Center for Hormonforstyrrende Stoffer

Litteraturgennemgang for perioden oktober 2015 – december 2015

Indhold

Humane studier ved Afd. for Vækst og Reproduktion, Rigshospitalet

Søgning er udført på PubMed og dækker perioden 21.september 2015 - 10. december 2015

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

I den listede bruttoliste er dobbeltgængere fjernet, ligesom hits der hører under kategorierne in vivo studier, in vitro studier eller wildlife er frasorteret. De kommenterede artikler er highlightet.

De udvalgte artikler koncentrerer sig i denne omgang om hormonforstyrrende stoffers påvirkning af kvinders reproduktive helbred. Der er således inkluderet artikler om phthalater og fertilitet, phthalater og sygdommen endometriose og PFAAs og testosteron hos teenagepiger. I den forbindelse vil vi henlede opmærksomheden på den just udgivne video fra FIGO (International Federation of Gynecology and Obstetrics) om hormonforstyrrende stoffers effekter på reproduktion. Se videoen her: http://bit.ly/TalkingToxics

Endelig har forskere fra Vækst og Reproduktion udgivet en omfattende artikel i tidsskriftet *Physiological Reviews*, der gøres opmærksom på nedenfor.

God læselyst!

Udvalgte publikationer

Possible Role of Phthalate in the Pathogenesis of Endometriosis: In Vitro, Animal, and Human Data.
Kim SH, Cho S, Ihm HJ, Oh YS, Heo SH, Chun S, Im H, Chae HD, Kim CH, Kang BM.
J Clin Endocrinol Metab. 2015 Dec;100(12):E1502-11. doi: 10.1210/jc.2015-2478. Epub 2015 Oct 6.

CONTEXT: Although phthalates were shown to have several negative effects on reproductive function in animals, its role in the pathogenesis of endometriosis remains to be elucidated.
OBJECTIVE: We aimed to investigate the in vitro and in vivo effects of di-(2-ethylhexyl)-phthalate (DEHP) and to compare the urinary levels of several phthalate metabolites between women with and without endometriosis.
DESIGN: For experimental studies, we used endometrial cell culture and nonobese diabetic/severe combined immunodeficiency (NOD/SCID) mouse models. We also performed a prospective case-control study for human sample analyses.
SETTING: The study was conducted at an academic center.
MAIN OUTCOME MEASURES: The activities of matrix metalloproteinase (MMP)-2 and 9, cellular invasiveness, phosphorylation of extracellular signal-regulated kinase (Erk), and expression of p21-activated kinase 4 were analyzed in endometrial cells treated with DEHP. The implant size was compared between NOD/SCID mice fed with and without DEHP. Urinary concentrations of several phthalate metabolites were compared between women with and without endometriosis.
RESULTS: In vitro treatment of endometrial cells with DEHP led to significant increases of MMP-2 and 9 activities, cellular invasiveness, Erk phosphorylation, and p21-activated kinase 4 expression. The size of the endometrial implant was significantly larger in the NOD/SCID mice fed with DEHP compared with those fed with vehicle. The urinary concentration of mono (2-ethyl-5-hydroxyhexyl) phthalate, mono (2-ethyl-5-oxohexyl) phthalate, and mono (2-ethyl-5-carboxyphentyl) phthalate were significantly higher in women with endometriosis compared with controls.
CONCLUSION: These findings strongly suggest that exposure to phthalate may lead to establishment of endometriosis by enhancing invasive and proliferative activities of endometrial cells.

Urinary Phthalate Metabolite Concentrations and Reproductive Outcomes among Women Undergoing in Vitro Fertilization: Results from the EARTH Study.
Hauser R, Gaskins AJ, Souter I, Smith KW, Dodge LE, Ehrlich S, Meeker JD, Calafat AM, Williams PL; Earth Study Team.
Environ Health Perspect. 2015 Nov 6. [Epub ahead of print]

