Bulletin de veille Perturbateurs Endocriniens N°14 - Mars 2022

La validation des informations fournies (exactitude, fiabilité, pertinence par rapport aux principes de prévention, etc.) est du ressort des auteurs des articles signalés dans la veille. Les informations ne sont pas le reflet de la position de l'INRS.

Les liens mentionnés dans le bulletin donnent accès aux documents sous réserve d'un abonnement à la ressource.

Exposition professionnelle

Potential occupational exposure of parents to endocrine disrupting chemicals, adverse birth outcomes, and the modification effects of multi-vitamins supplement and infant sex.

Zhang H, Li Y, Zhang X, Chen W, Liang Q, Li C, et al. *Ecotoxicol Environ Saf*. 2022 Mar 15;233:113314.

BACKGROUND: Maternal occupational exposure to endocrine disrupting chemicals (EDCs) may have adverse effect on birth outcomes. However, little is known about paternal EDCs exposure and the combined effect of parental exposure on birth outcomes. OBJECTIVES: To assess the effects of both maternal and paternal occupational EDCs exposure on adverse birth outcomes, and further explore if multi-vitamins supplement and infant sex modify the association. METHODS: We conducted a prospective cohort study of 5421 mother-father-newborn groups in Guangzhou, China. A questionnaire informed by a job exposure matrix (JEM) was applied to collect parental occupational EDCs exposure based on the type of work performed. We used logistic regression to estimate

association between parental EDCs exposure and birth outcomes (including preterm birth (PTB), low birth weight (LBW), birth defects and congenital heart defects (CHD)). Stratified analyses and Cochran Q tests were performed to assess the modifying effect of maternal multi-vitamins supplement use and infant sex. RESULTS: Compared with mothers unexposed, we found that mothers those exposed to EDCs were associated with increased odds of birth defects (aOR=1.70, 95% confidence interval (CI): 1.10-2.62), especially for those exposed for > 1.5 years (aOR= 3.00, 95% CIs: 1.78-5.03), or those with directly occupational exposed to EDCs (aOR= 2.94, 95% CIs: 1.72-5.04). Maternal exposure for > 1.5 years and direct exposure increased the risk of CHD, with aORs of 2.47 (1.21-5.02) and 2.79 (1.37-5.69), respectively. Stronger adverse effects were also observed when mothers and fathers were both exposed to EDCs. Paternal occupational EDCs exposure and exposure ≤ 1.5 years was associated with increased odds of LBW, with aORs of 2.14 (1.63-2.79) and 1.54 (1.10-2.15), respectively. When stratified by multi-vitamins supplement and infant sex, we observed slightly stronger effects for maternal exposure on birth defects/CHD as well as paternal EDCs exposure on PTB and LBW, among those without multi-vitamins supplement and among male babies, although the modification effects were not significant. CONCLUSION: Maternal exposure to EDCs was associated with greater odds of birth defects and CHD, while paternal exposure was mainly associated with greater odds of LBW. These effects tend to be stronger among mothers without multi-vitamins supplement and among male babies.

Lien vers l'article

What to Expect When Expecting in Lab: A Review of Unique Risks and Resources for Pregnant Researchers in the Chemical Laboratory.

Lane MKM, Garedew M, Deary EC, Coleman CN, Ahrens-Víquez MM, Erythropel HC, et al. *Chem Res Toxicol*. 2022 Feb 21;35(2):163-98.

Pregnancy presents a unique risk to chemical researchers due to their occupational exposures to chemical, equipment, and physical hazards in chemical research laboratories across science, engineering, and technology disciplines. Understanding "risk" as a function of hazard, exposure, and vulnerability, this review aims to critically examine the state of the science for the risks and associated recommendations (or lack thereof) for pregnant researchers in chemical laboratories (labs). Commonly encountered hazards for pregnant lab workers include chemical hazards (organic solvents, heavy metals, engineered nanomaterials, and endocrine disruptors), radiation hazards (ionizing radiation producing equipment and materials and nonionizing radiation producing equipment), and other hazards related to the lab environment (excessive noise, excessive heat, psychosocial stress, strenuous physical work, and/or abnormal working hours). Lab relevant doses and routes of exposure in the chemical lab environment along with literature and governmental recommendations or resources for exposure mitigation are critically assessed. The specific windows of vulnerability based on stage of pregnancy are described for each hazard, if available. Finally, policy gaps for further scientific research are detailed to enhance future guidance to protect pregnant lab workers.

Lien vers l'article

Towards a toxic-free environment: perspectives for chemical risk assessment approaches.

Bonzini M, Leso V, Iavicoli I. *Med Lav*. 2022 Feb 22;113(1):e2022004.

Regulatory frameworks to control chemical exposure in general living and occupational environments have changed exposure scenarios towards a widely spread contamination at relatively low doses in developed countries. In such evolving context, some critical aspects should be considered to update risk assessment and management strategies. Risk assessment in low-dose chemical exposure scenarios should take advantage of: toxicological investigations on emerging substances of interest, like those recognised as endocrine disruptors or increasingly employed nanoscale materials; human biological monitoring studies aimed to identify innovative biomarkers for known chemical exposure; "omic" technologies useful to identify hazards of chemicals and their modes of action. For updated risk assessment models, suitable toxicological studies, analyses of dose-responses at low-concentrations, environmental and biological monitoring of exposure, together with exposome studies, and the proper definition of susceptible populations may all provide helpful contributions. These may guide defining preventive measures to control the exposure and develop safe and sustainable chemicals by design. Occupational medicine can offer know-how and instruments to understand and manage such evolution towards a toxic-free environment to protect the safety and health of the workforce and, in turn, that of the general population.

Lien vers l'article

Epidémiologie

Impact of organochlorine pollutants on semen parameters of infertile men in Pakistan,
AMIR S., M. TZATZARAKIS, C. MAMOULAKIS, J. H. BELLO, S. EQANI, E. VAKONAKI, M. KARAVITAKIS, S. SULTAN, F. TAHIR, S. T. A. SHAH and A. TSATSAKIS,
Environmental Research 195 (Apr 2021),
Male infertility is a major problem with important socioeconomic consequences. It is associated with several pathological factors, including but not limited to endocrine disruption as a result of environmental pollution and the alarming decline in sperm count over the decades is indicative of involvement of many environmental and lifestyle changes around the globe. Organochlorine pollutants such as dichlorodiphenyltrichlorethanes (DDTs), polychlorinated biphenyls (PCBs) and hexachlorobenzene (HCB) disrupt male reproductive system but the exact effect of environmental exposure on semen parameters in human is still not clear. This study was designed to monitor PCBs, DDTs and HCB in hair, urine and serum samples of infertile and healthy fertile men. Solid-phase microextraction gas chromatography-mass spectrometry (SPME/GC-MS) was used to monitor analytes. All tested compounds were detected, indicating recent use/persistent accumulation. Hair samples revealed no significant association with serum/urine concentrations of the analytes, while serum/urine concentrations were significantly correlated positively. Concentrations were higher in serum compared to other samples. The levels of organochlorine pollutants were higher in infertile men compared to controls with few exceptions. Among PCBs, and DDTs, PCB-153 and pp?-DDT were detected in highest concentrations, respectively. op?-DDT and pp?-DDT levels were significantly higher in infertile men compared to controls. HCB was significantly correlated negatively with sperm motility in all samples. Serum concentrations of all compounds were higher in men with defective semen parameters compared to normospermics. Serum was the best biological sample for assessing health outcomes in relation to exposure levels. http://dx.doi.org/10.1016/j.envres.2021.110832

Electronic waste and their leachates impact on human health and environment: Global ecological threat and management,
ANKIT, L. SAHA, V. KUMAR, J. TIWARI, SWETA, S. RAWAT, J. SINGH and K. BAUDDH,
Environmental Technology & Innovation 24 (Nov 2021),
Electronic waste is an important part of solid waste management around the world. Being a large part of the solid waste, e-waste contains numerous hazardous components in the form of halogenated compounds like polychlorinated biphenyls (PCBs), tetrabromobisphenol A (TBBPA), polybrominated biphenyl (PBB), etc. along with other toxic materials which cause an adverse impact on the plants, microbes and human beings. One of the major toxic components of e-waste are heavy metals (HMs) like As, Cr, Cd, Cu, and Hg, which needs to be

handled carefully at the time of dismantling the e-wastes, being managed by informal sector in developing countries compounds the problem, also, the available disposal/treatment technologies of e-waste are inadequate, and they have a direct as well as indirect impact on human health and the environment. This review deals with the quantity of e-waste generated globally and how its different components affect important factors of the ecosystem like soil, plants, microbes, and animals, including humans. This review also deals the recovery of valuable metals using various methods. This review concludes that, there is a quintessential need to replace conventional traditional procedures with futuristic state of the art eco-friendly approaches to manage e-waste.
http://dx.doi.org/10.1016/j.eti.2021.102049

Association of Maternal-Neonatal Steroids With Early Pregnancy Endocrine Disrupting Chemicals and Pregnancy Outcomes,
BANKER M., M. PUTTABYATAPPA, P. O'DAY, J. M. GOODRICH, A. S. KELLEY, S. E. DOMINO, Y. R. SMITH, D. C. DOLINOY, P. X. K. SONG, R. J. AUCHUS and V. PADMANABHAN,
Journal of Clinical Endocrinology & Metabolism 106, no. 3 (Mar 2021): 665-687,
Context: Steroids play an important role in fetal development and parturition. Gestational exposures to endocrine-disrupting chemicals (EDCs) affect steroidal milieu and pregnancy outcomes, raising the possibility of steroids serving as biomarkers. Most studies have not addressed the impact of EDC mixtures, which are reflective of real life scenarios. Objective: Assess the association of maternal and neonatal steroids with pregnancy outcomes and early pregnancy EDC levels. Design: Prospective analysis of mother-infant dyads. Setting: University hospital. Participants: 121 mother-infant dyads. Main Outcome Measures: The associations of maternal and neonatal steroidal hormones from 121 dyads with pregnancy outcomes, the associations of first trimester EDCs individually and as mixtures with maternal and neonatal steroids in a subset of 56 dyads and the influence of body mass index (BMI), age, and offspring sex in modulating the EDC associations with steroids were determined. Results: Steroid-specific positive or negative associations with pregnancy measures were evident; many maternal first trimester EDCs were negatively associated with estrogens and positively with androgen/estrogen ratios; EDC-steroid associations were influenced by maternal age, pre-pregnancy BMI, and fetal sex; and EDCs individually and as mixtures showed direct and inverse fetal sex-dependent associations with maternal and neonatal steroids. Conclusions: This proof-of-concept study indicates association of steroids with pregnancy outcomes depending on maternal age, prepregnancy BMI, and fetal sex, with the effects of EDCs differing when considered individually or as mixtures. These findings suggest that steroidal hormonal measures have potential to serve as biomarkers of impact of EDC exposures and pregnancy outcome.
http://dx.doi.org/10.1210/clinem/dgaa909

Prenatal phthalate exposure in relation to placental corticotropin releasing hormone (pCRH) in the CANDLE cohort,
BARRETT E. S., M. CORSETTI, D. DAY, S. W. THURSTON, C. T. LOFTUS, C. J. KARR, K. KANNAN, K. Z. LEWINN, A. K. SMITH, R. SMITH, F. A. TYLAVSKY, N. R. BUSH and S. SATHYANARAYANA,
Environment International 160 (Feb 2022),
Context: Phthalates may disrupt maternal-fetal-placental endocrine pathways, affecting pregnancy outcomes and child development. Placental corticotropin releasing hormone (pCRH) is critical for healthy pregnancy and child development, but understudied as a target of endocrine disruption. Objective: To examine phthalate metabolite concentrations (as mixtures and individually) in relation to pCRH. Design: Secondary data analysis from a prospective cohort study. Setting: Prenatal clinics in Tennessee, USA. Patients: 1018 pregnant women (61.4% non-Hispanic Black, 32% non-Hispanic White, 6.6% other) participated in the CANDLE study and provided data. Inclusion criteria included: low-medical-risk singleton pregnancy, age 16-40, and gestational weeks 16-29. Intervention: None. Main outcome measures: Plasma pCRH at two visits (mean gestational ages 23.0 and 31.8 weeks) and change in pCRH between visits (Delta pCRH). Results: In weighted quantile sums (WQS) regression models, phthalate mixtures were associated with higher pCRH at Visit 1 (beta = 0.07, 95 %CI: 0.02, 0.11) but lower pCRH at Visit 2 (beta = 0.08, 95 %CI: 0.14, 0.02). In stratified analyses, among women with gestational diabetes (n = 59), phthalate mixtures were associated with lower pCRH at Visit 1 (beta = 0.17, 95 %CI: 0.35, 0.0006) and Visit 2 (beta = 0.35, 95 %CI: 0.50, 0.19), as well as greater Delta pCRH (beta = 0.16, 95 %CI: 0.07, 0.25). Among women with gestational hypertension (n = 102), phthalate mixtures were associated with higher pCRH at Visit 1 (beta = 0.20, 95 %CI: 0.03, 0.36) and Visit 2 (beta = 0.42; 95 %CI: 0.19, 0.64) and lower Delta pCRH (beta = 0.17, 95 %CI: 0.29, 0.06). Significant interactions between individual phthalate metabolites and pregnancy complications were observed. Conclusions: Phthalates may impact placental CRH secretion, with

differing effects across pregnancy. Differences in results between women with and without gestational diabetes and gestational hypertension suggest a need for further research examining whether women with pregnancy complications may be more vulnerable to endocrine-disrupting effects of phthalates.
http://dx.doi.org/10.1016/j.envint.2022.107078

Endocrine Disrupting Chemicals and Risk of Testicular Cancer: A Systematic Review and Meta-analysis,
BRAUNER E. V., Y. H. LIM, T. KOCH, C. S. ULDBJERG, L. S. GREGERSEN, M. K. PEDERSEN, H. FREDERIKSEN, J. H. PETERSEN, B. A. COULL, A. M. ANDERSSON, M. HICKEY, N. E. SKAKKEBAEK, R. HAUSER and A. JUUL,
Journal of Clinical Endocrinology & Metabolism 106, no. 12 (Dec 2021): E4834-E4860,
The incidence of many hormone-dependent diseases, including testicular cancer, has sharply increased in all high-income countries during the 20th century. This is not fully explained by established risk factors. Concurrent, increasing exposure to antiandrogenic environmental endocrine disrupting chemicals (EDCs) in fetal life may partially explain this trend. This systematic review assessed available evidence regarding the association between environmental EDC exposure and risk of testicular cancer (seminomas and nonseminomas). Following PRISMA guidelines, a search of English peer-reviewed literature published prior to December 14, 2020 in the databases PubMed and Embase (R) was performed. Among the 279 identified records, 19 were eligible for quality assessment and 10 for further meta-analysis. The completeness of reporting was high across papers, but over 50% were considered subject to potential risk of bias. Mean age at diagnosis was 31.9 years. None considered effects of EDC multipollutant mixtures. The meta-analyses showed that maternal exposure to combined EDCs was associated with a higher risk of testicular cancer in male offspring [summary risk ratios: 2.16, (95% CI:1.78-2.62), 1.93 (95% CI:1.49-2.48), and 2.78 (95% CI:2.27-3.41) for all, seminoma, and nonseminoma, respectively]. Similarly, high maternal exposures to grouped organochlorines and organohalogens were associated with higher risk of seminoma and nonseminoma in the offspring. Summary estimates related to postnatal adult male EDC exposures were inconsistent. Maternal, but not postnatal adult male, EDC exposures were consistently associated with a higher risk of testicular cancer, particularly risk of nonseminomas. However, the quality of studies was mixed, and considering the fields complexity, more prospective studies of prenatal EDC multipollutant mixture exposures and testicular cancer are needed. http://dx.doi.org/10.1210/clinem/dgab523

Reduced mitochondrial DNA copy number in occupational workers from brominated flame retardants manufacturing plants,
CHEN T., X. T. WANG, J. X. JIA, D. J. WANG, Y. X. GAO, X. YANG, S. X. ZHANG, P. Y. NIU and Z. X. SHI,
Science of the Total Environment 809 (Feb 2022),
Decabrominated diphenyl ether (BDE-209) and its substitute decabromodiphenyl ethane (DBDPE) are two flame retardants that have similar structure and are widely used in various industrial products. The accumulation and potential toxicity of them to human health have already aroused attention, and some research showed that they may affect mitochondrial function. Therefore, this study focused on the population with high exposure to brominated flame retardants (BFRs) and the related changes in mtDNA copy number (mtDNAcn) in whole blood. 334 blood samples were collected from three groups of people in Shandong Province, including 42 BDE-209 occupational exposure workers from the BDE-209 manufacturing plant, 131 DBDPE occupational exposure workers from the DBDPE manufacturing plant, and 161 non-BFRs occupational exposure residents from the BFRs contaminated area. We measured the levels of BDE-209, DBDPE in serum sample, and the mtDNAcn in whole blood sample and analyzed these data by multiple linear regression. The average concentrations of BDE-209, DBDPE and Sigma(BDE-209+ DBDPE) in BDE-209 occupational workers were 3510, 639 and 4600 ng/g lw, respectively; the average concentrations of BDE-209, DBDPE and Sigma(BDE-209+ DBDPE) in DBDPE occupational workers were 229, 4040 and 4470 ng/g lw, respectively; the average concentrations of BDE-209, DBDPE and Sigma(BDE-209+ DBDPE) in non-BFRs occupational exposure residents were 66.3, 45.7 and 137 ng/g lw, respectively. The relative mtDNAcn was 0.823 in BDE-209 occupational workers, 0.845 in DBDPE occupational workers and 0.989 in non-BFRs occupational exposure residents. A 10-fold increase in BDE-209, DBDPE concentrations was separately associated with a 0.068 and 0.063 decrease in mtDNAcn. Therefore, our study implied that BFRs may affect mitochondrial function. As increasing BFRs exposure has emerged in recent years, the relationship between BFRs exposure and mitochondrial function needs further study.
http://dx.doi.org/10.1016/j.scitotenv.2021.151086

Association of urinary organophosphate esters level with sex steroid hormones levels in adult males: A

nationwide study, NHANES 2013-2014,
CHEN Z. Y., S. QIU, C. C. ZHANG, Y. ZHAN, L. R. LIU, Y. G. BAO, B. CHEN, Y. J. BAI, X. N. ZHENG, Y. HUANG, K. JIN, P. HAN and Q. WEI,
Andrology 10, no. 3 (Mar 2022): 567-575,
Background Exposure to environmental pollution via different mechanisms is associated with multiple endocrine dysfunctions. Organophosphate esters (OPEs) are endocrine-disrupting chemicals that affect sex steroid hormones. Purpose We aimed to study the effect of OPEs and their metabolites, such as diphenyl phosphate (DPHP), bis(1,3-dichloro-2-propyl) phosphate (BDCPP), bis(2-chloroethyl) phosphate (BCEP), and dibutyl phosphate (DBUP), on sex steroid hormones in males. Design, setting, participants, and intervention This cross-sectional analytical study analyzed data from the 2013-2014 National Health and Nutrition Examination Survey among 763 male participants aged >= 20 years. Main outcome measures The relationships between the metabolites of OPEs and total testosterone, estradiol, sex hormone-binding globulin, and the ratio of total testosterone to estradiol (a parameter derived from total testosterone and estradiol) were evaluated using multivariate linear regression models that were adjusted for potential confounders. Results A total of 763 participants, with a mean age of 44.59 (+/- 15.59) years, were enrolled. Of these, 65.7% participants had non-Hispanic white ancestry, 9.83% had non-Hispanic black ancestry, and 15.97% had Hispanic ancestry. Participants with higher urinary level of DPHP had a lower level of total testosterone and estradiol. Moreover, higher urinary levels of BDCPP were associated with higher estradiol. Conclusion According to our study, which is based on a representative population of US adults, exposure to OPEs was significantly associated with altered sex hormone levels (total testosterone and estradiol). Further studies focused on the underlying mechanisms regarding the association between each metabolite and sex steroid hormones are required.
http://dx.doi.org/10.1111/andr.13149

Prenatal phthalates, gestational weight gain, and long-term weight changes among Mexican women,
DEIERLEIN A. L., H. T. WU, A. C. JUST, A. J. KUPSCO, J. M. BRAUN, E. OKEN, D. C. SORIA-CONTRERAS, A. CANTORAL, M. L. PIZANO, N. MCRAE, M. M. TELLEZ-ROJO, R. O. WRIGHT and A. A. BACCARELLI,
Environmental Research 209 (Jun 2022),
Background: Phthalates are endocrine disrupting chemicals that may influence weight status; however, few studies have considered weight gain during pregnancy and subsequent long-term weight changes in women. Objective: To determine associations of prenatal phthalate exposure with maternal weight during pregnancy and through up to seven years post-delivery. Methods: We analyzed 15 urinary phthalate biomarker concentrations during the 2nd and 3rd trimesters among 874 pregnant women enrolled in the Programming Research in Obesity, Growth Environment and Social Stress Study in Mexico City. We examined three time-specific maternal weight outcomes: gestational weight gain (between 2nd and 3rd trimesters), short-term weight (between 3rd trimester and 12 months post-delivery), and long-term weight (between 18 months and 6-7 years post-delivery). We used Bayesian Kernel Machine Regression (BKMR) to estimate associations for the total phthalate mixture, as well as multivariable linear mixed models for individual phthalate biomarkers. Results: As a mixture, 2nd trimester urinary phthalate biomarker concentrations were associated with somewhat lower gestational weight gain between the 2nd and 3rd trimesters (interquartile range, IQR, difference: -0.07 standard deviations, SD; 95% credible interval, CrI: -0.20, 0.06); multivariable regression and BKMR models indicated that this inverse association was primarily driven by mono-2-ethyl-5-carboxypentyl terephthalate (MECPTP). Prenatal (2nd and 3rd trimesters) urinary phthalate mixture concentrations were positively associated with maternal weight change through 12 months postpartum (IQR difference: 0.11 SD; 95% CrI: 0.00, 0.23); these associations persisted from 18 months to 6-7 years follow-up (IQR difference: 0.07 SD; 95% CrI: 0.04, 0.10). Postpartum weight changes were associated with mono-3-carboxypropyl phthalate (MCPP) and MECPTP. Conclusions: Prenatal phthalate exposure was inversely associated with gestational weight gain and positively associated with long-term changes in maternal weight. Further investigation is required to understand how phthalates may influence body composition and whether they contribute to the development of obesity and other cardiometabolic diseases in women. http://dx.doi.org/10.1016/j.envres.2022.112835

Association between Total and Individual PCB Congener Levels in Maternal Serum and Birth Weight of Newborns: Results from the Chiba Study of Mother and Child Health Using Weighted Quantile Sum Regression,
EGUCHI A., K. SAKURAI, M. YAMAMOTO, M. WATANABE, A. HISADA, T. TAKAHASHI, E. TODAKA and C. MORI,
International Journal of Environmental Research and Public Health 19, no. 2 (Jan 2022),

