Center for Hormonforstyrrende Stoffer

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Indhold

Humane studier ved Afd. for Vækst og Reproduktion, Rigshospitalet

Søgning er udført på PubMed og dækker perioden 11.december 2015 – 20 marts 2016

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 handler primært om phthalater. Phthalater i medicinsk udstyr, phthalater i forhold til fedme hos børn, og hvorvidt man kan undgå phthalater (og parabener og phenoler) ved at ændre forbrugsvaner. Endelig har vi kigget på en artikel om phenoler i frohold til forekomsten af misdannelser i kønsorganerne hos nyfødte drengebørn.

God læselyst!

Udvalgte publikationer

Prenatal phthalate exposures and body mass index among 4 to 7 year old children: A pooled analysis.
Buckley JP(1), Engel SM, Braun JM, Whyatt RM, Daniels JL, Mendez MA, Richardson DB, Xu Y, Calafat AM, Wolff MS, Lanphear BP, Herring AH, Rundle AG
Epidemiology. 2016 Jan 6. [Epub ahead of print]

BACKGROUND: Phthalates are hypothesized to cause obesity, but few studies have assessed whether prenatal phthalate exposures are related to childhood body mass index (BMI).
METHODS: We included 707 children from three prospective cohort studies enrolled in the United States between 1998 and 2006 who had maternal urinary phthalate metabolite concentrations measured during pregnancy, and measures of weight and height at ages 4 to 7 years. We calculated age- and sex-standardized BMI z-scores and classified children with BMI percentiles ≥85 as overweight/obese. We used mixed effects regression models to estimate associations between a 1-standard deviation increase in natural log phthalate metabolite concentrations and BMI zscores and overweight/obesity. We estimated associations in multiple metabolite models adjusted for confounders, and evaluated heterogeneity of associations by child's sex, race/ethnicity, and cohort
RESULTS: Mono-3-carboxypropyl phthalate (MCPP) concentrations were positively associated with overweight/obese status in children (odds ratio [95% credible interval] = 2.1 [1.2, 4.0]) but not with BMI z-scores (beta = -0.02 [-0.15, 0.11]). We did not observe evidence of obesogenic effects for other metabolites. However, monoethyl phthalate (MEP) and summed di-(2-ethylhexyl) phthalate metabolites (∑DEHP) concentrations were inversely associated with BMI z-scores among girls (MEP beta = -0.14 [-0.28, 0.00]; ∑DEHP beta = -0.12 [-0.27, 0.02]).
CONCLUSIONS: Maternal urinary MCPP, a non-specific metabolite of several phthalates, was positively associated with childhood overweight/obesity. Metabolites of diethyl phthalate and DEHP were associated with lower BMI in girls but not boys, suggesting prenatal exposures may have sexually dimorphic effects on physical development.

Comparative study on the migration of di-2-ethylhexyl phthalate (DEHP) and tri-2-ethylhexyl trimellitate (TOTM) into blood from PVC tubing material of a heart-lung machine
Eckert E, Münch F, Göen T, Purbojo A, Müller J, Cesnjevar R
Chemosphere. 2016 Feb;145:10-6. doi: 10.1016/j.chemosphere.2015.11.067. Epub 2015 Dec 1.

Medical devices like blood tubing often consist of PVC material that requires the addition of plasticizers. These plasticizers may migrate into the blood leading to an exposure of the patients. In this study the migration behavior of three different blood tubing sets (PVC material with two different plasticizers and silicone as control material) applied on a heart-lung machine standardly used for cardiopulmonary bypass (CPB) in children was studied. We analyzed the total plasticizer migration by analysis of both, the parent compounds as well as their primary degradation products in blood. Additionally, the total mass loss of the tubing over perfusion time was examined. The PVC tubing plasticized with DEHP (di-2-ethylhexyl phthalate) was found to have the highest mass loss over time and showed a high plasticizer migration rate. In comparison, the migration of TOTM (tri-2-ethylhexyl trimellitate) and its primary degradation products was found to be distinctly lower (by a factor of approx. 350). Moreover, it was observed that the storage time of the tubing affects the plasticizer migration rates. In conclusion, the DEHP substitute TOTM promises to be an effective alternative plasticizer for PVC medical devices particularly regarding the decreased migration rate during medical procedures.

