Bulletin de veille Perturbateurs Endocriniens N°17 - Novembre 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

The Health Status of Hispanic Agricultural Workers in Georgia and Florida.

Chicas RC, Elon L, Houser MC, Mutic A, Gallegos EI, Smith DJ, et al. *J Immigr Minor Health*. 2022 Oct;24(5):1129-36.

To examine the health status of Hispanic agricultural workers in Florida and Georgia. Health data from agricultural workers in the Farm Worker Family Health Program (June 2019) and research studies in Florida (May 2015 and May 2019) were examined. Data from 728 agricultural workers were collected through sociodemographic questionnaire and clinical data. In the Florida sample, 83% were overweight or obese, 70% elevated blood pressure, 60% met the definition of prediabetes. In Georgia, 64% were overweight or obese and 67% had elevated blood pressure. Weak correlations were observed between BMI and systolic blood pressure (unadjusted r = 0.20), diastolic blood pressure (unadjusted r = 0.19), and glucose (unadjusted r = 0.14). Adjusting for age and gender did not show statistically significant correlation between BMI and systolic and diastolic blood pressure or glucose. While BMI has been shown to be strongly associated with high blood pressure and

impaired glucose, we found a weak correlation among agricultural workers. Given the common and high use of pesticides and elevated rates of hypertension, impaired glucose, and adiposity in agricultural workers, the public health impact of this relationship may require and lead to occupational reform that protects the health of agricultural workers. Future studies should assess occupational and environmental factors and lifestyle differences between agricultural workers and the general population to better understand these discrepancies in health status.

Lien vers l'article

Environmental and occupational exposure of metals and female reproductive health.

Dutta S, Gorain B, Choudhury H, Roychoudhury S, Sengupta P. *Environ Sci Pollut Res Int*. 2022 Sep;29(41):62067-92.

Untainted environment promotes health, but the last few decades experienced steep upsurge in environmental contaminants posing detrimental physiological impact. The responsible factors mainly include the exponential growth of human population, havoc rise in industrialization, poorly planned urbanization, and slapdash environment management. Environmental degradation can increase the likelihood of human exposure to heavy metals, resulting in health consequences such as reproductive problems. As a result, research into metal-induced causes of reproductive impairment at the genetic, epigenetic, and biochemical levels must be strengthened further. These metals impact upon the female reproduction at all strata of its regulation and functions, be it development, maturation, or endocrine functions, and are linked to an increase in the causes of infertility in women. Chronic exposures to the heavy metals may lead to breast cancer, endometriosis, endometrial cancer, menstrual disorders, and spontaneous abortions, as well as pre-term deliveries, stillbirths. For example, endometriosis, endometrial cancer, and spontaneous abortions are all caused by the metalloestrogen cadmium (Cd); lead (Pb) levels over a certain threshold can cause spontaneous abortion and have a teratogenic impact; toxic amounts of mercury (Hg) have an influence on the menstrual cycle, which can lead to infertility. Impact of environmental exposure to heavy metals on female fertility is therefore a well-known fact. Thus, the underlying mechanisms must be explained and periodically updated, given the growing evidence on the influence of increasing environmental heavy metal load on female fertility. The purpose of this review is to give a concise overview of how heavy metal affects female reproductive health.

Lien vers l'article

Excretion time courses of lambda-cyhalothrin metabolites in the urine of strawberry farmworkers and effect of coexposure with captan.

Bossou YM, Côté J, Mahrouche L, Mantha M, El Majidi N, Furtos A, et al. *Arch Toxicol*. 2022 Sep;96(9):2465-86.

There are limited literature data on the impact of coexposure on the toxicokinetics of pesticides in agricultural workers. Using the largely employed pyrethroid lambda-cyhalothrin (LCT) and fungicide captan as sentinel pesticides, we compared individual temporal profiles of biomarkers of exposure to LCT in strawberry field workers following an application episode of LCT alone or in coexposure with captan. Participants provided all urine voided over a 3-day period after an application of a pesticide formulation containing LCT alone (E1) or LCT mixed with captan (E2), and in some cases following re-entry in treated field (E3). Pyrethroid metabolites were measured in all urine samples, in particular 3-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2-dimethyl-cyclopropanecarboxylic acid

(CFMP), 3-phenoxybenzoic acid (3-PBA), and 4-hydroxy-3-phenoxybenzoic acid (4-OH3PBA). There were no obvious differences in individual concentration-time profiles and cumulative excretion of metabolites (CFMP, 3-PBA, 4-OH3BPA) after exposure to LCT alone or in combination with captan. For most workers and exposure scenarios, CFMP was the main metabolite excreted, but time courses of CFMP in urine did not always follow that of 3-PBA and 4-OH3BPA. Given that the latter metabolites are common to other pyrethroids, this suggests that some workers were coexposed to pyrethroids other than LCT. For several workers and exposure scenarios E1 and E2, values of CFMP increased in the hours following spraying. However, for many pesticide operators, other peaks of CFMP were observed at later times, indicating that tasks other than spraying of LCT-containing formulations contributed to this increased exposure. These tasks were mainly handling/cleaning of equipment used for spraying (tractor or sprayer) or work/inspection in LCT-treated field according to questionnaire responses. Overall, this study provided novel excretion time course data for LCT metabolites valuable for interpretation of biomonitoring data in workers, but also showed that coexposure was not a major determinant of variability in exposure biomarker levels. Our analysis also pointed out the importance of measuring specific metabolites.

Lien vers l'article

Epidémiologie

Aryl hydrocarbon receptor activity in human breast milk and cryptorchidism: A case-control study within the prospective Norwegian HUMIS cohort br,
DESALEGN A. A., B. COLLET, N. ISZATT, H. STIGUM, T. K. JENSEN, L. JONKER, H. BESSELINK, B. VAN DER BURG and M. EGGESBO,
Environmental Research 214 (Nov 2022),
impact estrogen signaling by interacting with aryl hydrocarbon receptor (AhR) activity. Objective: To evaluate whether AhR activity in breast milk samples is associated with cryptorchidism. Method: We conducted a case-control study based on 199 mother-child pairs (n =91 cases/108 controls) selected from the Norwegian Human Milk Study (2002-2009). We defined cases for cryptorchidism based on maternal reports at 1-, 6-, 12-, and 24-months after birth. Chemically- and biologically stable AhR activity (pg 2,3,7,8- TCDD equivalent (TEQ)/g lipid) was determined by DR- CALUX (R) assay in the mothers' milk collected at a median of 33 (10th-90th percentile: 18-57) days after delivery. We used multivariate logistic regression to compare AhR activity levels between cases and controls, and linear regression separately, to establish the relationship with the presence of 27 potential EDCs measured in breast milk and AhR activity. Results: The average estimated daily intake (EDI) of dioxin and (dioxin-like (dl)-compounds via breast milk is 33.7 +/- 17.9 pg TEQ/kg bodyweight per day among Norwegian children. There were no significant differences in AhR activation in breast milk samples between cases with cryptorchidism and controls. Among the 27 chemicals measured in breast milk, AhR activity was (borderline) significantly associated with all dl-PCBs, three non- dioxin-like (ndl)-PCBs (PCB-74, PCB-180, PCB-194) and two organochlorine pesticides (OCPs; HCB, beta-HCH). No associations between AhR activity and brominated flame retardants (PBDEs) or poly- and perfluoroalkyl substances (PFASs). Conclusion: No association between AhR activity and cryptorchidism was found among Norwegian boys. The average EDI of dioxin and dl-compounds in exclusively breastfed Norwegian infants remains above the safety threshold and, therefore requires further reduction measures. Consistent with a possible role in the observed AhR activity, all dl-PCBs were associated with AhR activity whereas the association was null for either PBDEs or PFASs
https://doi.org/10.1016/j.envres.2022.113861