Maternal exposure to polychlorinated biphenyls (PCBs) during pregnancy is associated with a low birth weight; however, the congener-specific effects of PCB congeners are not well defined. In this study, we used maternal serum samples from the Chiba Study of Mother and Child Health (C-MACH) cohort, collected at 32 weeks of gestational age, to analyze the effects of PCB congener exposure on birth weight by examining the relationship between newborn birth weight and individual PCB congener levels in maternal serum (n = 291). The median total PCB level in the serum of mothers of male and female newborns at approximately 32 weeks of gestation was 39 and 37 ng g(-1) lipid wt, respectively. The effect of the total PCB levels and the effects of PCB congener mixtures were analyzed using a linear regression model and a generalized weighted quantile sum regression model (gWQS). The birth weight of newborns was significantly associated with maternal exposure to PCB mixtures in the gWQS model. The results suggest that exposure to PCB mixtures results in low newborn birth weight. However, specific impacts of individual PCB congeners could not be related to newborn birth weight. http://dx.doi.org/10.3390/ijerph19020694

Association of bisphenol A, bisphenol F, and bisphenol S with ADHD symptoms in children,
KIM J. I., Y. A. LEE, C. H. SHIN, Y. C. HONG, B. N. KIM and Y. H. LIM,
Environment International 161 (Mar 2022),
Background: Bisphenol A (BPA) has been linked to attention-deficit/hyperactivity disorder (ADHD) symptoms, but the neurotoxic effects of bisphenol substitutes such as bisphenol F (BPF) and S (BPS) have not been well investigated. We investigated the associations between BPA, BPF, and BPS with ADHD symptoms at multiple time points in children. Methods: The levels of BPA (at ages 4, 6, and 8), BPF (at ages 6 and 8), and BPS (at ages 6 and 8) were measured in 619 children. Because of the low detection frequency of BPF and BPS levels, participants were divided into categories (<or >= limit of detection (LOD) for BPF; < LOD, >= LOD and < median, or >= median for BPS). ADHD symptoms were assessed using the ADHD Rating Scale IV (ARS). The relationship between bisphenols and ARS scores was analyzed using Poisson regression models, and generalized additive models and piecewise regression models were further explored for BPA. Results: BPA was detected in most participants (>97%), whereas BPF and BPS were less frequently detected (age 6: 17.5% for BPF and 42.0% for BPS; age 8: 51.6% for BPF and 73.3% for BPS). Doubling in BPA levels was associated with increased ARS scores by 4.7% (95% confidence intervals [CI]: 0.5, 9.2) at age 6. The association was greater with BPA levels higher than 3.0 mu g/g creatinine (24.2% [95% CI: 15.5, 33.6] increase). The BPF >= LOD group had 10.8% (95% CI: 1.2, 21.4) higher ARS scores than the BPF < LOD group. The BPS >= median group had 11.4% (95% CI: 2.0, 21.7) higher ARS scores than the BPS < LOD group. Conclusion: All bisphenols, in particular those at or above the LOD or median levels, were associated with ADHD symptoms at age 6. Further prospective studies are warranted to determine causal inference. http://dx.doi.org/10.1016/j.envint.2022.107093

The Impact of Bisphenol A on Thyroid Function in Neonates and Children: A Systematic Review of the Literature,
KOUTAKI D., G. PALTOGLOU, A. VOURDOUMPA and E. CHARMANDARI,
Nutrients 14, no. 1 (Jan 2022),
Background: Bisphenol A (BPA) is an endocrine-disrupting chemical widely used in plastic products that may have an adverse effect on several physiologic functions in children. The aim of this systematic review is to summarize the current knowledge of the impact of BPA concentrations on thyroid function in neonates, children, and adolescents. Methods: A systematic search of Medline, Scopus, Clinical Trials.gov, Cochrane Central Register of Controlled Trials CENTRAL, and Google Scholar databases according to PRISMA guidelines was performed. Only case-control, cross-sectional, and cohort studies that assessed the relationship between Bisphenol A and thyroid function in neonates and children aged <18 years were included. Initially, 102 articles were assessed, which were restricted to 73 articles after exclusion of duplicates. A total of 73 articles were assessed by two independent researchers based on the title/abstract and the predetermined inclusion and exclusion criteria. According to the eligibility criteria, 18 full-text articles were selected for further assessment. Finally, 12 full-text articles were included in the present systematic review. Results: The presented studies offer data that suggest a negative correlation of BPA concentrations with TSH in children, a gender-specific manner of action, and a potential effect on proper neurodevelopment. However, the results are inconclusive with respect to specific thyroid hormone concentrations and the effect on thyroid autoimmunity. Conclusion: The potential negative effect of BPA in the developing thyroid gland of children that may affect proper neurodevelopment, suggesting the need to focus future research on designing studies that elucidate the underlying mechanisms and the effects of BPA in thyroid function in early life. http://dx.doi.org/10.3390/nu14010168

Exposure of childbearing-aged female to phthalates through the use of personal care products in China: An assessment of absorption via dermal and its risk characterization,
LI Y. Y., N. ZHENG, Y. LI, P. Y. LI, S. Y. SUN, S. J. WANG and X. SONG,
Science of the Total Environment 807 (Feb 2022),
Phthalates (PAEs) are widely used in personal care products (PCPs) and skin care packaging materials. Through national representative sampling, 328 childbearing-aged females in China were investigated by questionnaire, whose contact factors for 30 cosmetic products were collected. According to the daily exposure method and adverse cumulative effects of PAE exposure on female reproduction, we derived the ER alpha, ER beta binding, and AR anti-androgenic effects. The utilization rates of acne cleanser, acne cream, cleanser (non-acne), and cream (non-acne) in volunteers were 21.90%, 22.22%, 51.63%, and 51.96%, respectively. Examining the data for PAEs in PCPs, the content of DBP (dibutyl phthalate) in them was significantly higher for tubes (0.26 +/- 0.05 mu g/g) and other packaging (pump type and metal tube) (025 +/- 0.03 mu g/g) than bowl (0.17 +/- 0.04 mu g/g). The DBP content of acne cream (0.27 +/- 0.03 mu g/g) was significantly higher than that of non-acne cream (0.17 +/- 0.03 mu g/g); likewise, there was significantly more DEHP (di (2-ethylhexyl) phthalate) in acne cleanser (0.87 +/- 0.15 mu g/g) than non-acne cleanser (0.64 +/- 0.36 mu g/g). Students and office worker were the main consumers of PCPs; however, among all occupation groups, the daily exposure dose of PCPs for workers was highest (mean = 0.0004, 0.0002, 0.0009 mu g/kg bw/day for DEP (diethyl phthalate), DBP, and DEHP, respectively). The cumulative indices of PAEs' exposure revealed that the level of ERa and ER beta binding and AR anti-androgenic effects in workers was respectively 0.4935, 0.0186, and 0.2411 mu g/kg bw/day. The risk index (HITDI and HIRfDs) of DEP, DBP, and DEHP was lower than their corresponding reference value (hazard index <1), but using PCPs may cause potential health risks. Therefore, we should pay attention to the adverse effects of PAEs on female reproductive functioning. especially the cumulative exposure of females of childbearing age. http://dx.doi.org/10.1016/j.scitotenv.2021.150980

Single and mixed effects of prenatal exposure to multiple bisphenols on hemoglobin levels and the risk of anemia in pregnant women,
LIANG J., C. X. YANG, T. LIU, P. TANG, H. S. HUANG, H. N. WEI, Q. LIAO, J. H. LONG, X. Y. ZENG, S. LIU, D. P. HUANG and X. Q. QIU,
Environmental Research 207 (May 2022),
Introduction: Bisphenols have endocrine-disrupting effects, which may disrupt hemoglobin (Hb) homeostasis and lead to anemia. However, the effects of bisphenols on anemia remain unknown. Therefore, we assessed the effects of single-and multiple-exposure to bisphenols on Hb levels and anemia of pregnant women. Methods: The study involved 2035 pregnant women from Guangxi Zhuang Birth Cohort in China. Generalized linear regression, principal component analysis (PCA), quantile g-computation (Qgcomp), and Bayesian kernel machine regression (BKMR) were performed to examine the effects of serum bisphenols on Hb levels and the risk of anemia. Results: After adjustment, elevated bisphenol A (BPA) levels were correlated with decreased Hb concentrations (beta =-0.51; 95%CI:-0.92,-0.10) in the first trimester, and these correlations were more sensitive in mothers of males. Compared with the low-exposure group, bisphenol B (BPB) levels in the high-exposure group led to a 1.52 g/L (95%CI:-3.01,-0.03) decrease in Hb levels in the second trimester; tetrabromobisphenol A (TBBPA) levels in the high-exposure group led to a higher the risk of anemia in the third trimester (OR = 1.46; 95%CI: 1.07, 1.99); bisphenol F (BPF) in the high-exposure group led to lower Hb levels (beta =-2.42; 95%CI:-4.69,-0.14) in mothers of male fetuses in the third trimester. Qgcomp showed that elevated levels of bisphenol mixture was correlated with (beta =-1.42; 95%CI:-2.61,-0.24) decrease in Hb levels in the second trimester. PCA revealed a negative association between PC2 and Hb levels in the first trimester (beta =-0.89; 95%CI:-1.61,-0.17). Similarly, a negative relationship was observed between PC1 and Hb levels in the third trimester among mothers with male fetuses (beta =-1.00; 95%CI:-1.94,-0.06). Conclusions: Prenatal exposure to single and mixed bisphenols may decrease Hb levels and increase the risk of anemia during pregnancy, the associations may be greater in mothers with male fetuses than those with female fetuses.
http://dx.doi.org/10.1016/j.envres.2021.112625

The Effects of Environmental Contaminant Exposure on Reproductive Aging and the Menopause Transition,
NEFF A. M., M. J. LAWS, G. R. WARNER and J. A. FLAWS,

Current Environmental Health Reports (Purpose of Review Menopause marks the end of a woman's reproductive lifetime. On average, natural menopause occurs at 51 years of age. However, some women report an earlier age of menopause than the national average. This can be problematic for women who delay starting a family. Moreover, early onset of menopause is associated with increased risk of cardiovascular disease, depression, osteoporosis, and premature death. This review investigates associations between exposure to endocrine-disrupting chemicals (EDCs) and earlier onset of menopause. Recent Findings Recent data suggest exposure to certain EDCs may accelerate reproductive aging and contribute to earlier onset of menopause. Human and rodent-based studies identify positive associations between exposure to certain EDCs/environmental contaminants and reproductive aging, earlier onset of menopause, and occurrence of vasomotor symptoms. These findings increase our understanding of the detrimental effects of EDCs on female reproduction and will help lead to the development of strategies for the treatment/prevention of EDC-induced reproductive aging. http://dx.doi.org/10.1007/s40572-022-00334-y

Identifying environmental exposure profiles associated with timing of menarche: A two-step machine learning approach to examine multiple environmental exposures,
OSKAR S., M. S. WOLFF, S. L. TEITELBAUM and J. A. STINGONE,
Environmental Research 195 (Apr 2021),
Background: Variation in the timing of menarche has been linked with adverse health outcomes in later life. There is evidence that exposure to hormonally active agents (or endocrine disrupting chemicals; EDCs) during childhood may play a role in accelerating or delaying menarche. The goal of this study was to generate hypotheses on the relationship between exposure to multiple EDCs and timing of menarche by applying a two-stage machine learning approach. Methods: We used data from the National Health and Nutrition Examination Survey (NHANES) for years 2005-2008. Data were analyzed for 229 female participants 12-16 years of age who had blood and urine biomarker measures of 41 environmental exposures, all with >70% above limit of detection, in seven classes of chemicals. We modeled risk for earlier menarche (<12 years of age vs older) with exposure biomarkers. We applied a two-stage approach consisting of a random forest (RF) to identify important exposure combinations associated with timing of menarche followed by multivariable modified Poisson regression to quantify associations between exposure profiles ("combinations") and timing of menarche. Results: RF identified urinary concentrations of monoethylhexyl phthalate (MEHP) as the most important feature in partitioning girls into homogenous subgroups followed by bisphenol A (BPA) and 2,4-dichlorophenol (2,4-DCP). In this first stage, we identified 11 distinct exposure biomarker profiles, containing five different classes of EDCs associated with earlier menarche. MEHP appeared in all 11 exposure biomarker profiles and phenols appeared in five. Using these profiles in the second-stage of analysis, we found a relationship between lower MEHP and earlier menarche (MEHP <= 2.36 ng/mL vs >2.36 ng/mL: adjusted PR = 1.36, 95% CI: 1.02, 1.80). Combinations of lower MEHP with benzophenone-3, 2,4-DCP, and BPA had similar associations with earlier menarche, though slightly weaker in those smaller subgroups. For girls not having lower MEHP, exposure profiles included other biomarkers (BPA, enterodiol, monobenzyl phthalate, triclosan, and 1-hydroxypyrene); these showed largely null associations in the second-stage analysis. Adjustment for covariates did not materially change the estimates or CIs of these models. We observed weak or null effect estimates for some exposure biomarker profiles and relevant profiles consisted of no more than two EDCs, possibly due to small sample sizes in subgroups. Conclusion: A two-stage approach incorporating machine learning was able to identify interpretable combinations of biomarkers in relation to timing of menarche; these should be further explored in prospective studies. Machine learning methods can serve as a valuable tool to identify patterns within data and generate hypotheses that can be investigated within future, targeted analyses.
http://dx.doi.org/10.1016/j.envres.2020.110524

Assessment of polybrominated diphenyl ether contamination and associated human exposure risk at municipal waste dumping sites,
PALIYA S., A. MANDPE, M. S. KUMAR, S. KUMAR and R. KUMAR,
Environmental Geochemistry and Health (The reports concerning the occurrence and fate of polybrominated diphenyl ethers (PBDEs) at municipal solid waste (MSW) dumping sites are scarce, and considering the Indian context, no study has been conducted to assess PBDE contamination at MSW dumping sites and associated exposure and health risk. Therefore, in the present study, the concentration of PBDE congeners was investigated in soil samples amassed from MSW dumping sites of India and the factors affecting the dissemination of different PBDE congeners in soil were evaluated. Also, the human exposure and health risk through soil intake

and dermal contact were also evaluated the first time in India. The total PBDE concentrations from tri- to deBDE congeners in soil ranged from 6.81 to 33.67 mu g/g dw and showed a trend towards higher levels of PBDEs in the dumping sites of more populous cities. BDE 183 was found to be the main congener in the soil of the dumping sites. The congener profile in the soil exhibited the composition of the octa- and deBDE technical mixture and possibilities of biological and photodegradation of deBDE into lower brominated congeners. A significant correlation was observed between the measures of BDE 183 and BDE 209 congeners and carbon, nitrogen and hydrogen contents of the soil. The measured exposure doses of PBDEs through soil intake and dermal contact and the hazard index was estimated higher in children as compared to adults, which indicates the increased risk and susceptibility of infants and children to PBDE exposure. The results of the present study revealed that the MSW dumping sites in India are a sink of PBDEs and might have detrimental effects on human health. [GRAPHICS] . http://dx.doi.org/10.1007/s10653-022-01208-w

Endocrine Disrupting Chemicals and Premenstrual Syndrome in Female College Students in East Asia: A Multi-Country Study,
PARK J., J. J. LEE, S. PARK, H. LEE, S. NAM, S. LEE and H. LEE,
International Journal of Womens Health 14 (2022): 167-177,
Purpose: This study aimed to explore the severity of premenstrual syndrome (PMS) and to examine associated factors with PMS among East Asian female college students with regard to endocrine-disrupting chemical (EDC). Patients and Methods: This study was a cross-sectional design. An online survey was completed by 520 female college students in Hong Kong and Korea. The structured questionnaire included items measuring knowledge of EDCs, actions taken and willingness to minimize exposure to EDCs, interest in EDCs, prior education on EDCs, life stress, severity of PMS, and general and health-related characteristics. Multiple logistic regressions were performed. Results: The prevalence of severe PMS among the participants was 54.6%. Factors associated with severe PMS included a selfreported heavy menstrual flow, underweight, obesity, interpersonal relationship stress, actions taken to minimize exposure to EDCs, and interest in EDCs. Conclusion: This study provided the evidence of a negative association between severe PMS and the actions taken to minimize exposure to EDCs. To alleviate symptoms of PMS among young female adults, practical interventions, such as education to overcome barriers to preventing exposure to EDCs, are suggested. http://dx.doi.org/10.2147/ijwh.S349172

Current understandings and perspectives of petroleum hydrocarbons in Alzheimer's disease and Parkinson's disease: a global concern,
RAJENDRAN R., R. P. RAGAVAN, A. G. AL-SEHEMI, M. S. UDDIN, L. ALEYA and B. MATHEW,
Environmental Science and Pollution Research 29, no. 8 (Feb 2022): 10928-10949,
Over the last few decades, the global prevalence of neurodevelopmental and neurodegenerative illnesses has risen rapidly. Although the aetiology remains unclear, evidence is mounting that exposure to persistent hydrocarbon pollutants is a substantial risk factor, predisposing a person to neurological diseases later in life. Epidemiological studies correlate environmental hydrocarbon exposure to brain disorders including neuropathies, cognitive, motor and sensory impairments; neurodevelopmental disorders like autism spectrum disorder (ASD); and neurodegenerative disorders like Alzheimer's disease (AD) and Parkinson's disease (PD). Particulate matter, benzene, toluene, ethylbenzene, xylenes, polycyclic aromatic hydrocarbons and endocrine-disrupting chemicals have all been linked to neurodevelopmental problems in all class of people. There is mounting evidence that supports the prevalence of petroleum hydrocarbon becoming neurotoxic and being involved in the pathogenesis of AD and PD. More study is needed to fully comprehend the scope of these problems in the context of unconventional oil and natural gas. This review summarises in vitro, animal and epidemiological research on the genesis of neurodegenerative disorders, highlighting evidence that supports inexorable role of hazardous hydrocarbon exposure in the pathophysiology of AD and PD. In this review, we offer a summary of the existing evidence gathered through a Medline literature search of systematic reviews and meta-analyses of the most important epidemiological studies published so far.
http://dx.doi.org/10.1007/s11356-021-17931-3

Chemical Exposures via Personal Care Products and the Disproportionate Asthma Burden Among the US Black Population,
RALEY E., L. QUIROS-ALCALA and E. C. MATSUI,
Journal of Allergy and Clinical Immunology-in Practice 9, no. 9 (Sep 2021): 3290-3292,

An evolving body of literature links chemicals commonly found in personal care products (PCPs) to an increased risk of both developing asthma and worsening existing asthma. Phthalates, parabens, environmental phenols, such as triclosan and bisphenol A, and other endocrine-disrupting compounds have been implicated in asthma and related allergic conditions in epidemiological studies. Because Black individuals have increased exposure to these chemicals through hair care products and feminine hygiene products, disproportionate exposure to these chemicals through PCPs could contribute, in part, to the disproportionate asthma prevalence and morbidity among the U.S. Black population. Increased exposure to these chemicals among Black individuals is explained, in part, by more frequent use of hair care products that can contain higher concentrations of these chemicals and greater use of feminine hygiene products, which are also sources of exposure to these chemicals. Epidemiological evidence using urinary biomarkers of exposure demonstrates associations between PCPs and exposure to these chemicals and that the U.S. Black population has greater exposure to these chemicals than the non-Black population. Should chemical exposures through PCPs contribute to the excess burden of asthma among the U.S. Black population, reducing these exposures would reduce this disparity.
http://dx.doi.org/10.1016/j.jaip.2021.04.063

Environmental Pollution to Blame for Depressive Disorder?,
SEGOVIA-MENDOZA M., M. I. PALACIOS-ARREOLA, L. PAVON, L. E. BECERRIL, K. E. NAVA-CASTRO, O. AMADOR-MUNOZ and J. MORALES-MONTOR,
International Journal of Environmental Research and Public Health 19, no. 3 (Feb 2022),
Public concern has emerged about the effects of endocrine-disrupting compounds (EDCs) on neuropsychiatric disorders. Preclinical evidence suggests that exposure to EDCs is associated with the development of major depressive disorder (MDD) and could result in neural degeneration. The interaction of EDCs with hormonal receptors is the best-described mechanism of their biological activity. However, the dysregulation of the hypothalamic-pituitary-gonadal adrenal axis has been reported and linked to neurological disorders. At a worldwide level and in Mexico, the incidence of MDD has recently been increasing. Of note, in Mexico, there are no clinical associations on blood levels of EDCs and the incidence of the MDD. Methodology: Thus, we quantified for the first time the serum levels of parent compounds of two bisphenols and four phthalates in patients with MDD. The levels of di-ethyl-hexyl-phthalate (DEHP), butyl-benzyl-phthalate (BBP), di-n-butyl phthalate (DBP), and di-ethyl-phthalate (DEP), bisphenol A (BPA), and bisphenol S (BPS) in men and women with or without MDD were determined with a gas chromatograph-mass spectrometer. Results/conclusion: We found significant differences between concentrations of BBP between controls and patients with MDD. Interestingly, the serum levels of this compound have a dysmorphic behavior, being much higher in women (~500 ng/mL) than in men (<= 10 ng/mL). We did not observe significant changes in the serum concentrations of the other phthalates or bisphenols tested, neither when comparing healthy and sick subjects nor when they were compared by gender. The results point out that BBP has a critical impact on the etiology of MDD disorder in Mexican patients, specifically in women. http://dx.doi.org/10.3390/ijerph19031737

Maternal occupational exposure to endocrine-disrupting chemicals and urogenital anomalies in the offspring,
SPINDER N., J. E. H. BERGMAN, M. VAN TONGEREN, H. M. BOEZEN, H. KROMHOUT and H. E. K. DE WALLE,
Human Reproduction 37, no. 1 (Jan 2022): 142-151,
STUDY QUESTION: Is there an association between maternal occupational exposure to endocrine-disrupting chemicals (EDCs) early in pregnancy and subgroups of congenital anomalies of kidney and urinary tract (CAKUT), and hypospadias? SUMMARY ANSWER: Exposure to specific EDCs can increase the risk of CAKUT and no association with hypospadias was observed. WHAT IS KNOWN ALREADY: Previous studies showed an association between maternal occupational exposure to EDCs and hypospadias. However, little is known about the effect of these chemicals on the development of CAKUT, especially subgroups of urinary tract anomalies. STUDY DESIGN, SIZE, DURATION: For this case-control study, cases with urogenital anomalies from the European Concerted Action on Congenital Anomalies and Twins Northern Netherlands (Eurocat NNL) registry and non-malformed controls from the Lifelines children cohort (living in the same catchment region as Eurocat NNL) born between 1997 and 2013 were selected. This study included 530 cases with CAKUT, 364 cases with hypospadias, 7 cases with both a urinary tract anomaly and hypospadias and 5602 non-malformed controls. Cases with a genetic or chromosomal anomaly were excluded, and to avoid genetic correlation, we also excluded cases in which a sibling with the same defect was included. PARTICIPANTS/MATERIALS, SETTING, METHODS: Information on maternal occupation held early in pregnancy was collected via self-administered

questionnaires. Job titles were translated into occupational exposure to EDCs using a job-exposure matrix (JEM). Adjusted odds ratios (aORs) and 95% CIs were estimated to assess the association between maternal occupational exposure to EDCs (and to specific types of EDCs) and CAKUT and hypospadias. MAIN RESULTS AND THE ROLE OF CHANCE: For CAKUT and hypospadias, 23.1% and 22.9% of the cases were exposed to EDCs, respectively, whereas 19.8% of the controls were exposed. We found an association between maternal occupational exposure to organic solvents/alkylphenolic compounds and CAKUT (aOR 1.41, 95% CI 1.01-1.97) that became stronger when combinations of urinary tract anomalies co-occurred with other defects (aOR 7.51, 95% CI 2.41-23.43). An association was also observed for exposure to phthalates/benzophenones/parabens/siloxanes and CAKUT (aOR 1.56, 95% CI 1.06-2.29), specifically urinary collecting system anomalies (aOR 1.62, 95% CI 1.03-2.54) and combinations of urinary tract anomalies (aOR 2.90, 95% CI 1.09-7.71). We observed no association between EDC exposure and hypospadias. LIMITATIONS, REASONS FOR CAUTION: The different study designs of Eurocat NNL and Lifelines could have introduced differential information bias. Also, exposure misclassification could be an issue: it is possible that the actual exposure differed from the exposure estimated by the JEM. In addition, women could also have been exposed to other exposures not included in the analysis, which could have resulted in residual confounding by co-exposures. WIDER IMPLICATIONS OF THE FINDINGS: Women, their healthcare providers, and their employers need to be aware that occupational exposure to specific EDCs early in pregnancy may be associated with CAKUT in their offspring. An occupational hygienist should be consulted in order to take exposure to those specific EDCs into consideration when risk assessments are carried out at the workplace. STUDY FUNDING/COMPETING INTEREST(S): N.S. was paid by the Graduate School of Medical Sciences (MD/PhD programme), University Medical Center Groningen (UMCG), Groningen, the Netherlands. Eurocat Northern Netherlands is funded by the Dutch Ministry of Health, Welfare and Sports. The Lifelines Biobank initiative has been made possible by subsidy from the Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, the University Medical Center Groningen (UMCG the Netherlands), University Groningen and the Northern Provinces of the Netherlands. The authors report no conflict of interest. http://dx.doi.org/10.1093/humrep/deab205

