Center for Hormonforstyrrende Stoffer

Litteraturgennemgang for perioden oktober – december 2013

Indhold

Humane studier ved Afd. for Vækst og Reproduktion, Rigshospitalet

Søgning er udført på PubMed og dækker perioden 19. september 2013 – 11. december 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.

Denne gang handler de udvalgte artikler om tilbageregning fra urinkoncentrationer til et estimeret dagligt indtag af non-persistente, hormonforstyrrende stoffer, om målinger af phenoler i amnionvæske og moderen urin med henblik på at estimere fostrets eksponering, om danske og koreanske børns udsættelse for phthalater og om phthalat-eksponering og risiko for for tidlig fødsel. God læselyst!

Udvalgte publikationer

Considerations for estimating daily intake values of non-persistent environmental endocrine disruptors based on urinary biomonitoring data. Søeborg T, Frederiksen H, Andersson AM. Department of Growth and Reproduction, Rigshospitalet, Copenhagen University Hospital, Copenhagen, 2100, Denmark. Reproduction. 2013 Nov 28. [Epub ahead of print]

Introduction: Human exposure to chemicals may be estimated by back-calculating urinary concentrations resulting from biomonitoring studies if knowledge of the chemical's toxicokinetic properties is available.
Aim: To review available toxicokinetic data for back-calculating urinary concentrations into daily intake values for bisphenol A, phthalates, parabens and triclosan, and to identify knowledge gaps.
Methods: Human data was evaluated and supplied with relevant animal data. Focus was on recovery of the administered dose, the route of administration and on differences between humansand animals.
Results: Two human toxicokinetic studies are currently used to conclude that an oral dose of bisphenol A is recoverable in urine and that no free bisphenol A is present in plasma in spite of several contradicting biominotoring studies. Urinary recovery of an oral dose of phthalates in humans is complicated to assess due to extensive metabolism. In animals using 14C-marked phthalates, near-complete recovery is observed. An oral dose of 14C-marked parabens is also almost completely recovered in animals. In both humans and animals however, two unspecific metabolites are formed, which complicates the back-calculation of parabens in humans. The recovery of both oral and dermal triclosan in humans has been studied, but due to background levels of triclosan, the back-calculation is difficult to perform.
Conclusion: Due to limited data, reasonable estimates of daily intake values based on urinary data are often not possible to obtain. Several knowledge gaps were identified and new studies were suggested. The route of administration used in toxicokinetic studies often does not match realistic scenarios.

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. Inserm, Institut Albert Bonniot (U823), Team of Environmental Epidemiology applied to Reproduction and Respiratory Health, Grenoble, France. Environ Health Perspect. 2013 Oct;121(10):1225-31. doi: 10.1289/ehp.1206335. Epub 2013 Aug 9.

BACKGROUND: Maternal urinary biomarkers are often used to assess fetal exposure to phenols and their precursors. Their effectiveness as a measure of exposure in epidemiological studies depends on their variability during pregnancy and their ability to accurately predict fetal exposure.
OBJECTIVES: We assessed the relationship between urinary and amniotic fluid concentrations of nine environmental phenols, and the reproducibility of urinary concentrations, among pregnant women.
METHODS: Seventy-one women referred for amniocentesis were included. Maternal urine was collected at the time of the amniocentesis appointment and on two subsequent occasions. Urine and amniotic fluid were analyzed for 2,4- and 2,5-dichlorophenols, bisphenol A, benzophenone-3, triclosan, and methyl-, ethyl-, propyl-, and butylparabens using online solid phase extraction-high performance liquid chromatography-isotope dilution tandem mass spectrometry.
RESULTS: Only benzophenone-3 and propylparaben were detectable in more than half of the amniotic fluid samples; for these phenols,concentrations in amniotic fluid and maternal urine collected on the same day were positively correlated ($\rho = 0.53$ and 0.32, respectively). Otherphenols were detected infrequently in amniotic fluid (e.g., bisphenol A was detected in only two samples). The intraclass correlation coefficients (ICCs) of urinary concentrations in samples from individual women ranged from 0.48 and 0.62 for all phenols except bisphenol A (ICC = 0.11).

CONCLUSION: Amniotic fluid detection frequencies for most phenols were low. The reproducibility of urine measures was poor for bisphenol A, but good for the other phenols. Although a single sample may provide a reasonable estimate of exposure for some phenols, collecting multiple urine samples during pregnancy is an option to reduce exposure measurement error in studies regarding the effects of phenol prenatal exposure on health

Childhood exposure to DEHP, DBP and BBP under existing chemical management systems: A comparative study of sources of childhood exposure in Korea and in Denmark. Lee J, Lee JH, Kim CK, Thomsen M. Department of Environmental Science, Aarhus University, Roskilde, Denmark. Electronic address: jile@dmu.dk. Environ Int. 2013 Nov 21;63C:77-91. doi: 10.1016/j.envint.2013.10.020. [Epub ahead of print] PubMed PMID: 24270398.

In this paper, the cumulative risks of Di(2-ethylhexyl) phthalate (DEHP), Di-n-butyl phthalate (DBP), and Benzyl-butyl phthalate (BBP) to 2-year-old children in two countries: one European (Denmark) and one Asian (South Korea) were compared. Denmark does not produce phthalates as a raw material, while Korea produces more than 0.4million tons of the three above-mentioned phthalates each year. First, a comparative review of the existing phthalate regulations in the two countries was performed. Next, the level of childhood phthalate exposure from environmental and food sources was estimated using an exposure scenario approach. Then, the scenario based exposure level was compared with back-calculated exposure levels based on biomonitored urinary phthalate metabolite concentrations. The result verifies the existence of varying territorial human background exposure levels and the gap between exposure estimations based on exposure modeling and biomonitoring data.
Cumulative childhood risk levels in Denmark were lower than in Korea. For both countries, risk levels from back calculation were higher than those from scenario estimation. The median cumulative risk levels from scenario estimation and back calculation respectively were 0.24 and up to 0.5 in Denmark while 0.52 and up to 0.95 inKorea. Food and indoor dust were the main exposure sources for all three phthalates. In order to protect human health from cumulative risks of these phthalates, the exposure scenarios in existing regulations such as the EU REACH need to be strengthened. Moreover, based on the contributions from different exposure sources, national specific risk management tools need to be developed and strengthened, applying a systemic approach to promote sustainable material flows.