BACKGROUND: Evidence from both animal and human studies suggests that exposure to phthalates may be associated with adverse female reproductive outcomes.
OBJECTIVE: We evaluated the associations between urinary concentrations of phthalate metabolites and outcomes of assisted reproductive technologies (ART).
METHODS: This analysis included 256 women enrolled in the Environment and Reproductive Health (EARTH) prospective cohort study (2004-2012) who provided 1-2 urine samples per cycle prior to oocyte retrieval. We measured 11 urinary phthalate metabolites [mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), mono-2-ethyl-5-carboxypentyl phthalate (MECPP), mono-isobutyl phthalate (MiBP), mono-n-butyl phthalate (MBP), monobenzyl phthalate (MBzP), monoethyl phthalate (MEP), monocarboxyisooctyl phthalate (MCOP), and monocarboxyisononyl phthalate (MCNP), and mono(3-carboypropyl) phthalate (MCPP)]. We used

generalized linear mixed models to evaluate the association of urinary phthalate metabolites with IVF outcomes, accounting for multiple IVF cycles per woman.
RESULTS: In multivariate models, women in the highest as compared to lowest quartile of MEHP, MEHHP, MEOHP, MECPP, ∑DEHP (MEHP+MEHHP+MEOHP+MECPP) and MCNP had lower oocyte yield. Similarly, the number of mature (MII) oocytes retrieved was lower in the highest versus lowest quartile for these same phthalate metabolites. The adjusted difference (95% CI) in proportion of cycles resulting in clinical pregnancy and live birth between women in the fourth vs. first quartile of ∑DEHP were -0.19 (-0.29, -0.08) and -0.19 (-0.28, -0.08), respectively, and there was also a lower proportion of cycles resulting in clinical pregnancy and live birth for individual DEHP metabolites.
CONCLUSIONS: Urinary concentrations of DEHP metabolites were inversely ssociated with oocyte yield, clinical pregnancy and live birth following ART.

Prenatal Exposure to Perfluoroalkyl Acids and Serum Testosterone Concentrations at 15 Years of Age in Female ALSPAC Study Participants
Maisonet M, Calafat AM, Marcus M, Jaakkola JJ, Lashen H.
Environ Health Perspect. 2015 Dec;123(12):1325-30. doi: 10.1289/ehp.1408847. Epub 2015 Jun 2.

BACKGROUND: Exposure to perfluorooctane sulfonic acid (PFOS) or to perfluorooctanoic acid (PFOA) increases mouse and human peroxisome proliferator-activated receptor alpha (PPARα) subtype activity, which influences lipid metabolism. Because cholesterol is the substrate from which testosterone is synthesized, exposure to these substances has the potential to alter testosterone concentrations.
OBJECTIVES: We explored associations of total testosterone and sex hormone-binding globulin (SHBG) concentrations at age 15 years with prenatal exposures to PFOS, PFOA, perfluorohexane sulfonic acid (PFHxS), and perfluoronanoic acid (PFNA) in females.
METHODS: Prenatal concentrations of the perfluoroalkyl acids (PFAAs) were measured in serum collected from pregnant mothers at enrollment (1991-1992) in the Avon Longitudinal Study of Parents and Children (ALSPAC). The median gestational age when the maternal blood sample was obtained was 16 weeks (interquartile range, 11-28 weeks). Total testosterone and SHBG concentrations were measured in serum obtained from their daughters at 15 years of age. Associations between prenatal PFAAs concentrations and reproductive outcomes were estimated using linear regression models (n = 72).
RESULTS: Adjusted total testosterone concentrations were on average 0.18-nmol/L (95% CI: 0.01, 0.35) higher in daughters with prenatal PFOS in the upper concentration tertile compared with daughters with prenatal PFOS in the lower tertile. Adjusted total testosterone concentrations were also higher in daughters with prenatal concentrations of PFOA (β = 0.24; 95% CI: 0.05, 0.43) and PFHxS (β = 0.18; 95% CI: 0.00, 0.35) in the upper tertile compared with daughters with concentrations in the lower tertile. We did not find evidence of associations between PFNA and total testosterone or between any of the PFAAs and SHBG.
CONCLUSIONS: Our findings were based on a small study sample and should be interpreted with caution. However, they suggest that prenatal exposure to some PFAAs may alter testosterone concentrations in females.

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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 2015/09/31 to 2015/12/31 (Oktober 2015 og fremefter)
Efter at have fjernet genganger fra forrige litteraturopdateringslister, samt artikler der ikke hørte til under kategorien "in vitro" gav litteratursøgningen, med de angivne søgekriterier, tilsammen en liste med i alt 28 artikler.

Udvalgte publikationer

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

Den første artikel omhandler *in vitro* studier af persistente organiske miljøgiftes (POPs) evne til at påvirke aktiviteten af glucocorticoid receptoren (GR) og dermed påvirkning af glucocorticoid hormon systemet.

Den anden artikel omhandler et studie af to phthalaters (DNOP og DPhP) effekt på aktiviteten af UDP-glucuronosyltransferaser (UGTs), en gruppe phase II enzymer som spiller en vigtig rolle båder for metaboliseringen af fremmedstoffer men også endogene stoffer heriblandt visse hormoner.