Association between co-exposure to phenols and phthalates mixture and infertility risk in women,
ZHAN W. Q., H. YANG, J. ZHANG and Q. CHEN,
Environmental Research 215 (Dec 2022),
Background: Exposure to phenols and phthalates has been separately linked to increased risks of infertility in women of reproductive age. However, the combined effect of phenols and phthalates exposure on infertility has not been explored. Methods: Data from the National Health and Nutrition Examination Surveys (NHANES) were

used. A total of 857 women of reproductive age (18-45 years) with available information on urinary phenol and phthalate metabolites, reproductive questionnaires, and covariates were included in the present study. The definition of infertility was based on self-reports. Multivariable logistic regression, principal component analysis (PCA), and Bayesian kernel machine regression (BKMR) with stratified variable selection were applied to determine what associations were found between combined exposure to these mixtures and risk of infertility among women of reproductive age. Results: After adjusting for potential confounders, bisphenol A (BPA), mono(3-carboxypropyl) phthalate (MCPP) and four di(2-ethylhexyl) phthalate (DEHP) metabolites [mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP)] were positively associated with infertility. PCA revealed that the DEHP-BPA factor's PC score was significantly positively related to the likelihood of infertility [adjusted odds ratio (aOR) = 1.45; 1.08, 1.82]. The DEHP-BPA component consistently had the highest group posterior inclusion probability (PIP) in BKMR models. The BKMR model also found that MEOHP, MEHHP, and BPA were positively associated with infertility risk when the remaining combination concentrations were held at their median values. In addition, we observed that the probability of infertility increased dramatically as the quantiles of total mixture concentration increased. Conclusion: Our findings indicate that a combination of phenol and phthalate metabolites is linked to infertility among reproductive-age women. BPA and DEHP, in particular, are significantly related to the risk of infertility.
https://doi.org/10.1016/j.envres.2022.114244

Association between trimester-specific exposure to thirteen endocrine disrupting chemicals and preterm birth: Comparison of three statistical models,
CHEN Y. Y., H. XIAO, A. NAMAT, J. LIU, F. Y. RUAN, S. Q. XU, R. Z. LI and W. XIA,
Science of the Total Environment 851 (Dec 2022),
Background: Growing evidence indicated that maternal exposure to some endocrine disrupting chemicals (EDCs) may increase the risk of preterm birth (PTB). However, few studies have evaluated the joint effect of EDCs on PTB.Objectives: This study aimed to evaluate the associations of maternal EDCs mixture in the 1st, 2nd, and 3rd trimesters during pregnancy with PTB, and identify the vital components that mainly contribute to PTB.Methods: This study included 847 pregnant women that provided urine samples for all three trimesters. Urinary concentrations of thirteen EDC metabolites (four phthalates, two parabens, three phenols, and four benzotriazoles and benzothiazoles) were examined. Logistic regression model, quantile g-computation and Bayesian kernel machine re-gression (BKMR) models were applied to study the association.Results: Logistic regression model suggested that only bisphenol A (BPA) in the 1st trimester significantly increased the OR of PTB after adjusting for BPA exposure in the 2nd and 3rd trimesters. Quantile g-computation model identified that urinary EDCs mixture in the 1st trimester were positively associated with PTB [OR (95 % CI): 1.98 (1.10, 3.58)], and the most heavily weighted component for PTB was BPA (26 %), followed by mono-2ethylhexyl phthalate (MEHP) (22 %). BKMR model determined a significant association between EDCs mixture in the 1st trimester and PTB when all EDC concentrations were at or above their 55th percentile compared with the median. The BKMR model found that BPA and MEHP were associated with an increase in the estimated probability of PTB, when the other EDCs were held to their 50th and 75th percentiles, respectively, in the 1st trimester.Conclusions: The results of mixture analysis models indicated that exposure to higher EDCs mixture in the 1st trimester may increase the risk of PTB. BPA was considered as the most contributing factor for PTB among the detected EDCs.
https://doi.org/10.1016/j.scitotenv.2022.158236

Association of exposure to ambient particulate matter with maternal thyroid function in early pregnancy,
ZHANG X. C., A. HUELS, R. MAKUCH, A. F. ZHOU, T. ZHENG, W. XIA, A. GASKINS, J. MAKUCH, Z. ZHU, C. R. ZHU, Z. M. QIAN, S. Q. XU and Y. Y. LI,
Environmental Research 214 (Nov 2022),
Background: It is known that maternal thyroid dysfunction during early pregnancy can cause adverse pregnancy complications and birth outcomes. This study was designed to examine the association between ambient particulate matter with aerodynamic diameters <= 2.5 mu m (PM2.5) and particulate matter with aerodynamic diameters <= 10 mu m (PM10) exposure and maternal thyroid function during early pregnancy.Methods: This study was based on data from a birth cohort study of 921 pregnant women in China. We estimated associations between ambient PM2.5 and PM10 exposure during the first trimester of pregnancy (estimated with land-use regression models) and maternal thyroid hormone concentrations (free thyroxine (FT4), free tri-iodothyronine (FT3), and thyroid-stimulating hormone (TSH)) collected between weeks 10 and 17 of gesta-tion using linear

regression models adjusting for potential confounders. Ambient PM2.5 and PM10 concentrations were modeled per interquartile range (IQR) increment and as tertiles based on the distribution of the exposure levels. Results: An IQR increment (68 mu g/m3) in PM2.5 exposure was associated with a significant decrease in maternal FT4 levels (8 =-0.60, 95% CI:-1.07,-0.12); and a significant decrease in FT4/FT3 ratio (8 =-0.13, 95% CI:-0.25,-0.02). Further analyses showed that, relative to the lowest tertile, women in both the middle and highest tertiles of PM2.5 had significantly lower concentrations of maternal FT4 and FT4/FT3 ratio. No significant associations were found between PM2.5 and FT3 or TSH levels. PM10 exposure was not significantly associated with maternal thyroid function. Conclusions: Our study suggested that higher ambient PM2.5, not PM10, exposed during the first trimester of pregnancy were associated with a significant decrease in maternal serum FT4 concentrations and FT4/FT3 ratio. Studies in populations with different exposure levels are needed to replicate our study results. https://doi.org/10.1016/j.envres.2022.113942