Environmental Phthalate Exposure and Preterm Birth. Ferguson KK, McElrath TF, Meeker JD. Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor. JAMA Pediatr. 2013 Nov 18. doi: 10.1001/jamapediatrics.2013.3699. [Epub ahead of print]

IMPORTANCE: Preterm birth is a leading cause of neonatal mortality, with a variety of contributing causes and risk factors. Environmental exposures represent a group of understudied, but potentially important, factors. Phthalate diesters are used extensively in a variety of consumer products worldwide. Consequently, exposure in pregnant women is highly prevalent.
OBJECTIVE: To assess the relationship between phthalate exposure during pregnancy and preterm birth.
DESIGN, SETTING, AND PARTICIPANTS: This nested case-control study was conducted at Brigham and Women's Hospital, Boston, Massachusetts. Women were recruited for a prospective observational cohort study from 2006-2008. Each provided demographic data, biological samples, and information about birth outcomes. From within this group, we selected 130 cases of preterm birth and 352 randomly assigned control participants, and we analyzed urine samples from up to 3 time points during pregnancy for levels of phthalate metabolites.
EXPOSURE: Phthalate exposure during pregnancy.

MAIN OUTCOMES AND MEASURES: We examined associations between average levels ofphthalate exposure during pregnancy and preterm birth, defined as fewer than 37 weeks of completed gestation, as well as spontaneous preterm birth, defined as preterm preceded by spontaneous preterm labor or preterm premature rupture of the membranes (n = 57).
RESULTS: Geometric means of the di-2-ethylhexyl phthalate (DEHP) metabolites mono-(2-ethyl)-hexyl phthalate (MEHP) and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), as well as mono-n-butyl phthalate (MBP), were significantly higher in cases compared with control participants. In adjusted models, MEHP, MECPP, and Σ DEHP metabolites were associated with significantly increased odds of preterm birth. When spontaneous preterm births were examined alone, MEHP, mono-(2-ethyl-5-oxohexyl) phthalate, MECPP, Σ DEHP, MBP, and mono-(3-carboxypropyl) phthalate metabolite levels were all associated with significantly elevated odds of prematurity.
CONCLUSIONS AND RELEVANCE: Women exposed to phthalates during pregnancy have significantly increased odds of delivering preterm. Steps should be taken to decrease maternal exposure to phthalates during pregnancy.

Bruttoliste

Bisphenol A

1: Automated on-line column-switching high performance liquid chromatography isotope dilution tandem mass spectrometry method for the quantification of bisphenol A, bisphenol F, bisphenol S, and 11 other phenols in urine. Zhou X, Kramer JP, Calafat AM, Ye X. J Chromatogr B Analyt Technol Biomed Life Sci. 2013 Nov 13;944C:152-156. doi: 10.1016/j.jchromb.2013.11.009. [Epub ahead of print] PubMed PMID: 24316527.

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Phthalates

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Flame retardants

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Tributyltin / Triclosan / Triclocarban

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7: 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 Oct;121(10):1225-31. doi: 10.1289/ehp.1206335. Epub 2013 Aug 9. PubMed PMID: 23942273; PubMed Central PMCID: PMC3801458.

8: Temporal variability in urinary excretion of bisphenol A and seven other phenols in spot, morning, and 24-h urine samples. Lassen TH, Frederiksen H, Jensen TK, Petersen JH, Main KM, Skakkebæk NE, Jørgensen N, Kranich SK, Andersson AM. Environ Res. 2013 Oct;126:164-70. doi: 10.1016/j.envres.2013.07.001. Epub 2013 Aug 8. PubMed PMID: 23932849.

9: Biomarkers of human exposure to personal care products: results from the Flemish Environment and Health Study (FLEHS 2007-2011). Den Hond E, Paulussen M, Geens T, Bruckers L, Baeyens W, David F, Dumont E, Loots I, Morrens B, de Bellevaux BN, Nelen V, Schoeters G, Van Larebeke N, Covaci A. Sci Total Environ. 2013 Oct 1;463-464:102-10. doi: 10.1016/j.scitotenv.2013.05.087. Epub 2013 Jun 20. PubMed PMID: 23792252.

10: Urinary excretion of phthalate metabolites, phenols and parabens in rural and urban Danish mother-child pairs. Frederiksen H, Nielsen JK, Mørck TA, Hansen PW, Jensen JF, Nielsen O, Andersson AM, Knudsen LE. Int J Hyg Environ Health. 2013 Nov;216(6):772-83. doi: 10.1016/j.ijheh.2013.02.006. Epub 2013 Mar 13. PubMed PMID: 23528233.

11: Bisphenol A and other phenols in urine from Danish children and adolescents analyzed by isotope diluted TurboFlow-LC-MS/MS. Frederiksen H, Aksglaede L, Sorensen K, Nielsen O, Main KM, Skakkebaek NE,

Juul A, Andersson AM. Int J Hyg Environ Health. 2013 Nov;216(6):710-20. doi: 10.1016/j.ijheh.2013.01.007. Epub 2013 Mar 13. PubMed PMID: 23491025.

12: Widespread occurrence of bisphenol A diglycidyl ethers, p-hydroxybenzoic acid esters (parabens), benzophenone type-UV filters, triclosan, and triclocarban in human urine from Athens, Greece. Asimakopoulos AG, Thomaidis NS, Kannan K. Sci Total Environ. 2013 Nov 16;470-471C:1243-1249. doi: 10.1016/j.scitotenv.2013.10.089. [Epub ahead of print] PubMed PMID: 24246946.

13: Temporal variability in urinary excretion of bisphenol A and seven other phenols in spot, morning, and 24-h urine samples. Lassen TH, Frederiksen H, Jensen TK, Petersen JH, Main KM, Skakkebæk NE, Jørgensen N, Kranich SK, Andersson AM. Environ Res. 2013 Oct;126:164-70. doi: 10.1016/j.envres.2013.07.001. Epub 2013 Aug 8. PubMed PMID: 23932849.

14: Urinary excretion of phthalate metabolites, phenols and parabens in rural and urban Danish mother-child pairs. Frederiksen H, Nielsen JK, Mørck TA, Hansen PW, Jensen JF, Nielsen O, Andersson AM, Knudsen LE. Int J Hyg Environ Health. 2013 Nov;216(6):772-83. doi: 10.1016/j.ijheh.2013.02.006. Epub 2013 Mar 13. PubMed PMID: 23528233.

15: Bisphenol A and other phenols in urine from Danish children and adolescents analyzed by isotope diluted TurboFlow-LC-MS/MS. Frederiksen H, Aksglaede L, Sorensen K, Nielsen O, Main KM, Skakkebaek NE, Juul A, Andersson AM. Int J Hyg Environ Health. 2013 Nov;216(6):710-20. doi: 10.1016/j.ijheh.2013.01.007. Epub 2013 Mar 13. PubMed PMID: 23491025.

Endocrine disrupters

1: A plea for risk assessment of endocrine disrupting chemicals. Testai E, Galli CL, Dekant W, Marinovich M, Piersma AH, Sharpe RM. Toxicology. 2013 Dec 6;314(1):51-9. doi: 10.1016/j.tox.2013.07.018. Epub 2013 Aug 11. PubMed PMID: 23939142.