Reducing Phthalate, Paraben, and Phenol Exposure from Personal Care Products in Adolescent Girls: Findings from the HERMOSA Intervention Study

Harley KG, Kogut K, Madrigal DS, Cardenas M, Vera IA, Meza-Alfaro G, She J, Gavin Q, Zahedi R, Bradman A, Eskenazi B, Parra KL.

Environ Health Perspect. 2016 Mar 7. [Epub ahead of print]

BACKGROUND: Personal care products are a source of exposure to potentially endocrine disrupting chemicals such as phthalates, parabens, triclosan, and benzophenone-3 (BP-3) for adolescent girls.

METHODS: We enrolled 100 Latina girls in a youth-led, community-based participatory research intervention study to determine whether using personal care products whose labels stated they did not contain these chemicals for three days could lower urinary concentrations. Pre- and post-intervention urine samples were analyzed for phthalate metabolites, parabens, triclosan and BP-3 using high-performance liquid chromatography/tandem mass spectrometry.

RESULTS: Urinary concentrations of mono-ethyl phthalate (MEP) decreased by 27.4% (95% Confidence Interval (CI): -39.3, -13.2) on average over the 3 day intervention; no significant changes were seen in urinary concentrations of mono-n-butyl phthalate (MnBP) and mono-isobutyl phthalate (MiBP). Methyl and propyl paraben concentrations decreased by 43.9% (95% CI: -61.3, -18.8) and 45.4% (95% CI: -63.7, -17.9), respectively. Unexpectedly, concentrations of ethyl and butyl paraben concentrations increased, although concentrations were low overall and not detected in almost half the samples. Triclosan concentrations decreased by 35.7% (95% CI: -53.3, -11.6) and BP-3 concentrations decreased by 36.0% (95% CI: -51.0, -16.4).

DISCUSSION: This study demonstrates that techniques available to consumers, such as choosing personal care products that are labelled to be free of phthalates, parabens, triclosan, and BP-3, can reduce personal exposure to possible endocrine disrupting chemicals. Involving youth in the design and implementation of the study was key to recruitment, retention, compliance, and acceptability of the intervention.

Bisphenol A and other phenols in human placenta from children with cryptorchidism or hypospadias

Fernández MF, Arrebola JP, Jiménez-Díaz I, Sáenz JM, Molina-Molina J, Ballesteros O, Kortenkamp A, Olea N

Reprod Toxicol. 2016 Jan;59:89-95. doi: 10.1016/j.reprotox.2015.11.002. Epub 2015 Nov 19.

Embryo-foetal exposure to low doses of endocrine disrupting chemicals (EDCs) has been related to reproductive tract diseases in experimental animals but not convincingly in human populations. The aim of this case-control study was to explore the relationship between exposure to non-persistent EDCs during pregnancy and male genital development. Exposure to bisphenol-A (BPA), benzophenones (BPs) [BP-1, BP-2, BP-3, BP-6, BP-8 and 4-hydroxybenzophenone (4-OH-BP),] and parabens (PBs) [methyl-, ethyl-, propyl- and butyl-PB] was analyzed by means of ultra-high performance liquid chromatography-tandem mass spectrometry in placenta samples from a subsample of 28 cases and 51 healthy controls nested in a cohort of newborns recruited between 2000 and 2002. The multivariable regression analyses indicated a statistically significant association between exposure to BPA and propyl-PB and the risk of malformations [adjusted odd ratio (95% CIs) in the third tertile of exposure: 7.2 (1.5-35.5) and 6.4 (1.2-35.5) for BPA and propyl-PB, respectively].

