

Center for Hormonforstyrrende Stoffer

Litteraturgennemgang for perioden 1. september 2014 - 26. november 2014

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Humane studier ved Afd. for Vækst og Reproduktion, Rigshospitalet

Søgning er udført på PubMed og dækker perioden 1. september 2014 - 26. november 2014

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.

De udvalgte artikler koncentrerer sig i denne omgang om phthalater og bisphenol A. Enkelte af artiklerne kommenteres på engelsk, da det er en finsk PhD studerende i afdelingen, der har hjulpet med disse.

God læselyst!

Udvalgte publikationer

Bornehag CG(1), Carlstedt F, Jönsson BA, Lindh CH, Jensen TK, Bodin A, Jonsson C, Janson S, Swan SH

Prenatal Phthalate Exposures and Anogenital Distance in Swedish Boys.

Environ Health Perspect. 2014 Oct 29. [Epub ahead of print]

BACKGROUND: Phthalates are used as plasticizers in soft polyvinyl chloride (PVC) and in a large number of consumer products. Due to reported health risks, di-isobutyl phthalate (DiNP) has been introduced as a replacement for diethyl hexyl phthalate (DEHP) in soft PVC. This raises concerns since animal data suggest that DiNP may have anti-androgenic properties similar to DEHP. The anogenital distance (AGD) - the distance from the anus to the genitals - has been used to assess reproductive toxicity. **OBJECTIVE:** The objective of this study was to examine the associations between prenatal phthalate exposure and AGD in Swedish infants. **METHODS:** AGD was measured in 196 boys at age 21 months and first trimester urine was analyzed for ten phthalate metabolites of DEP, DBP, DEHP, BBzP as well as DiNP and creatinine. Data on covariates were collected by questionnaires. **RESULTS:** The most significant associations were found between the shorter of two AGD measures (anoscrotal distance, AGDas) and DiNP metabolites and strongest for oh-MMeOP and oxo-MMeOP. However, the AGDas reduction was small (4%) in relation to more than an interquartile increase in DiNP exposure. **CONCLUSIONS:** These findings call into question the safety of substituting DiNP for DEHP in soft PVC, particularly since a shorter male AGD has been shown to relate to male genital birth defects in children and impaired reproductive function in adult males and the fact that human levels of DiNP are increasing globally.

Araki A, Mitsui T, Miyashita C, Nakajima T, Naito H, Ito S, Sasaki S, Cho K, Ikeno T, Nonomura K, Kishi R.

Association between maternal exposure to di(2-ethylhexyl) phthalate and reproductive hormone levels in fetal blood: the Hokkaido study on environment and children's health.

PLoS One. 2014 Oct 8;9(10):e109039. doi: 10.1371/journal.pone.0109039.

eCollection 2014.

Prenatal di(2-ethylhexyl) phthalate (DEHP) exposure can produce reproductive toxicity in animal models. Only limited data exist from human studies on maternal DEHP exposure and its effects on infants. We aimed to examine the associations between DEHP exposure in utero and reproductive hormone levels in cord blood. Between 2002 and 2005, 514 pregnant women agreed to participate in the Hokkaido Study Sapporo Cohort. Maternal blood samples were taken from 23–35 weeks of gestation and the concentration of the primary metabolite of DEHP, mono(2-ethylhexyl) phthalate (MEHP), was measured. Concentrations of infant reproductive hormones including estradiol (E2), total testosterone (T), and progesterone (P4), inhibin B, insulin-like factor 3 (INSL3), steroid hormone binding globulin, follicle-stimulating hormone, and luteinizing hormone were measured from cord blood. Two hundred and two samples with both MEHP and hormone data were included in statistical analysis. The participants completed a self-administered questionnaire regarding information on maternal characteristics. Gestational age, birth weight and infant sex were obtained from birth records. In an adjusted linear regression analysis fit to all study participants, maternal MEHP levels were found to be associated with reduced levels of T/E2, P4, and inhibin B. For the stratified analyses for sex, inverse associations between maternal MEHP levels T/E2, P4, inhibin B, and INSL3 were statistically significant for males only. In addition, the MEHP quartile model showed a significant p-value trend for P4, inhibin B, and INSL3 decrease in males. Since inhibin B and INSL3 are major secretory products of Sertoli and Leydig cell, respectively, the results of this study suggest that DEHP exposure in utero may have adverse effects on both Sertoli and Leydig cell development in males, which agrees with

the results obtained from animal studies. Comprehensive studies investigating phthalates' exposure in humans, as well as their long-term effects on reproductive development are needed.

Jensen MS, Anand-Ivell R, Nørgaard-Pedersen B, Jönsson BA, Bonde JP, Hougaard DM, Cohen A, Lindh CH, Ivell R, Toft G.

Amniotic fluid phthalate levels and male fetal gonad function

Epidemiology. 2015 Jan;26(1):91-9. doi: 10.1097/EDE.0000000000000198.

BACKGROUND: Prenatal exposure to phthalates may pose a threat to human male reproduction. However, additional knowledge about the in vivo effect in humans is needed, and reported associations with genital abnormalities are inconclusive. We aimed to study prenatal di(2-ethylhexyl) phthalate (DEHP) and diisonyl phthalate (DiNP) exposure in relation to cryptorchidism, hypospadias, and human fetal Leydig cell function. **METHODS:** We studied 270 cryptorchidism cases, 75 hypospadias cases, and 300 controls. Second-trimester amniotic fluid samples were available from a Danish pregnancy-screening biobank ($n = 25,105$) covering 1980-1996. We assayed metabolites of DEHP and DiNP ($n = 645$) and steroid hormones ($n = 545$) by mass spectrometry. We assayed insulin-like factor 3 by immunoassay ($n = 475$) and analyzed data using linear or logistic regression. **RESULTS:** Mono(2-ethyl-5-carboxypentyl) phthalate (5cx-MEPP, DEHP metabolite) was not consistently associated with cryptorchidism or hypospadias. However, we observed an 18% higher (95% confidence interval [CI] = 5%-33%) testosterone level, and a 41% lower (-56% to -21%) insulin-like factor 3 level in the highest 5cx-MEPP tertile compared with the lowest. Mono(4-methyl-7-carboxyheptyl) phthalate (7cx-MMeHP, DiNP metabolite) showed elevated odds ratio point estimates for having cryptorchidism (odds ratio = 1.28 [95% CI = 0.80 to 2.01]) and hypospadias (1.69 [0.78 to 3.67]), but was not consistently associated with the steroid hormones or insulin-like factor 3. **CONCLUSIONS:** Data on the DEHP metabolite indicate possible interference with human male fetal gonadal function. Considering the DiNP metabolite, we cannot exclude (nor statistically confirm) an association with hypospadias and, less strongly, with cryptorchidism.