CEHOS Litteratur update *in vitro* og *in vivo* oktober–december 2013

DTU Fødevareinstituttet

In vitro studier ved DTU-FOOD

Søgt i Pubmed med følgende kriterier:" Endocrine disrupt* AND in vitro*" samt "Endocrine disrupt* AND expose* AND in vitro*","Paraben* AND in vitro*,"perfluor* OR polyfluor* AND in vitro*" og "Phthalat* AND in vitro*". Publiceret fra i perioden 2013/09/30 to 2013/12/31 (Oktober 2013 og fremefter).

Efter at have fjernet genganger fra forrige litteraturopdateringslister gav litteratursøgningen, med de angivne søgekriterier, tilsammen en liste med i alt 44 artikler plus 1 artikel, der ikke blev fundet af de valgte søgekriterier. De i alt 45 artikler (se bruttolisten længere nede i dokumentet) er blevet fordelt i 6 grupper:"Parabens","Various Nano-materials/compounds","Perflourinated and Polyflourinated compounds", Plastic derivatives" (BPA, Phthalates and others), "Pesticides/Fungicides/Insecticides" og " Various EDCs, Mixtures and Other endpoints".

Udvalgte publikationer

Ud fra bruttolisten (se længere nede i dokumentet) er 2 artikler blevet udvalgt til nærmere beskrivelse baseret på, at de beskriver resultater, der bidrager til ny eller yderligere viden om hormonforstyrrende stoffer.

Den første artikel omhandler in vitro studier til belysning af mulige mekanismer bag visse hormonforstyrrende stoffer effekt eller evne til at påvirke tidspunktet for pubertetsstart.

Den anden artikel omhandler et studie, der ved brug af 11 forskellige in vitro assays, har undersøgt 11 typer organophosphat flammehæmmere, for at undersøge om de har nogle af de samme hormonforstyrrende egenskaber, som er kendt fra andre typer af flammehæmmere.

Endocrine disrupting chemicals affect the, Gonadotropin releasing hormone neuronal network.

Mueller JK, Heger S.

Abstract

Endocrine disrupting chemicals have been shown to alter the pubertal process. The controlling levels of the Gonadotropin releasing hormone (GnRH) network involve GnRH itself, KiSS1, and the transcriptional regulators enhanced at puberty 1 (EAP1), Thyroid Transcription Factor 1 (TTF1), and Yin Yang 1 (YY1). While Genistein and Bisphenol A (BPA) have been shown to advance the advent of puberty, exposure to Dioxin delayed pubertal onset. Utilizing in vitro approaches, we observed that Genistein and BPA suppress inhibitory and activate stimulatory components of the GnRH network, while Dioxin exhibit an inhibitory effect at all regulatory hierarchical levels of the GnRH network. It repressed KiSS1, Gnrh, Ttf1 and Yy1 transcription via the xenobiotic response element (XRE), while EAP1 was not affected. Therefore, EDCs alter the neuroendocrine GnRH regulatory network at all hierarchical levels.

In vitro endocrine disruption potential of organophosphate flame retardants via human nuclear receptors.

Kojima H, Takeuchi S, Itoh T, Iida M, Kobayashi S, Yoshida T.

Abstract

Various organophosphate flame retardants (OPFRs) are widely used in building materials, textiles and electric appliances, and have been reported to cause indoor environmental pollution in houses and office buildings. In this study, using cell-based transactivation assays, we characterized the agonistic and/or antagonistic activities of 11 OPFRs against human nuclear receptors; estrogen receptor α (ERα), ERβ, androgen receptor (AR), glucocorticoid receptor (GR), thyroid hormone receptor α1 (TRα1), TRβ1, retinoic acid receptor α (RARα), retinoid X receptor α (RXRα), pregnane X receptor (PXR), peroxisome proliferator-activated receptor α (PPARα), and PPARγ. Of the 11 OPFRs tested, triphenyl phosphate (TPhP) and tricrecyl phosphate (TCP) showed ERα and/or ERβ agonistic activity. In addition, tributyl phosphate (TBP), tris(1,3-dichloro-2-propyl) phosphate (TDCPP), TPhP and TCP showed AR antagonistic activity, and TBP, tris(2-ethylhexyl) phosphate (TEHP), TDCPP, TPhP and TCP showed GR antagonistic activity. Furthermore, we found that seven compounds, TBP, tris(2-chloro-1-methylethyl) phosphate (TCPP), TEHP, tris(2-butoxyethyl) phosphate (TBEP), TDCPP, TPhP, and TCP, display PXR agonistic activity. However, none of test compounds showed agonistic or antagonistic activity against TRα/β, or agonistic activity against RARα, RXRα or PPARα/γ. Taken together, these results suggest that several OPFRs may have potential endocrine disrupting effects via ERα, ERβ, AR, GR and PXR.

Bruttolisten *in vitro*

Parabens

1.Oral Propylparaben Administration to Juvenile Male Wistar Rats Did Not Induce Toxicity in Reproductive Organs.
Gazin V, Marsden E, Marguerite F.
Toxicol Sci. 2013 Oct 10. [Epub ahead of print]

2.Single administration of butylparaben induces spermatogenic cell apoptosis in prepubertal rats.
Alam MS, Ohsako S, Kanai Y, Kurohmaru M.
Acta Histochem. 2013 Nov 13. doi:pii: S0065-1281(13)00194-3. 10.1016/j.acthis.2013.10.006. [Epub ahead of print]

Various Nano-materials/compounds

1.Intracellular pH Measurements Using Perfluorocarbon Nanoemulsions.
Patrick MJ, Janjic JM, Teng H, O'Hear MR, Brown CW, Stokum JA, Schmidt BF, Ahrens ET, Waggoner AS.
J Am Chem Soc. 2013 Nov 22. [Epub ahead of print]

2.Optimization of acoustic parameters and nanodroplet concentration for spatially controlled, reduced energy high intensity focused ultrasound ablation.
Puett AC, Phillips LC, Sheeran PS, Dayton PA.
J Acoust Soc Am. 2013 Nov;134(5):4051. doi: 10.1121/1.4830784.

3.Application of a hemolysis assay for analysis of complement activation by perfluorocarbon nanoparticles.
Pham CT, Thomas DG, Beiser J, Mitchell LM, Huang JL, Senpan A, Hu G, Gordon M, Baker NA, Pan D, Lanza GM, Hourcade DE.
Nanomedicine. 2013 Nov 8. doi:pii: S1549-9634(13)00588-1. 10.1016/j.nano.2013.10.012. [Epub ahead of print]

4.Dual perfluorocarbon nanodroplets enhance high intensity focused ultrasound heating and extend therapeutic window in vivo.
Phillips LC, Sheeran PS, Puett C, Timbie KF, Price RJ, Miller GW, Dayton PA.
J Acoust Soc Am. 2013 Nov;134(5):4049. doi: 10.1121/1.4830779.

5.Characterization of nanometric ultrasound contrast agents with a liquid perfluorocarbon core.
, Fattal E, Pepin C, Polidori A, Taulier N, Thomas JL, Tsapis N, Valier-Brasier T, Urbach W.
J Acoust Soc Am. 2013 Nov;134(5):4049.