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Wilson J, Friis Berntsen H, Elisabeth Zimmer K, Verhaegen S, Frizzell C, Ropstad E, Connolly L.
Toxicol Lett. 2015 Nov 17. pii: S0378-4274(15)30112-0. doi: 10.1016/j.toxlet.2015.11.014. [Epub ahead of print]

Persistent organic pollutants (POPs) are toxic substances, highly resistant to environmental degradation, which can bio-accumulate and have long-range atmospheric transport potential (UNEP, 2001). The majority of studies on endocrine disruption have focused on interferences on the sexual steroid hormones and so have overlooked disruption to glucocorticoid hormones. Here the endocrine disrupting potential of individual POPs and their mixtures has been investigated in vitro to identify any disruption to glucocorticoid nuclear receptor transcriptional activity. POP mixtures were screened for glucocorticoid receptor (GR) translocation using a GR redistribution assay (RA) on a CellInsight™ NXT high content screening (HCS) platform. A mammalian reporter gene assay (RGA) was then used to assess the individual POPs, and their mixtures, for effects on glucocorticoid nuclear receptor transactivation. POP mixtures did not induce GR translocation in the GR RA or produce an agonist response in the GR RGA. However, in the antagonist test, in the presence of cortisol, an individual POP, p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE), was found to decrease glucocorticoid nuclear receptor transcriptional activity to 72.5% (in comparison to the positive cortisol control). Enhanced nuclear transcriptional activity, in the presence of cortisol, was evident for the two lowest concentrations of perfluorodecanoic acid (PFOS) potassium salt (0.0147mg/ml and 0.0294mg/ml), the two highest concentrations of perfluorodecanoic acid (PFDA) (0.0025mg/ml and 0.005mg/ml) and the highest concentration of 2,2',4,4'-tetrabromodiphenyl ether (BDE-47) (0.0000858mg/ml). It is important to gain a better understanding of how POPs can interact with GRs as the disruption of glucocorticoid action is thought to contribute to complex diseases.

New insights into the risk of phthalates: Inhibition of UDP-glucuronosyltransferases
Liu X, Cao YF, Ran RX, Dong PP, Gonzalez FJ, Wu X, Huang T, Chen JX, Fu ZW, Li RS, Liu YZ, Sun HZ, Fang ZZ.
Chemosphere. 2015 Nov 5;144:1966-1972. doi: 10.1016/j.chemosphere.2015.10.076. [Epub ahead of print]

Wide utilization of phthalates-containing products results in the significant exposure of humans to these compounds. Many adverse effects of phthalates have been documented in rodent models, but their effects in humans exposed to these chemicals remain unclear until more mechanistic studies on phthalate toxicities can be carried out. To provide new insights to predict the potential adverse effects of phthalates in humans, the recent study investigated the inhibition of representative phthalates di-n-octyl ortho-phthalate (DNOP) and diphenyl phthalate (DPhP) towards the important xenobiotic and endobiotic-metabolizing UDP-glucuronosyltransferases (UGTs). An in vitro UGTs incubation system was employed to study the inhibition of DNOP and DPhP towards UGT isoforms. DPhP and DNOP weakly inhibited the activities of UGT1A1, UGT1A7, and UGT1A8. 100 μM of DNOP inhibited the activities of UGT1A3, UGT1A9, and UGT2B7 by 41.8% ($p < 0.01$), 45.6% ($p < 0.01$), and 48.8% ($p < 0.01$), respectively. 100 μM of DPhP inhibited the activity of UGT1A3, UGT1A6, and UGT1A9 by 81.8 ($p < 0.001$), 49.1% ($p < 0.05$), and 76.4% ($p < 0.001$), respectively. In silico analysis was used to explain the stronger inhibition of DPhP than DNOP towards UGT1A3 activity. Kinetics studies were carried out to determine mechanism of inhibition of UGT1A3 by DPhP. Both Dixon and Lineweaver-Burk plots showed the competitive inhibition of DPhP towards UGT1A3. The inhibition kinetic parameter (K_i) was calculated to be 0.89 μM. Based on the [I]/Ki standard ([I]/Ki < 0.1, low possibility; 1>[I]/Ki > 0.1, medium possibility; [I]/Ki > 1, high possibility), these studies predicted in vivo drug-drug interaction might occur when the plasma concentration of DPhP was above 0.089 μM. Taken together, this study reveals the potential for adverse effects of phthalates DNOP and DPhP as a result of UGT inhibition.