Hormann AM, Vom Saal FS, Nagel SC, Stahlhut RW, Moyer CL, Ellersieck MR, Welshons WV, Toutain PL, Taylor JA

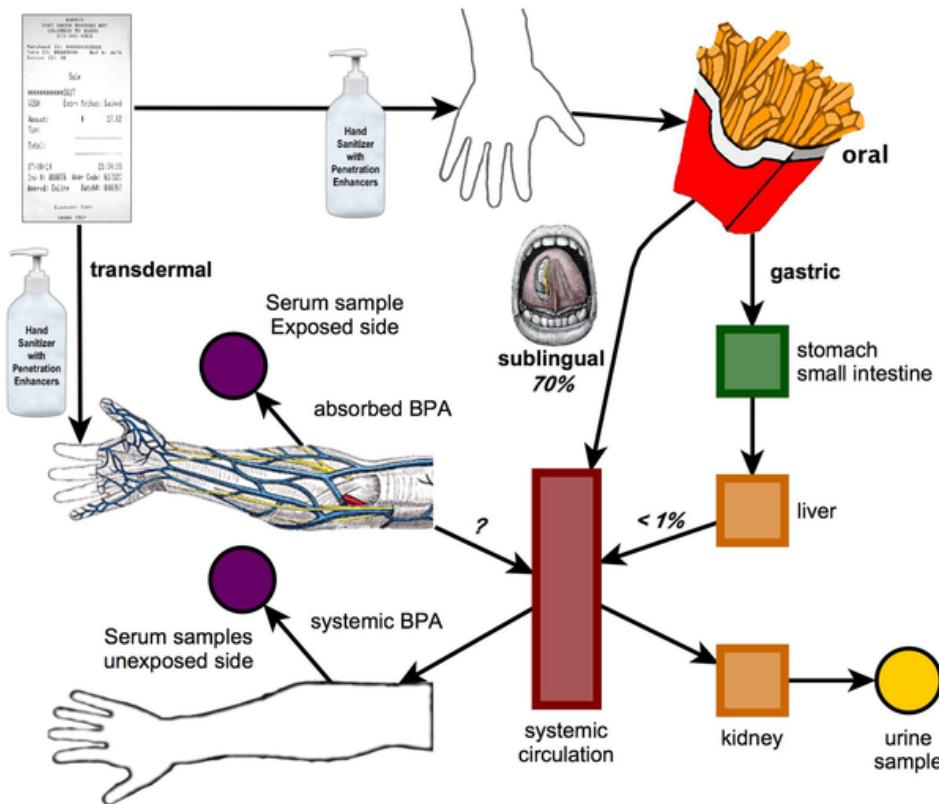
Holding Thermal Receipt Paper and Eating Food after Using Hand Sanitizer Results in High Serum Bioactive and Urine Total Levels of Bisphenol A (BPA)

PLoS One. 2014 Oct 22;9(10):e110509. doi: 10.1371/journal.pone.0110509. eCollection 2014.

Bisphenol A (BPA) is an endocrine disrupting environmental contaminant used in a wide variety of products, and BPA metabolites are found in almost everyone's urine, suggesting widespread exposure from multiple sources. Regulatory agencies estimate that virtually all BPA exposure is from food and beverage packaging. However, free BPA is applied to the outer layer of thermal receipt paper present in very high (

paper as a source of BPA exposure is that some commonly used hand sanitizers, as well as other skin care products, contain mixtures of dermal penetration enhancing chemicals that can increase by up to 100 fold the dermal absorption of lipophilic compounds such as BPA. We found that when men and women held thermal receipt paper immediately after using a hand sanitizer with penetration enhancing chemicals, significant free BPA was transferred to their hands and then to French fries that were eaten, and the combination of dermal and oral BPA absorption led to a rapid and dramatic average maximum increase (Cmax) in unconjugated (bioactive) BPA of ~720 ng/g total BPA/g andmatinine in urine within 90 min. The default method used by regulatory agencies to test for hazards posed by chemicals is intra-gastric gavage. For BPA this approach results in less than 1% of the administered dose being bioavailable in blood. It also ignores dermal absorption as well as sublingual absorption in the mouth that

both bypass first-pass liver metabolism. The elevated levels of BPA that we observed due to holding thermal paper after using a product containing dermal penetration enhancing chemicals have been related to an increased risk for a wide range of developmental abnormalities as well as diseases in adults.



J. Troisi, C. Mikelson, S. Richards, S. Symes, D. Adair, F. Zullo, M. Guida

Placental concentrations of bisphenol A and birth weight from births in the Southeastern U.S.

Placenta 35 (2014) 947-952

Introduction: Bisphenol A (BPA) is a weakly estrogenic compound that has been detected in a wide variety of food products and biological matrices (saliva, blood, urine, etc). Despite the potential risk of human exposure to BPA, little information exists concerning maternal and fetal exposure to BPA during pregnancy. The aim of this study is to evaluate the correlation between placental BPA concentration, infant birth weight and calculated birth weight centile, and several other maternal and infant parameters.

Methods: Placental sample were collected from 200 subjects. BPA levels were measured by isotope dilution GC-MS. Additional maternal and infant data were gathered from medical charts and were potential correlates with placental BPA levels.

Results: Placental BPA concentrations ranged from 4.4 ng/g to 273.9 ng/g in oven-dried tissue (average 103.4 ± 61.8 ng/g). There was a significant negative correlation between calculated birth weight centile and levels of placental BPA ($p < 0.05$). Low birth weight and small for gestational age infants also had significantly greater placental BPA concentrations as compared to normal weight infants and average/large for gestational age infants. Infants born to African American mothers also had greater placental BPA concentrations as compared to infants born to Hispanic mothers.

Discussion: Placental BPA concentrations are correlated with the growth potential of the fetus and may play a role in reduced fetal growth.