Bruttoliste

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J Environ Public Health. 2015;2015:571839. doi: 10.1155/2015/571839. Epub 2015 Dec 29.

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 i perioden 2015/12/31 to 2016/12/31.

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 50 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 phthalater, med henblik på at undersøge eventuel migration af phthalaterne mellem brøndene i celledyrkningsplader, der normalt anvendes i forbindelse med *in vitro* forsøg.

Den anden artikel omhandler et *in vitro* studie, der har til formål at undersøge de hormonforstyrrende effekter af syv organophosphat flammehæmmere (OPFRs), som i stigende grad anvendes som alternativer til de mere veldokumenteret skadelig BFRs. Effekterne af de syv OPFRs sammenlignes så med effekten en meget udbredte BFRs (BDE-47).

Migration of phthalates on culture plates - an important challenge to consider for in vitro studies.

Frohnert Hansen J, Boas M, Møller Brorson M, Frederiksen H, Hartoft-Nielsen ML, Krogh Rasmussen Å, Main KM, Feldt-Rasmussen U.
Scand J Clin Lab Invest. 2016 Apr;76(2):165-71. doi: 10.3109/00365513.2015.1110857. Epub 2016 Jan 12.

Phthalates are endocrine disruptors of the reproductive system and suspected to influence many other organ and hormone systems. They are also semi-volatile organic compounds present in the gas phase in the environment. Their mode of action has been investigated in numerous in vitro studies. Multi-well culture plates are typically used to study phthalates in cell cultures. In a pilot study, we observed evidence of phthalate migration in 24-well culture plates. As this has not previously been described, we investigated the phenomenon in more detail. Primary human thyroid epithelial cell cultures (n = 8 cultures) were exposed to either di-ethyl phthalate (DEP), di-n-butyl phthalate (DnBP), mono-n-butyl phthalate (MnBP) or di-(2-ethylhexyl) phthalate (DEHP). Measurement of phthalate metabolites by mass spectrometry demonstrated that the short-branched DEP was able to migrate to adjacent wells when added to cell culture plates. DnBP also seemed to be able to migrate, unlike the long-branched DEHP or the monoester MnBP which did not seem to have this ability. High background levels of phthalate metabolites were also observed, which might compromise results from low dose phthalate studies. In conclusion, the migration of phthalates which is probably caused by their volatile properties might lead to false interpretation of study results.

Organophosphate Flame Retardants Act as Endocrine-Disrupting Chemicals in MA-10 Mouse Tumor Leydig Cells.

Schang G, Robaire B, Hales BF.

Toxicol Sci. 2016 Jan 21. pii: kfw012.

The organophosphate flame retardants (OPFRs) have emerged as alternatives to banned brominated flame retardants but little is known about their possible activity as endocrine disruptors. Our goal was to compare the effects of 7 commonly used OPFRs in vitro on MA-10 mouse Leydig tumor cells to those of a major brominated flame retardant, 2,2',4,4'-tetrabromodiphenyl ether (BDE-47). The effects of OPFRs and BDE-47 on mitochondrial activity, cell counts, oxidative stress, steroid secretion and gene expression were investigated. BDE-47 and all 7 OPFRs tested significantly reduced MA-10 cell mitochondrial activity (concentrations ≥50 μM) and cell number (concentrations ≥10 μM). All of the OPFRs significantly increased (10 μM, 1.7-4.4-fold) superoxide production whereas BDE-47 had no significant effect. Basal progesterone production was significantly increased (10 μM, 1.5 to 3-fold) by 2-ethylhexyl diphenyl phosphate, isodecyl diphenyl phosphate, isopropylated triphenyl phosphate, tert-butylphenyl diphenyl phosphate, and tricresyl phosphate, while BDE-47, triphenyl phosphate and tri-o-cresyl phosphate had no effect. Interestingly, isopropylated triphenyl phosphate enhanced dbcAMP-stimulated steroid production (∼2-fold), while tri-o-cresyl phosphate decreased (∼2/3) LH-stimulated steroid production. Several OPFRs affected the expression of genes involved in the biosynthesis of progesterone. In conclusion, all the OPFRs tested affected mitochondrial activity, cell survival, and superoxide production. Basal or stimulated steroid secretion was affected by all of the OPFRs except triphenyl phosphate; BDE-47 had no effect. Hence, the OPFRs currently used as alternatives affect Leydig cells to a greater extent than the brominated flame retardants that they have replaced.