6. Pulmonary Toxicity of **Perfluorinated** Silane-Based Nanofilm Spray Products: Solvent Dependency.

Nørgaard AW, Hansen JS, Sørli JB, Levin M, Wolkoff P, Nielsen GD, Larsen ST.
Toxicol Sci. 2013 Nov 5. [Epub ahead of print]

Perflourinated and Polyflourinated compounds

1.Effects of perfluoroalkyl acids on the function of the thyroid hormone and the aryl hydrocarbon receptor.

Long M, Ghisari M, Bonefeld-Jørgensen EC.

Environ Sci Pollut Res Int. 2013 Nov;20(11):8045-56. doi: 10.1007/s11356-013-1628-7. Epub 2013 Mar 29.

2.**Perfluorooctanesulfonate** (PFOS) perturbs male rat Sertoli cell blood-testis barrier function by affecting F-actin organization via p-FAK-Tyr407 - an **in vitro** study.Wan HT, Mruk DD, Wong CK, Cheng CY.

Endocrinology. 2013 Oct 29. [Epub ahead of print]

3.Pefluorocarbon inhibition of bubble induced Ca2+ transients in an **in vitro** model of vascular gas embolism. Klinger AL, Kandel J, Pichette B, Eckmann DM.

Exp Biol Med (Maywood). 2013 Oct 16. [Epub ahead of print]

4. **Perfluorooctane** Sulfonate Disturbs Nanog Expression through miR-490-3p in Mouse Embryonic Stem Cells.

Xu B, Chen X, Mao Z, Chen M, Han X, Du G, Ji X, Chang C, Rehan VK, Wang X, Xia Y.
PLoS One. 2013 Oct 1;8(10):e74968. doi: 10.1371/journal.pone.0074968.

5. Looking for protein expression signatures in European eel peripheral blood mononuclear cells after in vivo exposure to **perfluorooctane** sulfonate and a real world field study.

Roland K, Kestemont P, Loos R, Tavazzi S, Paracchini B, Belpaire C, Dieu M, Raes M, Silvestre F.
Sci Total Environ. 2013 Oct 1;468-469C:958-967. doi: 10.1016/j.scitotenv.2013.07.110. [Epub ahead of print]

6. Dosimetric Anchoring of In Vivo and **In Vitro** Studies for **Perfluorooctanoate** and **Perfluorooctanesulfonate**.

Wambaugh JF, Setzer RW, Pitruzzello AM, Liu J, Reif DM, Kleinstreuer NC, Wang NC, Sipes N, Martin M, Das K, Dewitt JC, Strynar M, Judson R, Houck KA, Lau C.
Toxicol Sci. 2013 Nov 27. [Epub ahead of print]

Plastic derivatives (BPA, Phthalates and others)

1. Effects of 4-nonylphenol and bisphenol A on stimulation of cell growth via disruption of transforming growth factor-β signaling pathway in ovarian cancer models.

Park MA, Choi KC.
Chem Res Toxicol. 2013 Dec 5. [Epub ahead of print]

2.Bisphenol A promotes dendritic morphogenesis of hippocampal neurons through estrogen receptor-mediated ERK1/2 signal pathway.Xu X, Lu Y, Zhang G, Chen L, Tian D, Shen X, Yang Y, Dong F.

Chemosphere. 2014 Feb;96:129-37. doi: 10.1016/j.chemosphere.2013.09.063. Epub 2013 Nov 11.

3.Sperm impairments in adult vesper mice (Calomys laucha) caused by in utero exposure to bisphenol A.

Vilela J, Hartmann A, Silva EF, Cardoso T, Corcini CD, Varela-Junior AS, Martinez PE, Colares EP.

Andrologia. 2013 Oct 23. doi: 10.1111/and.12182. [Epub ahead of print]

4.**Endocrine disrupting** chemicals affect the, Gonadotropin releasing hormone neuronal network.

Mueller JK, Heger S.
Reprod Toxicol. 2013 Nov 6. doi:pii: S0890-6238(13)00366-3. 10.1016/j.reprotox.2013.10.011. [Epub ahead of print]

5.Skin permeation and metabolism of di(2-ethylhexyl) phthalate (DEHP).

Hopf NB, Berthet A, Vernez D, Langard E, Spring P, Gaudin R.
Toxicol Lett. 2013 Oct 16;224(1):47-53. doi: 10.1016/j.toxlet.2013.10.004. [Epub ahead of print]

6.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.

7.Size fraction effect on **phthalate** esters accumulation, bioaccessibility and **in vitro** cytotoxicity of indoor/outdoor dust, and risk assessment of human exposure.

Wang W, Wu FY, Huang MJ, Kang Y, Cheung KC, Wong MH.
J Hazard Mater. 2013 Oct 15;261:753-62. doi: 10.1016/j.jhazmat.2013.04.039. Epub 2013 May 2.

Pesticides/Fungicides/Insecticides

1.p,p'-DDE activates CatSper and compromises human sperm function at environmentally relevant concentrations.

Tavares RS, Mansell S, Barratt CL, Wilson SM, Publicover SJ, Ramalho-Santos J.
Hum Reprod. 2013 Dec;28(12):3167-77. doi: 10.1093/humrep/det372. Epub 2013 Sep 24.

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

A computational approach to mechanistic and predictive toxicology of pesticides.

Kongsbak K, Vinggaard AM, Hadrup N, Audouze K.

ALTEX. 2013 Sep 14. doi:pii: S1868696X1304241X. [Epub ahead of print]

Various EDCs, Mixtures and Other endpoints

1.127 TREATMENTS WITH DIVERSE **ENDOCRINE-DISRUPTING** CHEMICALS RESULTED IN THE INHIBITION OF OVARIAN TUMOR PROGRESSION VIA INTERRUPTION OF TRANSFORMING GROWTH FACTOR-β IN **IN VITRO** AND XENOGRAFTED MOUSE MODELS.

Lee HR, Go RE, Choi KC.
Reprod Fertil Dev. 2013 Dec;26(1):177. doi: 10.1071/RDv26n1Ab127.

2.A physiologically-based toxicokinetic model for the zebrafish Danio rerio.

Péry AR, Devillers J, Brochot C, Mombelli E, Palluel O, Piccini B, Brion F, Beaudouin R.
Environ Sci Technol. 2013 Dec 2. [Epub ahead of print]

3.The flavonoid chrysin, an **endocrine disrupter**, relaxes cholecystokinin- and KCl-induced tension in male guinea pig gallbladder strips through multiple signaling pathways.

Kline LW, Karpinski E.
Steroids. 2013 Nov 26. doi:pii: S0039-128X(13)00265-1. 10.1016/j.steroids.2013.11.012. [Epub ahead of print]

4.Binary Classification of a Large Collection of Environmental Chemicals from Estrogen Receptor Assays by QSAR and Machine Learning Methods. Zang Q, Rotroff D, Judson RS. J Chem Inf Model. 2013 Nov 26. [Epub ahead of print]

5.Assessment of wastewater and recycled water quality: A comparison of lines of evidence from in vitro, in vivo and chemical analyses.