Bruttoliste

Bisphenol A

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3: Gorrochategui E, Casas J, Pérez-Albaladejo E, Jáuregui O, Porte C, Lacorte S. Characterization of complex lipid mixtures in contaminant exposed JEG-3 cells using liquid chromatography and high-resolution mass spectrometry. *Environ Sci Pollut Res Int.* 2014 Oct;21(20):11907-16. doi: 10.1007/s11356-014-3172-5. Epub 2014 Jun 28. PubMed PMID: 24969426.

4: Celada LJ, Whalen MM. Effects of butyltins on mitogen-activated-protein kinase kinase kinase and Ras activity in human natural killer cells. *J Appl Toxicol.* 2014 Sep;34(9):1002-11. doi: 10.1002/jat.2921. Epub 2013 Sep 5. PubMed PMID: 24038145; PubMed Central PMCID: PMC3868639.

Endocrine disrupters

1: Boberg J, Johansson HK, Hadrup N, Dreisig K, Berthelsen L, Almstrup K, Vinggaard AM, Hass U. Perinatal exposure to mixtures of anti-androgenic chemicals causes proliferative lesions in rat prostate. *Prostate.* 2014 Oct 18. doi:10.1002/pros.22897. [Epub ahead of print] PubMed PMID: 25327291.

2: Vega A, Baptissart M, Martinot E, Saru JP, Baron S, Schoonjans K, Volle DH. Hepatotoxicity induced by neonatal exposure to diethylstilbestrol is maintained throughout adulthood via the nuclear receptor SHP. *Expert Opin Ther Targets.* 2014 Dec;18(12):1367-76. doi: 10.1517/14728222.2014.964209. Epub 2014 Sep 29. PubMed PMID: 25263461.

In vitro studier ved DTU Fødevareinstituttet

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 2014/08/30 to 2014/12/30 present (September 2014 og fremefter)

Efter at have fjernet genganger fra forrige litteraturopdateringslister gav litteratursøgningen, med de angivne søgekriterier, tilsammen en liste med i alt 35 artikler (Bruttolisten). Artiklerne er blevet fordelt i 4 grupper: ”Perflourinated and Polyflourinated compounds”, ”Plastic derivatives (BPA, Phthalates and others)”, ”Pesticides/Fungicides/Insecticides /Biocides” og ”Various EDCs, Mixtures and Other endpoints”.

Udvalgte publikationer

2 artikler er blevet udvalgt (fra bruttolisten) til nærmere beskrivelse baseret på, at de beskriver resultater der bidrager til ny eller yderligere viden om grupper af hormonforstyrrende stoffer.

Den første artikel beskriver et in vitro studie, hvor man har undersøgt den østrogene effekt af bisphenol A og to BPA alternativer BPS of polyethersulfone (PES), samt deres metabolitter.

Den anden artikel omhandler in vitro studier til at undersøge hormonforstyrrende effekter af en række godkendte og almindelig anvendte ikke-persistente pesticider.

[Estrogenic potency of bisphenol S, polyethersulfone and their metabolites generated by the rat liver S9 fractions on a MVLN cell using a luciferase reporter gene assay.](#)

Kang JS, Choi JS, Kim WK, Lee YJ, Park JW.

Abstract

Background:

Bisphenol A (BPA) is an applied chemical that is used in many industrial fields and is a potential endocrine disruption chemical (EDC) that is found in the environment. Bisphenol S (BPS) and polyethersulfone (PES) have been suggested as putative BPA alternatives. In this study, the estrogenic potency induced by the binding of 17-beta-estradiol (E2), BPA, BPS, PES and their metabolites formed by the rat liver S9 fraction to the human estrogen receptor (ER) was estimated.

Methods:

We used an in vitro bioassay based on the luciferase reporter assay in MVLN cells to evaluate the estrogenic activity of 17-beta-estradiol (E2), BPA, BPS, PES (E2: 0.001 to 0.3 nM; BPA, BPS and PES: 0.0001 to 5 microM) and their metabolites (E2: 0.05 microM; BPA, BPS and PES: 0.1 mM) according to incubation times (0, 20 and 40 min). After chemical treatment to MVLN cells for 72 hrs, and the cell viability and luciferase intensity induced were estimated, from which the estrogenic activity of the chemicals tested was evaluated.

Results:

BPA and BPS induced estrogenic activity whereas PES did not show any estrogenic activity in the concentrations tested. In an in vitro assay of metabolites, BPA metabolites displayed comparable estrogenic activity with BPA and metabolites of both BPS and PES showed increasing estrogenic activity.

Conclusions:

The results suggest that the metabolites of BPS and PES have estrogenic potential and the need for the assessment of both chemicals and their metabolites in other EDC evaluation studies. The estrogenic potency of PES and its metabolites is the first report in our best knowledge.

[Effect of nonpersistent pesticides on estrogen receptor, androgen receptor, and aryl hydrocarbon receptor.](#)

Medjakovic S, Zechling A, Gerster P, Ivanova MM, Teng Y, Klinge CM, Schildberger B, Gartner M, Jungbauer A.

Abstract

Nonpersistent pesticides are considered less harmful for the environment, but their impact as endocrine disruptors has not been fully explored. The pesticide Switch was applied to grape vines, and the maximum residue concentration of its active ingredients was quantified. The transactivation potential of the pesticides Acorit, Frupica, Steward, Reldan, Switch, Cantus, Teldor, and Scala and their active compounds (hexythiazox, mepanipyrim, indoxacarb, chlorpyrifos-methyl, cyprodinil, fludioxonil, boscalid, fenhexamid,

and pyrimethanil) were tested on human estrogen receptor α (ER α), androgen receptor (AR) and arylhydrocarbon receptor (AhR) in vitro. Relative binding affinities of the pure pesticide constituents for AR and their effect on human breast cancer and prostate cancer cell lines were evaluated. Residue concentrations of Switch's ingredients were below maximum residue limits. Fludioxonil and fenhexamid were ER α agonists (EC50 -values of 3.7 and 9.0 μ M, respectively) and had time-dependent effects on endogenous ER α -target gene expression (cyclin D1, progesterone receptor, and nuclear respiratory factor 1) in MCF-7 human breast cancer cells. Fludioxonil, mepanipyrim, cyprodinil, pyrimethanil, and chlorpyrifos-methyl were AhR-agonists (EC50 s of 0.42, 0.77, 1.4, 4.6, and 5.1 μ M, respectively). Weak AR binding was shown for chlorpyrifos-methyl, cyprodinil, fenhexamid, and fludioxonil. Assuming a total uptake which does not take metabolism and clearance rates into account, our in vitro evidence suggests that pesticides could activate pathways affecting hormonal balance, even within permitted limits, thus potentially acting as endocrine disruptors.