Association of per- and polyfluoroalkyl substances with thyroid homeostasis during pregnancy in the SELMA study,
DERAKHSHAN A., A. KORTENKAMP, H. SHU, M. A. C. BROEREN, C. H. LINDH, R. P. PEETERS, C. G. BORNEHAG, B. DEMENEIX and T. I. M. KOREVAAR,
Environment International 167 (Sep 2022),
Objectives: To investigate the association of exposure to per- and polyfluoroalkyl substances (PFAS) during early pregnancy with markers of the maternal thyroid system. Methods: Serum concentrations of seven PFAS as well as thyroid stimulating hormone (TSH), free and total thyroxine (FT4 and TT4), free and total triiodothyronine (FT3 and TT3) were measured in pregnant women in early pregnancy in the Swedish Environmental Longitudinal, Mother and child, Asthma and allergy (SELMA) study. Outcomes were concentrations of TSH and thyroid hormones, FT4/FT3 or TT4/TT3 ratios, TSH/FT4 ratio as a marker of the negative feedback loop, TT4/FT4 or TT3/FT3 ratios as markers of the binding of thyroid hormones to binding proteins. Results: The study population comprised 2,008 women with median (95% range) gestational age of 10 (6-14) weeks. There was no association between PFAS and TSH. Higher PFNA, PFDA, PFHpA and PFOA levels were associated with a higher FT4 (largest effect estimate for PFDA: beta [95% CI]: 0.27 [0.10 to 0.45], P = 0.002). Higher PFUnDA levels, but no other PFAS, were associated with a lower FT3 beta [95% CI]: -0.05 [-0.09 to -0.01], P = 0.005). Higher PFUnDA levels were associated with lower TT4 beta [95% CI]: -1.58 [-3.07 to -0.09]) and there was an inverted U-shaped association of PFOS with TT4 (P = 0.03). Higher PFDA, PFUnDA, PFHpA levels were associated with a lower TT3. Overall, higher PFAS concentrations were associated with a higher FT4/FT3 ratio and a higher TT4/TT3 ratio. There was no association of PFAS with the TSH/FT4 ratio. Higher concentrations of several PFAS were associated with lower TT4/FT4 and TT3/FT3 ratios. Conclusions: These findings translate results from experimental studies suggesting that exposure to PFAS may interfere with the thyroid system during pregnancy. Further experimental studies should take into account human evidence to better understand the potential underlying mechanisms of thyroid disruption by PFAS exposure. https://doi.org/10.1016/j.envint.2022.107420

Association of preconception mixtures of phenol and phthalate metabolites with birthweight among subfertile couples,
ZHANG Y., V. MUSTIELES, P. L. WILLIAMS, I. SOUTER, A. M. CALAFAT, M. DEMOKRITOU, A. LEE, S. VAGIOS, R. HAUSER and C. MESSERLIAN,
Environmental Epidemiology 6, no. 5 (Oct 2022),
Background: Although parental preconception exposure to some phenols and phthalates have been associated with reduced birthweight, few studies have examined these chemicals as complex mixtures. Methods: We included 384 mothers and 211 fathers (203 couples) who gave birth to 384 singletons from a prospective cohort of couples seeking fertility evaluation. Urinary concentrations of bisphenol A (BPA), parabens, and 11 phthalate metabolites including those of di(2-ethylhexyl) phthalate (DEHP) were examined. Birthweight was abstracted from delivery records. We used principal component analysis and Bayesian Kernel Machine Regression (BKMR) to examine maternal and paternal preconception mixtures in relation to singleton birthweight. We also fit couple-based BKMR with hierarchical variable selection to assess couples' joint mixtures in relation to birthweight. Results: PC scores of maternal and paternal preconception low molecular weight phthalates factor, and paternal preconception DEHP-BPA factor were associated with reduced birthweight. In BKMR models, we found that maternal preconception monoethyl phthalate and BPA concentrations, and paternal preconception mono-n-butyl phthalate concentrations were inversely associated with birthweight when the remaining mixture components were held at their median concentrations. In couple-based BKMR models, paternal preconception

biomarkers contributed more to couples' joint effect on birthweight compared with maternal preconception biomarkers. A decreasing trend of birthweight was observed across quantiles of maternal, paternal, and couples' total preconception mixture concentrations, respectively. Conclusions: Results from this preconception cohort of subfertile couples suggest a complex interplay between paternal and maternal preconception exposure to mixtures of nonpersistent chemicals, with both parental windows of exposure jointly contributing to reduced birthweight. https://doi.org/10.1097/ee9.0000000000000222

Associations Between Prenatal Urinary Biomarkers of Phthalate Exposure and Preterm Birth: A Pooled Study of 16 US Cohorts,
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JAMA Pediatrics 176, no. 9 (2022): 895-905,
Phthalate exposure is widespread among pregnant women and may be a risk factor for preterm birth.To investigate the prospective association between urinary biomarkers of phthalates in pregnancy and preterm birth among individuals living in the US.Individual-level data were pooled from 16 preconception and pregnancy studies conducted in the US. Pregnant individuals who delivered between 1983 and 2018 and provided 1 or more urine samples during pregnancy were included.Urinary phthalate metabolites were quantified as biomarkers of phthalate exposure. Concentrations of 11 phthalate metabolites were standardized for urine dilution and mean repeated measurements across pregnancy were calculated.Logistic regression models were used to examine the association between each phthalate metabolite with the odds of preterm birth, defined as less than 37 weeks of gestation at delivery (n = 539). Models pooled data using fixed effects and adjusted for maternal age, race and ethnicity, education, and prepregnancy body mass index. The association between the overall mixture of phthalate metabolites and preterm birth was also examined with logistic regression. G-computation, which requires certain assumptions to be considered causal, was used to estimate the association with hypothetical interventions to reduce the mixture concentrations on preterm birth.The final analytic sample included 6045 participants (mean [SD] age, 29.1 [6.1] years). Overall, 802 individuals (13.3%) were Black, 2323 (38.4%) were Hispanic/Latina, 2576 (42.6%) were White, and 328 (5.4%) had other race and ethnicity (including American Indian/Alaskan Native, Native Hawaiian, >1 racial identity, or reported as other). Most phthalate metabolites were detected in more than 96% of participants. Higher odds of preterm birth, ranging from 12% to 16%, were observed in association with an interquartile range increase in urinary concentrations of mono-n-butyl phthalate (odds ratio [OR], 1.12 [95% CI, 0.98-1.27]), mono-isobutyl phthalate (OR, 1.16 [95% CI, 1.00-1.34]), mono(2-ethyl-5-carboxypentyl) phthalate (OR, 1.16 [95% CI, 1.00-1.34]), and mono(3-carboxypropyl) phthalate (OR, 1.14 [95% CI, 1.01-1.29]). Among approximately 90 preterm births per 1000 live births in this study population, hypothetical interventions to reduce the mixture of phthalate metabolite levels by 10%, 30%, and 50% were estimated to prevent 1.8 (95% CI, 0.5-3.1), 5.9 (95% CI, 1.7-9.9), and 11.1 (95% CI, 3.6-18.3) preterm births, respectively.Results from this large US study population suggest that phthalate exposure during pregnancy may be a preventable risk factor for preterm delivery.
https://doi.org/10.1001/jamapediatrics.2022.2252

