposures. Effects of single compound exposures neither carried over, nor became additive in the antidepressant mixtures, and reproductive behavior was not affected. Analysis of brain tissues from the exposed fish suggested increased uptake of FLX, SER and BUP and minimal uptake of VEN when compared to exposure water concentrations. Furthermore, the only metabolite detected consistently in the brain tissues was norfluoxetine. Similar trends of uptake by brain tissue were observed when fish were exposed to antidepressant mixtures. The present study demonstrates that anatomy and physiology, but not reproductive behavior, can be disrupted by exposure to environmental concentrations of some antidepressants. The observation that antidepressant uptake into fish tissues is selective may have consequences on assessing the mode-of-action and effects of these compounds in future studies.

Artikel 3:

Title: The synthetic gestagen levonorgestrel impairs metamorphosis in Xenopus laevis by disruption of the thyroid system
Author(s): Lorenz Claudia; Contardo-Jara Valeska; Pflugmacher Stephan; et al.
Source: TOXICOLOGICAL SCIENCES Volume: 123 Issue: 1 Pages: 94-102

Abstract: Synthetic gestagens, including levonorgestrel (LNG), are active compounds in contraceptives, and several studies report their occurrence in surface waters. However, information about endocrine-disrupting effects in nontarget organisms is scarce. The present study investigated effects of LNG exposure on thyroid hormone–dependent metamorphosis of Xenopus laevis. Premetamorphic X. laevis tadpoles at Nieuwkoop and Faber (NF) stage 48 were exposed in a flow-through culture system to four LNG concentrations (10211, 10210, 1029, and 1028M) over the period of metamorphosis. At NF 58 and 66, tadpoles were examined sex specifically. Developmental time and organismal responses were recorded and correlated with molecular and histopathological endpoints. Exposure to 1028M LNG caused an inhibition of metamorphosis resulting in developmental arrest at early climax stages as giant tadpoles or tailed frogs. In brain-pituitary tissue of NF 58 tadpoles, gene expression of thyroid-stimulating hormone (b-subunit; TSHb), TH receptor b (TRb), and deiodinase type 3 (D3) was not changed. Instead, prolactin (PRL) messenger RNA (mRNA) was significantly increased by 1029M LNG in females and by 1028M LNG in both sexes. In NF 66 tadpoles, mRNA levels of TSHb mRNA were significantly increased in the 1029 and 1028M LNG treatment groups indicating a hypothyroid state. No changes of TRb, D3, and PRL gene expression were detected. Histopathological evaluation of thyroid gland sections revealed no typical sign of hypothyroidism but rather an inactivated appearance of the thyroid. In conclusion, our data demonstrate for the first time a completely new aspect of thyroid system disruption caused by synthetic gestagens in developing amphibians.

Bruttoliste:

Title: Adverse effects in wild fish living downstream from pharmaceutical manufacture discharges
Author(s): Sanchez Wilfried; Sremski William; Piccini Benjamin; et al.
Source: ENVIRONMENT INTERNATIONAL Volume: 37 Issue: 8 Pages: 1342-1348

Title: Thyroid axis disruption in juvenile brown trout (Salmo trutta) exposed to the flame retardant beta-tetrabromoethylcyclohexane (beta-TBECH) via the diet
Author(s): Park Bradley J.; Palace Vince; Wautier Kerry; et al.
Source: ENVIRONMENTAL SCIENCE & TECHNOLOGY Volume: 45 Issue: 18 Pages: 7923-7927

Title: Decreased vitellogenin inducibility and 17 beta-estradiol levels correlated with reduced egg production in killifish (Fundulus heteroclitus) from Newark Bay, NJ
Author(s): Bugel Sean M.; White Lori A.; Cooper Keith R.
Source: AQUATIC TOXICOLOGY Volume: 105 Issue: 1-2 Pages: 1-12

Title: Bezafibrate, a lipid-lowering pharmaceutical, as a potential endocrine disruptor in male zebrafish (Danio rerio)
Author(s): Velasco-Santamaria Yohana M.; Korsgaard Bodil; Madsen Steffen S.; et al.
Source: AQUATIC TOXICOLOGY Volume: 105 Issue: 1-2 Pages: 107-118