Leusch FD, Khan SJ, Gagnon MM, Quayle P, Trinh T, Coleman H, Rawson C, Chapman HF, Blair P, Nice H, Reitsema T.
Water Res. 2013 Oct 30. doi:pii: S0043-1354(13)00862-2. 10.1016/j.watres.2013.10.056. [Epub ahead of print]

6.RNA-Sequencing Analysis of TCDD-Induced Responses in Zebrafish Liver Reveals High Relatedness to In Vivo Mammalian Models and Conserved Biological Pathways.

Li ZH, Xu H, Zheng W, Lam SH, Gong Z.
PLoS One. 2013 Oct 30;8(10):e77292. doi: 10.1371/journal.pone.0077292.

7.The Use and Acceptance of Other Scientifically Relevant Information (OSRI) in the U.S. Environmental Protection Agency (EPA) **Endocrine Disruptor** Screening Program.

Bishop PL, Willett CE.
Birth Defects Res B Dev Reprod Toxicol. 2013 Oct 22. doi: 10.1002/bdrb.21077. [Epub ahead of print]

8.**Endocrine-Disrupting** Effects of Compounds in Danish Streams.

Long M, Strand J, Lassen P, Krüger T, Dahllöf I, Bossi R, Larsen MM, Wiberg-Larsen P, Bonefeld-Jørgensen EC.
Arch Environ Contam Toxicol. 2013 Oct 22. [Epub ahead of print]
9.A rapid screening test for **endocrine disrupting** chemicals using primary cell culture of the marine medaka.

Tse AC, Lau KY, Ge W, Wu RS.
Aquat Toxicol. 2013 Nov 15;144-145:50-8. doi: 10.1016/j.aquatox.2013.09.022. Epub 2013 Sep 30.

10.Characterization of the environmental quality of sediments from two estuarine systems based on different **in-vitro** bioassays.

Fernandes D, Pujol S, Pérez-Albaladejo E, Tauler R, Bebianno MJ, Porte C.
Mar Environ Res. 2013 Oct 8. doi:pii: S0141-1136(13)00169-4. 10.1016/j.marenvres.2013.09.019. [Epub ahead of print]

11.t4 Workshop Report: Lessons Learned, Challenges, and Opportunities: The U.S. **Endocrine Disruptor** Screening Program.

Juberg DR, Borghoff SJ, Becker RA, Casey W, Hartung T, Holsapple MP, Marty MS, Mihaich EM, Van Der Kraak G, Wade MG, Willett CE, Andersen ME, Borgert CJ, Coady KK, Dourson ML, Fowle JR, Gray LE, Lamb JC, Ortego LS, Schug TT, Toole CM, Zorrilla LM, Kroner OL, Patterson J, Rinckel LA, Jones BR.
ALTEX. 2013 Oct 10. doi:pii: S1868696X1309271X. [Epub ahead of print]

12.Current perspectives on the androgen 5 alpha-dihydrotestosterone (DHT) and 5 alpha-reductases in teleost fishes and amphibians.

Martyniuk CJ, Bissegger S, Langlois VS.
Gen Comp Endocrinol. 2013 Dec 1;194:264-74. doi: 10.1016/j.ygcen.2013.09.019. Epub 2013 Oct 3.

13.**In vitro endocrine disruption** and TCDD-like effects of three novel brominated flame retardants: TBPH, TBB, & TBCO.

Saunders DM, Higley EB, Hecker M, Mankidy R, Giesy JP.
Toxicol Lett. 2013 Nov 25;223(2):252-9. doi: 10.1016/j.toxlet.2013.09.009. Epub 2013 Sep 21.

14.Exposure to tributyltin induces endoplasmic reticulum stress and the unfolded protein response in zebrafish.

Komoike Y, Matsuoka M.
Aquat Toxicol. 2013 Oct 15;142-143:221-9. doi: 10.1016/j.aquatox.2013.08.017. Epub 2013 Sep 4.

15.**In vitro endocrine disruption** potential of organophosphate flame retardants via human nuclear receptors.

Kojima H, Takeuchi S, Itoh T, Iida M, Kobayashi S, Yoshida T.
Toxicology. 2013 Dec 6;314(1):76-83. doi: 10.1016/j.tox.2013.09.004. Epub 2013 Sep 17.

16.Effects of HO-/MeO-PBDEs on androgen receptor: **in vitro** investigation and helix 12-involved MD simulation.

Wang X, Yang H, Hu X, Zhang X, Zhang Q, Jiang H, Shi W, Yu H.
Environ Sci Technol. 2013 Oct 15;47(20):11802-9. doi: 10.1021/es4029364. Epub 2013 Oct 2.

17.Effects of global warming on fish reproductive endocrine axis, with special emphasis in pejerrey Odontesthes bonariensis.

Miranda LA, Chalde T, Elisio M, Strüssmann CA.

Gen Comp Endocrinol. 2013 Oct 1;192:45-54. doi: 10.1016/j.ygcen.2013.02.034. Epub 2013 Mar 13.

18.Detection of unique acoustic signatures for phase-change contrast agents used in medical imaging and therapy.

Sheeran PS, Martin KH, Hjelmquist JN, Matsunaga TO, Dayton PA.
J Acoust Soc Am. 2013 Nov;134(5):4050. doi: 10.1121/1.4830782.

19.Characterization of liquid-filled nanoparticles for detection and drug-delivery in tumors.

Taulier N, Payen T, Jafari S, Mamou J, Elias F, Tsapis N, Bridal L.
J Acoust Soc Am. 2013 Nov;134(5):4048. doi: 10.1121/1.4830773.

20.EU-wide monitoring survey on emerging polar organic contaminants in wastewater treatment plant effluents.

Loos R, Carvalho R, António DC, Comero S, Locoro G, Tavazzi S, Paracchini B, Ghiani M, Lettieri T, Blaha L, Jarosova B, Voorspoels S, Servaes K, Haglund P, Fick J, Lindberg RH, Schwesig D, Gawlik BM.
Water Res. 2013 Nov 1;47(17):6475-87. doi: 10.1016/j.watres.2013.08.024. Epub 2013 Sep 15.

21.**In vitro** and in vivo evaluations of a novel pulsed and controlled osmotic pump capsule.

Zhang W, Zhang L, Qu X, Zhu Z, Pan Y, Guan J, Pan W.
Drug Dev Ind Pharm. 2013 Dec 3. [Epub ahead of print]

22.Bioerodible system for sequential release of multiple drugs.

Sundararaj SC, Thomas MV, Dziubla TD, Puleo DA.
Acta Biomater. 2014 Jan;10(1):115-25. doi: 10.1016/j.actbio.2013.09.031. Epub 2013 Oct 1.