The Potential Relationship Between Environmental Endocrine Disruptor Exposure and the Development of Endometriosis and Adenomyosis,
STEPHENS V. R., J. T. RUMPH, S. AMELI, K. L. BRUNER-TRAN and K. G. OSTEEN,
Frontiers in Physiology 12 (Jan 2022),
Women with endometriosis, the growth of endometrial glands and stroma outside the uterus, commonly also exhibit adenomyosis, the growth of endometrial tissues within the uterine muscle. Each disease is associated with functional alterations in the eutopic endometrium frequently leading to pain, reduced fertility, and an increased risk of adverse pregnancy outcomes. Although the precise etiology of either disease is poorly understood, evidence suggests that the presence of endometriosis may be a contributing factor to the subsequent development of adenomyosis as a consequence of an altered, systemic inflammatory response. Herein, we will discuss the potential role of exposure to environmental toxicants with endocrine disrupting capabilities in the pathogenesis of both endometriosis and adenomyosis. Numerous epidemiology and experimental studies support a role for environmental endocrine disrupting chemicals (EDCs) in the development of endometriosis; however, only a few studies have examined the potential relationship between toxicant exposures and the risk of adenomyosis. Nevertheless, since women with endometriosis are also frequently found to have adenomyosis, discussion of EDC exposure and development of each of these diseases is relevant. We will discuss the potential mechanisms by which EDCs may act to promote the co-development of endometriosis and adenomyosis. Understanding the disease-promoting mechanisms of environmental toxicants related to endometriosis and adenomyosis is paramount to designing more effective treatment(s) and preventative strategies. http://dx.doi.org/10.3389/fphys.2021.807685

Interrelationships among growth hormone, thyroid function, and endocrine-disrupting chemicals on the susceptibility to attention-deficit/hyperactivity disorder,
WANG L. J., Y. H. HUANG, W. J. CHOU, S. Y. LEE, H. Y. CHANG, C. C. CHEN and H. R. CHAO,
European Child & Adolescent Psychiatry (Abnormal growth hormones and thyroid function may be linked to pathophysiology of attention-deficit/hyperactivity disorder (ADHD). Phthalates and bisphenol-A (BPA), two endocrine-disrupting chemicals (EDCs), may affect the human endocrine system. In this study, we aimed to perform a comprehensive investigation of whether growth hormone, thyroid function, and EDCs exhibited differential levels between ADHD patients and healthy controls. In total, 144 children with ADHD and 70 healthy

control subjects were enrolled. Their endocrine systems were evaluated using the serum levels of insulin-like growth factor-1 (IGF-1), IGF-binding protein-3 (IGFBP-3), thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), and Free T4. The urinary levels of EDCs, including monoethyl phthalate (MEP), mono-methyl phthalate (MMP), monoethylhexyl phthalate (MEHP), mono-n-butyl phthalate (MnBP), monobenzyl phthalate (MBzP), and BPA, were also examined. Patients with ADHD had lower IGF-1 levels than healthy controls ($p = 0.003$), but we observed no significant difference in IGFBP-3, TSH, T3, T4, or Free T4. Compared to the control group, patients with ADHD demonstrated higher MEHP levels ($p = 0.043$), MnBP ($p = 0.033$), and MBzP ($p = 0.040$). Furthermore, MEHP levels ($p < 0.001$) and BPA levels ($p = 0.041$) were negatively correlated with IGF-1 levels, while IGF-1 levels were negatively correlated with principal components consisting of ADHD clinical symptoms and neuropsychological performance variables. We suggest that MEHP exposure may be associated with decreased serum levels of IGF-1 and increased risk of ADHD. The mechanism underlying this association may be important for protecting children from environmental chemicals that adversely affect neurodevelopment. http://dx.doi.org/10.1007/s00787-021-01886-4

Sex differences in the association of measures of sexual maturation to common toxicants: Lead, dichloro-diphenyl-trichloroethane (DDT), dichloro-diphenyl-dichloroethylene (DDE), and polychlorinated biphenyls (PCBs),
WEST C. N., L. M. SCHELL and M. V. GALLO,
Annals of Human Biology 48, no. 6 (Aug 2021): 485-502,
Many studies of human toxicant exposure examine the hypothesis that human sexual maturation can be affected through endocrine disruption. Within this body of literature there is significant variation in the findings. Variation may be related to the differential effects by toxicants between males and females as well as variation in sample size, toxicant levels, and the timing of exposure. We review sexual maturation outcomes between males and females when exposed to lead, dichlorodiphenyldichloroethylene (DDE), dichloro-diphenyl-trichloroethane (DDT), and polychlorinated biphenyls (PCBs) using a systematic process to gather peer-reviewed studies published from January 1994 through December 2019 on the NCBI website's PubMed search engine. The review includes 34 studies, some comprised of multiple analyses, to compare effects on sexual maturation by sex. The analysis shows that both boys and girls have delayed sexual maturation in relation to lead exposure. There are differences in the direction of effects associated with DDE/DDT and PCB exposure in boys and girls. PCBs exist as congeners of many structural forms, and that variation is considered in this review. Dioxin-like and non-dioxin-like PCBs exposure directionality differed between boys and girls as well. Future investigations into the basis of sex variation in DDE/DDT and PCB relationships to sexual maturation are warranted.
http://dx.doi.org/10.1080/03014460.2021.1998623

Prenatal exposure to organochlorine pesticides and infant growth: A longitudinal study,
YANG C. H., J. FANG, X. J. SUN, W. X. ZHANG, J. X. LI, X. M. CHEN, L. YU, W. XIA, S. Q. XU, Z. W. CAI and Y. Y. LI,
Environment International 148 (Mar 2021),
Background: The association between exposure to organochlorine pesticides (OCPs) and infant growth has been reported contradictorily in previous studies. Few studies have investigated the effects of prenatal exposure to OCPs on infant growth assessed longitudinally at multiple time points. Objectives: The purpose of the study was to examine the associations between prenatal exposure to OCPs and infant growth at birth, 6, 12 and 24 months of age, and further to explore the potential sex-specific effects. Methods: The study population included 1039 mother-infant pairs who participated in a birth cohort study in Wuhan, China. The weight, length and body mass index (BMI) z-score of infants were measured and calculated at birth, 6, 12 and 24 months of age. The overweight status was defined as BMI z-score >= 85th percentile according to the standard of World Health Organization. The concentrations of OCPs were measured in cord serum, including hexachlorocyclohexanes (HCHs, consisted of alpha-HCH, beta-HCH, and gamma-HCH), p,p'-dichlorodiphenyltrichloroethane (p,p' -DDT) and its metabolites: p,p' -dichlorodiphenyldichloroethane (p,p' -DDD), and p,p'dichlorodiphenyldichloroethylene (p,p'-DDE). Generalized linear models were applied to estimate the associations of cord OCPs with infant growth parameters. A group-based semiparametric mixture model was used to estimate growth patterns of infants. Linear-mixed growth curve models were used to examine relationships between predicted growth trajectories and prenatal exposure to OCPs. Weighted quantile sum regression (WQSR) analyses were used to estimate the mixture effects of OCPs on infant growth. Results: Higher cord serum beta-HCH concentrations were associated with higher BMI z-score at 12 [ss = 0.07, 95% CI: 0.01, 0.13] and 24 months of age [beta = 0.08, 95% CI: 0.02, 0.14]. Similar patterns were observed for relationships of.-HCH [beta = 0.04, 95%CI: 0.01, 0.07] and p,p'-DDT

[beta = 0.03, 95% CI: 0.00, 0.06] with BMI z-score at 6 and 12 months of age, respectively. However, higher cord serum p,p' -DDE concentrations were associated with a reduction of BMI z-score at 6 months of age [beta = 0.07, 95% CI: 0.12, 0.01]. Cord serum beta-HCH was also positively associated with the risk of overweight at 12 months of age [RR = 1.16, 95% CI (1.02, 1.33), for the medium vs the lowest tertile]. Among girls, the effects of beta-HCH on BMI z-score and overweight status were stronger than boys at 12 and 24 months of age. No statistically significant relationships of other OCPs with infant growth were observed. Conclusions: Prenatal exposure to beta-HCH was associated with increased BMI z-score and higher risk of overweight status in infants especially at 12 and 24 months of age, which seemed to be stronger in girls.
http://dx.doi.org/10.1016/j.envint.2020.106374

Grandmothers' endocrine disruption during pregnancy, low birth weight, and preterm birth in third generation,
YIM G., A. ROBERTS, D. WYPIJ, M. A. KIOUMOURTZOGLOU and M. G. WEISSKOPF,
International Journal of Epidemiology 50, no. 6 (Dec 2021): 1886-1896,
Background: Diethylstilbestrol (DES) is an endocrine-disrupting pharmaceutical prescribed to pregnant women to prevent pregnancy complications between the 1940s and 1970s. Although DES has been shown in animal studies to have multigenerational effects, only two studies have investigated potential multigenerational effects in humans on preterm birth (PTB), and none on low birthweight (LBW)-major determinants of later life health. Methods: Nurses' Health Study (NHS) II participants (G1; born 1946-64) reported their mothers' (G0) use of DES while pregnant with them. We used cluster-weighted generalized estimating equations to estimate odds ratios (OR) and 95% confidence intervals (CI) for risk of LBW and PTB among the grandchildren by grandmother use of DES. G1 birth-weight and gestational age were considered to explore confounding by indication. Results: Among 54 334 G0-G1/grandmother-mother pairs, 973 (1.8%) G0 used DES during pregnancy with G1. Of the 128 275 G2 children, 4369 (3.4%) were LBW and 7976 (6.2%) premature. Grandmother (G0) use of DES during pregnancy was associated with an increased risk of G2 LBW [adjusted OR (aOR) = 3.09; 95% CI: 2.57, 3.72], that was reduced when restricted to term births (aOR = 1.59; 95% CI: 1.08, 2.36). The aOR for PTB was 2.88 (95% CI: 2.46, 3.37). Results were essentially unchanged when G1 birthweight and gestational age were included in the model, as well as after adjusting for other potential intermediate variables, such as G2 pregnancy-related factors. Conclusions: Grandmother use of DES during pregnancy is associated with an increased risk of LBW, predominantly through an increased risk of PTB. Results when considering G1 birth outcomes suggest this does not result from confounding by indication. http://dx.doi.org/10.1093/ije/dyab065

Toxicité sur l'homme

Comprehensive review of the impact of tris(2,3-dibromopropyl) isocyanurate (TBC or TDBP-TAZTO) on living organisms and the environment,
BAR M. and K. A. SZYCHOWSKI,
Environmental Geochemistry and Health (Tris(2,3-dibromopropyl) isocyanurate (TBC or TDBP-TAZTO) belongs to the group of brominated flame retardants (BFRs). The production of this compound is increasing due to the growing demand and wide application in electrical, electronic, musical instrument, and automotive component industries. The properties of TBC, e.g., the high octanol-air partition coefficient (Koa), high octanol-water partition coefficient (Kow), and high bioconcentration factor (BCF), indicate a possibility of its spread in aquatic and terrestrial ecosystems and bioaccumulation in living organisms. The presence of TBC has been confirmed in soil, sediments, river water, and such materials as microplastic, curtains, and e-waste devices. The compound has potential to bioaccumulate in the food chain of living organisms. TBC has been demonstrated to exert a harmful effect mainly on the nervous and endocrine systems, lungs, and liver. The possible mechanism of toxicity of the compound in the nervous system is based on the generation of oxidative stress by TBC leading to apoptosis of neuronal cells, while mitochondrial damage is considered to be responsible for changes in the respiratory organ. Moreover, the potential of mussels and earthworms to be bioindicators of TBC has been proven. Therefore, the literature review is focused on TBC properties and analysis of the identification and impact of the compound on the environment, living organisms, and human cell lines. Given the many toxic effects of TBC highlighted in the literature, there is a need for more profound research on the safety of TBC and methods for identification and

degradation of this compound. http://dx.doi.org/10.1007/s10653-022-01206-y

Estrogens-Origin of Centrosome Defects in Human Cancer?,
BUEHLER M. and A. STOLZ,
Cells 11, no. 3 (Feb 2022),
Estrogens are associated with a variety of diseases and play important roles in tumor development and progression. Centrosome defects are hallmarks of human cancers and contribute to ongoing chromosome missegragation and aneuploidy that manifest in genomic instability and tumor progression. Although several mechanisms underlie the etiology of centrosome aberrations in human cancer, upstream regulators are hardly known. Accumulating experimental and clinical evidence points to an important role of estrogens in deregulating centrosome homeostasis and promoting karyotype instability. Here, we will summarize existing literature of how natural and synthetic estrogens might contribute to structural and numerical centrosome defects, genomic instability and human carcinogenesis. http://dx.doi.org/10.3390/cells11030432

In vitro and in silico approach to study the hormonal activities of the alternative plasticizer tri-(2-ethylhexyl) trimellitate TEHTM and its metabolites,
DAHBI L., A. FARCE, N. KAMBIA, I. SEVERIN, T. DINE, E. MOREAU, V. SAUTOU and M. C. CHAGNON,
Archives of Toxicology 96, no. 3 (Mar 2022): 899-918,
Tri-(2-ethylhexyl) trimellitate (TEHTM) is a plasticizer for polyvinyl chloride (PVC) material used in medical devices. It is an alternative to di-(2-ethylhexyl) phthalate (DEHP), a well-known reprotoxic and endocrine disruptor. As plasticizers are known to easily migrate when in contact with fatty biological fluids, patient exposure to TEHTM is highly probable. However, there is currently no data on the potential endocrine-disrupting effects of its human metabolites. To evaluate the effects of TEHTM metabolites on endocrine activity, they were first synthesized and their effects on estrogen, androgen and thyroid receptors, as well as steroid synthesis, were investigated by combining in vitro and in silico approaches. Among the primary metabolites, only 4-MEHTM (4-mono-(2-ethylhexyl) trimellitate) showed agonist activities on ERs and TRs, while three diesters were TR antagonists at non-cytotoxic concentrations. These results were completed by docking experiments which specified the ER and TR isoforms involved. A mixture of 2/1-MEHTM significantly increased the estradiol level and reduced the testosterone level in H295R cell culture supernatants. The oxidized secondary metabolites of TEHTM had no effect on ER, AR, TR receptors or on steroid hormone synthesis. Among the fourteen metabolites, these data showed that two of them (4-MEHTM and 2/1-MEHTM) induced effect on hormonal activities in vitro. However, by comparing the concentrations of the primary metabolites found in human urine with the active concentrations determined in bioassays, it can be suggested that the metabolites will not be active with regard to estrogen, androgen, thyroid receptors and steroidogenesis-mediated effects.
http://dx.doi.org/10.1007/s00204-022-03230-4

The Environmental Pollutant Bromophenols Interfere With Sulfotransferase That Mediates Endocrine Hormones,
DAI Z. H., F. R. ZHAO, Y. LI, J. XU and Z. Y. LIU,
Frontiers in Endocrinology 12 (Jan 2022),
Bromophenols (BPs), known as an important environmental contaminant, can cause endocrine disruption and other chronic toxicity. The study aimed to investigate the potential inhibitory capability of BPs on four human sulfotransferase isoforms (SULT1A1, SULT1A3, SULT1B1 and SULT1E1) and interpret how to interfere with endocrine hormone metabolism. P-nitrophenol(PNP) was utilized as a nonselective probe substrate, and recombinant SULT isoforms were utilized as the enzyme resources. PNP and its metabolite PNP-sulfate were analyzed using a UPLC-UV detecting system. SULT1A1 and SULT1B1 were demonstrated to be the most vulnerable SULT isoforms towards BPs' inhibition. To determine the inhibition kinetics, 2,4,6-TBP and SULT1A3 were selected as the representative BPs and SULT isoform respectively. The competitive inhibition of 2,4,6-TBP on SULT1A3. The fitting equation was y=90.065x+1466.7, and the inhibition kinetic parameter (K-i) was 16.28 mu M. In vitro-in vivo extrapolation (IVIVE) showed that the threshold concentration of 2,4,6-TBP to induce inhibition of SULT1A3 was 1.628 mu M. In silico docking, the method utilized indicated that more hydrogen bonds formation contributed to the stronger inhibition of 3,5-DBP than 3-BP. In conclusion, our study gave the full description of the inhibition of BPs towards four SULT isoforms, which may provide a new perspective on the toxicity mechanism of BPs and further explain the interference of BPs on endocrine hormone metabolism.
http://dx.doi.org/10.3389/fendo.2021.814373

The potential implications of estrogenic and antioxidant-dependent activities of high doses of methyl paraben on MCF7 breast cancer cells,
ELSEHLY W. M., G. M. MOURAD, R. A. MEHANNA, M. A. KHOLIEF, N. A. EL-NIKHELY, A. K. AWAAD and M. H. ATTIA,
Journal of Biochemical and Molecular Toxicology (Methyl paraben (MP) is an endocrine-disrupting compound that possesses estrogenic properties and contributes to an aberrant burden of estrogen signaling in the human breast and subsequently increasing the risks for the development of breast cancer. The exact exposure, as well as the safe concentrations, are variable among daily products. The present study addresses the effects of exposure to escalated concentrations of MP on the proliferation of MCF-7 breast cancer cells in addition to exploring its other mechanisms of action. The study involved exposure of cultured MCF-7 breast cancer cells to seven MP concentrations, ranging from 40 to 800 mu M for 5 days. Cell viability, apoptosis, and proliferation were respectively assessed using crystal violet test, flow cytometric analysis, and quantitative real-time polymerase chain reaction for Ki-67 expression. The estradiol (E2) secretion and oxidative stress were also assessed and analyzed in correlation to MP's proliferation and cytotoxicity potentials. The results showed that the maximum proliferative concentration of MP was 800 mu M. At a concentration of 40 mu M and higher, MP induced increased expression of Ki-67, denoting enhanced proliferation of the cells in monolayer culture. A positive correlation between the detrimental oxidative stress effect of MP's tested concentrations, cell proliferation, and viability was demonstrated ($p < 0.05$). Our results indicated that MP at high doses induced sustained cell proliferation due to E2 secretion as well as its antioxidant activity. Accordingly, it was concluded that high and unpredicted exposure to MP might carry a carcinogenic hazard on estrogen receptor-positive breast cancer cells. http://dx.doi.org/10.1002/jbt.23012

Pregnant Women and Endocrine Disruptors: Role of P2X7 Receptor and Mitochondrial Alterations in Placental Cell Disorders,
FOUYET S., E. OLIVIER, P. LEPROUX, M. DUTOT and P. RAT,
Cells 11, no. 3 (Feb 2022),
In pregnant women, the lungs, skin and placenta are exposed daily to endocrine-disrupting chemicals (EDCs). EDCs induce multiple adverse effects, not only on endocrine organs, but also on non-endocrine organs, with the P2X7 cell death receptor being potentially the common key element. Our objective was first to investigate mechanisms of EDCs toxicity in both endocrine and non-endocrine cells through P2X7 receptor activation, and second, to compare the level of activation in lung, skin and placental cells. In addition, apoptosis in placental cells was studied because the placenta is the most exposed organ to EDCs and has essential endocrine functions. A total of nine EDCs were evaluated on three human cell models. We observed that the P2X7 receptor was not activated by EDCs in lung non-endocrine cells but was activated in skin and placenta cells, with the highest activation in placenta cells. P2X7 receptor activation and apoptosis are pathways shared by all tested EDCs in endocrine placental cells. P2X7 receptor activation along with apoptosis induction could be key elements in understanding endocrine placental and skin disorders induced by EDCs.
http://dx.doi.org/10.3390/cells11030495

Prenatal exposure to the phthalate DEHP impacts reproduction-related gene expression in the pituitary,
GE X. Y., K. WEIS, J. FLAWS and L. RAETZMAN,
Reproductive Toxicology 108 (Mar 2022): 18-27,
Phthalates are chemicals used in products including plastics, personal care products, and building materials, leading to widespread contact. Previous studies on prenatal exposure to Di-(2-ethylhexyl) phthalate (DEHP) in mice and humans demonstrated pubertal timing and reproductive performance could be affected in exposed offspring. However, the impacts at the pituitary, specifically regarding signaling pathways engaged and direct effects on the gonadotropins LH and FSH, are unknown. We hypothesized prenatal exposure to DEHP during a critical period of embryonic development (e15.5 to e18.5) will cause sex-specific disruptions in reproduction-related mRNA expression in offspring's pituitary due to interference with androgen and aryl hydrocarbon receptor (AhR) signaling. We found that prenatal DEHP exposure in vivo caused a significant increase in Fshb specifically in males, while the anti-androgen flutamide caused significant increases in both Lhb and Fshb in males. AhR target gene Cyp1b1 was increased in both sexes in DEHP-exposed offspring. In embryonic pituitary cultures, the DEHP metabolite MEHP increased Cyp1a1 and Cyp1b1 mRNA in both sexes and Cyp1b1 induction

was reduced by co-treatment with AhR antagonist. AhR reporter assay in GHFT1 cells confirmed MEHP can activate AhR signaling. Lhb, Fshb and Gnrhr mRNA were significantly decreased in both sexes by MEHP, but cotreatment with AhR antagonist did not restore mRNA levels in pituitary culture. In summary, our data suggest phthalates can directly affect the function of the pituitary by activating AhR signaling and altering gonadotropin expression. This indicates DEHP's impacts on the pituitary could contribute to reproductive dysfunctions observed in exposed mice and humans. http://dx.doi.org/10.1016/j.reprotox.2021.12.008