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Liu X, Cao YF, Ran RX, Dong PP, Gonzalez FJ, Wu X, Huang T, Chen JX, Fu ZW, Li RS, Liu YZ, Sun HZ, Fang ZZ.

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Herudover er der yderligere 1 artikel, som ikke blev fanget af de valgte søgekriterier:
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In vivo studier ved DTU Fødevareinstituttet

Søgning er udført på PubMed og dækker perioden Juli - ultimo September 2015

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 (endocrine disrupt*) AND risk assessment

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 36 artikler (Bruttolisten).

Udvalgte publikationer:

Udvalgte publikationer

To artikler er blevet udvalgt til nærmere beskrivelse (abstrakt og konklusion). Disse artikler er valgt fordi vi mener de bidrager til ny viden om hormonforstyrrende stoffer og her er der særligt fokus på phthalater og mix (Howdeshell et al. 2015) og Flutamid Lavdosis og non monotonicitet (Fussell et al. 2015).

Rigtig God læselyst.

Dose Addition Models Based on Biologically Relevant Reductions in Fetal Testosterone Accurately Predict Postnatal Reproductive Tract Alterations by a Phthalate Mixture in Rats.
Howdeshell KL, Rider CV, Wilson VS, Furr JR, Lambright CR, Gray LE Jr.
Toxicol Sci. 2015 Dec;148(2):488-502. doi: 10.1093/toxsci/kfv196. Epub 2015 Sep 8.

Challenges in cumulative risk assessment of anti-androgenic phthalate mixtures include a lack of data on all the individual phthalates and difficulty determining the biological relevance of reduction in fetal testosterone (T) on postnatal development. The objectives of the current study were 2-fold: (1) to test whether a mixture model of dose addition based on the fetal T production data of individual phthalates would predict the effects of a 5 phthalate mixture on androgen-sensitive postnatal male reproductive tract development, and (2) to determine the biological relevance of the reductions in fetal T to induce abnormal postnatal reproductive tract development using data from the mixture study. We administered a dose range of the mixture (60, 40, 20, 10, and 5% of the top dose used in the previous fetal T production study consisting of 300 mg/kg per chemical of benzyl butyl (BBP), di(n)butyl (DBP), diethyl hexyl phthalate (DEHP), di-isobutyl phthalate (DiBP), and 100 mg dipentyl (DPP) phthalate/kg; the individual phthalates were present in equipotent doses based on their ability to reduce fetal T production) via gavage to Sprague Dawley rat dams on GD8-postnatal day 3. We compared observed mixture responses to predictions of dose addition based on the previously published potencies of the individual phthalates to reduce fetal T production relative to a reference chemical and published postnatal data for the reference chemical (called DAref). In addition, we predicted DA (called DAall) and response addition (RA) based on logistic regression analysis of all 5 individual phthalates when complete data were available. DA ref and DA all accurately predicted the observed mixture effect for 11 of 14 endpoints. Furthermore, reproductive tract malformations were seen in 17-100% of F1 males when fetal T production was reduced by about 25-72%, respectively.

Investigations of putative reproductive toxicity of low-dose exposures to flutamide in Wistar rats
Fussell KC, Schneider S, Buesen R, Groeters S, Strauss V, Melching-Kollmuss S, van Ravenzwaay B.
Arch Toxicol. 2015 Dec;89(12):2385-402. doi: 10.1007/s00204-015-1622-6. Epub 2015 Nov 2.

The current investigation examines whether the model anti-androgenic substance flutamide is capable of disrupting endocrine homeostasis at very low doses. The data generated clarify whether a non-monotonic dose-response relationship exists to enhance the current debate about the regulation of endocrine disruptors. Moreover, it is part of a series of investigations assessing the dose-response relationship of single and combined administration of anti-androgenic substances. A pre-postnatal in vivo study design was chosen, which was compliant with regulatory testing protocols. The test design was improved by additional endpoints addressing hormone levels, morphology, and histopathological examinations. Doses were chosen to represent a clear effect level (2.5 mg/kg bw/d), a low endocrine effect level (LOAEL, 0.25 mg/kg bw/d), a NOAEL for endocrine effects (0.025 mg/kg bw/d), a further dose at 0.0025 mg/kg bw/d flutamide, as well as an "ADI" (0.00025 mg/kg bw/d or 100-fold below the NOAEL) for the detection of a possible non-monotonic dose-response curve. Anti-androgenic changes were observable at LOAEL and the clear effect dose level but not at lower exposures. Nipple retention appeared to be the most sensitive measure of anti-androgenic effects, followed by age at sexual maturation, anogenital distance/anogenital index and male sex organ weights, as well as gross and histopathological findings. The results of all five doses indicate the absence of evidence for effects at very low dose levels. A non-monotonic dose-response relationship was not evident for the anti-androgenic drug flutamide.