Bruttolisten

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Saillenfait AM, Ndiaye D, Sabaté JP.
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Gupta V, Singh S, Srivarstava M, Ahmad H, Pachauri SD, Khandelwal K, Dwivedi P, Dwivedi AK; CDRI communication no: 8635.

Drug Deliv. 2016 Jan;23(1):113-22. doi: 10.3109/10717544.2014.905882. Epub 2014 Apr 30.

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

Low-Dose Bisphenol-A Impairs Adipogenesis and Generates Dysfunctional 3T3-L1 Adipocytes
Ariemma F, D'Esposito V, Liguoro D, Oriente F, Cabaro S, Liotti A, Cimmino I, Longo M, Beguinot F, Formisano P, Valentino R.
PLoS One. 2016 Mar 4;11(3):e0150762. doi: 10.1371/journal.pone.0150762. eCollection 2016.

In Vivo studier ved DTU Fødevareinstituttet

Søgning er udført på PubMed og dækker perioden Januar - ultimo Marts 2016

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 51 artikler (Bruttolisten).

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 brug af TG 443 (Extenden One generation reproductive toxicity study) (Beekhuijzen et al. 2016)og effekter af Prochloraz (Melching-Kollmuss et al. 2016).

Rigtig God læselyst.

Ud fra bruttolisten (se længere nede i dokumentet) er udvalgt følgende 2 artikler til engelsk abstrakt og dansk resume.

Implementing the extended one-generation reproductive toxicity study (EOGRTS): important points to consider.

Beekhuijzen M, Barentsen H, Marsden E, Zmarowski A, Aujoulat M, Picut C, Sloter E. Crit Rev Toxicol. 2016 Apr;46(4):332-47. doi: 10.3109/10408444.2015.1137863. Epub 2016 Mar 3.

The hallmark of the extended one-generation reproductive toxicity study (EOGRTS) is that, based on certain criteria or triggers, selected offspring are assigned at weaning to different cohorts for further investigation of sexual maturation, reproductive organ integrity and function, neuropathological and behavioral endpoints, and/or immune function. The triggers allow for a more customizable design based directly on the data, while minimizing animal usage. Compared to the two-generation reproductive toxicity study, the EOGRTS design increases the number, extent, and duration of F1-offspring assessments resulting in more thorough and efficient utilization of the first generation while excluding the second generation of offspring unless triggered. Therefore, the EOGRTS has the potential to reduce the number of rats required by nearly 1200 animals per study. When performing the EOGRTS, the complexity of this study should not be underestimated and experienced flexible testing laboratories with sufficient resources and historical control data for all parameters are essential. The aim of this review is to discuss the important aspects of this challenging study design and to share our knowledge on the implementation of this study in our laboratories. In addition, we elaborate on the type of criteria for expansion of the study and logistical considerations. Altogether, this review can be used as guidance by other labs, study monitors, and registration officers.

Comparing effect levels of regulatory studies with endpoints derived in targeted anti-androgenic studies: example prochloraz.

Melching-Kollmuss S, Fussell KC, Schneider S, Buesen R, Groeters S, Strauss V, van Ravenzwaay B. Arch Toxicol. 2016 Feb 25.