Title: Generation of fluorescent zebrafish to study endocrine disruption and potential crosstalk between thyroid hormone and corticosteroids
Author(s): Terrien Xavier; Fini Jean-Baptiste; Demeneix Barbara A.; et al.
Source: AQUATIC TOXICOLOGY Volume: 105 Issue: 1-2 Pages: 13-20

Title: Low-dose exposure to alkylphenols adversely affects the sexual development of Atlantic cod (Gadus morhua): Acceleration of the onset of puberty and delayed seasonal gonad development in mature female cod
Author(s): Meier Sonnich; Morton H. Craig; Andersson Eva; et al.
Source: AQUATIC TOXICOLOGY Volume: 105 Issue: 1-2 Pages: 136-150

Title: The anti-estrogenic activity of sediments from agriculturally intense watersheds: Assessment using in vivo and in vitro assays
Author(s): Jeffries Marlo K. Sellin; Conoan Nicholas H.; Cox Marc B.; et al.
Source: AQUATIC TOXICOLOGY Volume: 105 Issue: 1-2 Pages: 189-198

Title: 17 alpha-Ethinyl estradiol affects anxiety and shoaling behavior in adult male zebra fish (Danio rerio)
Author(s): Reyhanian Nasim; Volkova Kristina; Hallgren Stefan; et al.
Source: AQUATIC TOXICOLOGY Volume: 105 Issue: 1-2 Pages: 41-48

Title: Short-term exposure to a treated sewage effluent alters reproductive behaviour in the three-spined stickleback (Gasterosteus aculeatus)
Author(s): Sebire Marion; Katsiadaki Ioanna; Taylor Nick G. H.; et al.
Source: AQUATIC TOXICOLOGY Volume: 105 Issue: 1-2 Pages: 78-88

Title: Ligula intestinalis infection is associated with alterations of both brain and gonad aromatase expression in roach (Rutilus rutilus)
Author(s): Boulange-Lecomte C.; Geraudie P.; Forget-Leray J.; et al.
Source: JOURNAL OF HELMINTHOLOGY Volume: 85 Issue: 3 Pages: 339-344

Title: Transcriptional regulatory dynamics of the hypothalamic-pituitary-gonadal axis and its peripheral pathways as impacted by the 3-beta HSD inhibitor trilostane in zebrafish (Danio rerio)
Author(s): Wang Rong-Lin; Bencic David; Lazorchak Jim; et al.
Source: ECOTOXICOLOGY AND ENVIRONMENTAL SAFETY Volume: 74 Issue: 6 Pages: 1461-1470

Title: Early life-stage and multigeneration toxicity study with bisphenol A and fathead minnows (Pimephales promelas)
Author(s): Staples Charles A.; Hall A. Tilghman; Friederich Urs; et al.
Source: ECOTOXICOLOGY AND ENVIRONMENTAL SAFETY Volume: 74 Issue: 6 Pages: 1548-1557

Title: Use of sex ratio of bream (Abramis brama L.) as an indicator of endocrine effects: Results from the German Environmental Specimen Bank
Author(s): Teubner Diana; Tarricone Kathrin; Veith Michael; et al.
Source: ECOLOGICAL INDICATORS Volume: 11 Issue: 5 Pages: 1487-1489

Title: Toxic influence of endocrine disruptor, carbendazim, on brain biochemical and haematological changes in the fresh water fish, Cyprinus carpio
Author(s): Govindassamy P.; Tiroumavalavane M.; Marcelline S. O.; et al.
Conference: 47th Congress of the European-Societies-of-Toxicology Location: Paris, FRANCE Date: AUG 28-31, 2011
Sponsor(s): European Soc Toxicol
Source: TOXICOLOGY LETTERS Volume: 205 Supplement: 1 Pages: S125-S125

Title: Low-dose effects and biphasic effect profiles: Is trenbolone a genotoxicant?
Author(s): Boettcher Melanie; Kosmehl Thomas; Braunbeck Thomas
Source: MUTATION RESEARCH-GENETIC TOXICOLOGY AND ENVIRONMENTAL MUTAGENESIS Volume: 723 Issue: 2 Pages: 152-157