Associations between repeated measurements of childhood triclosan exposure and physical growth at 7 years,
CHEN M. Y., Y. HU, C. LV, R. SHI, Y. ZHANG, W. F. TANG, X. D. YU, Y. TIAN and Y. GAO,
Chemosphere 307 (Nov 2022),
Background: Epidemiological studies suggested that triclosan (TCS) exposure was ubiquitous among children and could affect their physical growth. However, most studies relied on TCS exposure at single time point, and the impacts of multiple time points TCS exposure were unclear.Objectives: To estimate the associations between repeated TCS measurements in childhood (at ages 1, 2, 5, and 7 years) and physical growth at 7 years.Methods: This study included 206 children from Laizhou Wan Birth Cohort (LWBC), China. Urinary TCS con-centrations were detected at age of 1, 2, 5, and 7 years, and physical growth including height, weight, waist circumference, and fat percentage was measured at 7 years. Multiple informant models were applied to examine the relationships of repeated TCS measurements in childhood with physical growth, and stratified analysis by gender was performed. Results: The detection rates of TCS at age of 1, 2, 5, and 7 years were above 60%, with median declining from 0.89 to 0.33 mu g/g creatinine. We found TCS at 5 years was positively associated with waist-to-height ratio, and TCS at 7 years was positively associated with physical growth, including weight z-score, BMI z-score, waist circumference, waist-to-height ratio, and fat percentage. Moreover, the above associations for

weight z-score, BMI z-score, and fat percentage significantly varied by the period of exposure (pint < 0.05). After stratified by gender, positive associations were only found among boys.Conclusions: In our study, TCS levels decreased as children's age increased. TCS exposures at age of 5 and 7 years were positively associated with physical growth at 7 years, and these associations were only significant in boys. Given the relatively small sample size, our findings should be interpreted with caution until confirmed by further investigation.
https://doi.org/10.1016/j.chemosphere.2022.135970

Associations of prepubertal urinary phthalate metabolite concentrations with pubertal onset among a longitudinal cohort of boys,
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Environmental Research 212 (Sep 2022),
Background: Although phthalate exposures have been associated with adverse effects on male reproductive health, few studies have explored longitudinal associations with male pubertal development. Objectives: We examined the association of prepubertal urinary concentrations of phthalate metabolites with age at pubertal onset in a prospective cohort of Russian boys. Methods: At enrollment at ages 8-9 years, medical history, dietary, and demographic information was collected. At entry and annually, physical examinations and pubertal staging [Genitalia (G), Pubarche (P), and testicular volume (TV, in ml)] were conducted and spot urines were collected. Prepubertal urine samples (defined as either TV = 1, 2 and G = 1, 2 or TV = 3 and G = 1) were pooled for each boy and phthalate metabolite concentrations were quantified using isotope dilution LC-MS/MS at Moscow State University. We measured 15 metabolites including those from anti-androgenic parent phthalates (AAPs) such as di (2-ethylhexyl) (DEHP) and di-isononyl (DiNP) phthalates as well as monobenzyl (MBzP), mono-n-butyl (MnBP), and mono-isobutyl (MiBP) metabolites. We calculated the molar sums of DEHP (Sigma DEHP), DiNP (Sigma DiNP), and AAP (Sigma AAP) metabolites. Separate interval-censored models were used to assess associations of quartiles of prepubertal phthalate metabolites with each pubertal onset indicator, G2+, P2+ and TV > 3 mL, adjusted for covariates and urine specific gravity. Results: 304 boys had 752 prepubertal urine samples (median 2, range: 1-6) for pooling. In adjusted models, higher urinary AAPs were consistently associated with later pubertal onset (P2) with mean shifts ranging from 8.4 to 14.2 months for the highest versus lowest quartiles. Significantly later onset for G2 and TV > 3 mL was observed for higher versus lower quartiles of MiBP, MBzP, Sigma DEHP and Sigma DiNP. Conclusions: On average, boys with higher concentrations of prepubertal urinary AAPs had later pubertal onset by six months to over a year. The impact of AAPs on timing of male puberty may be attributable to disruption of androgen-dependent biological pathways.
https://doi.org/10.1016/j.envres.2022.113218

Benchmark dose approach in investigating the relationship between blood metal levels and reproductive hormones: Data set from human study,
BARALIC K., D. JAVORAC, D. MARIC, D. DUKIC-COSIC, Z. BULAT, E. A. MILJAKOVIC, M. ANDELKOVIC, B. ANTONIJEVIC, M. ASCHNER and A. B. DJORDJEVIC,
Environment International 165 (Jul 2022),
https://doi.org/10.1016/j.envint.2022.107313

Benchmark dose approach in investigating the relationship between blood metal levels and reproductive hormones: Data set from human study,
BARALIC K., D. JAVORAC, D. MARIC, D. DUKIC-COSIC, Z. BULAT, E. A. MILJAKOVIC, M. ANDELKOVIC, B. ANTONIJEVIC, M. ASCHNER and A. B. DJORDJEVIC,
Environment International 165 (Jul 2022),
The main objective of this research was to conduct a dose-response modeling between the internal dose of measured blood Cd, As, Hg, Ni, and Cr and hormonal response of serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The study included 207 male participants from subjects of 5 different cohorts (patients with prostate, testicular, and pancreatic cancer, patients suffering from various thyroid and metabolic disorders, as well as healthy volunteers), enrolled from January 2019 to May 2021 at the Clinical Centre of Serbia in Belgrade, Serbia. Benchmark dose-response modeling analysis was performed with the PROAST software version 70.1, showing the hormone levels as quantal data. The averaging technique was applied to compute the Benchmark dose (BMD) interval (BMDI), with benchmark response set at 10%.

Doseresponse relationships between metal/metalloid blood concentration and serum hormone levels were confirmed for all the investigated metals/metalloid and hormones. The narrowest BMDI was found for Cdtestosterone and Hg-LH pairs, indicative of high confidence in these estimates. Although further research is needed, the observed findings demonstrate that the BMD approach may prove to be significant in the dose-response modeling of human data. https://doi.org/10.1016/j.envint.2022.107313