23.Slow accumulation of mutations in Xpc(-/-) mice upon induction of oxidative stress.

Melis JP, Kuiper RV, Zwart E, Robinson J, Pennings JL, van Oostrom CT, Luijten M, van Steeg H.
DNA Repair (Amst). 2013 Dec;12(12):1081-6. doi: 10.1016/j.dnarep.2013.08.019. Epub 2013 Sep 29.

In vivo studier ved DTU - FOOD

Søgning er udført på PubMed og dækker perioden 25/9-10/12 2013

(Oktober - December 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 or BPA) OR ((perfluor* OR polyfluor*)AND in vivo).

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

Udvalgte publikationer

Tre artikler er blevet udvalgt til nærmere beskrivelse (abstrakt og konklusion). Disse 3 som dette kvartal er vores egne artikler er valgt fordi vi mener de bidrager til ny viden om kombinationseffekter hos unge dyr (Axelstad et al. 2013 online) og senere i livet (Isling et al 2013 Online). Den sidste bidrager til ny viden om lavdosiseffekter af Bisphenol A (Christiansen et al. 2013 Online).

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

Late life effects on **rat** reproductive system after developmental exposure to mixtures of **endocrine disrupters**.
Isling LK, Boberg J, Jacobsen PR, Mandrup KR, Axelstad M, Christiansen S, Vinggaard AM, Taxvig C, Kortenkamp A, Hass U.
Reproduction. 2013 Nov 28. [Epub ahead of print]

Abstract

This study examined late life effects of perinatal exposure of rats to a mixture of endocrine disrupting contaminants. Four groups of 14 time-mated Wistar rats were exposed by gavage from gestation day 7 to pup day 22 to a mixture of 13 anti-androgenic and estrogenic chemicals including phthalates, pesticides, UV-filters, bisphenol A, parabens and the drug paracetamol. The groups received vehicle (control), a mixture of all 13 chemicals at 150-times (TotalMix150) or 450-times (TotalMix450) high end human exposure, or a 450-times mixture of 9 predominantly anti-androgenic chemicals (AAMix450). Onset of puberty and estrous cyclicity at 9 and 12 months of age was assessed. Significantly fewer females showed regular estrus cyclicity at 12 months of age in the TotalMix450 and AAMix450 groups compared to controls. In 19 months old male offspring, epididymal sperm counts were lower than controls and in ventral prostate, an over-representation of findings related to hyperplasia was observed in exposed groups compared to controls particularly in the group dosed with anti-androgens. A higher incidence of pituitary adenoma at 19 months of age was found in males and females in the AAMix450 group. Developmental exposure of rats to the highest dose of a human relevant mixture of endocrine disrupters induced adverse effects late in life manifested as earlier female reproductive senescence, reduced sperm counts, higher score for prostate atypical hyperplasia and higher

incidence of pituitary tumors. These delayed effects highlight the need for further studies on the role of endocrine disrupters in hormone-related disorders in aging humans.

Endocrine disrupting contaminant mixtures induce adverse developmental effects in pre-weaning rats.
Axelstad M, Christiansen S, Boberg J, Scholze M, Jacobsen PR, Isling LK, Kortenkamp A, Hass U.
Reproduction. 2013 Dec 2. [Epub ahead of print]

Abstract
Reproductive toxicity was investigated in rats after developmental exposure to a mixture of 13 endocrine disrupting contaminants, including pesticides, plastic- and cosmetic ingredients, and paracetamol. The mixture was composed on the basis of information about high end human exposures, and dose levels reflecting 100, 200 and 450 times this exposure were tested. Compounds were also grouped according to their estrogenicity or anti-androgenicity, and their joint effects were tested at two different doses, with each group reflecting 200 or 450 times human exposure. In addition, a single paracetamol dose was tested (350 mg/kg/day). All exposures and a vehicle were administered by oral gavage to time-mated Wistar dams rats throughout gestation and lactation, and their offspring were assessed for reproductive effects at birth and in prepuberty.
The mixture doses which included the anti-androgenic compounds, affected the male offspring by causing decreased anogenital distance, increased nipple retention and reduced ventral prostate weights, at both medium and high doses. Additionally, the weights of the levator ani/bulbocavernosus muscle (LABC) were decreased at the high anti-androgen mixture dose. No effects were seen after exposure to the estrogenic chemicals alone, whereas males exposed solely to paracetamol showed decreased LABC weights and increased nipple retention. Thus adverse reproductive effects were observed at mixtures reflecting 200 times high end human exposure, which is relatively close to the safety margin covered by the regulatory uncertainty factor of 100. This suggests that highly exposed human population groups may not be sufficiently protected against mixtures of endocrine disrupting chemicals.

Low dose effects of **BPA** on early sexual development of male and female rats.
Christiansen S, Axelstad M, Boberg J, Vinggaard AM, Pedersen GA, Hass U.
Reproduction. 2013 Dec 2. [Epub ahead of print]

Abstract

Bisphenol A (BPA) is widely detected in human urine and blood. BPA has been reported to impair many endpoints for reproductive and neurological development; however, it is controversial whether BPA has effects in the μg/kg dose range. The aim of the current study was to examine the influence of BPA on early male and female sexual development at dose levels covering both regulatory NOAELs (5 and 50 mg/kg bw/day) as well as doses in the μg/kg dose range (0.025 and 0.25 mg/kg bw/day).

Time-mated Wistar rats (n=22) were gavaged during pregnancy and lactation from gestation day 7 to pup day (PD) 22 with 0; 0.025; 0.25; 5 or 50 mg/kg bw/day BPA. From 0.250 mg/kg and above, male anogenital distance was significantly decreased, whereas decreased female anogenital distance was seen from 0.025 mg/kg bw/day and above. Moreover, the incidence of nipple retention in males

appeared dose-relatedly increased and the increase was statistically significant at 50 mg/kg/day. No significant changes in reproductive organ weights in the 16-day-old males and females and no signs of maternal toxicity were seen. The decreased anogenital distance at birth in both sexes indicates effects on prenatal sexual development and provides new evidence of low-dose adverse effects of BPA in rats in the μg/kg dose range.

The NOAEL in this study is clearly below the NOAEL of 5 mg/kg for BPA that is used as the basis for establishment of the current Tolerable Daily Intake (TDI) by EFSA, thus a reconsideration of the current TDI of BPA appears warranted.