Title: Towards a system level understanding of non-model organisms sampled from the environment: A network biology approach
Author(s): Williams Tim D.; Turan Nil; Diab Amer M.; et al.
Source: PLOS COMPUTATIONAL BIOLOGY Volume: 7 Issue: 8 Article Number: e1002126

Title: Accumulation and debromination of decabromodiphenyl ether (BDE-209) in juvenile fathead minnows (Pimephales promelas) induces thyroid disruption and liver alterations
Author(s): Noyes Pamela D.; Hinton David E.; Stapleton Heather M.
Source: TOXICOLOGICAL SCIENCES Volume: 122 Issue: 2 Pages: 265-274

Title: Organochlorine concentrations in franciscana dolphins, Pontoporia blainvillei, from Brazilian waters
Author(s): Lailson-Brito Jose; Dorneles Paulo Renato; Azevedo-Silva Claudio Eduardo; et al.
Source: CHEMOSPHERE Volume: 84 Issue: 7 Pages: 882-887

Title: Health status of native fish (Percilia gillissi and Trichomycterus areolatus) downstream of the discharge of effluent from a tertiary-treated elemental chlorine-free pulp mill in Chile
Author(s): Chiang Gustavo; McMaster Mark E.; Urrutia Roberto; et al.
Source: ENVIRONMENTAL TOXICOLOGY AND CHEMISTRY Volume: 30 Issue: 8 Pages: 1793-1809

Title: Cloning and expression of the translocator protein (18 kDa), voltage-dependent anion channel, and diazepam binding inhibitor in the gonad of largemouth bass (Micropterus salmoides) across the reproductive cycle
Author(s): Doperalski Nicholas J.; Martyniuk Christopher J.; Prucha Melinda S.; et al.
Source: GENERAL AND COMPARATIVE ENDOCRINOLOGY Volume: 173 Issue: 1 Pages: 86-95

Title: Bisphenol A modulates expression of sex differentiation genes in the self-fertilizing fish, Kryptolebias marmoratus
Author(s): Rhee Jae-Sung; Kim Bo-Mi; Lee Chang Joo; et al.
Source: AQUATIC TOXICOLOGY Volume: 104 Issue: 3-4 Pages: 218-229

Title: Effect of the organochlorine pesticide endosulfan on GnRH and gonadotrope cell populations in fish larvae
Author(s): Piazza Yanina G.; Pandolfi Matias; Lo Nostro Fabiana L.
Source: ARCHIVES OF ENVIRONMENTAL CONTAMINATION AND TOXICOLOGY Volume: 61 Issue: 2 Pages: 300-310

Title: Vitellogenin-like gene expression in freshwater amphipod Gammarus fossarum (Koch, 1835): functional characterization in females and potential for use as an endocrine disruption biomarker in males
Author(s): Xuereb Benoit; Bezin Laurent; Chaumot Arnaud; et al.
Source: ECOTOXICOLOGY Volume: 20 Issue: 6 Pages: 1286-1299

Title: A review of studies on androgen and estrogen exposure in fish early life stages: effects on gene and hormonal control of sexual differentiation
Author(s): Leet Jessica K.; Gall Heather E.; Sepulveda Maria S.
Source: JOURNAL OF APPLIED TOXICOLOGY Volume: 31 Issue: 5 Pages: 379-398

Title: Use of GC x GC/TOF-MS and LC/TOF-MS for metabolomic analysis of Hyalella azteca chronically exposed to atrazine and its primary metabolite, desethylatrazine
Author(s): Ralston-Hooper Kimberly J.; Adamec Jiri; Jannash Amber; et al.
Source: JOURNAL OF APPLIED TOXICOLOGY Volume: 31 Issue: 5 Pages: 399-410

Title: Drifting towards the surface: A shift in newborn pipefish's vertical distribution when exposed to the synthetic steroid ethinylestradiol
Author(s): Sarria M. P.; Santos M. M.; Reis-Henriques M. A.; et al.
Source: CHEMOSPHERE Volume: 84 Issue: 5 Pages: 618-624