Bisphenol A analogues in associations with serum hormone levels among reproductive-aged Chinese men,
ZENG J. Y., P. P. CHEN, C. LIU, Y. L. DENG, Y. MIAO, M. ZHANG, F. P. CUI, T. T. LU, T. SHI, K. D. YANG, C. J. LIU and Q. ZENG,
Environment International 167 (Sep 2022),
Background: Bisphenol A (BPA) as an endocrine disrupting chemical has been shown to alter reproductive endocrine function, but little is known on its analogues such as bisphenol F (BPF) and bisphenol S (BPS) with increasing usage and exposure. Objective: To explore the associations between exposures to BPA, BPF and BPS and serum reproductive hormones among reproductive-aged Chinese men. Methods: We measured BPA, BPF and BPS concentrations in repeated urine samples and multiple reproductive hormones in the serum samples collected from 462 men attending an infertility clinic in Wuhan, China. Linear regression models were applied to assess the associations between averaged urinary BPA, BPF and BPS levels and serum hormone concentrations, and restricted cubic spline (RCS) models were further utilized to explore potential non-linear associations. We also examined potential modifying effects by age and body mass index (BMI). Results: There was little evidence of associations between BPA exposure and altered reproductive hormones. However, we found that elevated BPF and BPS exposures were in negative associations with estrogen (E2) levels and E2/T (total testosterone) ratio (all P for trends < 0.05), and that elevated BPS exposure was negatively associated with SHBG levels (P for trend = 0.09). Based on the RCS models, these linear negative associations except that between BPS exposure and E2/T ratio were further confirmed. In stratified analyses, BPF and BPS exposures in relation to reduced E2 and E2/T ratio were more pronounced among men aged > 30 years, whereas their associations with reduced SHBG levels were more pronounced among men aged <= 30. Also, BPS exposure in negative association with FSH only emerged among men with BMI >= 24 kg/m(2) (P for interaction = 0.03). Conclusion: BPF and BPS exposures were negatively associated with male serum E2, E2/T ratio and SHBG levels, and these associations varied by age and BMI. https://doi.org/10.1016/j.envint.2022.107446

Developmental programming: Impact of prenatal bisphenol-A exposure on liver and muscle transcriptome of female,
PUTTABYATAPPA M., N. SAADAT, V. R. ELANGOVAN, J. DOU, K. BAKULSKI and V. PADMANABHAN,
Toxicology and Applied Pharmacology 451 (Sep 2022),
Gestational Bisphenol A (BPA) exposure leads to peripheral insulin resistance, and hepatic and skeletal muscle oxidative stress and lipotoxicity during adulthood in the female sheep offspring. To investigate transcriptional changes underlying the metabolic outcomes, coding and non-coding (nc) RNA in liver and muscle from 21-month-old control and prenatal BPA-treated (0.5 mg/kg/day from days 30 to 90 of gestation; Term: 147 days) female sheep were sequenced. Prenatal BPA-treatment dysregulated: expression of 194 genes (138 down, 56 up) in liver and 112 genes (32 down, 80 up) in muscle (FDR < 0.05 and abs log2FC > 0.5); 155 common gene pathways including mitochondrial-related genes in both tissues; 1415 gene pathways including oxidative stress and lipid biosynthetic process specifically in the liver (FDR < 0.01); 192 gene pathways including RNA biosynthetic processes in muscle (FDR < 0.01); 77 lncRNA (49 down, 28 up), 14 microRNAs (6 down, 8 up), 127 snoRNAs (63 down, 64 up) and 55 snRNAs (15 down, 40 up) in the liver while upregulating 6 lncRNA and dysregulating 65 snoRNAs (47 down, 18 up) in muscle (FDR < 0.1, abs log2FC > 0.5). Multiple ncRNA correlated with LCORL, MED17 and ZNF41 mRNA in liver but none of them in the muscle. Discriminant analysis identified (p < 0.05) PECAM, RDH11, ABCA6, MIR200B, and MIR30B in liver and CAST, NOS1, FASN, MIR26B, and MIR29A in muscle as gene signatures of gestational BPA exposure. These findings provide mechanistic clues into the development and/or maintenance of the oxidative stress and lipid accumulation and potential for development of mitochondrial and fibrotic defects contributing to the prenatal BPA-induced metabolic dysfunctions. https://doi.org/10.1016/j.taap.2022.116161

Effect of perfluoroalkyl exposure in pregnancy and infancy on intrauterine and childhood growth and anthropometry. Sub study from COPSAC2010 birth cohort,
SEVELSTED A., G. GURDENIZ, D. RAGO, C. E. T. PEDERSEN, J. A. LASKY-SU, A. CHECA, P. ZHANG, C. E. WHEELOCK, S. S. NORMANN, D. M. KRISTENSEN, M. A. RASMUSSEN, J. SCHULLEHNER, K. SDOUGKOU, J. W. MARTIN, J. STOKHOLM, K. BONNELYKKE, H. BISGAARD and B. CHAWES,
Ebiomedicine 83 (Sep 2022),
Background Perfluoroalkyl substances PFOS and PFOA are persistent and bioaccumulative exogenous chemicals in the human body with a range of suspected negative health effects. It is hypothesised that exposure during prenatal and early postnatal life might have particularly detrimental effects on intrauterine and childhood growth. In a Dan-ish longitudinal mother-child cohort we investigate effect of PFOS and PFOA in pregnancy and infancy on intrauter-ine and childhood growth and anthropometry. Methods COPSAC2010 is an ongoing population based mother-child cohort of 738 pregnant women and their children followed from 24 week gestation with longitudinal deep clinical phenotyping until age 10 years. In this observational cohort sub study plasma PFOS and PFOA concentrations were semi-quantified by untargeted metabolomics in the mothers at week 24 and 1 week postpartum and in the children at ages 6 and 18 months and calibrated using a targeted pipe-line. We examined associations to intrauterine and childhood growth and anthropometry, including interactions with child sex. Untargeted and targeted blood metabolomics profiles were integrated to investigate underlying mechanisms. Findings Pregnancy plasma PFOA concentrations were associated with lower birth size -0.19 [-0.33; -0.05] BMI z-score per 1-ng/mL and increased childhood height (z-scored) at age 6: 0.18 [0.05; 0.31], but there was no association between childs' own infancy plasma PFOA concentration and height. Pregnancy plasma PFOS concentrations were also associated with lower birth BMI (-0.04 [-0.08; -0.01]), but in childhood pregnancy plasma PFOS con-centration interacted with child sex on BMI and fat percentage at 6 years with negative associations in girls and positive in boys. The effect of maternal plasma PFOS concentration on lower girl BMI was borderline mediated through increasing child plasma lactosyl-ceramide levels (p-mediation=0.08). Similarly the effect of maternal plasma PFOS concentration on higher boy fat percentage was borderline mediated through increasing child plasma lactosyl-ceramide levels (p-mediation=0.07). Infancy concentrations of plasma PFOS associated with lower height in childhood, -0.06 z-score at age 6 [-0.19; -0.03]. Interpretation Higher PFOS and PFOA plasma concentrations during pregnancy had detrimental effects on fetal growth. The effects on childhood growth were not similar as PFOA increased child height, opposite of PFOS in mul-tipollutant models suggesting a differing fetal programming effect. Sex specific growth effects were borderline medi-ated through an altered lactosyl-ceramide metabolism, proposing a possible mechanism of PFOS that has long-lasting health consequences in this observational study.Funding All funding received by COPSAC are listed on www.copsac.com. The Lundbeck Foundation (Grant no R16 -A1694); The Novo Nordic Foundation (Grant nos NNF20OC0061029, NNF170C0025014, NNF180C0031764) The Ministry of Health (Grant no 903516); Danish Council for Strategic Research (Grant no 0603-00280B) and The Capital Region Research Foundation have provided core support to the COPSAC research center. Effort from JALS is supported by R01HL123915, R01HL141826, and R01HL155742 from NIH/NHLBI. CEW was supported by the Swedish Heart Lung Foundation (HLF 20180290, HLF 20200693). BC has received funding for this project from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation pro-gramme (grant agreement No. 946228). The funding agencies did not have any role in design and conduct of the study; collection, management, and interpretation of the data; or preparation, review, or approval of the manuscript.
https://doi.org/10.1016/j.ebiom.2022.104236