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Gelbke HP, Banton M, Leibold E, Pemberton M, Samson SL.
Crit Rev Toxicol. 2015 Oct;45(9):727-64. doi: 10.3109/10408444.2015.1064091. Epub 2015 Sep 25.

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Howdeshell KL, Rider CV, Wilson VS, Furr JR, Lambright CR, Gray LE Jr.
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Søgningen er udført på Web of Knowledge (all databases) og dækker perioden 29/9 - 8/12 2015.

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.
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, der omhandler parabener.

Udvalgte publikationer

Environmental chemicals active as human antiandrogens do not activate a stickleback androgen receptor but enhance a feminising effect of oestrogen in roach.
Lange A, Sebire M, Rostkowski P, Mizutani T, Miyagawa S, Iguchi T, Hill EM, Tyler CR.
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ABSTRACT: Sexual disruption is reported in wild fish populations living in freshwaters receiving discharges of wastewater treatment works (WwTW) effluents and is associated primarily with the feminisation of males by exposure to oestrogenic chemicals. Antiandrogens could also contribute to the feminisation of male fish, but there are far less data supporting this hypothesis and almost nothing is known for the effects of oestrogens in combination with antiandrogens in fish. We conducted a series of in vivo exposures in two fish species to investigate the potency on reproductive-relevant endpoints of the antiandrogenic antimicrobials triclosan (TCS), chlorophene (CP) and dichlorophene (DCP) and the resin, abietic acid (AbA), all found widely in WwTW effluents. We also undertook exposures with a mixture of antiandrogens and a mixture of antiandrogens in combination with the oestrogen 17α-ethinyloestradiol (EE2). In stickleback (Gasterosteus aculeatus), DCP showed a tendency to reduce spiggin induction in females androgenised by dihydrotestosterone (DHT), but these findings were not conclusive. In roach (Rutilus rutilus), exposures to DCP (178 days), or a mixture of TCS, CP and AbA (185 days), or to the model antiandrogen flutamide (FL,178 days) had no effect on gonadal sex ratio or on the development of the reproductive ducts. Exposure to EE2 (1.5 ng/L, 185 days) induced feminisation of the ducts in 17% of the males and in the mixture of antiandrogens (TCS, CP, AbA) in combination with EE2, almost all (96%) of the males had a feminized reproductive ducts. In stickleback androgen receptor (ARα and ARβ) transactivation assays, the model antiandrogens, FL and procymidone inhibited 11-ketotestosterone (11-KT) induced receptor activation, but none of the human antiandrogens, TCS, CP, DCP and AbA had an effect. These data indicate that antimicrobial antiandrogens in combination can contribute to the feminisation process in exposed males, but they do not appear to act through the androgen receptor in fish.

Acute exposure to synthetic pyrethroids causes bioconcentration and disruption of the hypothalamus-pituitary-thyroid axis in zebrafish embryos.
Tu W, Xu C, Lu B, Lin C, Wu Y, Liu W.

ABSTRACT: Synthetic pyrethroids (SPs) have the potential to disrupt the thyroid endocrine system in mammals; however, little is known of the effects of SPs and underlying mechanisms in fish. In the current study, embryonic zebrafish were exposed to various concentrations (1, 3 and 10 μg/L) of bifenthrin (BF) or λ-cyhalothrin (λ-CH) until 72 h post fertilization, and body condition, bioaccumulation, thyroid hormone levels and transcription of related genes along the hypothalamus–pituitary–thyroid (HPT) axis examined. Bodyweightwas significantly decreased in the λ-CH exposure groups, but not the BF exposure groups. BF and λ-CH markedly accumulated in the larvae, with concentrations ranging from 90.7 to 596.8 ng/g. In both exposure groups, alterations were observed in thyroxine (T4) and triiodothyronine (T3) levels. In addition, the majority of the HPT axis-related genes examined, including CRH, TSHβ, TTR, UGT1ab, Pax8, Dio2 and TRα, were significantly upregulated in the presence of BF. Compared to BF, λ-CH induced different transcriptional regulation patterns of the tested genes, in particular, significant stimulation of TTR, Pax8, Dio2 and TRα levels alongwith concomitant downregulation of Dio1. Molecular docking analyses revealed that at the atomic level, BF binds to thyroid hormone receptor (TRα) protein more potently than λ-CH, consequently affecting HPT axis signal transduction. In vitro and in silico experiments disclosed that during the early stages of zebrafish development, BF and λ-CH have the potential to disrupt thyroid endocrine system.