Bruttolisten *in vivo* (delt ind i emner)

Parabens

1.Oral Propylparaben Administration to Juvenile Male Wistar **Rats** Did Not Induce Toxicity in Reproductive Organs.
Gazin V, Marsden E, Marguerite F.
Toxicol Sci. 2013 Oct 10. [Epub ahead of print]

Plastic derivatives (BPA, Phthalates and others)

BPA

1.Low dose effects of **BPA** on early sexual development of male and female rats.
Christiansen S, Axelstad M, Boberg J, Vinggaard AM, Pedersen GA, Hass U.
Reproduction. 2013 Dec 2. [Epub ahead of print] **(valgt)**

2.Low dose of bisphenol A impairs the reproductive axis of prepuberal male **rats**.
Gámez JM, Penalba R, Cardoso N, Ponzo O, Carbone S, Pandolfi M, Scacchi P, Reynoso R.
J Physiol Biochem. 2013 Nov 24. [Epub ahead of print]

3.A multi-generational study on low-dose BPA exposure in Wistar **rats**: Effects on maternal behavior, flavor intake and development.
Sofiane B, Raymond B, Claire C, Mireille F, Laurence D, Bruno P, Latifa AN, Marie-Chantal CL.
Neurotoxicol Teratol. 2013 Nov 20. doi:pii: S0892-0362(13)00217-1. 10.1016/j.ntt.2013.11.002. [Epub ahead of print]

4.Indole-3-carbinol attenuates the deleterious gestational effects of bisphenol A exposure on the prostate gland of male F1 **rats**.
Brandt JZ, Silveira LT, Grassi TF, Anselmo-Franci JA, Fávaro WJ, Felisbino SL, Barbisan LF, Scarano WR.
Reprod Toxicol. 2013 Nov 17;43C:56-66. doi: 10.1016/j.reprotox.2013.11.001. [Epub ahead of print]

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Bodin J, Kocbach Bølling A, Becher R, Kuper F, Lovik M, Nygaard UC.
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Vilela J, Hartmann A, Silva EF, Cardoso T, Corcini CD, Varela-Junior AS, Martinez PE, Colares EP. Andrologia. 2013 Oct 23. doi: 10.1111/and.12182. [Epub ahead of print]

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Kuwahara R, Kawaguchi S, Kohara Y, Cui H, Yamashita K.
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Horm Behav. 2013 Sep;64(4):598-604. doi: 10.1016/j.yhbeh.2013.08.014. Epub 2013 Sep 1.

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Katchy A, Pinto C, Jonsson P, Nguyen-Vu T, Pandelova M, Riu A, Schramm KW, Samarov D, Gustafsson JA, Bondesson M, Williams C.
Toxicol Sci. 2013 Nov 27. [Epub ahead of print]

15.Low dose of **bisphenol A** impairs the reproductive axis of prepuberal male rats.
Gámez JM, Penalba R, Cardoso N, Ponzo O, Carbone S, Pandolfi M, Scacchi P, Reynoso R.
J Physiol Biochem. 2013 Nov 24. [Epub ahead of print]

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Bodin J, Kocbach Bølling A, Becher R, Kuper F, Lovik M, Nygaard UC.
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19.**Bisphenol A** and human health: A review of the literature.
Rochester JR.
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Diaz Weinstein S, Villafane JJ, Juliano N, Bowman RE.
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Teeguarden JG, Hanson-Drury S.
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Phthalates and others

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Mangala Priya V, Mayilvanan C, Akilavalli N, Rajesh P, Balasubramanian K.
Cardiovasc Toxicol. 2013 Dec 3. [Epub ahead of print]

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Herreros MA, Encinas T, Torres-Rovira L, Garcia-Fernandez RA, Flores JM, Ros JM, Gonzalez-Bulnes A.
Environ Toxicol Pharmacol. 2013 Nov;36(3):1141-9. doi: 10.1016/j.etap.2013.09.020. Epub 2013 Oct 12.

3.A critical assessment of the endocrine susceptibility of the human testis to **phthalates** from fetal life to adulthood.
Albert O, Jégou B.
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Rajesh P, Balasubramanian K.
Hum Exp Toxicol. 2013 Oct 15. [Epub ahead of print]

Pesticides/Fungicides/Insecticides

1.o-p'-DDT-mediated uterotrophy and gene expression in immature C57BL/6 **mice** and Sprague-Dawley **rats**.
Kwekel JC, Forgacs AL, Williams KJ, Zacharewski TR.
Toxicol Appl Pharmacol. 2013 Oct 3. doi:pii: S0041-008X(13)00424-9. 10.1016/j.taap.2013.09.024. [Epub ahead of print]

2.Prepubertal exposure to arsenic(III) suppresses circulating insulin-like growth factor-1 (IGF-1) delaying sexual maturation in female **rats**.
Reilly MP, Saca JC, Hamilton A, Solano RF, Rivera JR, Whitehouse-Innis W, Parsons JG, Dearth RK.
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3. Dynamic postnatal developmental and sex-specific neuroendocrine effects of prenatal PCBs in **rats**.
Walker DM, Goetz BM, Gore AC.
Mol Endocrinol. 2013 Nov 27. [Epub ahead of print]

Various EDCs, Mixtures and Other endpoints

1. **Endocrine disrupting** contaminant mixtures induce adverse developmental effects in pre-weaning **rats**.
Axelstad M, Christiansen S, Boberg J, Scholze M, Jacobsen PR, Isling LK, Kortenkamp A, Hass U.
Reproduction. 2013 Dec 2. [Epub ahead of print] **valgt**

2.Late life effects on **rat** reproductive system after developmental exposure to mixtures of **endocrine disrupters**.
Isling LK, Boberg J, Jacobsen PR, Mandrup KR, Axelstad M, Christiansen S, Vinggaard AM, Taxvig C, Kortenkamp A, Hass U.
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3.Mixture effects at very low doses with combinations of anti-androgenic pesticides, antioxidants, industrial pollutant and chemicals used in personal care products.
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Walker DM, Goetz BM, Gore AC.
Mol Endocrinol. 2013 Nov 27. [Epub ahead of print]

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11. Evaluation of a Screening System for Obesogenic Compounds: Screening of **Endocrine Disrupting** Compounds and Evaluation of the PPAR Dependency of the Effect.
Pereira-Fernandes A, Demaegdt H, Vandermeiren K, Hectors TL, Jorens PG, Blust R, Vanparys C.
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15.Expression and methylation status of female-predominant GH-dependent liver genes are modified by neonatal androgenization in female **mice**.
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Juberg DR, Borghoff SJ, Becker RA, Casey W, Hartung T, Holsapple MP, Marty MS, Mihaich EM, Van Der Kraak G, Wade MG, Willett CE, Andersen ME, Borgert CJ, Coady KK, Dourson ML, Fowle JR, Gray LE, Lamb JC, Ortego LS, Schug TT, Toole CM, Zorrilla LM, Kroner OL, Patterson J, Rinckel LA, Jones BR.
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Wildlife studier ved Biologisk Institut, Syddansk Universitet (SDU)

Søgningen er udført på Web of Knowledge (all databases) og dækker perioden 23/9 2013 – 11/12 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 fire artikler til medtagelse af abstract og yderligere kommentarer.

Udvalgte publikationer

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.
Tre artikler (**artikel 2+3+4)** inkluderer undersøgelser af parabener og er, grundet Miljøstyrelsens ønskede fokus på denne stofgruppe, alle medtaget til kort yderligere kommentering på trods af, at to af studierne (**artikel 3+4)** primært omhandler de toksiske effekter af stofferne.