Comparative Neurodevelopment Effects of Bisphenol A and Bisphenol F on Rat Fetal Neural Stem Cell Models,
GILL S. and V. M. R. KUMARA,
Cells 10, no. 4 (Apr 2021),
Bisphenol A (BPA) is considered as one of the most extensively synthesized and used chemicals for industrial and consumer products. Previous investigations have established that exposure to BPA has been linked to developmental, reproductive, cardiovascular, immune, and metabolic effects. Several jurisdictions have imposed restrictions and/or have banned the use of BPA in packaging material and other consumer goods. Hence, manufacturers have replaced BPA with its analogues that have a similar chemical structure. Some of these analogues have shown similar endocrine effects as BPA, while others have not been assessed. In this investigation, we compared the neurodevelopmental effects of BPA and its major replacement Bisphenol F (BPF) on rat fetal neural stem cells (rNSCs). rNSCs were exposed to cell-specific differentiation media with non-cytotoxic doses of BPA or BPF at the range of 0.05 mu M to 100 mu M concentrations and measured the degree of cell proliferation, differentiation, and morphometric parameters. Both of these compounds increased cell proliferation and impacted the differentiation rates of oligodendrocytes and neurons, in a concentration-dependent manner. Further, there were concentration-dependent decreases in the maturation of oligodendrocytes and neurons, with a concomitant increase in immature oligodendrocytes and neurons. In contrast, neither BPA nor BPF had any overall effect on cellular proliferation or the cytotoxicity of astrocytes. However, there was a concentration-dependent increase in astrocyte differentiation and morphological changes. Morphometric analysis for the astrocytes, oligodendrocytes, and neurons showed a reduction in the arborization. These data show that fetal rNSCs exposed to either BPA or BPF lead to comparable changes in the cellular differentiation, proliferation, and arborization processes. http://dx.doi.org/10.3390/cells10040793

Benzo a pyrene impairs the migratory pattern of human gonadotropin-releasing-hormone-secreting neuroblasts,
GUARNIERI G., M. BECATTI, P. COMEGLIO, L. VIGNOZZI, M. MAGGI, G. B. VANNELLI and A. MORELLI,
European Journal of Histochemistry 65 (2021),
Benzo[a]pyrene (BaP) is a widespread pollutant that can act as an endocrine disrupting compound (EDC) and interferes with reproductive function. The central regulatory network of the reproductive system is mediated by gonadotropin-releasing hormone (GnRH) neurons, which originate in the olfactory placode and, during ontogenesis, migrate into the hypothalamus. Given the importance of the migratory process for GnRH neuron maturation, we investigated the effect of BaP (10 mu M for 24 h) on GnRH neuroblasts isolated from the human fetal olfactory epithelium (FNCB4). BaP exposure significantly reduced the mRNA level of genes implicated in FNCB4 cell migration and affected their migratory ability. Our findings demonstrate that BaP may interfere with the central neuronal network controlling human reproduction affecting GnRH neuron maturation.
http://dx.doi.org/10.4081/ejh.2021.3282

Linking bisphenol potential with deleterious effect on immune system: a review,
JAIN R., A. JAIN, S. JAIN, S. S. THAKUR and S. K. JAIN,
Nucleus-India (Bisphenol A (BPA) environmental exposure during the life stage of an organism can influence immune cell development and may cause disease in later life. The harmful health impacts of BPA exposure pinpoint multiple mechanisms for BPA-induced toxicity, further exacerbated by reports of a biphasic response. BPA exposure and its chronic negative consequences, as well as their links to endocrine disruption and epigenetic changes, reveal that shifts in DNA methylation patterns, histone modifications, and microRNA alteration modify the epigenome in a tissue-specific manner. BPA has immunotoxic properties observed during in vitro and in vivo studies. It is reported that BPA exhibits adverse health effects due to immunotoxicity, which may lead to immune disorders. In vitro and in vivo study confirms that bisphenol impairs both innate and

adaptive immune mechanism which in turn interferes with cellular and humoral activities. The present review focus upon BPA mediated disturbances in the immune system including immune cells development, inflammation, its related pathways and ability to impair mature immune system.
http://dx.doi.org/10.1007/s13237-022-00383-6

Effects of Endocrine Disruptors o,p '-Dichlorodiphenyltrichloroethane, p,p '-Dichlorodiphenyltrichloroethane, and Endosulfan on the Expression of Estradiol-, Progesterone-, and Testosterone-Responsive MicroRNAs and Their Target Genes in MCF-7 Cells,
KALININA T., V. KONONCHUK, L. KLYUSHOVA and L. GULYAEVA,
Toxics 10, no. 1 (Jan 2022),
Many studies have shown that dichlorodiphenyltrichloroethane (DDT) exposure raises breast cancer risk. Another insecticide with similar properties is endosulfan, which has been actively used in agriculture after DDT prohibition. Previously, we have identified some estradiol-, progesterone-, and testosterone-sensitive microRNAs (miRNAs, miRs). Because DDT and endosulfan have estrogenic, antiandrogenic, and antiprogesterone properties, we hypothesized that these miRNAs are affected by the insecticides. We quantified relative levels of miRNAs and expression levels of their target genes in breast cancer MCF-7 cells treated with p,p '-DDT, o,p '-DDT, or endosulfan. We also quantified miR-19b expression, which, as previously shown, is regulated by estrogen. Here, we observed that miR-19b expression increased in response not only to estradiol but also to testosterone and progesterone. Treatment of MCF-7 cells with p,p '-DDT or endosulfan decreased the protein levels of apoptosis regulators TP53INP1 and APAF1. In cells treated with o,p '-DDT, the TP53INP1 amount decreased after 24 h of incubation, but increased after 48 h of incubation with insecticide. OXTR expression, which is known to be associated with breast carcinogenesis, significantly diminished under the exposure of all insecticides. In cells treated with p,p '-DDT or o,p '-DDT, the observed changes were accompanied by alterations of the levels of hormone-responsive miRNAs: miR-324, miR-190a, miR-190b, miR-27a, miR-193b, and miR-19b. http://dx.doi.org/10.3390/toxics10010025

The effect of endocrine disrupting chemicals on the vitronectin-receptor (integrin alpha(v)beta(3))-mediated cell adhesion of human umbilical vein endothelial cells,
KENDA M., U. P. FONOVIC, J. KOS and M. S. DOLENC,
Toxicology in Vitro 79 (Mar 2022),
Endocrine disrupting chemicals (EDCs) are associated with cancer development and progression due to their promotion of increased cell invasiveness and metastasis formation. However, the effects of EDCs on cell adhesion mediated through integrins have not been well studied to date. Their actions are implicated by binding sites for hormones on the vitronectin receptor (VTNR; or integrin alpha(v)beta(3)), which is involved in tumor angiogenesis and metastasis. VTNR-expressing human umbilical vein endothelial cells (HUVECs) were used to determine the effects of EDCs and endogenous hormones on cell adhesion to vitronectin-coated surfaces, and on VTNR activation. Cell adhesion was significantly increased for bisphenol A, triclocarban, and triclosan (10, 100 nM; $p < 0.05$), with similar trends for bisphenols AF and S (10, 100 nM; $p > 0.05$). No changes in cell adhesion were seen for 5 alpha-dihydrotestosterone, 17 beta-estradiol, triiodothyronine, imatinib and paroxetine. These data indicate that EDC-mediated increases in HUVEC adhesion to vitronectin are not mediated through androgenic, estrogenic, or thyroid activities, nor through activation of VTNR. Although these effects of EDCs on HUVEC adhesion require further investigation of the underlying mechanism(s) of action to define their biological relevance, the low-dose effects and nonmonotonic responses revealed here define the need for further investigation of these EDCs. http://dx.doi.org/10.1016/j.tiv.2021.105275

Effects of triclosan exposure on placental extravillous trophoblast motility, relevant IGF2/H19 signaling and DNA methylation-related enzymes of HTR-8/SVneo cell line,
MA R., N. TANG, L. P. FENG, X. WANG, J. W. ZHANG, X. REN, Y. T. DU and F. X. OUYANG,
Ecotoxicology and Environmental Safety 228 (Dec 2021),
Triclosan (TCS) is an antimicrobial agent widely used in personal care products and a potential endocrine disruptor chemical (EDC). TCS can pass through the placental barrier. Any influence of EDCs on epigenetic changes of placenta and embryo may bring profound impact on later health. This study aimed to investigate the effects of TCS exposure on cell proliferation and migration, and the expression of imprinted genes IGF2/H19 and DNA methylation-related enzymes in human placental extravillous trophoblast cell line HTR-8/SVneo. After

exposure to TCS levels of 0 (DMSO Control), 10(-11), 10(-18), 10(-9), 10(-8), 10(-7), 10(-6), 10(-5), 3 x 10(-5), 6 x 10(-5), 10(-4) M and incubated for up to 36 h, cell proliferation and migration were examined by CCK-8, EdU incorporation assay and wound healing assay; the mRNA levels of IGF2, H19, DNA methyltransferases (Dnmt3a, Dnmt3b and Dnmt1), ten-eleven translocation enzymes (Tet1, Tet2 and Tet3) and IGF2 Receptor (IGF2R) were analyzed by qRT-PCR. The protein levels of IGF2 were measured by Western blot and ELISA. The cell viability turned to decline at TCS treatment of 3 x 10(-5) M and above (all $p < 0.05$, compared to the DMSO Control). The cell migration decreased at TCS 10(-5) and 3 x 10(-5) M treatment ($p < 0.05$), but consistently unchanged at low dose of TCS from 10(-9) to 10(-7) M ($p > 0.05$). TCS treatments below cytotoxicity doses (< 10(-5) M) did not significantly alter the mRNA levels of IGF2, Dnmt1, Dnmt3a, Dnmt3b, Tet1, Tet2 and Tet3, compared to DMSO Control treatment (all $p > 0.05$). The transcription level of H19 was up-regulated by TCS at 3 x 10(-5) M. TCS at 10(-7) and 6 x 10(-5) M increased the protein level of IGF2 in cell supernatant. Our data suggest that high TCS exposure may suppress HTR-8/SVneo cells viability and migration, increase H19 gene expressions and IGF2 protein secretion. The exact mechanism of TCS action in human trophoblast needs further studies.
http://dx.doi.org/10.1016/j.ecoenv.2021.113051

Impact of bisphenol A (BPA) on cells and tissues at the human materno-fetal interface,
MANZAN-MARTINS C. and L. PAULESU,
Tissue & Cell 73 (Dec 2021),
Bisphenol A (BPA) is an endocrine disruptor extensively used in the production of polycarbonate plastics and epoxy resins and a component of liquid and food containers. It is a hazard in the prenatal period because of its presence in the placenta, fetal membranes, amniotic fluid, maternal and fetal blood and its ability to cross the placenta and reach the fetus. Estimation of the risk of BPA exposure during in utero life is extremely important in order to prevent complications of pregnancy and fetal growth. This review describes in vitro models of the human materno-fetal interface. It also outlines the effects of BPA at doses indicated as "physiological", namely at the concentrations found in the general population, and at "supraphysiological" and "subphysiological" doses, i.e. above and below the physiological range. This work will help clarify the discrepancies observed in studies on the effects of BPA on human reproduction and pregnancy, and it will be useful for the choice of appropriate in vitro models for future studies aimed at identifying the potential impact of BPA on specific functional processes.
http://dx.doi.org/10.1016/j.tice.2021.101662

Impacts of endocrine disrupting chemicals on reproduction in wildlife and humans,
MARLATT V. L., S. BAYEN, D. CASTANEDA-CORTES, G. DELBES, P. GRIGOROVA, V. S. LANGLOIS, C. J. MARTYNIUK, C. D. METCALFE, L. PARENT, A. RWIGEMERA, P. THOMSON and G. VAN DER KRAAK,
Environmental Research 208 (May 2022),
Endocrine disrupting chemicals (EDCs) are ubiquitous in aquatic and terrestrial environments. The main objective of this review was to summarize the current knowledge of the impacts of EDCs on reproductive success in wildlife and humans. The examples selected often include a retrospective assessment of the knowledge of reproductive impacts over time to discern how the effects of EDCs have changed over the last several decades. Collectively, the evidence summarized here within reinforce the concept that reproduction in wildlife and humans is negatively impacted by anthropogenic chemicals, with several altering endocrine system function. These observations of chemicals interfering with different aspects of the reproductive endocrine axis are particularly pronounced for aquatic species and are often corroborated by laboratory-based experiments (i.e. fish, amphibians, birds). Noteworthy, many of these same indicators are also observed in epidemiological studies in mammalian wildlife and humans. Given the vast array of reproductive strategies used by animals, it is perhaps not surprising that no single disrupted target is predictive of reproductive effects. Nevertheless, there are some general features of the endocrine control of reproduction, and in particular, the critical role that steroid hormones play in these processes that confer a high degree of susceptibility to environmental chemicals. New research is needed on the implications of chemical exposures during development and the potential for long-term reproductive effects. Future emphasis on field-based observations that can form the basis of more deliberate, extensive, and long-term population level studies to monitor contaminant effects, including adverse effects on the endocrine system, are key to addressing these knowledge gaps.
http://dx.doi.org/10.1016/j.envres.2021.112584

Extravillous trophoblast migration and invasion: Impact of environmental chemicals and

pharmaceuticals,
MEAKIN C., E. S. BARRETT and L. M. ALEKSUNES,
Reproductive Toxicology 107 (Jan 2022): 60-68,
During pregnancy, the migration and invasion of extravillous trophoblasts (EVTs) into the maternal uterus is essential for proper development of the placenta and fetus. During the first trimester, EVTs engraft and remodel maternal spiral arteries allowing for efficient blood flow and the transfer of essential nutrients and oxygen to the fetus. Aberrant migration of EVTs leading to either shallow or deep invasion into the uterus has been implicated in a number of gestational pathologies including preeclampsia, fetal growth restriction, and placenta accreta spectrum. The migration and invasion of EVTs is well-coordinated to ensure proper placentation. However, recent data point to the ability of xenobiotics to disrupt EVT migration. These xenobiotics include heavy metals, endocrine disrupting chemicals, and organic contaminants and have often been associated with adverse pregnancy outcomes. In most instances, xenobiotics appear to reduce EVT migration; however, there are select examples of enhanced motility after chemical exposure. In this review, we provide an overview of the 1) current experimental approaches used to evaluate EVT migration and invasion in vitro, 2) ability of environmental chemicals and pharmaceuticals to enhance or retard EVT motility, and 3) signaling pathways responsible for altered EVT migration that are sensitive to disruption by xenobiotics.
http://dx.doi.org/10.1016/j.reprotox.2021.11.008

Ortho-substituted PCB 153: effects in CHO-K1 cells,
MILETIC M., T. MURATI, B. SIMIC, N. BILANDZIC, A. BROZOVIC and I. KMETIC,
Arhiv Za Higijenu Rada I Toksikologiju-Archives of Industrial Hygiene and Toxicology 72, no. 4 (Dec 2021): 326-332,
Non-planar di-ortho-substituted PCB 153 (2,2',4,4',5,5'-hexachlorobiphenyl), one of the most abundant PCB congeners in the environment and in biological and human tissues, has been identified as potential endocrine disruptor affecting the reproductive and endocrine systems in rodents, wildlife, and humans. The aim of this study was to gain a deeper insight into its mode/mechanism of action in Chinese hamster ovary K1 cells (CHO-K1). PCB 153 (10-100 mu mol/L) inhibited CHO-K1 cell proliferation, which was confirmed with four bioassays (Trypan Blue, Neutral Red, Kenacid Blue, and MTT), of which the MTT assay proved the most sensitive. PCB 153 also induced ROS formation in a dose-dependent manner. Apoptosis was seen after 6 h of exposure to PCB 153 doses >= 50 mu mol/L, while prolonged exposure resulted in the activation of the necrotic pathway. PCB 153-induced disturbances in normal cell cycle progression were time-dependent, with the most significant effects occurring after 72 h. http://dx.doi.org/10.2478/aiht-2021-72-3588

Long-term in vitro exposure of human granulosa cells to the mixture of endocrine disrupting chemicals found in human follicular fluid disrupts steroidogenesis,
NENADOV D. S., B. TESIC, S. FA, K. POGRMIC-MAJKIC, D. KOKAI, B. STANIC and N. ANDRIC,
Toxicology in Vitro 79 (Mar 2022),
Most in vitro studies examine the effects of a single ED or a mixture of EDs on granulosa cells using short-term exposure; however, this approach is unlikely to reflect long-term, real-life exposures that are common in humans. We established an in vitro model that mimics long-term exposure of granulosa cells to real-life ED mixture. Human granulosa cells, HGrC1, were exposed to the mixture consisting of bisphenol A, polychlorinated biphenyl 153, benzo[a]pyrene, and perfluorooctanesulfonate in concentrations found in human follicular fluid (MIX) for 48 h and 4 weeks. Only long-term exposure to MIX decreased estradiol production after 2 and 3 weeks, and CYP19A1 protein after 2 weeks of exposure. By week 4, the cells restored estradiol production and CYP19A1 protein level. MIX increased basal progesterone production after 3 and 4 weeks of exposure but did not affect STAR and CYP11A1 mRNA. Cells that had been exposed to MIX for 4 weeks showed augmentation of forskolinstimulated progesterone production. These results demonstrate that only long-term exposure to MIX alters steroidogenesis in HGrC1. This study also revealed that adverse effects of MIX on steroidogenesis in HGrC1 occurred a few weeks into MIX exposure and that this effect can be transient.
http://dx.doi.org/10.1016/j.tiv.2021.105302

Comparative evaluation of the effects of bisphenol derivatives on oxidative stress parameters in HepG2 cells,
OZYURT B., G. OZKEMAHLI, A. YIRUN, A. B. OZYURT, M. BACANLI, N. BASARAN, B. KOCER-GUMUSEL and P.

ERKEKOGLU,
Drug and Chemical Toxicology (Bisphenol A (BPA) BPA is an endocrine-disrupting chemical that has a wide range of uses. Exposure to BPA can be by oral, inhalation, and parenteral routes. Although its use in several products is limited, there is still concern on its adverse health effects, particularly for susceptible populations like children. Alternative bisphenols, such as bisphenol S (BPS) and bisphenol F (BPF), are now being used instead of BPA, although there is little information on the toxicity of these bisphenols. BPF is used as a plasticizer in the production of several industrial materials as well as in the coating of drinks and food cans. BPS is used in curing fast-drying epoxy glues, as a corrosion inhibitor and as a reactant in polymer reactions. In this study, the possible toxic effects of BPA, BPS, and BPF in HepG2 cells were evaluated comparatively. For this purpose, their effects on cytotoxicity, production of intracellular reactive oxygen species (ROS), oxidant/antioxidant parameters, and DNA damage have been examined. The cytotoxicity potentials of different bisphenols were found to be as BPS > BPF > BPA. All bisphenol derivatives caused increases in intracellular ROS production. We observed that all bisphenol derivatives cause an imbalance in some oxidant/antioxidant parameters. Bisphenols also caused significant DNA damage in order of BPF > BPA > BPS. We can suggest that both of the bisphenol derivatives used as alternatives to BPA also showed similar toxicities and may not be considered as safe alternatives. Mechanistic studies are needed to elucidate this issue. http://dx.doi.org/10.1080/01480545.2022.2028823

Endocrine-disrupting effects of bisphenols on urological cancers,
PELLERIN E., C. CANEPARO, S. CHABAUD, S. BOLDUC and M. PELLETIER,
Environmental Research 195 (Apr 2021),
Bisphenols are endocrine-disrupting chemicals found in a broad range of products that can modulate hormonal signalling pathways and various other biological functions. These compounds can bind steroid receptors, e.g. estrogen and androgen receptors, expressed by numerous cells and tissues, including the prostate and the bladder, with the potential to alter their homeostasis and normal physiological functions. In the past years, exposure to bisphenols was linked to cancer progression and metastasis. As such, recent pieces of evidence suggest that endocrine-disrupting chemicals can lead to the development of prostate cancer. Moreover, bisphenols are found in the urine of the wide majority of the population. They could potentially affect the bladder's normal physiology and cancer development, even if the bladder is not recognized as a hormone-sensitive tissue. This review will focus on prostate and bladder malignancies, two urological cancers that share standard carcinogenic processes. The description of the underlying mechanisms involved in cell toxicity, and the possible roles of bisphenols in the development of prostate and bladder cancer, could help establish the putative roles of bisphenols on public health. http://dx.doi.org/10.1016/j.envres.2020.110485

Comparing effects and action mechanisms of BPA and BPS on HTR-8/SVneo placental cells,
PROFITA M., E. FABBRI, E. SPISNI and P. VALBONESI,
Biology of Reproduction 105, no. 5 (Nov 2021): 1355-1364,
Bisphenol A (BPA) is one of the most investigated compound as a suspected endocrine disrupting chemical. It has been found at nM concentrations in the maternal serum, cord serum, and amniotic fluid and also permeates placental tissues. Attempts are being made to replace BPA with the analog Bisphenol S (BPS). Also BPS was found in maternal and umbilical cord serum, and urine samples from a large population of pregnant women. A few studies investigated BPA impact on the placentation process, and even less are available for BPS. This work aimed to elucidate and compare the effects of BPA and BPS on physiological functions of HTR-8/SVneo cells, derived from extravillous trophoblast of first-trimester pregnancy. Proliferation and migration ability of trophoblast cells were assessed in vitro after exposure to BPA or BPS (10(-13)-10(-3) M). Further, induction of the inflammatory response by the bisphenols was studied. To provide insight into the molecular pathways implicated in the responses, experiments were carried out in the presence or absence of tamoxifen as estrogen receptors (ERs) blocker, and U0126 as ERK1/2 phosphorylation inhibitor. Data indicate that BPA significantly affects both proliferation and migration of HTR8/SVneo cells, through ER and ERK1/2 mediated processes. Differently, BPS only acts on proliferation, again through ER and ERK1/2 mediated processes. BPS, but not BPA, induces secretion of interleukins 6 and 8. Such effect is inhibited by blocking ERK1/2 phosphorylation. To the best of our knowledge, these are the first data showing that BPS affects trophoblast functions through ER/MAPK modulation. Summary sentence Bisphenol A and its analog bisphenol S, emerging contaminants founded in human serum and placental fluids, significantly affected the biological functions of HTR-8/SVneo cells, through estrogen receptors and MAPK mediated processes. http://dx.doi.org/10.1093/biolre/ioab139