Bruttoliste

Perflourinated and Polyflourinated compounds

1. [Exposure to perfluorinated compounds: in vitro study on thyroid cells.](#)
Coperchini F, Pignatti P, Lacerenza S, Negri S, Sideri R, Testoni C, de Martinis L, Cottica D, Magri F, Imbriani M, Rotondi M, Chiovato L.
Environ Sci Pollut Res Int. 2014 Sep 4. [Epub ahead of print]
2. [Chronic Exposure to Perfluorooctane Sulfonate Induces Behavior Defects and Neurotoxicity through Oxidative Damages, In Vivo and In Vitro.](#)
Chen N, Li J, Li D, Yang Y, He D.
PLoS One. 2014 Nov 20;9(11):e113453. doi: 10.1371/journal.pone.0113453. eCollection 2014.
3. [Vaporization dynamics of volatile perfluorocarbon droplets: a theoretical model and in vitro validation.](#)
Doinikov AA, Sheeran PS, Bouakaz A, Dayton PA.
Med Phys. 2014 Oct;41(10):102901. doi: 10.1111/1.4894804.
4. [Analysis of apoptosis induced by perfluorooctane sulfonates \(PFOS\) in mouse Leydig cells in vitro.](#)
Zhang DY, Xu XL, Shen XY, Ruan Q, Hu WL.
Toxicol Mech Methods. 2014 Oct 13:1-5. [Epub ahead of print]
5. [In vitro surfactant and perfluorocarbon aerosol deposition in a neonatal physical model of the upper conducting airways.](#)
Goikoetxea E, Murgia X, Serna-Grande P, Valls-i-Soler A, Rey-Santano C, Rivas A, Antón R, Basterretxea FJ, Miñambres L, Méndez E, Lopez-Arraiza A, Larrabe-Barrena JL, Gomez-Solaetxe MA.
PLoS One. 2014 Sep 11;9(9):e106835. doi: 10.1371/journal.pone.0106835. eCollection 2014.
6. [Inhalation and oral toxicokinetics of 6:2 FTOH and its metabolites in mammals.](#)
Russell MH, Himmelstein MW, Buck RC.
Chemosphere. 2014 Aug 30;120C:328-335. doi: 10.1016/j.chemosphere.2014.07.092. [Epub ahead of print]

Plastic derivatives" (BPA, Phthalates and others)

1. [Inhibitory Effects of Bisphenol-A on Neural Stem Cells Proliferation and Differentiation in the Rat Brain Are Dependent on Wnt/β-Catenin Pathway.](#)
Tiwari SK, Agarwal S, Seth B, Yadav A, Ray RS, Mishra VN, Chaturvedi RK.
Mol Neurobiol. 2014 Nov 9. [Epub ahead of print]
2. [Estrogenic potency of bisphenol S, polyethersulfone and their metabolites generated by the rat liver S9 fractions on a MVLN cell using a luciferase reporter gene assay.](#)
Kang JS, Choi JS, Kim WK, Lee YJ, Park JW.
Reprod Biol Endocrinol. 2014 Nov 4;12(1):102. doi: 10.1186/1477-7827-12-102.
3. [Bisphenol A stimulates human lung cancer cell migration via upregulation of matrix metalloproteinases by GPER/EGFR/ERK1/2 signal pathway.](#)
Zhang KS, Chen HQ, Chen YS, Qiu KF, Zheng XB, Li GC, Yang HD, Wen CJ.
Biomed Pharmacother. 2014 Sep 18. pii: S0753-3322(14)00116-4. doi: 10.1016/j.biopha.2014.09.003. [Epub ahead of print]
4. [Bisphenol A, oocyte maturation, implantation, and IVF outcome: review of animal and human data.](#)
Machtinger R, Orvieto R.
Reprod Biomed Online. 2014 Oct;29(4):404-10. doi: 10.1016/j.rbmo.2014.06.013. Epub 2014 Jul 10.

5. [Screening of bisphenol A, triclosan and paraben analogues as modulators of the glucocorticoid and androgen receptor activities.](#)

Kolšek K, Gobec M, Mlinarič Raščan I, Sollner Dolenc M. Toxicol In Vitro. 2014 Sep 2;29(1):8-15. doi: 10.1016/j.tiv.2014.08.009. [Epub ahead of print]

6. [Mixture effects of nonylphenol and di-n-butyl phthalate \(monobutyl phthalate\) on the tight junctions between Sertoli cells in male rats in vitro and in vivo.](#)

Hu Y, Wang R, Xiang Z, Qian W, Han X, Li D. Exp Toxicol Pathol. 2014 Sep 4. pii: S0940-2993(14)00093-1. doi: 10.1016/j.etp.2014.07.003. [Epub ahead of print]

7. [Genotoxicity of phthalates.](#)

Erkekoglu P, Kocer-Gumusel B. Toxicol Mech Methods. 2014 Sep 23:1-11. [Epub ahead of print]

8. [Impact of di-ethylhexylphthalate exposure on metabolic programming in P19 ECC-derived cardiomyocytes.](#)

Schaedlich K, Schmidt JS, Kwong WY, Sinclair KD, Kurz R, Jahnke HG, Fischer B. J Appl Toxicol. 2014 Oct 29. doi: 10.1002/jat.3085. [Epub ahead of print]

9. [In vitro evaluation of the quality of blood products collected and stored in systems completely free of di\(2-ethylhexyl\)phthalate-plasticized materials.](#)

Lagerberg JW, Gouwerok E, Vlaar R, Go M, de Korte D. Transfusion. 2014 Oct 21. doi: 10.1111/trf.12870. [Epub ahead of print]

10. [Di-\(2-ethylhexyl\) phthalate accelerates atherosclerosis in apolipoprotein E-deficient mice.](#)

Zhao JF, Hsiao SH, Hsu MH, Pao KC, Kou YR, Shyue SK, Lee TS. Arch Toxicol. 2014 Oct 2. [Epub ahead of print]

11. [Curcumin influences semen quality parameters and reverses the di\(2-ethylhexyl\)phthalate \(DEHP\)-induced testicular damage in mice.](#)

Glombik K, Basta-Kaim A, Sikora-Polaczek M, Kubera M, Starowicz G, Styrna J. Pharmacol Rep. 2014 Oct;66(5):782-7. doi: 10.1016/j.pharep.2014.04.010. Epub 2014 Apr 30.