Artikel 1: Effects of Bisphenol S Exposure on Endocrine Functions and Reproduction of Zebrafish. Ji, K.; Hong, S.; Kho, Y.; and Choi, K. 2013. Environmental Science & Technology 47, 8793-8800.

Abstract: While bisphenol S (BPS) has been frequently detected both in environment and biota, limited information is available on their effects of endocrine system. In the present study, adult zebrafish pairs were exposed to 0.5, 5, and 50 μg/L of BPS for 21 d, and the effects on reproduction, sex steroid hormones, and transcription of the genes belonging to the hypothalamic-

pituitarygonad (HPG) axis were investigated. The adverse effects on performances of F1 generation were further examined with or without subsequent exposure to BPS. Egg production and the gonadosomatic index in female fish were significantly decreased at ≥0.5 μg/L BPS. Plasma concentrations of 17β-estradiol were significantly increased in both male and female fish. In male fish, however, significant decreases of testosterone concentration were observed along with up-regulation of cyp19a and down-regulation of cyp17 and 17βhsd transcripts. Parental exposure to BPS resulted in delayed and lesser rates of hatching even when they were hatched in clean water. Continuous BPS exposure in the F1 embryos resulted in worse hatchability and increased malformation rates compared to those without BPS exposure. Our observations showed that exposure to low level BPS could affect the feedback regulatory circuits of HPG axis and impair the development of offspring.

Artikel 2: Transcriptome alterations in zebrafish embryos after exposure to environmental estrogens and anti-androgens can reveal endocrine disruption.
Schiller, V.; Wichmann, A.; Kriehuber, R.; Schafers, C.; Fischer, R.; and Fenske, M. 2013. Reproductive toxicology 42, 210-223.

Abstract: Exposure to environmental chemicals known as endocrine disruptors (EDs) is in many cases associated with an unpredictable hazard for wildlife and human health. The identification of endocrine disruptive properties of chemicals certain to enter the aquatic environment relies on toxicity tests with fish, assessing adverse effects on reproduction and sexual development. The demand for quick, reliable ED assays favored the use of fish embryos as alternative test organisms. We investigated the application of a transcriptomics-based assay for estrogenic and anti-androgenic chemicals with zebrafish embryos. Two reference compounds, 17α-ethinylestradiol and flutamide, were tested to evaluate the effects on development and the transcriptome after 48 h-exposures. Comparison of the transcriptome response with other estrogenic and anti-androgenic compounds (genistein, bisphenol A, methylparaben, linuron, prochloraz, propanil) showed commonalities and differences in regulated pathways, enabling us to classify the estrogenic and anti-androgenic potencies. This demonstrates that different mechanism of ED can be assessed already in fish embryos.

Artikel 3: Gene expression responses for detecting sublethal effects of xenobiotics and whole effluents on a Xenopus laevis embryo assay.
San Segundo, L.; Martini, F.; and Victoria Pablos, M. 2013. Environmental Toxicology and Chemistry 32, 2018-2025.

Abstract: In the present study, the authors investigated the effects of bisphenol A, chlorpyrifos, methylparaben, and 2 effluent samples from wastewater treatment plants located in the province of Madrid, Spain, on the messenger RNAexpression of specific genes involved in early development (ESR1, pax6, bmp4, and myf5) and a gene involved in the general stress response (hsp70) during Xenopus laevis embryo development. Gene expression was analyzed after 4 h, 24 h, and 96 h of exposure by semiquantitative reverse-transcriptase–polymerase chain reaction. Concentration ranges of the compounds and dilutions for the samples were selected to cause morphological alterations in embryos after 96 h of exposure. Transcript levels of ESR1, pax6, and hsp70 were differentially altered at early developmental stages with patterns specific to the contaminant and the

exposure time. However, further studies are needed to establish transcript levels of specific genes as biomarkers of sublethal effects in an environmental risk-assessment framework. Besides, studies including more generic responses, such as genes encoding antioxidant enzymes, together with genes related to embryonic development have to be developed to look for a battery of mechanistic endpoints for the evaluation of chemical exposure at the molecular level in a first-tier assessment.

Artikel 4: Embryonic exposure of medaka (Oryzias latipes) to propylparaben: Effects on early development and post-hatching growth.
Gonzalez-Doncel, M.; Garcia-Maurino, J. E.; San Segundo, L.; Beltran, E. M.; Sastre, S.; and Fernandez Torija, C. 2014. Environmental pollution 184, 360-369.

Abstract: Here we proposed a battery of non-invasive biomarkers and a histological survey to examine physiological/anatomical features in embryos, eleutheroembryos (13 days post-fertilization, dpf), and larvae (28 e42 dpf) of medaka to investigate the effects of embryonic exposure to propylparaben (PrP). Concentrations <1000 μg PrP/L didn't exert early or late toxic effects. However, survivorship was affected at 4000 μg/L in eleutheroembryos and at ≥1000 mg/L in larvae. Histological alterations were found in 37.5% of eleutheroembryos exposed to 4000 μg PrP/L. Morphometric analysis of the gallbladder revealed significant dilation at ≥400 mg/L throughout embryo development. Ethoxyresorufin-O-deethylase (EROD), as indicator of cytochrome P4501A activity, didn't reveal induction/inhibition although its combination with a P4501A agonist (i.e. β-naphthoflavone) resulted in a synergic EROD response. Results suggest a low toxicity of PrP for fish and support the use of fish embryos and eleutheroembryos as alternatives of in vivo biomarkers indicative of exposure/toxicity.

Bruttoliste

Alkylphenoler

Environmental concentration of nonylphenol alters the development of urogenital and visceral organs in avian model.
Roig, B.; Cadiere, A.; Bressieux, S.; Biau, S.; Faure, S.; and de Santa Barbara, P. 2014. Environment international 62, 78-85.

Multiple factors in marine environments affecting lobster survival, development, and growth, with emphasis on alkylphenols: a perspective.
Laufer, H.; Chen, M.; Baclaski, B.; Bobbitt, J. M.; Stuart, J. D.; Zuo, Y.; and Jacobs, M. W. 2013. Canadian Journal of Fisheries and Aquatic Sciences 70, 1588-1600.

Exposure to Estrogenic Chemicals Induces Ectopic Expression of vtg in the Testis of Rainbowfish, Melanotaenia fluviatilis.
Shanthanagouda, A.; Nugegoda, D.; Hassell, K.; and Patil, J. 2013. Bulletin of Environmental Contamination and Toxicology 91, 438-443.

Parabener

Embryonic exposure of medaka (Oryzias latipes) to propylparaben: Effects on early development and post-hatching growth.
Gonzalez-Doncel, M.; Garcia-Maurino, J. E.; San Segundo, L.; Beltran, E. M.; Sastre, S.; and Fernandez Torija, C. 2014. Environmental pollution 184, 360-369.

Plastblødgørere

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