Comparative analysis of two methodological approaches to the study of endocrine disruptor alpha-cypermethrin reproductive toxicity,
SHEPELSKA N. R., M. G. PRODANCHUK and Y. V. KOLIANCHUK,
Regulatory Mechanisms in Biosystems 12, no. 4 (2021): 724-732,
At present, one of the main threats to humanity is undoubtedly endocrine disruptors (ED), since they directly disrupt the processes of ensuring homeostasis, which are identical to the very essence of the concept of health, considered in valeology as the ability to maintain age-appropriate stability in conditions of sharp changes in quantitative and qualitative parameters of the triune flow of sensory, verbal and structural information. Pesticides can disrupt the physiological functioning of many endocrine chains, including the endocrine mechanisms that ensure reproductive health. The study aimed to compare the results of our studies of alpha-cypermethrin reproductive toxicity in the test system for studying gonadotoxic activity with data obtained in the test system "Three Generation Reproduction Study". The studies were performed on male and female Wistar Han rats with two generic samples of alpha-cypemrethrin from different manufacturers at doses of 0.2,1.0 and 3.0 mg/kg body weight The exposure lasted 11 (males) and 10 (females) weeks. During the last two weeks of exposure the state of the estrous cycle, duration and frequency of each stage in females was studied. After the end of treatment functional parameters of the state of the gonads in males and the ability of animals to reproduce were examined. hi males, the total sperm count, the absolute and relative number of motile germ cells, and the number of pathologically altered forms were evaluated. The results of the study showed that exposure of male and female Wistar Han rats to alpha-cypemrethrin at doses of 0.2-3.0 mg/kg during gametogenesis had a toxic effect on the reproductive system characterized by impaired gonadal and reproductive functions. hi our studies, alpha-cypemrethrin was found to have reproductive toxicity (reduced number of corpora luteum and live fetuses, increased absolute and relative postimplantation death, reduced average weight of fetuses and litters) and endocrine-disruptive effect, having a pronounced antiandrogenic effect on males. Obvious signs of endocrine reproductive disorders (changes in testis and epididymis weight, deterioration in semen parameters, altered length of separate stages of the estrous cycle) were observed in both females and males. However, studies in a test system of three-generations did not reveal a reproductive and endocrine-disruptive effect of cypermethrin, the toxicity of which was recognized as equivalent to the toxicity of alphacypermethrin. The obtained results showed higher sensitivity, informative and diagnostic significance of the methods for studying gonadotoxicity than the methodology of reproductive toxicity studies in the test system "Three Generation Reproduction Study". http://dx.doi.org/10.15421/0221100

Effects of bone marrow-derived mesenchymal stem cells exposed to endocrine-disrupting chemicals on the differentiation of umbilical cord blood hematopoietic stem cells,
SOLTANI A., S. ABROUN, F. ABBASNEJADSHANI and M. A. GHOLAMPOUR,
Environmental Science and Pollution Research (Endocrine-disrupting chemicals (EDCs), a class of peripheral toxic substances, can cause many environmental and clinical side effects, particularly on the human body's endocrine system. Bisphenol A (BPA) and diethylhexyl phthalate (DEHP) are two well-known EDCs in the medicine industry. However, there are no comprehensive studies on their effects on hematopoiesis. Hence, this study aimed to investigate the effect of these two aforementioned substances on the clonogenic capacity of umbilical cord blood hematopoietic stem cells (CB-HSCs). The HSCs which express CD34 + were isolated from umbilical cord blood by the magnetic-activated cell sorting (MACS) system. To investigate the effects of different optimized concentrations of BPA and DEHP, CB-CD34(+) HSCs were exposed to EDCs in semisolid medium. For evaluation of coexposures, CB-CD34(+) HSCs were cocultured with bone marrow-derived mesenchymal stem cells (BM-MSCs) in the presence of BPA and DEHP. Finally, the number and types of colonies were evaluated after 14 days. Statistical analysis was performed by GraphPad Prism through ANOVA. CB-HSC treated by BPA and DEHP showed a lower absolute colony count than the control group ($P < 0.05$). Decrease in clonogenic potential of HSCs was more significant in coculture condition by MSCs. In particular, there was a significant decrease in the BFU-E colonies in comedicated-derived fractions ($P < 0.0001$). In the presence of EDCs such as BPA and DEHP, the patterns of differentiation in CD34(+) CB-HSCs changed from suppressed erythroid differentiation toward stimulated myelogenesis pathways. http://dx.doi.org/10.1007/s11356-021-17787-7

In Vitro characterization of the endocrine disrupting effects of per- and poly-fluoroalkyl substances (PFASs) on the human androgen receptor,
TACHACHARTVANICH P., E. R. A. SINGAM, K. A. DURKIN, J. D. FURLOW, M. T. SMITH and M. A. LA MERRILL,

Journal of Hazardous Materials 429 (May 2022),
Per- and poly-fluoroalkyl substances (PFASs) are used extensively in a broad range of industrial applications and consumer products. While a few legacy PFASs have been voluntarily phased out, over 5000 PFASs have been produced as replacements for their predecessors. The potential endocrine disrupting hazards of most emerging PFASs have not been comprehensively investigated. In silico molecular docking to the human androgen receptor (hAR) combined with machine learning techniques were previously applied to 5206 PFASs and predicted 23 PFASs bind the hAR. Herein, the in silico results were validated in vitro for the five candidate AR ligands that were commercially available. Three manufactured PFASs namely (9-(nonafluorobutyl)- 2,3,6,7-tetrahydro-1 H,5 H,11 H-pyrano[2,3-f]pyrido[3,2,1-ij]quinolin-11-one (NON), 2-(heptafluoropropyl)- 3-phenylquinoxaline (HEP), and 2,2,3,3,4,4,5,5,5-nonafluoro-N-(4-nitrophenyl)pentanamide (NNN) elicited significant antiandrogenic effects at relatively low concentrations. We further investigated the mechanism of AR inhibition and found that all three PFASs inhibited AR transactivation induced by testosterone through a competitive binding mechanism. We then examined the antiandrogenic effects of these PFASs on AR expression and its responsive genes. Consistently, these PFASs significantly decreased the expression of PSA and FKBP5 and increased the expression of AR, similar to the effects elicited by a known competitive AR inhibitor, hydroxyflutamide. This suggests they are competitive antagonists of AR activity and western blot analysis revealed these PFASs decreased intracellular AR protein in androgen sensitive human prostate cancer cells. Hence, the findings presented here corroborate our published in silico approach and indicate these emerging PFASs may adversely affect the human endocrine system. http://dx.doi.org/10.1016/j.jhazmat.2022.128243

In vitro impact of genistein and mono(2-ethylhexyl) phthalate (MEHP) on the eicosanoid pathway in spermatogonial stem cells,
TRAN-GUZMAN A., R. MORADIAN, H. Y. CUI and M. CULTY,
Reproductive Toxicology 107 (Jan 2022): 150-165,
Perinatal exposures to endocrine disrupting chemicals (EDCs) alter the male reproductive system. Infants are exposed to genistein (GEN) through soy-based formula, and to Mono(2-ethylhexyl) Phthalate (MEHP), metabolite of the plasticizer DEHP. Spermatogonial stem cells (SSCs) are formed in infancy and their integrity is essential for spermatogenesis. Thus, understanding the impact of EDCs on SSCs is critical. Prostaglandins (PGs) are inflammatory mediators synthesized via the eicosanoid pathway starting with cyclooxygenases (Coxs), that regulate physiological and pathological processes. Our goal was to study the eicosanoid pathway in SSCs and examine whether it was disrupted by GEN and MEHP, potentially contributing to their adverse effects. The mouse C18-4 cell line used as SSC model expressed high levels of Cox1 and Cox2 genes and proteins, and eicosanoid pathway genes similarly to levels measured in primary rat spermatogonia. Treatments with GEN and MEHP at 10 and 100 mu M decreased Cox1 gene and protein expression, whereas Cox2, phospholipase A2, prostaglandin synthases transcripts, PGE2, PGF2a and PGD2 were upregulated. Simultaneously, the transcript levels of spermatogonia progenitor markers Foxo1 and Mcam and differentiated spermatogonial markers cKit and Stra8 were increased. Foxo1 was also increased by EDCs in primary rat spermatogonia. This study shows that the eicosanoid pathway is altered during SSC differentiation and that exposure to GEN and MEHP disrupts this process, mainly driven by GEN effects on Cox2 pathway, while MEHP acts through an alternative mechanism. Thus, understanding the role of Cox enzymes in SSCs and how GEN and MEHP exposures alter their differentiation warrants further studies. http://dx.doi.org/10.1016/j.reprotox.2021.12.007

EDC-induced mechanisms of immunotoxicity: a systematic review,
VIDAL O. S., D. DEEPIKA, M. SCHUHMACHER and V. KUMAR,
Critical Reviews in Toxicology 51, no. 7 (Aug 2021): 634-652,
Endocrine-disrupting chemicals (EDCs) refer to a group of chemicals that cause adverse effects in human health, impairing hormone production and regulation, resulting in alteration of homeostasis, reproductive, and developmental, and immune system impairments. The immunotoxicity of EDCs involves many mechanisms altering gene expression that depend on the activation of nuclear receptors such as the aryl hydrocarbon receptor (AHR), the estrogen receptor (ER), and the peroxisome proliferator-activated receptor (PPAR), which also results in skin and intestinal disorders, microbiota alterations and inflammatory diseases. This systematic review aims to review different mechanisms of immunotoxicity and immunomodulation of T cells, focusing on T regulatory (Treg) and Th17 subsets, B cells, and dendritic cells (DCs) caused by specific EDCs such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), bisphenols (BPs) and polyfluoroalkyl substances (PFASs). To achieve this objective, a systematic study was conducted searching various databases including PubMed and Scopus to find

in-vitro, in-vivo, and biomonitoring studies that examine EDC-dependent mechanisms of immunotoxicity. While doing the systematic review, we found species- and cell-specific outcomes and a translational gap between in-vitro and in-vivo experiments. Finally, an adverse outcome pathway (AOP) framework is proposed, which explains mechanistically toxicity endpoints emerging from different EDCs having similar key events and can help to improve our understanding of EDCs mechanisms of immunotoxicity. In conclusion, this review provides insights into the mechanisms of immunotoxicity mediated by EDCs and will help to improve human health risk assessment. http://dx.doi.org/10.1080/10408444.2021.2009438

Multi- and transgenerational biochemical effects of low-dose exposure to bisphenol A and 4-nonylphenol on testicular interstitial (Leydig) cells,
XIA B. T., Y. HE, Y. GUO, J. L. HUANG, X. J. TANG, J. R. WANG, Y. TAN and P. DUAN,
Environmental Toxicology (Bisphenol A (BPA) and 4-nonylphenol (NP) are well-known endocrine-disrupting chemicals (EDCs) that have been proven to affect Leydig cell (LC) functions and testosterone production, but whether BPA and NP have multi- and transgenerational biochemical effects on Leydig cells (LCs) is unknown. Fourier transform infrared (FTIR) spectroscopy is a powerful analytical technique that enables label-free and non-destructive analysis of the tissue specimen. Herein we employed FTIR coupled with chemometrics analysis to identify biomolecular changes in testicular interstitial (Leydig) cells of rats after chronic exposure to low doses of BPA and NP. Cluster segregations between exposed and control groups were observed based on the fingerprint region of 1800-900 cm(-1) in all generations. The main biochemical alterations for segregation were amide I, amide II and nucleic acids. BPA and NP single and co-exposure induced significant differences in the ratio of amide I to amide II compared to the corresponding control group in all generations. BPA exposure resulted in remarkable changes of cellular gene transcription and DNA oxidative damage across all generations. Direct exposure to BPA, NP, and BPA&NP of F0 and F1 generations could significantly decrease lipid accumulation in LCs in the F2 and F3 generations. The overall findings revealed that single or co-exposure to BPA and NP at environmental concentrations affects the biochemical structures and properties of LCs.
http://dx.doi.org/10.1002/tox.23462

Bisphenol A induces pyroptotic cell death via ROS/NLRP3/Caspase-1 pathway in osteocytes MLO-Y4,
ZHANG Y., M. YAN, W. Y. SHAN, T. ZHANG, Y. C. SHEN, R. R. ZHU, J. FANG and H. J. MAO,
Food and Chemical Toxicology 159 (Jan 2022),
Bisphenol A (BPA), a ubiquitous endocrine-disrupting chemical, is commonly used as a plasticizer to manufacture various food packaging materials. Evidence has demonstrated that BPA disturbed bone health. However, few studies focused on the effect of BPA on osteocytes, making up over 95% of all the bone cells. Here, we reported that BPA inhibited the cell viability of MLO-Y4 cells, and increased apoptosis in a dose-dependent manner. Furthermore, BPA up-regulated protein expressions of speck-like protein containing CARD (ASC), NLRP3, cleaved caspase-1 (Casp-1 p20) and cleaved gasdermin D (GSDMD-N), and increased the ratios of interleukin (IL)-113/pro-IL-113 and IL-18/pro-IL-18 in MLO-Y4 cells. BPA enhanced levels of lactate dehydrogenase (LDH), IL113 and IL-18 in culture supernatants. This pyroptotic death and the NLPR3 inflammasome activation were reversed by the caspase-1 inhibitor VX765 or the NLRP3 inflammasome inhibitor MCC950. Furthermore, BPA stimulated the production of intracellular reactive oxygen species (ROS), mitochondrial ROS (mtROS), elevated malondialdehyde (MDA) level and decreased superoxide dismutase (SOD) activity, which led to oxidative damage in MLO-Y4 cells. The ROS scavenger N-acetylcysteine (NAC) or the mitochondrial antioxidant MitoTEMPO inhibited the NLPR3 inflammasome activation and pyroptotic death induced by BPA. Collectively, our data suggest that BPA causes pyroptotic death of osteocytes via ROS/NLRP3/Caspase-1 pathway. http://dx.doi.org/10.1016/j.fct.2021.112772

Evaluation de l'exposition

Determination of Endocrine Disruptor Bisphenol-A Leakage from Differ-ent Matrices of Dental Resin-based Composite Materials,
AL-TANNAK N. F., F. ALZOUBI, F. M. KAREEM and L. NOVOTNY,
Current Pharmaceutical Analysis 18, no. 3 (2022): 305-315,

Background: Bisphenol A (BPA) derivatives monomers as resins are common components in dental restorative materials and materials used for orthodontic treatment. However, they are a source for BP-A leakage, which can affect adult and child health as an endocrine disruptor. Objectives: This study aimed to investigate the level of BPA leakage from four selected weights (0.1, 0.2, 0.3, 0.4 mg) of five different resin combinations used in dental restorative materials. Methods: The resin combinations were cured with light for 20 seconds, kept in 1 mL of acetonitrile, and sonicated for 30 minutes. Separation was achieved by using BEH C18 (1.7 mu m, 2.1 x 100 mm) analytical column (Waters (R) Acquity UPLC) and a mobile phase composed of water and acetonitrile (68:32 v/v). Moreover, Waters (R) Xevo G2-SQToF coupled with Waters (R) Acquity UPLC system with binary Solvent Manager (I-Class) via electrospray ionization (ESI) interface was used to confirm peaks identities. Results: BPA was detected in all resin combinations and in all selected sample weights. However, BP A was below the limit of quantification (LOQ) in all selected weights of the Filtek Z350 XT Universal Restorative System. The results show that BPA is still released from selected dental resin combinations available in the market despite the general concern about its potential adverse effects. Conclusion: Nevertheless, the amounts of BPA were within the acceptable levels indicated by the U.S. Environmental Protection Agency and the U.S. Department of Health and Human Services National Toxicology Program and represent a very small contribution to the total BPA exposure. The use of alternative materials such as high-viscosity glass ionomers, inorganic biomaterials, and ceramic would be ideal and healthier for adults and children. http://dx.doi.org/10.2174/1573412917666210525114226

Endocrine-disrupting chemicals used as common plastic additives: Levels, profiles, and human dietary exposure from the Indian food basket,
CHAKRABORTY P., G. K. BHARAT, O. GAONKAR, M. MUKHOPADHYAY, S. CHANDRA, E. H. STEINDAL and L. NIZZETTO,
Science of the Total Environment 810 (Mar 2022),
Endocrine-disrupting chemicals (EDCs) such as phthalic acid esters (PAEs) and bisphenol A (BPA) are the most widely used plastic additives in polymeric materials. These EDCs are ubiquitously distributed in the environment. Hence selected PAEs and BPA were investigated in twenty-five food types and drinking water (supply and packaged) from the metropolitan city, Delhi, and the peri-urban areas of a non-metropolitan city, Dehradun. Except cabbage and orange, the sum of thirteen PAEs (Sigma(13)PAEs) and BPA in all the other food types were significantly higher in Delhi over Dehradun ($p < 0.01$). Highest mean Sigma(13)PAEs (665 ng/g) and BPA (73 ng/g) were observed in cottage cheese and potatoes, respectively followed by fish (PAEs - 477 ng/g, BPA - 16 ng/g). Supply water from the west zone of Delhi was found to contain the highest concentration of BPA (309 ng/L) and Sigma(13)PAEs (5765 ng/L) with the dominance of diethyl phthalate (DEP). Based on the compositional profile and compound-wise principal component analysis, environmental contamination and food processing were attributed as significant sources of most priority PAEs in food samples. Di-ethyl hexyl phthalate (DEHP) was over 100-fold higher in the bottled water from local brands than composite bottled water samples. Packaging material was identified as a source for di-n-butyl phthalate (DnBP) in packaged food. This study observed the highest estimated daily dietary intake (EDI) in the high-fat-containing food products viz., cottage cheese, and fish from north Delhi. High bioaccumulation of BPA can be a possible reason for elevated EDI in vegetables and local fish of Delhi. Unlike Dehradun, EDI for Sigma(13)PAEs and BPA was slightly higher for the non-vegetarian adult when compared to the vegetarian adult. DEHP and DnBP exhibited the highest estimated estrogenic potential for bottled water from local brands. Dietary exposure due to six priority PAEs contamination in food stuffs was two to four-fold higher in Delhi than Dehradun for adult man and woman.
http://dx.doi.org/10.1016/j.scitotenv.2021.152200

Determination of contamination levels for multiple endocrine disruptors in hair froma non-occupationally exposed population living in Liege (Belgium),
CLAESSENS J., C. PIRARD and C. CHARLIER,
Science of the Total Environment 815 (Apr 2022),
Today, the interest in hair as alternative matrix for human biomonitoring of environmental pollutants has increased, but available data on chemical levels in hair remain scarce. In this study, the measurement of 2 bisphenols (A and S), 3 parabens (methyl-, ethyl- and propylparabens) and 8 perfluroralkyl compounds (PFCs) namely perfluoroctanesulfonate (PFOS), perfluorohexanesulfonate (PFHxS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluroroheptanoic acid (PFHpA), perfluoropentanoic acid (PFPeA) and perfluorohexanoic acid (PFHxA) was carried out, using a thoroughly validated UPLC-MS/MS method, in the hair from 114 adults living in Liege (Belgium) and surrounding areas.

Themost frequently quantified compounds in the population were: bisphenol S (97.4%, median = 31.9 pg.mg(-1)), methylparaben (94.7%, median = 28.9 pg.mg(-1)), bisphenol A (93.9%, median = 46.6 pg.mg(-1)), ethylparaben (66.7%, median = 5.2 pg.mg(-1)), propylparaben (54.8%, median = 16.4 pg.mg(-1)) and PFOA (46.4%, median < 0.2 pg.mg(-1)). The other PFCs were detected only in few samples although current exposure of the Belgian population to PFCs was previously demonstrated using blood analyses. Nonparametric statistical analyses were performed to evaluate the influence of gender, hair treatments and hair length, but no significant difference was observed. Only age was positively correlated with the propylparaben contamination. Although blood seems to remain more suitable for PFCs exposure assessment, the results of this study suggest that hair can be an appropriate matrix for biomonitoring of organic pollutants such as parabens or bisphenols. http://dx.doi.org/10.1016/j.scitotenv.2021.152734

Association of urinary triclosan, methyl triclosan, triclocarban, and 2,4-dichlorophenol levels with anthropometric and demographic parameters in children and adolescents in 2020 (case study: Kerman, Iran),
NASAB H., S. RAJABI, M. MIRZAEE and M. HASHEMI,
Environmental Science and Pollution Research (Endocrine-disrupting chemicals (EDCs) can be a major risk factor for noncommunicable illnesses, especially when children are exposed to them. The purpose of this study was to assess the urine concentrations of triclosan (TCS), methyl triclosan (MTCS), triclocarban (TCC), and 2,4-dichlorophenol (2,4-DCP) and its association with anthropometric and demographic parameters in children and adolescents aged 6-18 living in Kerman, Iran, in 2020. A GC/MS instrument was used to measure the concentrations of the analytes. TCS, MTCS, TCC, and 2,4-DCP geometric mean concentrations (mu g/L) were 4.32 +/- 2.08, 1.73 +/- 0.88, 4.66 +/- 10.25, and 0.19 +/- 0.14, respectively. TCS, MTCS, TCC, and 2,4-DCP were shown to have a positive and significant association with BMI z-score and BMI (p-value < 0.01). TCS and MTCS have a positive, strong, and substantial association (p-value < 0.01, r = 0.74). There was no significant association between the waist circumference (WC) and the analytes studied. In addition, there was a close association between analyte concentration and demographic parameters (smoking, education, income, etc.) overall. In Kerman, Iran, the current study was the first to look into the association between TCS, MTCS, TCC, and 2,4-DCP analytes and anthropometric and demographic data. The levels of urinary TCS, MTCS, TCC, 2,4-DCP, and anthropometric parameters in children and adolescents are shown to have a significant association in this study. However, because the current study is cross-sectional and it is uncertain if a single experiment accurately reflects long-term exposure to these analytes, more research is needed to determine the impact of these analyses on the health of children and adolescents. http://dx.doi.org/10.1007/s11356-021-18466-3

Bisphenol A Release from Dental Composites and Resin-Modified Glass Ionomers under Two Polymerization Conditions,
TICHY A., M. SIMKOVA, R. VRBOVA, A. ROUBICKOVA, M. DUSKOVA and P. BRADNA,
Polymers 14, no. 1 (Jan 2022),
Bisphenol A (BPA)-based monomers are commonly contained in dental resin-based materials. As BPA is an endocrine disruptor, its long-term release from restorative composites and resin-modified glass ionomers (RM-GICs) under two polymerization conditions was measured in this study. Specimens of two conventional composites containing BPA-based monomers, two "BPA-free" composites, and two RM-GICs were polymerized from one side for 20 s at 1300 mW/cm(2) or for 5 s at 3000 mW/cm(2). The amounts of BPA released in artificial saliva and methanol after 1, 4, 9, 16, 35, 65, 130, and 260 days were measured using liquid chromatography-tandem mass spectrometry. The highest amounts of BPA were released from conventional composites, followed by RM-GICs, while the least was released from "BPA-free" composites. Amounts of released BPA were significantly higher in methanol and decreased gradually after the first day. Fast polymerization (5 s at 3000 mW/cm(2)) resulted in a significantly higher release of BPA after 1 day, but the effect of polymerization conditions was not significant overall. In conclusion, fast polymerization increased the initial release of BPA, but the released amounts were significantly lower than the current tolerable daily intake (4 mu g/kg body weight/day) even in methanol, representing the worst-case scenario of BPA release. http://dx.doi.org/10.3390/polym14010046

Méthodes

Organophosphate ester metabolites in human breast milk determined by online solid phase extraction coupled to high pressure liquid chromatography tandem mass spectrometry,
CHEN M. Q., J. KOEKKOEK and M. LAMOREE,
Environment International 159 (Jan 2022),
The analysis of metabolites of organophosphate esters (OPEs) in human breast milk is essential to evaluate OPE and OPE metabolite exposure of newborns. In the current study, an analytical method which only needs a small amount of breast milk (100 mu l) was developed and validated for six diester metabolites and three hydroxylated metabolites applying salt-induced liquid-liquid extraction (SI-LLE) and dispersive solid phase extraction (d-SPE) for sample preparation and online solid phase extraction coupled to high pressure chromatography tandem mass spectrometry (online-SPE-HPLC-MS/MS) for quantitative measurement. The final method consisted of an extraction with formic acid (FA)/acetonitrile (1:200, v/v) and a cleanup with C18 d-SPE. The final extracts were trapped on a C18 cartridge with application of a wash step of 2 ml 0.1% FA milli-Q/methanol (98:2, v/v). Method detection limits (MDLs) ranging from 21.7 ng/l for BBOEHEP to 500 ng/l for BCIPP and average recoveries ranging from 58% for 5-OH-EHDPHP to 120% for BCIPP were achieved. Thirty-three breast milk samples from the LINC (Linking EDCs in maternal Nutrition to Child health) cohort collected in three distinct areas in The Netherlands were analyzed using the validated method. BCEP, BCIPP, BCIPHPP, BDCIPP, and 5-OHEHDPHP were not detected in any of the samples, while BBOEP was the most frequently detected metabolite with a concentration range of <MDL to l.47 ng/ml, followed by DPhP and BBOEHEP, detected in ranges of <MDL to 0.09 and <MDL to 0.027 ng/ml. The results indicated that OPEs entering the human body are only to a limited extent excreted via breast milk. http://dx.doi.org/10.1016/j.envint.2021.107049