Prochloraz is an imidazole fungicide, and its regulatory toxicological data package has been primarily generated in the 1990s. More recently, studies have been published demonstrating an interaction with

hormone receptors/steroidogenesis and effects with an endocrine mode of action. In the present study, prochloraz has been investigated in a comprehensive in vivo study including relevant elements of current regulatory reproduction toxicity studies and additional mechanistic parameters. Prochloraz was administered per gavage in oil from GD 6 to PND 83 to pregnant and lactating Wistar rats and their respective offspring, at doses of 0.01 mg/kg bw/day (acceptable daily intake of prochloraz), 5 mg/kg bw/day [expected no-observed-effect-level (NOEL)] and 30 mg/kg bw/day. At 30 mg/kg bw/day maternal and offspring effects (decreased viability, lower number of live offspring) were seen including a delayed entry into male puberty (+1 day) accompanied by lower male offspring body weights, increased anogenital distance/index in females and transiently retained nipples in males at PND 12 (not seen at PND 20). The only finding at the "expected NOEL" was increased incidences of transiently retained nipples in males which are not considered adverse. No effects were seen in the low-dose group. There was no evidence for a non-monotonic dose-response curve or effects at low levels.

Bruttolisten

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Palanza P, Nagel SC, Parmigiani S, Vom Saal FS.
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2. Burden of disease and costs of exposure to endocrine disrupting chemicals in the European Union: an updated analysis.
Trasande L, Zoeller RT, Hass U, Kortenkamp A, Grandjean P, Myers JP, DiGangi J, Hunt PM, Rudel R, Sathyanarayana S, Bellanger M, Hauser R, Legler J, Skakkebaek NE, Heindel JJ.
Andrology. 2016 Mar 22. doi: 10.1111/andr.12178. [Epub ahead of print]

3. Endocrine Disruption: Computational Perspectives on Human Sex Hormone-Binding Globulin and Phthalate Plasticizers.
Sheikh IA, Turki RF, Abuzenadah AM, Damanhouri GA, Beg MA.
PLoS One. 2016 Mar 10;11(3):e0151444. doi: 10.1371/journal.pone.0151444. eCollection 2016.

4. Stereoselectivity and the potential endocrine disrupting activity of di-(2-ethylhexyl)phthalate(DEHP) against human progesterone receptor: a computational perspective.
Sheikh IA.
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Wildlife studier ved Biologisk Institut, Syddansk Universitet (SDU)

Søgningen er udført på Web of Knowledge (all databases) og dækker perioden 8/12 2015 – 29/3 2016.

Søgeprofilen kombinerer:	”Endocrine disrupt*” and	Fish* Amphibia* Bird* OR avia* Invertebrat* Mollus* Gastropod* Insect* Crustacea* Echinoderm* Ursus Reptil* OR alligator Whal* OR seal* OR dolphin*

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

Udvalgte artikler

Thyroid disruption in zebrafish (Danio rerio) larvae: Different molecular response patterns lead to impaired eye development and visual functions.
Baumann L, Ros A, Rehberger K, Neuhauss SC, Segner H.
Aquatic Toxicology. 172: 44-55. 2016.

The vertebrate thyroid system is important for multiple developmental processes, including eye development. Thus, its environmentally induced disruption may impact important fitness-related parameters like visual capacities and behaviour. The present study investigated the relation between molecular effects of thyroid disruption and morphological and physiological changes of eye development in zebrafish (Danio rerio). Two test compounds representing different molecular modes of thyroid disruption were used: propylthiouracil (PTU), which is an enzyme-inhibitor of thyroid hormone synthesis, and tetrabromo-bisphenol A (TBBPA), which interacts with the thyroid hormone receptors. Both chemicals significantly altered transcript levels of thyroid system-related genes (TRα, TRβ, TPO, TSH, DIO1, DIO2 and DIO3) in a compound-specific way. Despite these different molecular response patterns, both treatments resulted in similar pathological alterations of the eyes such as reduced size, RPE cell diameter and pigmentation, which were concentration-dependent. The morphological changes translated into impaired visual performance of the larvae: the optokinetic response was significantly and concentration-dependently decreased in both treatments, together with a significant increase of light preference of PTU-treated larvae. In addition, swimming activity was impacted. This study provides first evidence that different modes of molecular action of the thyroid disruptors can be associated with uniform apical responses. Furthermore, this study is the first to show that pathological eye development, as it can be induced by exposure to thyroid disruptors, indeed translates into impaired visual capacities of zebrafish early life stages.