Exploring associations between urine levels of phthalates and autism spectrum disorder symptoms: a case-control study in Tianjin, China,
HAN Y., S. H. JIN, L. Y. LIU, Z. Y. QU, L. GAO, P. Y. LI, W. J. XIONG and X. ZHANG,
Environmental Science and Pollution Research 29, no. 53 (Nov 2022): 80805-80816,
https://doi.org/10.1007/s11356-022-21526-x

Exploring associations between urine levels of phthalates and autism spectrum disorder symptoms: a case-control study in Tianjin, China,
HAN Y., S. H. JIN, L. Y. LIU, Z. Y. QU, L. GAO, P. Y. LI, W. J. XIONG and X. ZHANG,
Environmental Science and Pollution Research 29, no. 53 (Nov 2022): 80805-80816,
Autism spectrum disorder (ASD) comprises a group of neurodevelopmental disorders. The etiology of autism remains unclear, but a growing body of evidence indicates that phthalates play a role in its pathogenesis. The

aim of this study was to compare the urine levels of phthalates in children with ASD and healthy children. We also explored whether phthalates have an effect on ASD symptoms. The participants in this study included 101 children with ASD (79 boys and 22 girls) and 101 sex- and age-matched controls. The levels of phthalates were analyzed by gas chromatography-mass spectrometry (GC-MS). We detected significant differences in monoethyl phthalate (MEP) levels between the severe ASD and control groups ($p < 0.05$). Mono-n-butyl phthalate (MBP) concentration was positively correlated with language skill impairment in ASD (beta: 0.387, $p = 0.041$). MEP levels were associated with the CARS "Imitation" score in all children (OR: 1.470). MBP levels were associated with the "Nonverbal Communication" score among boys (OR: 1.233), and MEP levels were associated with the "Nonverbal Communication" score among girls (OR: 2.648). MEP levels were related to the CARS total score after adjustment for sex (beta: 1.524, $p = 0.047$). Compared with the reference mono(2-ethylhexyl) phthalate (MEHP) group, children with ASD in the medium-exposure group had an OR of 3.370 for aggravating ASD severity. These results suggested that increased exposure to phthalates contributes to more ASD symptoms and that there are potentially sex-specific associations. These findings warrant further confirmation.
https://doi.org/10.1007/s11356-022-21526-x

Exposure to Bisphenol A increases malignancy risk of thyroid nodules in overweight/obese patients,
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Environmental Pollution 316 (Jan 2023),
Bisphenol A (BPA) is a widespread thyroid disruptor, but evidence about an association with thyroid cancer is weak. Excess body weight is a risk factor for thyroid cancer and affects activity of endocrine disruptors. Aim of the study was to investigate the association between BPA exposure and thyroid cancer, verifying the effect modification related to body weight.We performed a multicentre, cross-sectional study including consecutive patients referring for nodular goiter. The quantitative determination of BPA in serum samples was performed through high performance liquid chromatography system, coupled in tandem with ultraviolet and fluorescence detection.Ninety-six patients were included: 55 benign nodules, 41 thyroid cancers, 28 normal weight, and 68 overweight/obese. BPA was detected in 79 subjects. In the overall study population and in the group with BMI<25 kg/m2 BPA exposure was not significantly correlated to thyroid cancer ($p = 0.08$ and 0.759, respectively). In the group with BMI >= 25 kg/m2, BPA-exposed subjects showed significantly higher risk of malignancy (OR: 5.3, $p = 0.028$). At multivariate analysis, such association was independent of smoking, alcohol consumption, occupational exposure, and phthalates exposure ($p = 0.021$ and 0.016, respectively), but was lost after adjustment for the presence of metabolic syndrome ($p = 0.089$). In overweight/obese subjects, BPA exposure was significantly associated with higher thyroid stimulating hormone levels.Our study suggests that BPA exposure is a risk factor for thyroid cancer in overweight/obese subjects.
https://doi.org/10.1016/j.envpol.2022.120478

Exposure to polycyclic aromatic hydrocarbons during pregnancy and breast tissue composition in adolescent daughters and their mothers: a prospective cohort study,
KEHM R. D., E. J. WALTER, S. OSKAR, M. L. WHITE, P. TEHRANIFAR, J. B. HERBSTMAN, F. PERERA, L. LILGE, R. L. MILLER and M. B. TERRY,
Breast Cancer Research 24, no. 1 (Jul 2022),
Background Polycyclic aromatic hydrocarbons (PAH), which are found in air pollution, have carcinogenic and endocrine disrupting properties that might increase breast cancer risk. PAH exposure might be particularly detrimental during pregnancy, as this is a time when the breast tissue of both the mother and daughter is undergoing structural and functional changes. In this study, we tested the hypothesis that ambient PAH exposure during pregnancy is associated with breast tissue composition, measured one to two decades later, in adolescent daughters and their mothers. Methods We conducted a prospective analysis using data from a New York City cohort of non-Hispanic Black and Hispanic mother-daughter dyads (recruited 1998-2006). During the third trimester of pregnancy, women wore backpacks containing a continuously operating air sampling pump for two consecutive days that measured ambient exposure to eight carcinogenic higher molecular weight nonvolatile PAH compounds (sigma 8 PAH) and pyrene. When daughters (n = 186) and mothers (n = 175) reached ages 11-20 and 29-55 years, respectively, optical spectroscopy (OS) was used to evaluate measures of breast tissue composition (BTC) that positively (water content, collagen content, optical index) and negatively (lipid content) correlate with mammographic breast density, a recognized risk factor for breast cancer. Multivariable linear regression was used to evaluate associations between ambient PAH exposure and BTC,

overall and by exposure to household tobacco smoke during pregnancy (yes/no). Models were adjusted for race/ethnicity, age, and percent body fat at OS. Results No overall associations were found between ambient PAH exposure (sigma 8 PAH or pyrene) and BTC, but statistically significant additive interactions between sigma 8 PAH and household tobacco smoke exposure were identified for water content and optical index in both daughters and mothers (interaction p values < 0.05). sigma 8 PAH exposure was associated with higher water content (beta(daughters) = 0.42, 95% CI = 0.15-0.68; beta(mothers) = 0.32, 95% CI = 0.05-0.61) and higher optical index (beta(daughters) = 0.38, 95% CI = 0.12-0.64; beta(mothers) = 0.38, 95% CI = 0.12-0.65) in those exposed to household tobacco smoke during pregnancy; no associations were found in non-smoking households (interaction p values < 0.05). Conclusions Exposure to ambient sigma 8 PAH and tobacco smoke during pregnancy might interact synergistically to impact BTC in mothers and daughters. If replicated in other cohorts, these findings might have important implications for breast cancer risk across generations. https://doi.org/10.1186/s13058-022-01546-8