Ultrasensitive detection and risk assessment of di(2-ethylhexyl) phthalate migrated from daily-use plastic products using a nanostructured electrochemical aptasensor,
LEE K., N. G. GURUDATT, W. HEO, K. A. HYUN and H. I. JUNG,
Sensors and Actuators B-Chemical 357 (Apr 2022),
Di(2-ethylhexyl) phthalate (DEHP) is an endocrine-disrupting chemical that induces numerous health problems when present in the human body in trace amounts. Therefore, for the simple and highly sensitive monitoring of migrated DEHP from daily-use plastic products into water sources, a gold-nanoflowers (AuFs)-structured electrochemical aptasensor was designed in this study. The morphologies of the well-defined AuFs-modified electrodes were investigated and the refined surface indicated enhanced electrochemical properties. DEHP was captured using methylene-blue (MB)-conjugated aptamer immobilized onto the AuFs-structured surface. The devised sensing platform exhibited a low detection limit (2.3 x 10-2 pg/mL) and a broad dynamic range (0.5 x 100 to 1 x 106 pg/mL). As a proof of concept, the designed aptasensor was successfully utilized as a monitoring tool to detect DEHP migration from plastic products, analyzing the migrated DEHP levels between 2.76 x 102 and 7.75 x 103 pg/mL. Furthermore, human exposure risk assessment via drinking water for ten items revealed that the carcinogenic risk values of four products exceeded the acceptable level, indicating the vulnerability of human health to even trace amounts of short-term-migrating DEHP. Consequently, our aptasensor shows tremendous potential for monitoring DEHP migrated from real samples with the reliable performance and the high sensitivity. http://dx.doi.org/10.1016/j.snb.2022.131381

Methods for the analysis of endocrine disrupting chemicals in selected environmental matrixes,
METCALFE C. D., S. BAYEN, M. DESROSIERS, G. MUNOZ, S. SAUVE and V. YARGEAU,
Environmental Research 206 (Apr 2022),
Endocrine disrupting chemicals (EDCs) are heterogenous in structure, chemical and physical properties, and their capacity to partition into various environmental matrixes. In many cases, these chemicals can disrupt the endocrine systems of vertebrate and invertebrate organisms when present at very low concentrations. Therefore, sensitive and varied analytical methods are required to detect these compounds in the environment. This review summarizes the analytical methods and instruments that are most used to monitor for EDCs in selected environmental matrixes. Only those matrixes for which there is a clear link between exposures and endocrine effects are included in this review. Also discussed are emerging methods for sample preparation and advanced analytical instruments that provide greater selectivity and sensitivity.

http://dx.doi.org/10.1016/j.envres.2021.112616

Optimization of an ultrasound-assisted extraction method for the determination of parabens and bisphenol homologues in human saliva by liquid chromatography-tandem mass spectrometry,
MOSCOSO-RUIZ I., Y. GALVEZ-ONTIVEROS, S. CANTARERO-MALAGON, A. RIVAS and A. ZAFRA,
Microchemical Journal 175 (Apr 2022),
Parabens and bisphenols are endocrine disrupting chemicals (EDCs) widely used in our daily lives. The main route of human exposure to these compounds is through the diet. This makes human saliva an important matrix for identification of these contaminants and evaluation of human exposure. In this work a multiresidue method to determine the presence of methyl-, ethyl-, propyl-, isopropyl-, butyl-and isobutylparaben; and bisphenol A, B, C, E, F, M, P, S, Z, AP, AF and FL in human saliva samples has been developed. Sample treatment involves an initial step of protein precipitation in acidic medium and a second step of analyte extraction. Extraction parameters were optimized using univariant and multivariant strategies. Microwave assisted extraction (MAE) and ultrasound assisted extraction (UAE) were compared and UAE was chosen the optimal extraction technique. The compounds were analyzed by ultra-high performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS). The calibration in matrix was applied and the limits of detection and quantification were from 0.1 to 0.4 ng g(-1) and from 0.3 to 1.0 ng g(-1), respectively. Accuracy was evaluated in terms of recovery (85.6 to 113.5%) with a relative standard deviation < 15% in all cases. The analytical method was successfully applied to quantify the target EDCs in ten human saliva samples, with some parabens being the most frequently detected compounds. http://dx.doi.org/10.1016/j.microc.2021.107122

High throughput screening of bisphenols and their mixtures under conditions of low-intensity adipogenesis of human mesenchymal stem cells (hMSCs),
NORGREN K., A. TUCK, A. V. SILVA, P. BURKHARDT, M. OBERG and V. M. KOS,
Food and Chemical Toxicology 161 (Mar 2022),
In vitro models of adipogenesis are phenotypic assays that most closely mimic the increase of adipose tissue in obesity. Current models, however, often lack throughput and sensitivity and even report conflicting data regarding adipogenic potencies of many chemicals. Here, we describe a ten-day long adipogenesis model using high content analysis readouts for adipocyte number, size, and lipid content on primary human mesenchymal stem cells (MSC) sensitive enough to compare bisphenol A derivatives quantitatively in a robust and high throughput manner. The number of adipocytes was the most sensitive endpoint capable of detecting changes of 20% and was used to develop a benchmark concentration model (BMC) to quantitatively compare eight bisphenols (tested at 0.1-100 mu M). The model was applied to evaluate mixtures of bisphenols obtaining the first experimental evidence of their additive effect on human MSC adipogenesis. Using the relative potency factors (RPFs), we show how a mixture of bisphenols at their sub-active concentrations induces a significant adipogenic effect due to its additive nature. The final active concentrations of bisphenols in tested mixtures reached below 1 mu M, which is within the concentration range observed in humans. These results point to the need to consider the toxicity of chemical mixtures. http://dx.doi.org/10.1016/j.fct.2022.112842

Prokaryotic expression of human-sourced and zebrafish-sourced protein kinase A alpha catalytic subunits combined with in vitro and in silico assay,
QIAO K., Y. JIANG, T. T. HU, S. Y. LI and W. J. GUI,
Ecotoxicology and Environmental Safety 228 (Dec 2021),
The extensively studied cAMP-dependent protein kinase A (PKA) is involved in the regulation of critical cell processes, including metabolism, gene expression, and cell proliferation. Therefore, PKA has been viewed increasingly as potential target for variety of drugs and environmental endocrine disruptors. Consequentially, the preparation of PKA protein became an important initial step for the subsequent exploration of PKA's character in endocrine disrupting effects of pesticides. To investigate PKA protein, which is potential to be the environmental endocrine toxicity target of triazole fungicides, a strategy to heterologously express protein kinase A catalytic alpha subunit of human (hPKAc alpha) and zebrafish (zPKAc alpha) in Escherichia coli (E. coli) BL21(DE3) host cells was demonstrated. After optimizing conditions and protein purification, we successfully obtained enzymatically active hPKAc alpha and zPKAc alpha. Western blot analysis indicated that the recombinant hPKAc alpha and zPKAc alpha still retained their characteristic antigenicity and binding activity, while in vitro kinase activity assays revealed that the recombinant hPKAc alpha and zPKAc alpha maintained enzyme activity. By in

silico methods including homology modelling and molecular docking, the affinity of ligands and the models of hPKAc alpha and zPKAc alpha were further tested. The present study offered a valuable method to achieve the prokaryotic expression of a eukaryotic protein kinase and laid a foundation to facilitate further investigation of toxicological target of triazole pesticides. http://dx.doi.org/10.1016/j.ecoenv.2021.113023

Xenobiotics-Division and Methods of Detection: A Review,
STEFANAC T., D. GRGAS and T. L. DRAGICEVIC,
Journal of Xenobiotics 11, no. 4 (Dec 2021): 130-141,
Xenobiotics are compounds of synthetic origin, usually used for domestic, agricultural, and industrial purposes; in the environment, they are present in micropollutant concentrations and high concentrations (using ng/L to mu g/L units). Xenobiotics can be categorized according to different criteria, including their nature, uses, physical state, and pathophysiological effects. Their impacts on humans and the environment are non-negligible. Prolonged exposure to even low concentrations may have toxic, mutagenic, or teratogenic effects. Wastewater treatment plants that are ineffective at minimizing the release of xenobiotic compounds are one of the main sources of xenobiotics in the environment (e.g., xenobiotic compounds reach the environment, affecting both humans and animals). In order to minimize the negative impacts, various laws and regulations have been adopted in the EU and across the globe, with an emphasis on xenobiotics removal from the environment, in a way that is economically, environmentally, and socially acceptable, and will not result in their accumulation, or creation of compounds that are more harmful. Detection methods allow detecting even small concentrations of xenobiotics in samples, but the problem is the diversity and mix of compounds present in the environment, in which it is not known what their effects are). In this review, the division of xenobiotics and their detection methods will be presented. http://dx.doi.org/10.3390/jox11040009

Rodent Model of Gender-Affirming Hormone Therapies as Specific Tool for Identifying Susceptibility and Vulnerability of Transgender People and Future Applications for Risk Assessment,
TASSINARI R. and F. MARANGHI,
International Journal of Environmental Research and Public Health 18, no. 23 (Dec 2021),
Transgenders (TGs) are individuals with gender identity and behaviour different from the social norms; they often undergo gender-affirming hormone therapy (HT). HT for TG men involves testosterone treatment and, for TG women, oestrogen plus androgen-lowering agents. Due-but not limited-to the lifelong lasting HT, usually TG people experience several physical and behavioural conditions leading to different and specific susceptibility and vulnerability in comparison to general population, including the response to chemical contaminants present in daily life. In particular, the exposure to the widespread endocrine disrupters (EDs) may affect hormonal and metabolic processes, leading to tissue and organ damage. Since the endocrine system of TG people is overstimulated by HT and, often, the targets overlap with ED, it is reasonable to hypothesize that TG health deserves special attention. At present, no specific tools are available to study the toxicological effects of environmental contaminants, including EDs, and the potential long-term consequences of HT on TG people. In this context, the development of adequate and innovative animal models to mimic gender-affirming HT have a high priority, since they can provide robust data for hazard identification in TG women and men, leading to more reliable risk assessment. http://dx.doi.org/10.3390/ijerph182312640

ER/AR Multi-Conformational Docking Server: A Tool for Discovering and Studying Estrogen and Androgen Receptor Modulators,
WANG F., S. HU, D. Q. MA, Q. Y. LI, H. C. LI, J. Y. LIANG, S. CHANG and R. KONG,
Frontiers in Pharmacology 13 (Jan 2022),
The prediction of the estrogen receptor (ER) and androgen receptor (AR) activity of a compound is quite important to avoid the environmental exposures of endocrine-disrupting chemicals. The Estrogen and Androgen Receptor Database (EARDB,) provides a unique collection of reported ER alpha, ER beta, or AR protein structures and known small molecule modulators. With the user-uploaded query molecules, molecular docking based on multi-conformations of a single target will be performed. Moreover, the 2D similarity search against known modulators is also provided. Molecules predicted with a low binding energy or high similarity to known ER alpha, ER beta, or AR modulators may be potential endocrine-disrupting chemicals or new modulators. The server provides a tool to predict the endocrine activity for compounds of interests, benefiting for the ER and AR drug design and endocrine-disrupting chemical identification. http://dx.doi.org/10.3389/fphar.2022.800885

Agenda

Journée d'étude: Perturbateurs endocriniens: les conséquences de l'exposition pour les travailleurs et leurs enfants
Jeudi 5 mai 2022 - SPF Emploi, Travail et Concertation sociale
https://evenements.emploi.belgique.be/fr/evenements-du-spf/journee-detude-perturbateurs-endocriniens-les-consequences-de-lexposition-pour
Au cours de cette journée d'étude, des experts médicaux donneront des précisions sur les effets possibles des perturbateurs endocriniens sur la santé, tant des travailleurs que de leurs enfants. De grands groupes de travailleurs sont quotidiennement exposés à divers produits qui peuvent avoir des effets nocifs sur la santé. Souvent, les effets nocifs de ces substances peuvent être estimés et inclus dans l'analyse des risques dans le contexte du travail, dans le but de protéger les travailleurs contre ces substances. Cependant, c'est moins souvent le cas pour certaines substances chimiques, comme les perturbateurs endocriniens, dont les propriétés et les effets ne sont pas toujours bien connus pour évaluer correctement les risques dans le contexte du travail. Les perturbateurs endocriniens sont des produits chimiques qui interfèrent avec le fonctionnement normal de notre système hormonal et qui peuvent provoquer diverses affections médicales graves. Au cours de cette journée d'étude, nous discuterons spécifiquement des conséquences possibles de l'exposition à ces substances nocives sur la santé des travailleurs et de leurs enfants.
Au cours de cette journée d'étude, des experts médicaux donneront des précisions sur les effets possibles des perturbateurs endocriniens sur la santé, tant des travailleurs que de leurs enfants. En outre, nous aborderons certaines caractéristiques toxicologiques des perturbateurs endocriniens et la manière dont cela peut affecter l'estimation de l'exposition sur le lieu de travail. Nous passerons brièvement en revue la législation pertinente sur le bien-être au travail et proposerons un guide pratique pouvant être utilisé pour informer les travailleurs et divers autres acteurs sur l'exposition aux perturbateurs endocriniens dans un contexte professionnel.
Des exemples concrets de différents secteurs ayant une expérience de la gestion des perturbateurs endocriniens seront examinés en détail. Nous chercherons des moyens d'améliorer la sécurité des travailleurs en contact avec les perturbateurs endocriniens. L'objectif est que ces expériences servent d'inspiration à d'autres secteurs.

Politique, actualité, société et évaluation du caractère PE des substances

Registry of SVHC intentions until outcome : 1,1'-[ethane-1,2-diylbisoxy]bis[2,4,6-tribromobenzene],
ECHA (mars 2022),
The registry of SVHC intentions until outcome aims to make interested parties aware of the substances for which an SVHC dossier is planned to be submitted to ECHA.
Substance : 1,1'-[ethane-1,2-diylbisoxy]bis[2,4,6-tribromobenzene]
Scope : Endocrine disrupting properties (Article 57(f) - environment) and vPvB (Article 57e).
Submitter: Spain
Expected date of submission : 04/08/2022 https://echa.europa.eu/fr/registry-of-svhc-intentions

New substance evaluation conclusions published : tert-butyl methyl ether.,
ECHA (mars 2022),
Tert-butyl methyl ether (EC 216-653-1, CAS 1634-04-4), added to the CoRAP list in 2014 and evaluated by France. Intial grounds of concern : Potential endocrine disruptor
High (aggregated) tonnage andWide dispersive use. Status : Concluded :
7.10.2. Endocrine disruption - Human health
ED properties of MTBE for human health have been examined in 2014-2015 in the context of SEv. Numerous data

indicates effects of MTBE on circulating hormones, in particular testosterone, corticosterone and LH. However, a consistent mode of action that could be associated with these changes has not been identified. A decrease in serum testosterone is observed in many studies following oral exposure to high doses of MTBE but it has not been studied by inhalation. The hypothesis that MTBE can have a direct high-dose solvent effect, which would destroy testosterone by dissolution is not considered relevant as increase in serum corticosterone are observed. Based on this data, it has not been considered to request additional data. ED properties of MTBE for human health may require further consideration based on new data and will be reassessed by the endocrine disruptors working group of ANSES and discussed in an upcoming RMOA
7.10.3. Conclusion on endocrine disrupting properties (combined/separate)
For the environmental part, even if an estrogenic activity was observed in male fish (vitellogenin induction), there were no adverse effects observed in vivo. In the absence of
adverse effects, endocrine disruption cannot be demonstrated for fish. For the Human Health Part, based on the data evaluated during SEv, ED related effects could only be seen at very high doses (effects at doses above the limit dose, 1000 mg/kg bw/d) and without a consistent mode of action. The concern was not sufficient to request further testing. ED properties of MTBE for human health may require further consideration based on new data and will be re-assessed by the endocrine disruptors working group of ANSES and discussed in an upcoming RMOA.
https://echa.europa.eu/fr/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e18068d70b?utm_source=echa-weekly&utm_medium=email&utm_campaign=weekly&utm_content=20220316&_cldee=bmF0aGFsaWUudG91bGVtb25kZUBpbnJzLmZy&recipientid=lead-44d9ccac935ceb118128005056b9310e-5bfb7b50da0241d8a3e201116f2142f8&esid=0a436145-19a5-ec11-8136-005056952b31

Avis sur deux projets de décrets d'application de la loi AGEC relatifs à la mise à disposition des informations permettant d'identifier pour le consommateur les substances dangereuses (dont les perturbateurs endocriniens) contenues dans certains produits.,
HCSP Haut conseil de la santé publique (mars 2022),
La loi n° 2020-105 du 10 février 2020 relative à la lutte contre le gaspillage et à l'économie circulaire, dite AGEC prévoit le recours à des décrets pris en Conseil d'Etat pour fixer les modalités d'application de la mise à disposition des informations permettant d'identifier pour le consommateur les substances dangereuses contenues dans certains produits mis sur le marché. Considérant les enjeux pour la santé humaine de cette loi, le HCSP a participé à la consultation publique en rendant un avis sur les 2 projets de textes suivants. Le projet de décret relatif à la mise à disposition des informations permettant d'identifier les perturbateurs endocriniens dans un produit par voie électronique Le HCSP recommande que soit rendu obligatoire en parallèle un affichage sur les produits au moyen d'une étiquette colorée associée à une lettre selon une échelle directement et aisément identifiable par tous lors de l'acte d'achat. A cet effet, le HCSP présente en annexe de son avis le principe de construction d'un Indice de composition chimique. Le projet de décret relatif à l'identification des substances dangereuses dans les produits générateurs de déchets Ce texte prévoit que cette obligation s'applique aux substances extrêmement préoccupantes inscrites sur la liste mentionnée par le règlement (CE) n° 1907/2006 et aux substances recommandées par l'Anses. Le HCSP recommande que cette obligation s'applique également aux substances CMR de catégorie 2 et à celles suspectées de propriétés de perturbation endocrinienne.
https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=1166

Pesticides Perturbateurs endocriniens : Il faut agir !,
Générations futures (mars 2022),
La Commission européenne a adopté des critères d'identification des perturbateurs endocriniens pour les substances actives biocides et pour les pesticides. Ces textes s'appliquent depuis 2018 et sont sensés permettre l'exclusion du marché des substances pouvant avoir des effets de perturbation du système endocrinien. Problème : les critères d'évaluation adoptés en 2017 par l'UE après 9 années d'attente exigent un niveau de preuve très élevé ne retenant que les perturbateurs endocriniens « connus » et « présumés ». Il n'existe pas de catégorie identifiant les perturbateurs « suspectés », contrairement aux Cancérogènes Mutagènes et Reprotoxiques (CMR). C'est à dire ceux pour lesquels toutes les preuves ne sont pas réunies. Mais ces preuves ont-elles été recherchées ? Et avec quels tests ? Les associations Alerte des Médecins sur les Pesticides (AMLP) et Générations Futures ont voulu vérifier ce que l'adoption de ces critères avait changé en pratique. Elles ont pris pour exemple 13 substances actives dont les autorisations arrivaient à terme en 2021. Pourquoi ces substances ? Parce que l'EFSA (Autorité européenne de sécurité de l'alimentation, chargée de l'homologation des substances)

les avaient repérées comme perturbant l'axe thyroïdien dans une étude de 2013. Et qu'elles sont retrouvées dans l'alimentation des français si l'on en croit les travaux de l'Anses (EAT2 et EATi). L'agence européenne avait donc repéré ces substances 5 ans avant l'adoption du règlement sur les PE. Les substances étudiées (Cyprodinil, Fenbuconazole, Mepanipyrim, Pyrimethanil, Ziram, Spinosad, Cyproconazole, Myclobutanil, Diethofencarb, Fenoxycarb, Boscalid, Folpel, Metribuzin) ont toutes un effet sur l'axe thyroïdien. La plupart ont un mécanisme d'action pouvant perturber le système endocrinien, mais celui-ci est systématiquement écarté, et aucun test validé n'est disponible pour le prouver ! https://www.generations-futures.fr/actualites/perturbateur-thyroidien/

Towards a paradigm shift in environmental health decision-making: a case study of oxybenzone,
MATOUSKOVA K. and L. N. VANDENBERG,
Environmental Health 21, no. 1 (Jan 2022),
Background Technological advancements make lives safer and more convenient. Unfortunately, many of these advances come with costs to susceptible individuals and public health, the environment, and other species and ecosystems. Synthetic chemicals in consumer products represent a quintessential example of the complexity of both the benefits and burdens of modern living. How we navigate this complexity is a matter of a society's values and corresponding principles. Objectives We aimed to develop a series of ethical principles to guide decision-making within the landscape of environmental health, and then apply these principles to a specific environmental chemical, oxybenzone. Oxybenzone is a widely used ultraviolet (UV) filter added to personal care products and other consumer goods to prevent UV damage, but potentially poses harm to humans, wildlife, and ecosystems. It provides an excellent example of a chemical that is widely used for the alleged purpose of protecting human health and product safety, but with costs to human health and the environment that are often ignored by stakeholders. Discussion We propose six ethical principles to guide environmental health decision-making: principles of sustainability, beneficence, non-maleficence, justice, community, and precautionary substitution. We apply these principles to the case of oxybenzone to demonstrate the complex but imperative decision-making required if we are to address the limits of the biosphere's regenerative rates. We conclude that both ethical and practical considerations should be included in decisions about the commercial, pervasive application of synthetic compounds and that the current flawed practice of cost-benefit analysis be recognized for what it is: a technocratic approach to support corporate interests. http://dx.doi.org/10.1186/s12940-021-00806-y

An ounce of prevention is worth a pound of cure: time to focus on preconception workplace reproductive health,
MESSERLIAN C., Y. ZHANG, Y. SUN, Y. X. WANG and V. MUSTIELES,
Human Reproduction 37, no. 1 (Jan 2022): 1-4,
Few opportunities exist in environmental reproductive medicine where we can have a direct impact on offspring health. Prevention of adverse child health outcomes has received less attention than understanding their etiology. Yet, the preconception and early pregnancy periods afford a unique opportunity to intervene and limit early life exposures that may result in harm with potentially lifelong consequences. Workplace exposures—whose largest burden involves reproductive-aged women and men—have been hard to investigate largely because of the complexity of measurement and challenges with follow-up. Case–control designs lend themselves to studying rare and often devastating outcomes, including birth defects. In the study by Spinder et al. (2021), published in this issue of Human Reproduction, the authors tackle a complex area of birth defects research using a nested case–control design by leveraging two large independent cohorts—the European Concerted Action on Congenital Anomalies and Twins in Northern Netherlands (Eurocat NNL) and the Lifelines http://dx.doi.org/10.1093/humrep/deab263