Title: Development of enzyme-linked immunosorbent assays for plasma vitellogenin in Chinese rare minnow (Gobiocypris rarus)
Author(s): Luo Wenru; Zhou Qunfang; Jiang Guibin
Source: CHEMOSPHERE Volume: 84 Issue: 5 Pages: 681-688

Title: Selective uptake and biological consequences of environmentally relevant antidepressant pharmaceutical exposures on male fathead minnows
Author(s): Schultz Melissa M.; Painter Meghan M.; Bartell Stephen E.; et al.
Source: AQUATIC TOXICOLOGY Volume: 104 Issue: 1-2 Pages: 38-47

Title: Disruption of the salmon reproductive endocrine axis through prolonged nutritional stress: Changes in circulating hormone levels and transcripts for ovarian genes involved in steroidogenesis and apoptosis
Author(s): Yamamoto Yoji; Luckenbach J. Adam; Goetz Frederick W.; et al.
Source: GENERAL AND COMPARATIVE ENDOCRINOLOGY Volume: 172 Issue: 3 Pages: 331-343

Title: Apparent rapid loss of endocrine disruptors from wetlands used to store either tertiary treated sewage effluent or stormwater runoff
Author(s): Norris Andrew; Burgin Shelley
Source: WATER AIR AND SOIL POLLUTION Volume: 219 Issue: 1-4 Pages: 285-295

Title: Occurrence of sexual hormones in sediments of mangrove in Brazil
Author(s): Froehner Sandro; Machado Karina Scurupa; Stefen Elisa; et al.
Source: WATER AIR AND SOIL POLLUTION Volume: 219 Issue: 1-4 Pages: 591-599

Title: Genotoxic effects in erythrocytes of Oreochromis niloticus exposed to nanograms-per-liter concentration of 17 beta-estradiol (E(2)): An assessment using micronucleus test and comet assay
Author(s): Sponchiado Graziela; Fortunato de Lucena Reynaldo Eliana Mara; de Andrade Any Caroline B.; et al.
Source: WATER AIR AND SOIL POLLUTION Volume: 218 Issue: 1-4 Pages: 353-360

Title: Effects of a short-term exposure to the fungicide prochloraz on endocrine function and gene expression in female fathead minnows (Pimephales promelas)
Author(s): Skolness Sarah Y.; Durhan Elizabeth J.; Garcia-Reyero Natalia; et al.
Source: AQUATIC TOXICOLOGY Volume: 103 Issue: 3-4 Pages: 170-178

Title: Demasculinization of male fish by wastewater treatment plant effluent
Author(s): Vajda Alan M.; Barber Larry B.; Gray James L.; et al.
Source: AQUATIC TOXICOLOGY Volume: 103 Issue: 3-4 Pages: 213-221

Title: Prenatal and concurrent exposure to halogenated organic compounds and gene expression of CYP17A1, CYP19A1, and oestrogen receptor alpha and beta genes
Author(s): Karmaus Wilfried; Osuch Janet Rose; Landgraf Jeff; et al.
Source: OCCUPATIONAL AND ENVIRONMENTAL MEDICINE Volume: 68 Issue: 6 Pages: 430-437

Title: Antiestrogenicity and estrogenicity in leachates from solid waste deposits
Author(s): Svenson Anders; Sjoholm Sofia; Allard Ann-Sofie; et al.
Source: ENVIRONMENTAL TOXICOLOGY Volume: 26 Issue: 3 Pages: 233-239

Title: Dietary Mercury has no observable effects on thyroid-mediated processes and fitness-related traits in wood frogs
Author(s): Wada Haruka; Bergeron Christine M.; McNabb F. M. Anne; et al.
Source: ENVIRONMENTAL SCIENCE & TECHNOLOGY Volume: 45 Issue: 18 Pages: 7915-7922

Title: The synthetic gestagen levonorgestrel impairs metamorphosis in Xenopus laevis by disruption of the thyroid system
Author(s): Lorenz Claudia; Contardo-Jara Valeska; Pflugmacher Stephan; et al.
Source: TOXICOLOGICAL SCIENCES Volume: 123 Issue: 1 Pages: 94-102