Pesticides/Fungicides/Insecticides/Biocides

1. [Antiandrogenic Mechanisms of Pesticides in Human LNCaP Prostate and H295R Adrenocortical Carcinoma Cells.](#)

Robitaille CN, Rivest P, Sanderson JT. Toxicol Sci. 2014 Oct 15. pii: kfu212. [Epub ahead of print]

2. [Effective attenuation of atrazine-induced histopathological changes in testicular tissue by antioxidant N-phenyl-4-aryl-polyhydroquinolines.](#)

Chandak N, Bhardwaj JK, Zheleva-Dimitrova D, Kitanov G, Sharma RK, Sharma PK, Saso L. J Enzyme Inhib Med Chem. 2014 Sep 29:1-8. [Epub ahead of print]

3. [Effect of nonpersistent pesticides on estrogen receptor, androgen receptor, and aryl hydrocarbon receptor.](#)
Medjakovic S, Zochling A, Gerster P, Ivanova MM, Teng Y, Klinge CM, Schildberger B, Gartner M, Jungbauer A.

Environ Toxicol. 2014 Oct;29(10):1201-16. doi: 10.1002/tox.21852. Epub 2013 Feb 23.

4. [Utilization of microfluidic V-junction device to prepare surface itraconazole adsorbed nanospheres.](#)

Kucuk I, Ahmad Z, Edirisonghe M, Orlu-Gul M.
Int J Pharm. 2014 Sep 10;472(1-2):339-46. doi: 10.1016/j.ijpharm.2014.06.023. Epub 2014 Jun 16.

Various EDCs, Mixtures and Other endpoints

1. [Exposures, mechanisms, and impacts of endocrine-active flame retardants.](#)

V Dishaw L, J Macaulay L, Roberts SC, Stapleton HM.

Curr Opin Pharmacol. 2014 Oct 9;19C:125-133. doi: 10.1016/j.coph.2014.09.018. [Epub ahead of print]
Review.

2. [Detection of immunotoxic effects of estrogenic and androgenic endocrine disrupting compounds using splenic immune cells of the female three-spined stickleback, Gasterosteus aculeatus \(L.\).](#)

Bado-Nilles A, Techer R, Porcher JM, Geffard A, Gagnaire B, Betouille S, Sanchez W.

Environ Toxicol Pharmacol. 2014 Sep;38(2):672-83. doi: 10.1016/j.etap.2014.08.002. Epub 2014 Aug 13.

3. [Exposure to paper mill effluent at a site in North Central Florida elicits molecular-level changes in gene expression indicative of progesterone and androgen exposure.](#)

Brockmeier EK, Jayasinghe BS, Pine WE, Wilkinson KA, Denslow ND.

PLoS One. 2014 Sep 8;9(9):e106644. doi: 10.1371/journal.pone.0106644. eCollection 2014.

4. [Toxicogenomic analysis of the ability of brominated flame retardants TBBPA and BDE-209 to disrupt thyroid hormone signaling in neural cells.](#)

Guyot R, Chatonnet F, Gillet B, Hughes S, Flamant F.

Toxicology. 2014 Nov 5;325:125-32. doi: 10.1016/j.tox.2014.08.007. Epub 2014 Aug 27.

5. [Assessment of the sensitizing potency of preservatives with chance of skin contact by the loose-fit coculture-based sensitization assay \(LCSA\).](#)

Sonnenburg A, Schreiner M, Stahlmann R.

Arch Toxicol. 2014 Nov 14. [Epub ahead of print]

6. [Establishment, Characterization, and Toxicological Application of Loggerhead Sea Turtle \(*Caretta caretta*\) Primary Skin Fibroblast Cell Cultures.](#)

Webb SJ, Zychowski GV, Bauman SW, Higgins BM, Raudsepp T, Gollahon LS, Wooten KJ, Cole JM, Godard-Codding CA.

Environ Sci Technol. 2014 Nov 10. [Epub ahead of print]

7. [A bioinspired omniphobic surface coating on medical devices prevents thrombosis and biofouling.](#)

Leslie DC, Waterhouse A, Berthet JB, Valentin TM, Watters AL, Jain A, Kim P, Hatton BD, Nedder A, Donovan K, Super EH, Howell C, Johnson CP, Vu TL, Bolgen DE, Rifai S, Hansen AR, Aizenberg M, Super M, Aizenberg J, Ingber DE.

Nat Biotechnol. 2014 Nov;32(11):1134-40. doi: 10.1038/nbt.3020. Epub 2014 Oct 12.

8. [Thrombin-inhibiting nanoparticles rapidly constitute versatile and detectable anticlotting surfaces.](#)

Myerson JW, He L, Allen JS, Williams T, Lanza G, Tollesen D, Caruthers S, Wickline S.

Nanotechnology. 2014 Oct 3;25(39):395101. doi: 10.1088/0957-4484/25/39/395101. Epub 2014 Sep 9.

9. [Effects of Polychlorinated Biphenyls 28, 30 and 118 on Bovine Spermatozoa In Vitro.](#)

Yurdakok B, Tekin K, Daskin A, Filazi A.

Reprod Domest Anim. 2014 Nov 15. doi: 10.1111/rda.12447. [Epub ahead of print]

10. [Induction of mesenchymal stem cell differentiation and cartilage formation by cross-linker-free collagen microspheres.](#)

Mathieu M, Vigier S, Labour MN, Jorgensen C, Belamie E, Noël D.

Eur Cell Mater. 2014 Sep 2;28:82-96; discussion 96-7.