Toxicopathological effects of the sunscreen UV filter, oxybenzone (benzophenone-3), on coral planulae and cultured primary cells and its environmental contamination in Hawaii and the U.S. Virgin Islands.
Downs CA, Kramarsky-Winter E, Segal R, Fauth J, Knutson S, Bronstein O, Ciner FR, Jeger R, Lichtenfeld Y, Woodley CM, Pennington P, Cadenas K, Kushmaro A, Loya Y.

ABSTRACT: Benzophenone-3 (BP-3; oxybenzone) is an ingredient in sunscreen lotions and personal-care products that protects against the damaging effects of ultraviolet light. Oxybenzone is an emerging contaminant of concern in marine environments—produced by swimmers and municipal, residential, and boat/ship wastewater discharges. We examined the effects of oxybenzone on the larval form (planula) of the coral Stylophora pistillata, as well as its toxicity in vitro to coral cells from this and six other coral species. Oxybenzone is a photo-toxicant; adverse effects are exacerbated in the light. Whether in darkness or light, oxybenzone transformed planulae from a motile state to a deformed, sessile condition. Planulae exhibited an increasing rate of coral bleaching in response to increasing concentrations of oxybenzone. Oxybenzone is a genotoxicant to corals, exhibiting a positive relationship between DNA-AP lesions and increasing oxybenzone concentrations. Oxybenzone is a skeletal endocrine disruptor; it induced ossification of the planula, encasing the entire planula in its own skeleton. The LC50 of planulae exposed to oxybenzone in the light for an 8- and 24-h exposure was 3.1 mg/L and 139 µg/L, respectively. The LC50s for oxybenzone in darkness for the same time points were 16.8 mg/L and 779 µg/L. Deformity EC20 levels (24 h) of planulae exposed to oxybenzone were 6.5 µg/L in the light and 10 µg/L in darkness. Coral cell LC50s (4 h, in the light) for 7 different coral species ranges from 8 to 340 µg/L, whereas LC20s (4 h, in the light) for the same species ranges from 0.062 to 8 µg/L. Coral reef contamination of oxybenzone in the U.S. Virgin Islands ranged from 75 µg/L to 1.4 mg/L, whereas Hawaiian sites were contaminated between 0.8 and 19.2 µg/L. Oxybenzone poses a hazard to coral reef conservation and threatens the resiliency of coral reefs to climate change.

Endocrine-disrupting effect of the ultraviolet filter benzophenone-3 in zebrafish, Danio rerio.
Kinnberg KL, Petersen GI, Albrektsen M, Minghlani M, Awad SM, Holbech BF, Green JW, Bjerregaard P, Holbech H.

ABSTRACT: The chemical ultraviolet (UV) filter benzophenone-3 (BP-3) is suspected to be an endocrine disruptor based on results from in vitro and in vivo testing. However, studies including endpoints of endocrine adversity are lacking. The present study investigated the potential endocrine-disrupting effects of BP-3 in zebrafish (Danio rerio) in the Fish Sexual Development Test (Organisation for Economic Co-operation and Development TG 234) and a 12-d adult male zebrafish study. In TG 234, exposure from 0 d to 60 d posthatch caused a monotone dose-dependent skewing of the phenotypic sex ratio toward fewer males and more female zebrafish (no observed effect concentration [NOEC]: 191 µg/L, lowest observed effect concentration [LOEC]: 388 µg/L). Besides, gonad maturation was affected in both female fish (NOEC 191 µg/L, LOEC 388 µg/L) and male fish (NOEC 388 µg/L, LOEC 470 µg/L). Exposure to BP-3 did not affect the vitellogenin concentration in TG 234. After 12 d exposure of adult male zebrafish, a slight yet significant increase in the vitellogenin concentration was observed at 268 µg/L but not at 63 µg/L and 437 µg/L BP-3. Skewing of the sex ratio is a marker of an endocrine-mediated mechanism as well as a marker of adversity, and therefore the conclusion of the present study is that BP-3 is an endocrine-disrupting chemical in accordance with the World Health Organization's definition.

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