Becoming with Toxicity: Chemical Epigenetics as "Racializing and Sexualizing Assemblage",
PACKER M.,
Hypatia-a Journal of Feminist Philosophy 37, no. 1 (2022): 2-26,
In this article I think through Black feminism and queer theory to critically analyze toxicology. I focus on toxicology's conception of endocrine-disrupting chemicals (EDCs), a class of toxicants that can cause epigenetic changes leading to inheritable health issues. I suggest that Black feminist interventions are particularly necessary for the study of toxicants because multiply marginalized populations are disproportionately more exposed to

EDCs. The structural preconditions that generate this uneven, racialized, and sexualized toxic body-burden threaten to turn cultural constructions of race and sex (epistemologies) into biological realities (ontologies). My discursive analysis of key scientific texts on toxicology, EDCs, and epigenetics underscores how Eurocentric biases and eugenic logics permeate and co-constitute biochemical matter. I further argue that these texts' un/articulated norms regarding the human, sexual behavior, and evolutionary fitness undermine the usefulness of toxicological assessments for environmental justice. I close by urging scientist scholar-activists to reconceive the study of toxicants. A Black feminist approach to toxicity, I suggest, would not only situate chemical exposures in their sociopolitical contexts, but also radically revision what it means to be human. http://dx.doi.org/10.1017/hyp.2021.68

Toxicité sur les animaux

Bisphenol A reveals its obesogenic effects through disrupting glucose tolerance, oxidant-antioxidant balance, and modulating inflammatory cytokines and fibroblast growth factor in zebrafish,
BELER M., D. CANSIZ, I. UNAL, U. V. USTUNDAG, E. DANDIN, E. AK, A. A. ALTURFAN and E. EMEKLI-ALTURFAN,
Toxicology and Industrial Health 38, no. 1 (Jan 2022): 19-28,
Obesogens affect lipid metabolism, and genetic or epigenetic factors may also contribute to the progression of obesity. Endocrine-disrupting chemicals (EDCs) are the most striking among obesogens. Bisphenol A (BPA) is an estrogenic EDC used in food containers, adhesives, dye powders, and dental fillers. We aimed to elucidate molecular mechanisms of BPA's obesogenic effects focusing on obesogenic pathways in the liver including fibroblast growth factor (FGF) and Dnmt3a which is its epigenetic regulator, oxidant-antioxidant status, and inflammatory cytokines. Zebrafish were divided into three groups as control, low-dose BPA (1 mu m BPA), and high-dose BPA groups (10 mu m BPA). At the end of 30 days, oral glucose tolerance test (OGTT) was performed, fasting blood glucose levels were measured, and hepatopancreas tissues were taken. Malondialdehyde (MDA) levels, superoxide dismutase (SOD), glutathione S-transferase (GST), and nitric oxide (NO) activities were examined in the hepatopancreas. Inflammatory cytokines, lepa, fgf21, and dnmt3a expressions were determined by RT-PCR. BPA exposure increased the body weights, il1ss, tnf alpha, il6, lepa, fgf21, and dnmt3a expressions, impaired glucose tolerance, and oxidant-antioxidant status in a dose-dependent manner. Hepatocyte degeneration, lipid vacuolization, and vasocongestion were observed in both BPA-exposed groups. Our study suggests impaired glucose tolerance, oxidant-antioxidant balance, increased inflammatory response, fgf21 expression, and dnmt3a expressions as the possible mechanisms for the BPA-induced obesity model in zebrafish. http://dx.doi.org/10.1177/07482337211054372

Effects of chronic exposure to bisphenol A in adult female mice on social behavior, vasopressin system, and estrogen membrane receptor (GPER1),
BONALDO B., A. CASILE, M. BETTARELLI, S. GOTTI, G. PANZICA and M. MARRAUDINO,
European Journal of Histochemistry 65 (2021),
Bisphenol A (BPA), an organic synthetic compound found in some plastics and epoxy resins, is classified as an endocrine disrupting chemical. Exposure to BPA is especially dangerous if it occurs during specific "critical periods" of life, when organisms are more sensitive to hormonal changes (i.e., intrauterine, perinatal, juvenile or puberty periods). In this study, we focused on the effects of chronic exposure to BPA in adult female mice starting during pregnancy. Three months old C57BL/6J females were orally exposed to BPA or to vehicle (corn oil). The treatment (4 mu g/kg body weight/day) started the day 0 of pregnancy and continued throughout pregnancy, lactation, and lasted for a total of 20 weeks. BPA-treated dams did not show differences in body weight or food intake, but they showed an altered estrous cycle compared to the controls. In order to evidence alterations in social and sociosexual behaviors, we performed the Three-Chamber test for sociability, and analyzed two hypothalamic circuits (well-known targets of endocrine disruption) particularly involved in the control of social behavior: the vasopressin and the oxytocin systems. The test revealed some alterations in the displaying of social behavior: BPA-treated dams have higher locomotor activity compared to the control dams, probably a signal of high level of anxiety. In addition, BPA-treated dams spent more time interacting with no-tester females than with no-tester males. In brain sections, we observed a decrease of vasopressin immunoreactivity (only in the paraventricular and suprachiasmatic nuclei) of BPA-treated females, while we did not find any alteration of the oxytocin system. In parallel, we have also observed, in the same hypothalamic

nuclei, a significant reduction of the membrane estrogen receptor GPER1 expression.
http://dx.doi.org/10.4081/ejh.2021.3272

Prenatal exposure to a mixture of phthalates accelerates the age-related decline in reproductive canacity but may not anect direct biomarkers of ovarian aging in the F1 generation of female mice,
BREHM E. and J. A. FLAWS,
Environmental Epigenetics 7, no. 1 (Oct 2021),
Phthalates are used in many consumer products, leading to daily human exposure. Although many studies focus on single phthalates, humans are exposed to mixtures of phthalates. Our laboratory created a phthalate mixture consisting of six different phthalates and found that it negatively affected female reproduction and accelerated some biomarkers of reproductive aging. However, it was unknown if prenatal exposure to the mixture accelerates the natural decline in reproductive capacity and ovarian aging in mice. Therefore, we tested the hypothesis that prenatal exposure to a phthalate mixture accelerates the age-related decline in reproductive capacity and biomarkers of ovarian aging in the F1 generation of mice. Pregnant CD-1 dams were orally dosed with control or phthalate mixture (20 mu g/kg/day-200 mg/kg/day) daily from gestational day 10-birth. The F1 female pups were aged to 11-13 months, and then estrous cyclicity and breeding trials were conducted at 11 and 13 months. Ovaries were collected from the F1 females at 13 months to examine biomarkers of ovarian aging. Prenatal exposure to the phthalate mixture decreased the time the F1 females spent in proestrus and the ability of the F1 females to give birth at 11 and 13 months of age compared to control. In contrast, prenatal exposure to the mixture did not affect biomarkers of direct aging of the ovary in the F1 generation. Collectively, our data show that prenatal phthalate mixture exposure accelerates the natural age-related decline in reproductive capacity but may not affect some biomarkers of ovarian aging in the F1 generation.
http://dx.doi.org/10.1093/eep/dvab010

Chronic low BPS exposure through diet impairs in vitro embryo production parameters according to metabolic status in the ewe,
DESMARCHAIS A., O. TETEAU, N. KASAL-HOC, J. COGNIE, O. LASSERRE, P. PAPILLIER, M. LACROIX, C. VIGNAULT, P. JARRIER-GAILLARD, V. MAILLARD, A. BINET, M. T. PELLICER-RUBIO, S. FRERET and S. ELIS,
Ecotoxicology and Environmental Safety 229 (Jan 2022),
Bisphenol A (BPA), an endocrine disruptor, has been replaced by structural analogues including bisphenol S (BPS). BPA and BPS exhibited similar effects regarding reproductive functions. Moreover, metabolic status and lipid metabolism are related to female fertility and could worsen BPS effects. The objective was to determine BPS in vivo effects on folliculogenesis and embryo production after chronic exposure through diet, and the influence of metabolic status in adult ewes. Sixty primiparous 2.5 year-old ewes, undergoing a restricted or well fed diet, were exposed to BPS (0, 4 or 50 mu g/kg/day) for at least three months. After hormonal oestrus synchronisation and ovarian stimulation, ewes were subjected to ovum pick-up (OPU) procedures to collect immature oocytes, that underwent in vitro maturation, fertilisation and embryo production. Body weight, body condition score and plasma glucose were higher in well-fed compared to restricted ewes, while plasma NEFA was lower during the 4-5 months after the beginning of the diets. Plasma progesterone levels increased on day 5 before OPU session in well-fed compared to restricted ewes. No effect of BPS dose was observed on follicle population, plasma AMH levels and embryo production numbers and rates. However, a significant diet x BPS dose interaction was reported for cleaved embryos, > 4-cell embryos, blastocyst and early blastocyst numbers, and plasma triiodothyronine levels. Our study showed that a contrasted diet did not affect follicle population nor embryo production in adult ewes but could affect the quality and progesterone secretion of the corpus luteum. Chronic low BPS exposure had no effect on follicular population and oocyte competence. Nevertheless, the significant diet x dose interactions observed on embryo production suggest that BPS effect is modulated by metabolic status. Further studies are required to assess the risk of BPS exposure for public reproductive health.
http://dx.doi.org/10.1016/j.ecoenv.2021.113096

Protective effect of the association of curcumin with piperine on prostatic lesions: New perspectives on BPA-induced carcinogenesis,
FACINA C. H., S. G. P. CAMPOS, T. F. R. RUIZ, R. M. GOES, P. S. L. VILAMAIOR and S. R. TABOGA,
Food and Chemical Toxicology 158 (Dec 2021),
Bisphenol A (BPA) is a chemical agent which can exert detrimental effects on the male reproductive system,

especially the prostate gland. In this study we described the efficacy of the dietary agent curcumin, alone or combined with piperine, to suppress the impact of BPA on the prostate. Adult gerbils were divided into nine experimental groups (n = 7 each group), regarding control (water and oil), exposed to BPA (50 mu g/kg/day in water) or curcumin (100 mg/kg) and/or piperine (20 mg/kg). To evaluate the effects of the phytotherapic agents, the other groups received oral doses every two days, BPA plus curcumin (BCm), piperine (BP), and curcumin + piperine (BCmP). BPA promoted prostatic inflammation and morphological lesions in ventral and dorsolateral prostate lobes, associated with an increase in androgen receptor-positive cells and nuclear atypia, mainly in the ventral lobe. Curcumin and piperine helped to minimize these effects. BPA plus piperine or curcumin showed a reduction in nuclear atypical phenotype, indicating a beneficial effect of phytochemicals. Thus, these phytochemicals minimize the deleterious action of BPA in prostatic lobes, especially when administered in association. The protective action of curcumin and piperine consumption is associated with weight loss, anti-inflammatory potential, and control of prostate epithelial cell homeostasis.
http://dx.doi.org/10.1016/j.fct.2021.112700

Effects of perinatal exposure to endocrine-disrupting chemicals on the reproductive system of F3 generation male rodents: a meta-analysis,
HE H., W. J. CHEN, Y. WEI, T. F. ZHANG, W. F. GENG and J. X. ZHAI,
Environmental Science and Pollution Research (To explore the relationship between perinatal exposure to endocrine-disrupting chemicals and the male reproductive system of F3 generation, and to evaluate the toxicological effects of endocrine-disrupting chemicals on the reproductive system of F3 generation male rodents. PubMed and Web of Science databases were searched to obtain the studies; overall risk ratios (RRs) with 95% confidence intervals (95% CIs) were used to evaluate the relationship between exposure to endocrine-disrupting chemicals and reproductive system damage in F3 generation male rodents. Nine studies were included for analysis. Endocrine-disrupting chemicals are significantly associated with the reproductive system of male rodents of F3 generation, especially the testis (RR = 3.13, 95% CI: 2.05, 4.76), prostate (RR = 2.26, 95% CI: 1.27, 4.00), and kidney (RR = 2.83, 95% CI: 1.77, 4.52), but the current analysis does not prove that EDCs are the adverse factors for puberty abnormalities. The results indicated that the overall associations between atrazine (RR = 3.06, 95% CI: 1.10, 8.51, P = 0.032), DDT (RR = 6.26, 95% CI: 1.56, 25.08, P = 0.010), pesticide and insect repellent mixture (permethrin and DEET) (RR = 2.23, 95% CI: 1.34, 3.69, P = 0.002), and vinclozolin (RR = 4.71, 95% CI: 2.74, 8.10, P = 0.000) and reproductive system damage in F3 generation male rodents were statistically significant. Our study indicated that EDCs have an atavistic effect on the male reproductive system, and we should pay attention to the long-term effects of environmental exposure to endocrine disruptors in future generations. http://dx.doi.org/10.1007/s11356-021-18338-w

p Association of Early Pubertal Onset in Female Rats With Inhalation of Lavender Oil,
KIM Y. M. and H. H. LIM,
Journal of Korean Medical Science 37, no. 2 (Jan 2022),
Background: Central precocious puberty (CPP) is caused by early activation of the hypothalamic-pituitary-gonadal axis but its major cause remains unclear. Studies have indicated an association between chronic environmental exposure to endocrine-disrupting chemicals and pubertal onset. Essential oil is widely used in homes worldwide for relief of Methods: To evaluate this association, we compared the hormone levels and timing of vaginal opening (VO) in female rats exposed to lavender oil (LO) through different routes (study groups: control, LO nasal spray [LS], and indoor exposure to LO [LE]) during the prepubertal period. The body weights of the animals were also compared every 3 days until the day of VO, at which time gonadotropin levels and internal organ weights were assessed. Results: The LS group showed early VO at 33.8 +/- 1.8 days compared with the control (38.4 +/- 2.9 days) and LE (36.6 +/- 1.5 days) groups. Additionally, luteinizing hormone levels were significantly higher in the LE and LS groups than those in the control group. Body weights did not differ significantly among the groups. Conclusion: Inhalation exposure to an exogenic simulant during the prepubertal period might trigger early pubertal onset in female rats. Further evaluation of exposure to other endocrine-disrupting chemicals capable of inducing CPP through the skin, orally, and/or nasally is warranted.
http://dx.doi.org/10.3346/jkms.2022.37.e9

Effects of Lead on Reproduction Physiology and Liver and Gonad Histology of Male Cyprinus carpio,
KORKMAZ C., O. AY, A. E. DONMEZ, B. DEMIRBAG and C. ERDEM,

Bulletin of Environmental Contamination and Toxicology Sera 17 beta-estradiol (E2), 11-ketotesteron (11-KT) and 17,20-beta-dihydroxy-4-pregnen-3-one (17,20 beta P) levels and hepatoso- matic-gonadosomatic indexes (HSI-GSI) were determined after exposing male C. carpio to 0.13 and 0.26 mg L-1 lead after 7, 14 and 21 days. Histological changes in liver and gonad tissues of male C. carpio were also determined. Sera E2, 11-KT and 17,20 beta P levels of male fish although showed differences from the control fish, these differences were not statistically significant. This was also true for the HSI values, the GSI values however, decreased on day 7 under the effect of 0.26 mg L-1 Pb. Dilatation in bile duct and sinusoids and lymphocyte infiltration were observed under histopathological examination. Low intensities of fibrosis were detected in testis tissues. Exposure to low concentrations of Pb did not cause endocrine disrupting and extensive histopathologic effects in C. carpio at the exposure periods tested. http://dx.doi.org/10.1007/s00128-021-03426-x

Combined effect of unfolded protein response and circZc3h4, circRNA Scar in mouse ovary and uterus damage induced by procymidone,
LI R., B. Y. XIN, Q. WANG, Z. WANG, H. FU, Z. L. YAN and Y. F. ZHU,
Ecotoxicology and Environmental Safety 229 (Jan 2022),
Procymidone (PCM) is a fungicide commonly used to prevent and control plant diseases, and it is also an environmental endocrine disruptor that has a typical anti-androgen effect on the function and/or structure of the vertebrate reproductive system. The activation of the unfolded protein response (UPR) will fold the protein correctly to ensure the cell's survival. PCM regulates GRP78 by affecting the level of hormones, and there is a regulatory relationship between the UPR, the circRNAs and the miRNAs. In vivo experiments, PCM (suspended in soybean oil) was orally administered to adolescent female mice for 21 days in 3 different doses of 50 mg kg(-1)day(-1) (low dose), 100 mg kg(-1) day(-1) (medium dose) and 200 mg kg(-1) day(-1) (high dose) to cause ovaries and uteruses damage, and in vitro experiments, various doses of PCM from 0.33 x 10(-5) (low dose) to 1 x 10(-5) (medium dose) then 3 x 10(-5) M (high dose) were used to induce injury on the ovaries and uteri of the mice. We found out that both in vivo and in vitro, PCM caused dose-dependent damages to the ovaries and uteri, increased their circRNA Scar levels and decreased circZc3h4 abundance. Also, all UPR signaling pathways in the low-dose group and some in the middle-dose group were activated. It is speculated that UPR may antagonize the partial ovarian and uterine damage in adolescent mice induced by PCM at doses less than NOAEL via changes in circZc3h4 and circRNA Scar. http://dx.doi.org/10.1016/j.ecoenv.2021.113068

Cypermethrin inhibits Leydig cell development and function in pubertal rats,
LI S. J., Y. WANG, C. ZOU, Q. Q. ZHU, Y. Y. WANG, H. Q. CHEN, W. J. YANG, Y. H. TU, H. N. YAN, X. H. LI and R. S. GE,
Environmental Toxicology (Cypermethrin is a broad-spectrum pyrethroid insecticide that is widely used. It may induce adverse endocrine-disrupting effects on the male reproductive system. Whether cypermethrin can disrupt Leydig cell development and function in the late puberty remains elusive. The objective of this study was to explore the effect of cypermethrin exposure to male rats on the development and function of Leydig cells in late puberty and explore the underlying mechanism. Thirty-six male Sprague-Dawley rats (age of 35 days) were gavaged with cypermethrin (0, 12.5, 25, and 50 mg/kg/day) from postnatal day 35-49. Cypermethrin significantly lowered serum testosterone level while elevating serum luteinizing hormone level at a dose of 50 mg/kg, without altering serum follicle-stimulating hormone level. Cypermethrin markedly decreased CYP11A1-positive Leydig cell number at 50 mg/kg without affecting SOX9-positive Sertoli cell number. It significantly down-regulated the expression of Leydig cell genes, Lhcgr, Star, Cyp11a1, and Cyp17a1 and their proteins, while up-regulating the expression of Sertoli cell genes, Dhh and Amh, and their proteins, at doses of 12.5-50 mg/kg. In addition, cypermethrin significantly increased malondialdehyde level while lowering the expression of Sod1 and Sod2 and their proteins at 50 mg/kg. Cypermethrin markedly induced reactive oxidative species at a concentration of 200 mu M and reduced mitochondrial membrane potential at 25 mu M and higher concentrations after 24 h of treatment to primary Leydig cells in vitro. In conclusion, cypermethrin inhibits the development and function of Leydig cells in male rats in late puberty. http://dx.doi.org/10.1002/tox.23473

Oxysterols Profile in Zebrafish Embryos Exposed to Triclocarban and Propylparaben-A Preliminary Study,
MEROLA C., A. VREMERE, F. FANTI, A. IANNETTA, G. CAIONI, M. SERGI, D. COMPAGNONE, S. LORENZETTI, M. PERUGINI and M. AMORENA,
International Journal of Environmental Research and Public Health 19, no. 3 (Feb 2022),

Oxysterols have long been considered as simple by-products of cholesterol metabolism, but they are now fully designed as bioactive lipids that exert their multiple effects through their binding to several receptors, representing endogenous mediators potentially involved in several metabolic diseases. There is also a growing concern that metabolic disorders may be linked with exposure to endocrine-disrupting chemicals (EDCs). To date, there are no studies aimed to link EDCs exposure to oxysterols perturbation-neither in vivo nor in vitro studies. The present research aimed to evaluate the differences in oxysterols levels following exposure to two metabolism disrupting chemicals (propylparaben (PP) and triclocarban (TCC)) in the zebrafish model using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). Following exposure to PP and TCC, there were no significant changes in total and individual oxysterols compared with the control group; however, some interesting differences were noticed: 24-OH was detected only in treated zebrafish embryos, as well as the concentrations of 27-OH, which followed a different distribution, with an increase in TCC treated embryos and a reduction in zebrafish embryos exposed to PP at 24 h post-fertilization (hpf). The results of the present study prompt the hypothesis that EDCs can modulate the oxysterol profile in the zebrafish model and that these variations could be potentially involved in the toxicity mechanism of these emerging contaminants. http://dx.doi.org/10.3390/ijerph19031264

Protracted Impairment of Maternal Metabolic Health in Mouse Dams Following Pregnancy Exposure to a Mixture of Low Dose Endocrine-Disrupting Chemicals, a Pilot Study,
MERRILL A. K., T. ANDERSON, K. CONRAD, E. MARVIN, T. JAMES-TODD, D. A. CORY-SLECHTA and M. SOBOLEWSKI,
Toxics 9, no. 12 (Dec 2021),
Pregnancy, a period of increased metabolic demands coordinated by fluctuating steroid hormones, is an understudied critical window of disease susceptibility for later-life maternal metabolic health. Epidemiological studies have identified associations between exposures to various endocrine-disrupting chemicals (EDCs) with an increased risk for metabolic syndrome, obesity, and diabetes. Whether such adverse outcomes would be heightened by concurrent exposures to multiple EDCs during pregnancy, consistent with the reality that human exposures are to EDC mixtures, was examined in the current pilot study. Mouse dams were orally exposed to relatively low doses of four EDCs: (atrazine (10 mg/kg), bisphenol-A (50 mu g/kg), perfluorooctanoic acid (0.1 mg/kg), 2,3,7,8-tetrachlorodibenzo-p-dioxin (0.036 mu g/kg)), or the combination (MIX), from gestational day 7 until birth or for an equivalent 12 days in non-pregnant females. Glucose intolerance, serum lipids, weight, and visceral adiposity were assessed six months later. MIX-exposed dams exhibited hyperglycemia with a persistent elevation in blood glucose two hours after glucose administration in a glucose tolerance test, whereas no such effects were observed in MIX-exposed non-pregnant females. Correspondingly, MIX dams showed elevated serum low-density lipoprotein (LDL). There were no statistically significant differences in weight or visceral adipose; MIX dams showed an average visceral adipose volume to body volume ratio of 0.09, while the vehicle dams had an average ratio of 0.07. Collectively, these findings provide biological plausibility for the epidemiological associations observed between EDC exposures during pregnancy and subsequent maternal metabolic dyshomeostasis, and proof of concept data that highlight the importance of considering complex EDC mixtures based of off common health outcomes, e.g., for increased risk for later-life maternal metabolic effects following pregnancy. http://dx.doi.org/10.3390/toxics9120346