11. [In Vitro Antibacterial Activity, Gas Chromatography-Mass Spectrometry Analysis of Woodfordia fruticosa Kurz. Leaf Extract and Host Toxicity Testing With In Vitro Cultured Lymphocytes From Human Umbilical Cord Blood.](#)
Dubey D, Patnaik R, Ghosh G, Padhy RN.
Osong Public Health Res Perspect. 2014 Oct;5(5):298-312. doi: 10.1016/j.phrp.2014.08.001. Epub 2014 Sep 6.
12. [Inhibition of PPAR \$\alpha\$ attenuates vimentin phosphorylation on Ser-83 and collapse of vimentin filaments during exposure of rat Sertoli cells in vitro to DBP.](#)
Zhang X, Liu W, Yang H, Tan L, Ao L, Liu J, Cao J, Cui Z.
Reprod Toxicol. 2014 Oct 4. pii: S0890-6238(14)00252-4. doi: 10.1016/j.reprotox.2014.09.015. [Epub ahead of print]
13. [Enteric-coated capsule containing \$\beta\$ -galactosidase-loaded polylactic acid nanocapsules: enzyme stability and milk lactose hydrolysis under simulated gastrointestinal conditions.](#)
He H, Zhang X, Sheng Y.
J Dairy Res. 2014 Nov;81(4):479-84. doi: 10.1017/S0022029914000491. Epub 2014 Sep 29.
14. [Transcriptomic characterization of C57BL/6 mouse embryonic stem cell differentiation and its modulation by developmental toxicants.](#)
Gao X, Yourick JJ, Sprando RL.
PLoS One. 2014 Sep 23;9(9):e108510. doi: 10.1371/journal.pone.0108510. eCollection 2014.

In Vivo studier ved DTU Fødevareinstituttet

(September- primo December 2014)

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 ((PFAS* OR Perfluor*) AND toxicity).

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

Udvalgte publikationer

Tre artikler er blevet udvalgt til nærmere beskrivelse (abstrakt og konklusion) og en artikel kun med abstract. Disse artikler er valgt fordi vi mener de bidrager til ny viden om hormonforstyrrende stoffer. Den første artikel er fra Sharpes gruppe og ser på AGD og om dette endepunkt kan ændres ved hormonpåvirkning i voksne gnavere (Mitchell et al 2014). De 2 næste artikler er fra det store EU projekt CONTAMED, dels om prostata effekter og om brystvævsforandringer efter mix eksponering (Boberg et al. og Mandrup et al 2014). Den sidste artikel (kun abstract) er et review der har til formål at bygge bro mellem den akademiske forskning og den regulatoriske risikovurdering af kemikalier (Beronius et al. 2014).

Ud fra bruttolisten (se længere nede i dokumentet) er udvalgt følgende 4 artikler til engelsk abstrakt og/eller dansk resume og kommentarer.

[Anogenital distance \(AGD\) plasticity in adulthood: Implications for its use as a biomarker of fetal androgen action.](#)

Mitchell RT, Mungall W, McKinnell C, Sharpe RM, Cruickshanks L, Milne L, Smith LB. Endocrinology. 2014 Nov 6:en20141534. [Epub ahead of print]

Abstract

Androgen action during the fetal masculinization-programming window (MPW) determines the maximum potential for growth of androgen-dependent organs (e.g. seminal vesicles, prostate, penis, perineum) and is reflected in anogenital distance (AGD). As such, determining AGD in postnatal life has potential as a lifelong easily accessible biomarker of overall androgen action during the MPW. However, whether the perineum remains androgen-responsive in adulthood and thus responds plastically to perturbed androgen drive remains unexplored. To determine this, we treated adult male rats with either the anti-androgen Flutamide, or the estrogen Diethylstilbestrol (DES) for five weeks, followed by a four-week wash-out period of no treatment. We determined AGD, and its correlate anogenital index (AGI; AGD relative to bodyweight), at weekly intervals across this period and compared this to normal adult rats (male and female), castrated male rats, and appropriate vehicle controls. These data showed that, in addition to reducing circulating testosterone and seminal vesicle weight, castration significantly reduced AGD (by ~17%), demonstrating that there is a degree of plasticity in AGD in adulthood. Flutamide treatment increased circulating testosterone yet also reduced seminal vesicle weight due to local antagonism of androgen receptor. Despite this suppression, surprisingly, Flutamide treatment had no effect on AGD at any time-point. In contrast, whilst DES treatment suppressed circulating testosterone and reduced seminal vesicle weight, it also induced a significant reduction in AGD (by ~11%), which returned to normal one week after cessation of DES treatment. We conclude that AGD in adult rats exhibits a degree of plasticity, which may be mediated by modulating local androgen/estrogen action. The implications of these findings regarding the use of AGD as a life-long clinical biomarker of fetal androgen action are discussed.

[Mixtures of environmentally relevant endocrine disrupting chemicals affect mammary gland development in female and male rats.](#)

Mandrup KR, Johansson HK, Boberg J, Pedersen AS, Mortensen MS, Jørgensen JS, Vinggaard AM, Hass U. Reprod Toxicol. 2014 Oct 8. pii: S0890-6238(14)00253-6. doi: 10.1016/j.reprotox.2014.09.016. [Epub ahead of print]

Abstract

Estrogenic chemicals are able to alter mammary gland development in female rodents, but little is known on the effects of anti-androgens and mixtures of endocrine disrupting chemicals (EDCs) with dissimilar modes of action. Pregnant rat dams were exposed during gestation and lactation to mixtures of environmentally relevant EDCs with estrogenic, anti-androgenic or dissimilar modes of action (TotalMix) of 100-, 200- or 450-fold high end human intake estimates. Mammary glands of prepubertal and adult female and male offspring were examined. Oestrogens increased mammary outgrowth in prepubertal females and the mRNA level of matrix metalloproteinase-3, which may be a potential biomarker for increased outgrowth. Mixtures

of EDCs gave rise to ductal hyperplasia in adult males. Adult female mammary glands of the TotalMix group showed morphological changes possibly reflecting increased prolactin levels. In conclusion both estrogenic and anti-androgenic chemicals given during foetal life and lactation affected mammary glands in the offspring.

Perinatal exposure to mixtures of anti-androgenic chemicals causes proliferative lesions in rat prostate.

Boberg J, Johansson HK, Hadrup N, Dreisig K, Berthelsen L, Almstrup K, Vinggaard AM, Hass U. Prostate. 2014 Oct 18. doi: 10.1002/pros.22897. [Epub ahead of print]

Abstract

BACKGROUND. Elevated levels of endogenous or exogenous estrogens during fetal life can induce permanent disturbances in prostate growth and predispose to precancerous lesions. Recent studies have indicated that also early anti-androgen exposure may affect prostate cancer risk.