UV-filter benzophenone-3 inhibits agonistic behavior in male Siamese fighting fish (Betta splendens).
Chen TH, Wu YT, Ding WH.
Ecotoxicology. 25(2): 302-309. 2016.

Benzophenone-3 (BP-3) is a widely used organic UV-filter compound. Despite the frequent occurrence of BP-3 in aquatic environments, little is known about its effect on fish behavior. The aim of this study was to investigate the endocrine disrupting effects of BP-3 in male fighting fish (Betta splendens) with a focus on agonistic behavior. Male fighting fish were exposed to 10, 100, and 1000 μg/L BP-3, as well as a solvent control (0.1 % ethanol) and a positive control (100 ng/L 17α-ethynylestradiol, EE2), for 28 days. At the beginning and the end of exposure, standard length and body mass of the fish were measured for calculating the condition factor (CF). In addition, spontaneous swimming activity (total distance moved) and agonistic behavior (maximum velocity and duration of opercular display in front of a mirror) were also quantified. At the end of exposure, the fish gonads were sampled for gonadosomatic index (GSI) measurement and histology. After the exposure, CF was significantly decreased in the 1000 μg/L BP-3 groups. Spontaneous swimming activity was not affected. However, maximum velocity was significantly reduced in the EE2 and 1000 μg/L BP-3 treatments; duration of opercular display was significantly decreased in the EE2 and 10 and 1000 μg/L BP-3 treatments. GSI was not significantly different between groups. There was a slight but statistically significant decrease of relative proportion of mature spermatozoa in testicular tissue in the 100 μg/L BP-3 treatment. Collectively, our results demonstrate that BP-3 can disrupt agonistic behavior of male fighting fish, indicating the endocrine disrupting activity of this compound.

Toxicological responses following short-term exposure through gavage feeding or water-borne exposure to Dechlorane Plus in zebrafish (Danio rerio).

Kang H, Moon HB, Choi K.

Chemosphere. 146: 226-232. 2016.

Dechlorane Plus (DP) is a chlorinated flame retardant widely used worldwide, and has been reported in environment and humans. However, only limited information is currently available on its toxicity on aquatic organisms. In this study, we employed zebrafish to evaluate possible toxicological responses including oxidative stress and endocrine disruption following exposure to DP. DP was dissolved in corn oil and was delivered to adult male zebrafish via gavage feeding. Delivery of DP was carried out twice on days 0 and 2, at up to 3 μg/g fish wet weight. Body residue level of DP in the fish at day 6 was within a range that has been reported in hot spot areas of China. On day 6, blood, liver, testis, and brain were collected and were evaluated for oxidative damage and endocrine disruption. Following DP exposure, hepatic catalase activity significantly increased, implying its oxidative damage potential. In addition, plasma thyroxine (T4) concentrations increased along with up-regulation of corticotropin releasing hormone and thyroid stimulating hormone β genes in brain. Following DP exposure, transcriptional responses of sex hormone related genes in brain were observed, suggesting possible sex hormone disrupting potentials of DP. However, water-borne exposure to DP up to 267 μg/L among the embryo and larval fish did not show any adverse effects on hatching time and transcription of thyroid hormone related genes. Our observations indicate for the first time that DP disrupts thyroid hormone balance of zebrafish by altering regulatory pathways in the brain.

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