Impact of Pesticides on Cancer and Congenital Malformation: A Systematic Review,
MELANDA V. S., M. E. A. GALICIOLLI, L. S. LIMA, B. C. FIGUEIREDO and C. S. OLIVEIRA,
Toxics 10, no. 11 (Nov 2022),
Pesticide exposure has deleterious effects on human health and development; however, no review has been conducted on human exposure to pesticides and the risk of congenital malformations and cancer in the same cohort. We systematically reviewed the evidence for this relationship following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. Four databases, namely, PubMed, Scopus, Cochrane Library, and BVS, were searched for studies deposited till July 2020 that examined the influence of pesticide exposure on congenital malformations and cancer outcomes in the same cohort. Seven studies were systematically included in this review. Among these, four were case-control studies, two were cross-sectional studies, and one was a longitudinal cohort study. The sources of contamination were food, water, or exposure during agricultural work. A link between the occurrence of cancer, congenital malformations, and exposure to pesticides was observed in most studies. https://doi.org/10.3390/toxics10110676

The Influence of Triclosan on the Thyroid Hormone System in Humans-A Systematic Review,
HOMBURG M., A. K. RASMUSSEN, L. RAMHOJ and U. FELDT-RASMUSSEN,
Frontiers in Endocrinology 13 (Jun 2022),
https://doi.org/10.3389/fendo.2022.883827

The Influence of Triclosan on the Thyroid Hormone System in Humans-A Systematic Review,
HOMBURG M., A. K. RASMUSSEN, L. RAMHOJ and U. FELDT-RASMUSSEN,
Frontiers in Endocrinology 13 (Jun 2022),
Objectives: Triclosan is an antibacterial agent suspected to disrupt the endocrine system. The aim of this study was to investigate the influence of triclosan on the human thyroid system through a systematic literature review of human studies. Methods: Eligibility criteria and method of analysis were registered at Prospero (registration number: CRD42019120984) before a systematic search was conducted in Pubmed and Embase in October 2020. Seventeen articles were found eligible for inclusion. Thirteen studies were observational, while four had a triclosan intervention. Participants consisted of pregnant women in eight studies, of men and non-pregnant women in seven studies and of chord samples/newborns/children/adolescents in six studies. The outcomes were peripheral thyroid hormones and thyroid-stimulating hormone (TSH) in blood samples. Results: Several studies found a negative association between triclosan and triiodothyronine and thyroxine, and a positive association with TSH; however, the opposite associations or no associations were also found. In general, the studies had limited measurement timepoints of thyroid outcomes, and the interventional studies used low concentrations of triclosan. Thus, study design limitations influence the quality of the dataset and it is not yet possible to conclude whether triclosan at current human exposure levels adversely affects the thyroid hormone system. Conclusions: Further larger studies with more continuity and more elaborate outcome measurements of thyroid function are needed to clarify whether triclosan, at current exposure levels, affects the human thyroid hormone system. https://doi.org/10.3389/fendo.2022.883827

Longitudinal effects of prenatal exposure to plastic-derived chemicals and their metabolites on asthma and lung function from childhood into adulthood,
FOONG R. E., P. FRANKLIN, F. SANNA, G. L. HALL, P. D. SLY, E. B. THORSTENSEN, D. A. DOHERTY, J. A. KEELAN and R. J. HART,
Respirology (Background and Objective Environmental exposure to phthalates and bisphenol A (BPA), chemicals used in the production of plastics, may increase risk for asthma and allergies. However, little is known about the long-term effects of early life exposure to these compounds. We investigated if prenatal exposure to these compounds was associated with asthma, allergy and lung function outcomes from early childhood into adulthood in a cohort study. Methods Maternal serum samples collected from 846 pregnant women in the Raine Study were assayed for BPA and phthalate metabolites. The children of these women were followed up at 5, 13 and 22 years where spirometry and respiratory questionnaires were conducted to determine asthma and allergy status. Lung function trajectories were derived from longitudinal spirometry measurements. Multinomial logistic regression and weighted quantile sum regression was used to test associations of individual and chemical mixtures with asthma phenotypes and lung function trajectories. Results Effects of prenatal BPA and phthalates on asthma phenotypes were seen in male offspring, where BPA was associated with increased risk for persistent asthma, while mono-iso-butyl phthalate and mono-iso-decyl phthalate was associated with increased risk for adult asthma. Prenatal BPA had no effect on lung function trajectories, but prenatal phthalate exposure was associated with improved lung function. Conclusion Prenatal BPA exposure was associated with increased likelihood of persistent asthma in males, while prenatal phthalate exposure was associated with increased likelihood of adult asthma in males. Results suggest that prenatal exposure to prenatal BPA and phthalates affect asthma risk, particularly in males, however lung function was not adversely affected.
https://doi.org/10.1111/resp.14386

Mixed exposure to phenol, parabens, pesticides, and phthalates and insulin resistance in NHANES: A mixture approach,
BAI J. J., Y. D. Y. MA, Y. D. ZHAO, D. H. YANG, S. MUBARIK and C. H. YU,
Science of the Total Environment 851 (Dec 2022),
Purpose: The effects of environmental chemicals on insulin resistance have attracted extensive attention. Previous studies typically focused on the single chemical effects. This study adopted three different models to analyze the mixed effects of nine common chemicals (one phenol, two parabens, two chlorophenols and four phthalates) on insulin resistance. Methods: Urinary concentrations of chemicals were extracted from National Health and Nutrition Examination Survey (NHANES) 2009-2016. Insulin resistance was assessed using homeostatic model assessment (HOMA) and defined as HOMA-IR > 2.6. The generalized linear regression (GLM), weighted quantile sum regression (WQS) and Bayesian kernel machine regression models (BKMR) were applied to assess the relationship between chemical mixture and HOMA-IR or insulin resistance. Results: Of the 2067 participants included, 872 (42.19 %) were identified as insulin resistant. In single-chemical GLM model, di-2-ethylhexyl phthalate (DEHP) had the highest parameter (beta/OR, 95 % CIs) of 0.21 (quartile 4, 0.12- 0.29) and 1.95 (quartile 4, 1.39- 2.74). Similar results were observed in the multi-chemical models, with DEHP (quartile 4) showing the positive relationship with HOMA-IR (0.18, 0.08- 0.28) and insulin resistance (1.76, 1.17- 2.64). According to WQS models, the WQS indices were significantly positively correlated with both HOMA-IR (beta: 0.07, 95 % CI: 0.03- 0.12) and insulin resistance (OR: 1.25, 95 % CI: 1.03- 1.53). DEHP was the top-weighted chemical positively correlated with both HOMA-IR and insulin resistance. In the BKMR model, the joint effect was also positively correlated with both outcomes. DEHP remained the main contributor to the joint effect, consistent with WQS analysis. Conclusion: Our findings suggested that these chemical mixtures had the positive joint effects on both HOMA-IR and insulin resistance, with DEHP being the potentially predominant driver. The inter-validation of the three models may indicate that reducing the DEHP concentration could improve glucose homeostasis and reduce the risk of insulin resistance. However, further studies are recommended to deepen our findings and elucidate the mechanisms of insulin resistance and chemical mixture.
https://doi.org/10.1016/j.scitotenv.2022.158218