METHODS. We examined the influence of perinatal exposure to mixtures of anti-androgenic and estrogenic chemicals on prostate development. Wistar rats were exposed from gestation day 7 to postnatal day 22 to a mixture of 8 anti-androgenic compounds (AAMix), a mixture of four estrogenic compounds (EMix), or paracetamol or a mixture of all 13 compounds (TotalMix) in mixture ratios reflecting human exposure levels.

RESULTS. Ventral prostate weights were reduced by the TotalMix and AAMix in pre-pubertal rats. Histological changes in prostate appeared with increasing age and indicated a shift from the normal age-dependent epithelial atrophy towards hyperplasia. These lesions showed similarities to pre-cancerous lesions in humans. Increased proliferation was observed already in pre-puberty and it was hypothesized that this could be associated with reduced ER β signaling, but no clear conclusions could be made from gene expression studies on ER β related pathways. The influences of the estrogenic chemicals and paracetamol on prostate morphology were minor, but in young adulthood the estrogen mixture reduced ventral prostate mRNA levels of Igf1 and paracetamol reduced the mRNA level of Pbpc3.

CONCLUSIONS. Mixtures of endocrine disrupters relevant for human exposure was found to elicit persistent effects on the rat prostate following perinatal exposure, suggesting that human perinatal exposure to environmental chemicals may increase the risk of prostate cancer later in life.

Bridging the gap between academic research and regulatory health risk assessment of Endocrine Disrupting Chemicals.

Beronius A, Hanberg A, Zilliacus J, Rudén C.

Curr Opin Pharmacol. 2014 Dec;19C:99-104. doi: 10.1016/j.coph.2014.08.005. Epub 2014 Sep 18. Review.

Valgt (abstract)

Abstract

Regulatory risk assessment is traditionally based primarily on toxicity studies conducted according to standardized and internationally validated test guidelines. However, health risk assessment of endocrine disrupting chemicals (EDCs) is argued to rely on the efficient integration of findings from academic research. The aim of this review was to provide an overview of current developments to facilitate the use of academic research in regulatory risk assessment of chemicals and how certain aspects of study design and reporting are particularly important for the risk assessment process. By bridging the gap between academic research and regulatory health risk assessment of EDCs, scientific uncertainty in risk assessment conclusions can be reduced, allowing for better targeted policy decisions for chemical risk reduction.

Bruttoliste

Plastic derivatives (BPA, Phthalates and others)

BPA (and alternatives)

1. Developmental programming: prenatal BPA treatment disrupts timing of LH surge and ovarian follicular wave dynamics in adult sheep.

Veiga-Lopez A, Beckett EM, Abi Salloum B, Ye W, Padmanabhan V.
Toxicol Appl Pharmacol. 2014 Sep 1;279(2):119-28. doi: 10.1016/j.taap.2014.05.016. Epub 2014 Jun 9.

2. Sperm impairments in adult vespertilio 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. 2014 Nov;46(9):971-8. doi: 10.1111/and.12182. Epub 2013 Oct 23.

3. Adolescent bisphenol-A exposure decreases dendritic spine density: role of sex and age.

Bowman RE, Luine V, Khandaker H, Villafane JJ, Frankfurt M.
Synapse. 2014 Nov;68(11):498-507. doi: 10.1002/syn.21758. Epub 2014 Jul 15.

4. Bisphenol a regulates the estrogen receptor alpha signaling in developing hippocampus of male rats through estrogen receptor.

Xu XB, He Y, Song C, Ke X, Fan SJ, Peng WJ, Tan R, Kawata M, Matsuda K, Pan BX, Kato N.
Hippocampus. 2014 Dec;24(12):1570-80. doi: 10.1002/hipo.22336. Epub 2014 Aug 13

5. Food intolerance at adulthood after perinatal exposure to the endocrine disruptor bisphenol A.

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17. Occurrences, toxicities, and ecological risks of benzophenone-3, a common component of organic sunscreen products: a mini-review.

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Wildlife studier ved Biologisk Institut, Syddansk Universitet

Søgningen er udført på Web of Knowledge (all databases) og dækker perioden 16/8 - 1/12 2014.

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*

Udvalgte publikationer

Fra bruttolisten (længere nede i dokumentet) er udvalgt tre artikler til medtagelse af abstract og yderligere kommentarer.

Kriterierne for udvælgelsen af publikationer til kommentering er, at de bidrager til ny viden omkring effekter af og virkningsmekanismer for hormonforstyrrende stoffer i 'wildlife' og/eller at de repræsenterer vigtig viden, som vurderes at have særlig interesse for Miljøstyrelsen bl.a. i forbindelse med styrelsens fokus på udvikling af testmetoder. Desuden kommenteres artikler, der omhandler 'nye' stoffer og miljøfaktorer, der har vist sig hormonforstyrrende; specielt hvis disse har relevans for danske forhold. Endelig medtages efter Miljøstyrelsens ønske artikler omhandlende parabener.

Artikel 1: Direct and indirect responses of a freshwater food web to a potent synthetic oestrogen.
Kidd, K. A.; Paterson, M. J.; Rennie, M. D.; Podemski, C. L.; Findlay, D. L.; Blanchfield, P. J.; and Liber, K. 2014. Philosophical Transactions of the Royal Society B-Biological Sciences 369

Abstract: Endocrine-disrupting chemicals (EDCs) in municipal effluents directly affect the sexual development and reproductive success of fishes, but indirect effects on invertebrate prey or fish predators through reduced predation or prey availability, respectively, are unknown. At the Experimental Lakes Area in northwestern Ontario, Canada, a long-term, whole-lake experiment was conducted using a before-after-control-impact design to determine both direct and indirect effects of the synthetic oestrogen used in the birth control pill, 17 α -ethynodiol (EE2). Algal, microbial, zooplankton and benthic invertebrate communities showed no declines in abundance during three summers of EE2 additions (5–6 ng l⁻¹), indicating no direct toxic effects. Recruitment of fathead minnow (*Pimephales promelas*) failed, leading to a near-extirpation of this species both 2 years during (young-of-year, YOY) and 2 years following (adults and YOY) EE2 additions. Body condition of male lake trout (*Salvelinus namaycush*) and male and female white sucker (*Catostomus commersonii*) declined before changes in prey abundance, suggesting direct effects of EE2 on this endpoint. Evidence of indirect effects of EE2 was also observed. Increases in zooplankton, *Chaoborus*, and emerging insects were observed after 2 or 3 years of EE2 additions, strongly suggesting indirect effects mediated through the reduced abundance of several small-bodied fishes. Biomass of top predator lake trout declined by 23–42% during and after EE2 additions, most probably an indirect effect from the loss of its prey species, the fathead minnow and slimy sculpin (*Cottus cognatus*). Our results demonstrate that small-scale studies focusing solely on direct effects are likely to underestimate the true environmental impacts of oestrogens in municipal wastewaters and provide further evidence of the value of whole-ecosystem experiments for understanding indirect effects of EDCs and other aquatic stressors.