Developmental and Hepatic Gene Expression Changes in Chicken Embryos Exposed to p-Tert-Butylphenyl Diphenyl Phosphate and Isopropylphenyl Phosphate via Egg Injection,
NGUYEN P., F. PAGE-LARIVIERE, K. WILLIAMS, J. O'BRIEN and D. CRUMP,
Environmental Toxicology and Chemistry 41, no. 3 (Mar 2022): 739-747,
Organophosphate flame retardants (OPFRs) are used in a variety of products such as clear coats, resins, and plastics; however, research into their toxicological effects is limited. p-Tert-butylphenyl diphenyl phosphate (BPDP) and isopropylphenyl phosphate (IPPP) are two OPFRs that were prioritized for whole-animal toxicological studies based on observed effects in cultured avian hepatocytes in a previous study. The present study investigates the toxicity of BPDP and IPPP in chicken embryos at different developmental stages by evaluating morphological and gene expression endpoints. Chicken eggs were exposed via air cell injection to 0-250 mu g/g (nominal) of either compound and then artificially incubated. At day 11 (midincubation), liver samples were collected for mRNA expression analysis; and at day 20 (1 day prehatch), morphological measurements and liver samples for transcriptomic evaluation were collected. At 250 mu g/g, gallbladder size was significantly reduced for both compounds, head/bill length and tarsus length were significantly decreased, and liver somatic index

was significantly increased following IPPP exposure only. No effects on mortality were observed up to the highest administered concentration for either chemical. Using a ToxChip polymerase chain reaction array, we report significant differences in hepatic gene expression for both compounds and time points; the most pronounced transcriptomic effects occurred at midincubation. Genes related to xenobiotic metabolism, bile acid/cholesterol regulation, and oxidative stress were significantly dysregulated. Given these changes observed throughout avian embryonic development, further research into the long-term effects of BPDP and IPPP are warranted, especially as they pertain to liver cholestasis. Environ Toxicol Chem 2022;00:1-9. (c) 2021 Her Majesty the Queen in Right of Canada. Environmental Toxicology and Chemistry (c) 2021 SETAC. Reproduced with the permission of the Minister of Environment and Climate Change Canada. http://dx.doi.org/10.1002/etc.5274

Developmental exposure to the DE-71 mixture of polybrominated diphenyl ether (PBDE) flame retardants induce a complex pattern of endocrine disrupting effects in rats,
RAMHOJ L., K. MANDRUP, U. HASS, T. SVINGEN and M. AXELSTAD,
Peerj 9 (Jan 2022),
Polybrominated diphenyl ethers (PBDEs) are legacy compounds with continued widespread human exposure. Despite this, developmental toxicity studies of DE-71, a mixture of PBDEs, are scarce and its potential for endocrine disrupting effects in vivo is not well covered. To address this knowledge gap, we carried out a developmental exposure study with DE-71. Pregnant Wistar rat dams were exposed to 0, 40 or 60 mg/kg bodyweight/day from gestation day 7 to postnatal day 16, and both sexes were examined. Developmental exposure affected a range of reproductive toxicity endpoints. Effects were seen for both male and female anogenital distances (AGD), with exposed offspring of either sex displaying around 10% shorter AGD compared to controls. Both absolute and relative prostate weights were markedly reduced in exposed male offspring, with about 40% relative to controls. DE-71 reduced mammary gland outgrowth, especially in male offspring. These developmental in vivo effects suggest a complex effect pattern involving anti-androgenic, anti-estrogenic and maybe estrogenic mechanisms depending on tissues and developmental stages. Irrespective of the specific underlying mechanisms, these in vivo results corroborate that DE-71 causes endocrine disrupting effects and raises concern for the effects of PBDE-exposure on human reproductive health, including any potential long-term consequences of disrupted mammary gland development. http://dx.doi.org/10.7717/peerj.12738

Alteration of Extracellular Matrix Components in the Anterior Pituitary Gland of Neonatal Rats Induced by a Maternal Bisphenol A Diet during Pregnancy,
SANANNAM B., S. LOOPRASERTKUL, S. KANLAYAPRASIT, N. KITKUMTHORN, T. SARACHANA and D. JINDATIP,
International Journal of Molecular Sciences 22, no. 23 (Dec 2021),
The extracellular matrix (ECM) plays crucial roles in the anterior pituitary gland via the mechanism of cell-ECM interaction. Since bisphenol A (BPA), a well-known endocrine disruptor, can cross through the placenta from mother to fetus and bind with estrogen receptors, cell populations in the neonatal anterior pituitary gland could be the target cells affected by this chemical. The present study treated maternal rats with 5000 mu g/kg body weight of BPA daily throughout the pregnancy period and then investigated the changes in ECM-producing cells, i.e., pericytes and folliculostellate (FS) cells, including their ECM production in the neonatal anterior pituitary at Day 1. We found that pericytes and their collagen synthesis reduced, consistent with the increase in the number of FS cells that expressed several ECM regulators-matrix metalloproteinase (MMP) 9 and the tissue inhibitors of metalloproteinase (TIMP) family. The relative MMP9/TIMP1 ratio was extremely high, indicating that the control of ECM homeostasis was unbalanced. Moreover, transmission electron microscopy showed the unorganized cell cluster in the BPA-treated group. This study revealed that although the mother received BPA at the "no observed adverse effect" level, alterations in ECM-producing cells as well as collagen and the related ECM balancing genes occurred in the neonatal anterior pituitary gland. http://dx.doi.org/10.3390/ijms222312667

Cyantraniliprole impairs reproductive parameters by inducing oxidative stress in adult female wistar rats,
SCARTON S. R. D., F. TSUZUKI, M. T. GUERRA, D. P. DOS SANTOS, A. C. DOS SANTOS, A. T. B. GUIMARAES, A. N. C. SIMAO, C. C. L. BEU and G. S. A. FERNADES,
Reproductive Toxicology 107 (Jan 2022): 166-174,
Cyantraniliprole is a synthetic insecticide used to control pests of up to 23 different types of crops. It is able to modulate ryanodine-like calcium channels, which are widely found in the organism of insects and mammals. The objective of this research was to verify the possible reproductive effects of adult female Wistar rats exposure to

cyantraniliprole. Animals (67 days old) were exposed to the chemical at doses of 10 or 150 mg/kg/day, orally, for 28 consecutive days (control animals received only the vehicle). Vaginal secretions were collected during the exposure period to assess the regularity of the estrous cycle; the liver, kidneys, pituitary gland, adrenal gland, uterus, and ovaries were collected and weighed; reproductive organs were assessed for histopathological evaluation and for biochemical markers of oxidative stress and progesterone plasma level was measured. Both doses caused negative changes in the morphology and redox system of the uterus and ovaries. Animals exposed to 10 mg/kg also exhibited higher level of plasma progesterone, elevated levels of lipid peroxidation in reproductive organs, increased superoxide dismutase activity in the uterus and glutathione peroxidase activity on the ovary, while the 150 mg/kg group exhibited an increment in estrous cycle length and diminished uterine glandular epithelium. Based on these results, we conclude that cyantraniliprole may have acted as an endocrine disruptor, and its effects are mediated by oxidative stress. http://dx.doi.org/10.1016/j.reprotox.2021.12.009

Disruption of developmental programming with long-term consequences after exposure to a glyphosate-based herbicide in a rat model,
SCHIMPF M. G., M. M. MILESI, M. V. ZANARDI and J. VARAYOUD,
Food and Chemical Toxicology 159 (Jan 2022),
Glyphosate-based herbicides (GBHs) have been associated with endocrine disrupting effects on reproductive organs. We examined whether postnatal exposure to GBH affects developmental programming of the uterus with long-term consequences. Female Wistar pups received vehicle (control) or GBH (2 mg of glyphosate/kg/day) from postnatal day (PND) 1 to PND7, where the developing uterus is highly sensitive to endocrine disruption. Short-, mid- and long-term effects were evaluated on PND8, PND120 and PND600, respectively. GBH induced hyperplasia and epigenetic alterations in the uterus of neonatal females (PND8). DNA hypermethylation, enrichment of H3K9me3 and reductions of H3K27me3 at regulatory regions of the morphoregulatory gene Hoxa10 resulted in gene downregulation. In young adult females (PND120), GBH increased 1713-estradiol (E2) and decreased progesterone (P4) serum levels, altering estrous cyclicity. Aged females (PND600) exposed to GBH developed leiomyoma and pre-neoplastic glandular lesions in the uterus. Vaginal rhabdomyosarcoma and intrahepatic bile duct adenoma were also observed. In conclusion, neonatal exposure to GBH altered the expression and induced hypermethylation of the Hoxa10 gene in uterine tissue at early life, and increased E2/P4 ratio serum level at middle-age. We propose that epigenetic reprogramming of Hoxa10 in association with hormonal imbalance could be among the possible mechanisms underlying the long-term adverse effects detected in GBH-exposed rats. http://dx.doi.org/10.1016/j.fct.2021.112695

Exposure to low-dose bisphenol A induces spleen damage in a murine model: Potentially through oxidative stress?,
SHAIBI T., H. BALOG, R. ALGHAZEER, M. OTHMAN, A. BENJAMA, M. ELHENSHERI, B. LWALEED and M. GRIW,
Open Veterinary Journal 12, no. 1 (2022): 23-32,
Background: During early life, exposure to environmental toxicants, including endocrine disruptor bisphenol A (BPA), can be detrimental to the immune system. To our knowledge, a few researches have looked at the effects of developing BPA exposures on the spleen. Aim: The murine model was developed to investigate the underlying molecular mechanisms and mode of BPA actions on the spleen subsequent to prolonged early-life exposure to BPA. Methods: Immature (3-week-old) male and female Swiss Albino mice were intraperitoneally injected with 50 mu g/kg BPA in corn oil or corn oil alone for 6 weeks. Mouse spleens were harvested and examined histologically at 10 weeks old (adulthood). Results: We observed neurobehavioral impairments and a significant increase in peripheral monocyte and lymphocyte counts in mice (males and females). Moreover. several spleen abnormalities in both male and female mice were observed in adulthood. BPA-treated mice's histopathological results revealed toxicity in the form of significantly active germinal centers of the white pulp and a few apoptotic cells. There was also a notable invasion of the red pulp by eosinophils and lymphocytes that were significantly higher than normal. Agarose gel electrophoresis provided further evidence of intemucleosomal DNA fragmentation and apoptosis in the splenic tissues of BPA-treated mice compared to controls. In addition, there were increased levels of the lipid peroxidation malondialdehyde end-product, a marker of oxidative lipid damage, in the spleens of BPA-treated mice compared to controls. Conclusion: Our study provides evidence that oxidative stress injury induced by early-life exposures to BPA could contribute to a range of splenic tissue damages during adulthood. http://dx.doi.org/10.5455/OVJ.2022.v12.i1.4

Effects of Pubertal Exposure to Butyl Benzyl Phthalate, Perfluorooctanoic Acid, and Zeranol on Mammary Gland Development and Tumorigenesis in Rats,
SU Y. R., J. SANTUCCI-PEREIRA, N. M. DANG, J. KANEFSKY, V. RAHULKANNAN, M. HILLEGASS, S. JOSHI, H. GURDOGAN, Z. CHEN, V. BESSONNEAU, R. RUDEL, J. SER-DOLANSKY, S. S. SCHNEIDER and J. RUSSO,
International Journal of Molecular Sciences 23, no. 3 (Feb 2022),
Endocrine-disrupting chemicals (EDCs)-including butyl benzyl phthalate (BBP), perfluorooctanoic acid (PFOA), and zeranol (alpha-ZAL, referred to as ZAL hereafter)-can interfere with the endocrine system and produce adverse effects. It remains unclear whether pubertal exposure to low doses of BBP, PFOA, and ZAL has an impact on breast development and tumorigenesis. We exposed female Sprague Dawley rats to BBP, PFOA, or ZAL through gavage for 21 days, starting on day 21, and analyzed their endocrine organs, serum hormones, mammary glands, and transcriptomic profiles of the mammary glands at days 50 and 100. We also conducted a tumorigenesis study for rats treated with PFOA and ZAL using a 7,12-dimethylbenz[a]anthracene (DMBA) model. Our results demonstrated that pubertal exposure to BBP, PFOA, and ZAL affected endocrine organs and serum hormones, and induced phenotypic and transcriptomic changes. The exposure to PFOA + ZAL induced the most phenotypic and transcriptomic changes in the mammary gland. PFOA + ZAL downregulated the expression of genes related to development at day 50, whereas it upregulated genes associated with tumorigenesis at day 100. PFOA + ZAL exposure also decreased rat mammary tumor latency, reduced the overall survival of rats after DMBA challenge, and affected the histopathology of mammary tumors. Therefore, our study suggests that exposure to low doses of EDCs during the pubertal period could induce changes in the endocrine system and mammary gland development in rats. The inhibition of mammary gland development by PFOA + ZAL might increase the risk of developing mammary tumors through activation of signaling pathways associated with tumorigenesis. http://dx.doi.org/10.3390/ijms23031398

Prenatal Octamethylcyclotetrasiloxane Exposure Impaired Proliferation of Neuronal Progenitor, Leading to Motor, Cognition, Social and Behavioral Functions,
TRAN D. N., S. M. PARK, E. M. JUNG and E. B. JEUNG,
International Journal of Molecular Sciences 22, no. 23 (Dec 2021),
Cyclic siloxane octamethylcyclotetrasiloxane (D4) has raised concerns as an endocrine-disrupting chemical (EDC). D4 is widely used in detergent products, cosmetics, and personal care products. Recently, robust toxicological data for D4 has been reported, but the adverse effects of D4 on brain development are unknown. Here, pregnant mice on gestational day 9.5 were treated daily with D4 to postnatal day 28, and the offspring mice were studied. The prenatal D4-treated mice exhibited cognitive dysfunction, limited memory, and motor learning defect. Moreover, prenatal D4 exposure reduced the proliferation of neuronal progenitors in the offspring mouse brain. Next, the mechanisms through which D4 regulated the cell cycle were investigated. Aberrant gene expression, such as cyclin-dependent kinases CDK6 and cyclin-dependent kinase inhibitor p27, were found in the prenatal D4-treated mice. Furthermore, the estrogen receptors ERa and ERb were increased in the brain of prenatal D4-treated mice. Overall, these findings suggest that D4 exerts estrogen activity that affects the cell cycle progression of neuronal progenitor cells during neurodevelopment, which may be associated with cognitive deficits in offspring. http://dx.doi.org/10.3390/ijms222312949

Implications of peroxisome proliferator-activated receptor gamma (PPARY) with the intersection of organophosphate flame retardants and diet-induced obesity in adult mice,
VAIL G. M., S. N. WALLEY, A. YASREBI, A. MAENG, T. J. DEGROAT, K. M. CONDE and T. A. ROEPKE,
Journal of Toxicology and Environmental Health-Part a-Current Issues 85, no. 9 (May 2022): 381-396,
Previously, organophosphate flame retardants (OPFRs) were demonstrated to dysregulate homeostatic parameters of energy regulation within an adult mouse model of diet-induced obesity. Using the same OPFR mixture consisting of 1 mg/kg/day of each triphenyl phosphate, tricresyl phosphate, and tris(1,3-dichloro-2-propyl)phosphate, the current study examined the role of peroxisome proliferator-activated receptor gamma (PPAR gamma) in OPFR-induced disruption by utilizing mice with brain-specific deletion of PPAR gamma (PPAR gamma KO) fed either a low-fat diet (LFD) or high-fat diet (HFD). Body weight and composition, feeding behavior, glucose and insulin tolerance, circulating peptide hormones, and expression of hypothalamic genes associated with energy homeostasis were recorded. When fed HFD, the effects of OPFR on body weight and feeding behavior observed in the previous wild-type (WT) study were absent in mice lacking neuronal PPAR gamma. This posits PPAR gamma as an important target for eliciting OPFR disruption in a diet-induced obesity model. Interestingly, female PPAR gamma KO mice, but not males, experienced many novel OPFR effects not

noted in WT mice, including decreased fat mass, altered feeding behavior and efficiency, improved insulin sensitivity, elevated plasma ghrelin and hypothalamic expression of its receptor. Taken together, these data suggest both direct roles for PPAR gamma in OPFR disruption of obese mice and indirect sensitization of pathways alternative to PPAR gamma when neuronal expression is deleted.
http://dx.doi.org/10.1080/15287394.2021.2023716

Dietary Exposure to Flame Retardant Tris (2-Butoxyethyl) Phosphate Altered Neurobehavior and Neuroinflammatory Responses in a Mouse Model of Allergic Asthma,
WIN-SHWE T. T., R. YANAGISAWA, T. T. LWIN, F. KAWAKAMI, E. KOIKE and H. TAKANO,
International Journal of Molecular Sciences 23, no. 2 (Jan 2022),
Tris (2-butoxyethyl) phosphate (TBEP) is an organophosphate flame retardant and used as a plasticizer in various household products such as plastics, floor polish, varnish, textiles, furniture, and electronic equipment. However, little is known about the effects of TBEP on the brain and behavior. We aimed to examine the effects of dietary exposure of TBEP on memory functions, their-related genes, and inflammatory molecular markers in the brain of allergic asthmatic mouse models. C3H/HeJSlc male mice were given diet containing TBEP (0.02 (TBEP-L), 0.2 (TBEP-M), or 2 (TBEP-H) mu g/kg/day) and ovalbumin (OVA) intratracheally every other week from 5 to 11 weeks old. A novel object recognition test was conducted in each mouse at 11 weeks old. The hippocampi were collected to detect neurological, glia, and immunological molecular markers using the real-time RT-PCR method and immunohistochemical analyses. Mast cells and microglia were examined by toluidine blue staining and ionized calcium-binding adapter molecule (Iba)-1 immunoreactivity, respectively. Impaired discrimination ability was observed in TBEP-H-exposed mice with or without allergen. The mRNA expression levels of N-methyl-D aspartate receptor subunits Nr1 and Nr2b, inflammatory molecular markers tumor necrosis factor-alpha oxidative stress marker heme oxygenase 1, microglia marker Iba1, and astrocyte marker glial fibrillary acidic protein were significantly increased in TBEP-H-exposed mice with or without allergen. Microglia and mast cells activation were remarkable in TBEP-H-exposed allergic asthmatic mice. Our results indicate that chronic exposure to TBEP with or without allergen impaired object recognition ability accompanied with alteration of molecular expression of neuronal and glial markers and inflammatory markers in the hippocampus of mice. Neuron-glia-mast cells interaction may play a role in TBEP-induced neurobehavioral toxicity.
http://dx.doi.org/10.3390/ijms23020655

Differential Expression Profiles and Potential Intergenerational Functions of tRNA-Derived Small RNAs in Mice After Cadmium Exposure,
ZENG L., J. Z. ZHOU, Y. W. ZHANG, X. F. WANG, M. WANG and P. SU,
Frontiers in Cell and Developmental Biology 9 (Jan 2022),
Cadmium (Cd) is a toxic heavy metal and ubiquitous environmental endocrine disruptor. Previous studies on Cd-induced damage to male fertility mainly focus on the structure and function of testis, including cytoskeleton, blood-testis barrier, and steroidogenesis. Nevertheless, to date, no studies have investigated the effects of Cd exposure on sperm epigenetic inheritance and intergenerational inheritance. In our study, we systematically revealed the changes in sperm tRNA-derived small RNAs (tsRNA) profiles and found that 14 tsRNAs (9 up-regulated and 5 down-regulated) were significantly altered after Cd exposure. Bioinformatics of tsRNA-mRNA-pathway interactions revealed that the altered biological functions mainly were related to ion transmembrane transport, lipid metabolism and cell membrane system. In addition, we focused on two stages of early embryo development and selected two organs to study the impact of these changes on cell membrane system, especially mitochondrion and lysosome, two typical membrane-enclosed organelles. Surprisingly, we found that the content of mitochondrion was significantly decreased in 2-cell stage, whereas remarkably increased in the morula stage. The contents of mitochondrion and lysosome were increased in the testes of 6-day-old offspring and livers of adult offspring, whereas remarkably decreased in the testes of adult offspring. This provides a possible basis to further explore the effects of paternal Cd exposure on offspring health.
http://dx.doi.org/10.3389/fcell.2021.791784

The association between bisphenol A exposure and oxidative damage in rats/mice: A systematic review and meta-analysis,
ZHANG H., R. F. YANG, W. Y. SHI, X. ZHOU and S. J. SUN,
Environmental Pollution 292 (Jan 2022),
Numerous studies reported that BPA could cause oxidative damage to different tissues in rats/mice. This study

aimed to perform a systematic review and meta-analysis of BPA exposure on oxidative damage in rats/mice. A comprehensive literature search was conducted using PubMed, Embase, and Web of Science databases from their inception date until July 18, 2020. 20 eligible articles were included in this study. The results showed that BPA could significantly increase the level of MDA (SMD, 16.88; 95%CI, 12.06-21.71), but there was a significant reduction in the contents of antioxidants, such as GR (-10.46,-13.91 --7.02),CAT (-8.48,-11.66 --5.30),GPx (-9.37,-11.95 --6.80),GST (-7.59,-14.51 --0.67),GSH (-10.64,-13.96 --7.33),and SOD (-6.48,-8.37 --4.58)in rats/mice. Our study provided clear evidence that BPA exposure could significantly induce oxidative damage in rats/mice. And we also found that the degree of oxidative damage was related to BPA dose, target tissue, intervention means, and exposure duration of BPA. http://dx.doi.org/10.1016/j.envpol.2021.118444

Maternal Perinatal Exposure to Dibutyl Phthalate Promotes Ovarian Dysfunction in Adult Female Offspring via Downregulation of TGF-beta 2 and TGF-beta 3,
ZHANG J., K. Y. ZHOU, R. CHENG, M. N. YANG, X. Y. SHEN, X. Y. LUO and L. Z. XU,
Reproductive Sciences (Maternal exposure to dibutyl phthalate (DBP) may result in ovarian dysfunction in female offspring. However, the underlying mechanisms remain elusive. Pregnant Sprague-Dawley rats were intraperitoneally injected with different doses of DBP, estradiol, and corn oil from gestational day 7 until the end of lactation. The reproductive characteristics, mRNA, and protein expression of ovaries for the adult female offspring were compared. KGN cells were cultured in vitro with DBP, estrogen receptor antagonist, or ALK-5 inhibitor. Genes, proteins, estradiol, and progesterone expressed by KGN, cell proliferation, and apoptosis were measured respectively. Maternal perinatal exposure to DBP induced prolonged estrous period, increased secondary follicles, significant decreased mRNA, and protein levels of TGF-beta 2, TGF-beta 3, and TGF-beta R II in ovaries of the adult female offspring, but none difference for serum levels of sex hormones, ovarian TGF-beta 1, and estrogen receptor. The mRNA levels of LHR, FSHR, and CYP19a in ovaries were also decreased. DBP might decrease the mRNA of TGF-beta 2, TGF-beta 3, and TGF-beta R II of KGN. DBP can inhibit the mRNA of CYP19 at 24 h, which might be blocked by the estrogen receptor antagonist, whose effects were attenuated at 48 h. DBP combined with FSH might time-dependently regulate the gene expression of TGF- beta R II, inhibitory at 24 h, but stimulative at 48 h, which could be blocked by the ALK5 inhibitor. However, the protein expressed by KGN was not influenced by DBP. DBP stimulated the proliferation of KGN at 24 h, which could be blocked by estrogen receptor antagonist, but attenuated at 48 h. The progesterone in culture medium secreted by KGN was decreased by DBP at 24 h. Maternal perinatal exposure to DBP induced decreased gene expression of TGF-beta signaling and functional proteins in ovaries of the adult female offspring. Molecular cross-talk between estrogen receptor and TGF-beta signaling pathway may play role in the mechanism of granulosa dysfunction induced by DBP. http://dx.doi.org/10.1007/s43032-021-00785-y