Title: The Fungicide chlorothalonil is nonlinearly associated with corticosterone levels, immunity, and mortality in amphibians
Author(s): McMahon Taegan A.; Halstead Neal T.; Johnson Steve; et al.
Source: ENVIRONMENTAL HEALTH PERSPECTIVES Volume: 119 Issue: 8 Pages: 1098-1103

Title: Effects of 4-tert-octylphenol on Xenopus tropicalis in a long term exposure
Author(s): Porter Karen L.; Olmstead Allen W.; Kumsher David M.; et al.
Source: AQUATIC TOXICOLOGY Volume: 103 Issue: 3-4 Pages: 159-169

Title: Cloning of estrogen receptor alpha and aromatase cDNAs and gene expression in turtles (Chrysemys picta and Pseudemys scripta) exposed to different environments
Author(s): Marquez Emily C.; Traylor-Knowles Nikki; Novillo-Villajos Apolonia; et al.
Source: COMPARATIVE BIOCHEMISTRY AND PHYSIOLOGY C-TOXICOLOGY & PHARMACOLOGY Volume: 154 Issue: 3 Pages: 213-225

Title: Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on steroid concentrations in blood and gonads of chicken embryo
Author(s): Sechman Andrzej; Hrabia Anna; Lis Marcin W.; et al.
Source: TOXICOLOGY LETTERS Volume: 205 Issue: 2 Pages: 190-195

Title: Behavioural responses to human-induced environmental change
Author(s): Tuomainen Ulla; Candolin Ulrika
Source: BIOLOGICAL REVIEWS Volume: 86 Issue: 3 Pages: 640-657

Title: Effects of the pharmaceuticals gemfibrozil and diclofenac on the marine mussel (Mytilus spp.) and their comparison with standardized toxicity tests
Author(s): Schmidt Wiebke; O'Rourke Kathleen; Hernan Robert; et al.
Source: MARINE POLLUTION BULLETIN Volume: 62 Issue: 7 Pages: 1389-1395

Title: Two-generation effects of the chitin synthesis inhibitor, teflubenzuron, on the aquatic midge Chironomus riparius
Author(s): Tassou Koffi T.; Schulz Ralf
Source: ECOTOXICOLOGY AND ENVIRONMENTAL SAFETY Volume: 74 Issue: 5 Pages: 1203-1209

Title: The effects of organotin on female gastropods
Author(s): Titley-O'Neal Cassander P.; Munkittrick Kelly R.; MacDonald Bruce A.
Source: JOURNAL OF ENVIRONMENTAL MONITORING Volume: 13 Issue: 9 Pages: 2360-2388

Title: Comparative effects of butyl benzyl phthalate (BBP) and di(2-ethylhexyl) phthalate (DEHP) on the aquatic larvae of Chironomus riparius based on gene expression assays related to the endocrine system, the stress response and ribosomes
Author(s): Planello Rosario; Herrero Oscar; Luis Martinez-Guitarte Jose; et al.
Source: AQUATIC TOXICOLOGY Volume: 105 Issue: 1-2 Pages: 62-70

Title: Occurrence and concentrations of pharmaceutical compounds in groundwater used for public drinking-water supply in California
Author(s): Fram Miranda S.; Belitz Kenneth
Source: SCIENCE OF THE TOTAL ENVIRONMENT Volume: 409 Issue: 18 Pages: 3409-3417

Title: Experimentally nonylphenol-polluted diet induces the expression of silent genes VTG and ER alpha in the liver of male lizard Podarcis sicula
Author(s): Verderame Mariailaria; Prisco Marina; Andreuccetti Piero; et al.
Source: ENVIRONMENTAL POLLUTION Volume: 159 Issue: 5 Special Issue: SI Pages: 1101-1107

Title: Organochlorine compound residues in the eggs of broad-snouted caimans (Caiman latirostris) and correlation with measures of reproductive performance
Author(s): Stoker C.; Repetti M. R.; Garcia S. R.; et al.
Source: CHEMOSPHERE Volume: 84 Issue: 3 Pages: 311-317