Artikel 2: Endocrine disrupting effects of benzotriazole in rare minnow (*Gobiocypris rarus*) in a sex-dependent manner. Liang, X.; Wang, M.; Chen, X.; Zha, J.; Chen, H.; Zhu, L.; and Wang, Z. 2014. Chemosphere 112, 154-162.

Abstract: Benzotriazole (BT), an anticorrosive agent, is widely used in industrial applications and household dishwashing agents. Despite its reported toxicity to aquatic organisms, little is known about its endocrine disrupting effects. In this study, adult Chinese rare minnows (*Gobiocypris rarus*)

were exposed to 0.05, 0.5, and 5 mg L⁻¹ BT for 28 d. The pathological damage in liver was associated with hypertrophy of the hepatocytes, nuclei pyknosis and vacuolization at 5 mg L⁻¹ groups. Additionally, the degeneration of the ovary and the stimulation of spermatogenesis were observed at 5 mg L⁻¹ groups. The plasma 17 β -estradiol level was significantly increased in the males but decreased in the females at 5 mg L⁻¹ ($p < 0.05$). In the brain, the up-regulation of CYP19B, GnRHs, and LH β mRNA was detected across all doses ($p < 0.05$). In the gonad, the transcriptional levels of StAR, CYP11A, 3 β HSD, CYP17, 17 β HSD, and CYP19A were generally decreased in the males at 5 mg L⁻¹ ($p < 0.05$), whereas these genes, except for 3 β HSD, were significantly increased in females at all concentrations ($p < 0.05$). Moreover, the expression level of VTG in the livers from all exposure groups was significantly increased compared with controls ($p < 0.05$). Taken together, our results indicate that BT could adversely affect the rare minnows in a sex-dependent manner.

Artikel 3: Development and validation of an OECD reproductive toxicity test guideline with the pond snail *Lymnaea stagnalis* (Mollusca, Gastropoda). Ducrot, V.; Askem, C.; Azam, D.; Brettschneider, D.; Brown, R.; Charles, S.; Coke, M.; Collinet, M.; Delignette-Muller, M.L.; Forfait-Dubuc, C.; Holbech, H.; Hutchinson, T.; Jach, A.; Kinnberg, K.L.; Lacoste, C.; Le Page, G.; Matthiessen, P.; Oehlmann, J.; Rice, L.; Roberts, E.; Ruppert, K.; Davis, J.E.; Veauvy, C.; Weltje, L.; Wortham, R.; Lagadic L. 2014. *Regul Toxicol Pharmacol*. [Epub ahead of print].

Abstract: The OECD test guideline development program has been extended in 2011 to establish a partial life-cycle protocol for assessing the reproductive toxicity of chemicals to several mollusk species, including the great pond snail *Lymnaea stagnalis*. In this paper, we summarize the standard draft protocol for a reproduction test with this species, and present inter-comparison results obtained in a 56-day prevalidation ring-test using this protocol. Seven European laboratories performed semi-static tests with cultured snails of the strain Renilys® exposed to nominal concentrations of cadmium chloride (from 53 to 608 μ gCdL⁻¹). Cd concentrations in test solutions were analytically determined to confirm accuracy in the metal exposure concentrations in all laboratories. Physico-chemical and biological validity criteria (namely dissolved oxygen content >60% ASV, water temperature 20±1°C, control snail survival >80% and control snail fecundity >8 egg-masses per snail over the test period) were met in all laboratories which consistently demonstrated the reproductive toxicity of Cd in snails using the proposed draft protocol. Effect concentrations for fecundity after 56 days were reproducible between laboratories (68<EC_{50-56d}<124 μ gL⁻¹) and were consistent with literature data. EC_{50-56d} and EC_{10-56d} values were comprised within a factor of 1.8 and 3.6, respectively, which is in the range of acceptable variation defined for reference chemicals in OECD test guidelines for invertebrates. The inter-laboratory reproducibility coefficient of variation (CV) for the Cd LC_{50-56d} values was 8.19%. The inter-laboratory comparison of fecundity within the controls gave a CV of 29.12%, while exposure to Cd gave a CV of 25.49% based on the EC_{50-56d} values. The OECD has acknowledged the success of this prevalidation exercise and a validation ring-test involving 14 laboratories in Europe, North- and South-America is currently being implemented using four chemicals (Cd, prochloraz, trenbolone and tributyltin).

Bruttoliste

Alkylphenoler

Alkylphenolic contaminants in the diet: *Sparus aurata* juveniles hepatic response.
Traversi, I.; Gioacchini, G.; Scorolli, A.; Mita, D.; Carnevali, O.; and Mandich, A. 2014. General and Comparative Endocrinology 205, 185-196.

Bisphenol A

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Low-dose bisphenol A disrupts gonad development and steroidogenic genes expression in adult female rare minnow *Gobiocypris rarus*.
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Toxic Effects of Bisphenol A on Early Life Stages of Japanese Medaka (*Oryzias latipes*).
Sun, L.; Lin, X.; Jin, R.; Peng, T.; Peng, Z.; and Fu, Z. 2014. Bulletin of Environmental Contamination and Toxicology 93, 222-227.

Phthalater

The effects on steroidogenesis and histopathology of adult male Japanese quails (*Coturnix coturnix japonica*) testis following pre-pubertal exposure to di(n-butyl) phthalate (DBP).
Bello, U. M.; Madekurozwa, M. C.; Groenewald, H. B.; Aire, T. A.; and Arukwe, A. 2014. Comparative Biochemistry and Physiology C-Toxicology & Pharmacology 166, 24-33.

Identification of Drosophila-Based Endpoints for the Assessment and Understanding of Xenobiotic-Mediated Male Reproductive Adversities.
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UV-filtre

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Occurrences, toxicities, and ecological risks of benzophenone-3, a common component of organic sunscreen products: A mini-review.

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