Phenols, Parabens, Phthalates and Puberty: a Systematic Review of Synthetic Chemicals Commonly Found in Personal Care Products and Girls' Pubertal Development,
RIVERA-NUNEZ Z., C. W. KINKADE, Y. T. ZHANG, A. ROCKSON, E. V. BANDERA, A. A. M. LLANOS and E. S. BARRETT,
Current Environmental Health Reports (Purpose of Review Exposure to endocrine disrupting chemicals through personal care products (PCPs) is widespread and may disrupt hormone-sensitive endpoints, such as timing of

puberty. Given the well-documented (and ongoing) decline in age at menarche in many populations, we conducted a systematic review of the epidemiological literature on exposure to chemicals commonly found in PCPs (including certain phthalates, phenols, and parabens) in relation to girls' pubertal development. Recent Findings The preponderance of research on this topic has examined phthalate exposures with the strongest evidence indicating that prenatal monoethyl phthalate (MEP) concentrations may be associated with slightly earlier timing of puberty, including age at menarche. Findings examining peri-pubertal phthalate exposures and pubertal outcomes were less consistent as were studies of prenatal and peri-pubertal phenol exposures. Very few studies had examined parabens in relation to girls' pubertal development. Common study limitations included potential exposure misclassification related to use of spot samples and/or mistimed biomarker assessment with respect to the outcomes. The role of body size as a mediator in these relationships remains unresolved. Overall, evidence of associations between chemical exposures in PCPs and girls' pubertal development was conflicting. When associations were observed, effect sizes were small. Nevertheless, given the many environmental, social, and behavioral factors in the modern environment that may act synergistically to accelerate timing of puberty, even marginal changes may be cause for concern, with implications for cancer risk, mental health, and cardiometabolic disease in later life. https://doi.org/10.1007/s40572-022-00366-4

Phthalate Exposures and Placental Health in Animal Models and Humans: A Systematic Review,
SEYMORE T. N., Z. RIVERA-NUNEZ, P. A. STAPLETON, J. J. ADIBI and E. S. BARRETT,
Toxicological Sciences 188, no. 2 (Jul 2022): 153-179,
Phthalates are ubiquitous compounds known to leach from the plastic products that contain them. Due to their endocrine-disrupting properties, a wide range of studies have elucidated their effects on reproduction, metabolism, neurodevelopment, and growth. Additionally, their impacts during pregnancy and on the developing fetus have been extensively studied. Most recently, there has been interest in the impacts of phthalates on the placenta, a transient major endocrine organ critical to maintenance of the uterine environment and fetal development. Phthalate-induced changes in placental structure and function may have significant impacts on the course of pregnancy and ultimately, child health. Prior reviews have described the literature on phthalates and placental health; however to date, there has been no comprehensive, systematic review on this topic. Here, we review 35 papers (24 human and 11 animal studies) and summarize phthalate exposures in relation to an extensive set of placental measures. Phthalate-related alterations were reported for placental morphology, hormone production, vascularization, histopathology, and gene/protein expression. The most consistent changes were observed in vascular and morphologic endpoints, including cell composition. These changes have implications for pregnancy complications such as preterm birth and intrauterine growth restriction as well as potential ramifications for children's health. This comprehensive review of the literature, including common sources of bias, will inform the future work in this rapidly expanding field.
https://doi.org/10.1093/toxsci/kfac060

Positive association between dietary exposure to polybrominated diphenyl ethers and breast cancer risk in the French E3N cohort: The role of vegetable oil consumption,
FRENOY P., C. MARQUES, T. FIOLET, G. CANO-SANCHO, G. SEVERI and F. R. MANCINI,
Environment International 167 (Sep 2022),
Exposure to endocrine-disrupting chemicals, like Polybrominated diphenyl ethers (PBDEs), is suspected of playing a role in the occurrence of breast cancer. Moreover, there is growing evidence that food chemical contaminants, especially lipophilic ones such as PBDEs, could interact with different components of the diet. The objective of the present study was to assess the association between dietary intake of PBDEs and breast cancer risk in the French E3N cohort study, and to investigate the potential modification of this association by vegetable oil consumption. The study included 67 879 women. Intakes of eight PBDEs were estimated using food consumption data from a validated semi-quantitative food frequency questionnaire, and food contamination levels measured by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES). Cox proportional hazards models were used to estimate Hazard Ratios (HR) and 95% Confidence Intervals (CI) for the association between total PBDEs dietary intake and breast cancer risk. Interaction measures for vegetable oil consumption were estimated on both additive and multiplicative scales. The women were followed for a maximum of 21.4 years, and 5 686 developed an incident breast cancer. A positive linear trend was highlighted between dietary intake of PBDEs in quintile groups and breast cancer risk, borderline with statistical significance (p-trend = 0.06, HRQ5VSQ1 and 95% CI: 1.09 [0.99;1.20]). Interaction measures for vegetable oil consumption were significant in both additive and multiplicative scales. Higher effect sizes of the

association were highlighted in high consumers of vegetable oil, i.e. >= 4.6 g/day (HRQ5vsQ1 and 95% CI: 1.23 [1.08; 1.40]), and almost no effect were found in low consumers (HRQ5vsQ1 and 95% CI: 0.97 [0.86; 1.10]). Highlighting such interactions between nutrients and chemicals is crucial to develop efficient dietary recommendations to limit the negative health effects associated with exposure to food chemical contaminants.
https://doi.org/10.1016/j.envint.2022.107444

Pre and postnatal exposure to mercury and sexual development in 9-year-old children in Spain: The role of brain-derived neurotrophic factor,
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Environmental Research 213 (Oct 2022),
Early exposure to mercury has been related to endocrine disruption. Steroid hormones play a crucial role in neural cell migration, differentiation, etc., as well as protecting against several neurotoxic compounds. We investigate the relation between mercury exposure and children's sexual development, and we evaluate the possible influence of different brain-derived neurotrophic factor (BDNF) polymorphisms on this association. Our study sample comprised 412 9-year-old children participating in the INMA cohort (2004-2015). Mercury concentrations were measured at birth (cord blood) and at 4 and 9 years of age (hair). Sexual development was assessed by levels of sex steroid hormones (estradiol and testosterone) in saliva and the Tanner stages of sex development at 9 years (categorized as 1: prepuberty and >1: pubertal onset). Covariates and confounders were collected through questionnaires during pregnancy and childhood. Polymorphisms in the BDNF gene were genotyped in cord blood DNA. Multivariate linear regression analyses were performed between mercury levels and children's sexual development by sex. Effect modification by genetic polymorphisms and fish intake was assessed. We found marginally significant inverse associations between postnatal exposure to mercury (at 9 years) and testosterone levels (p[95%CI] = -0.16[-0.33,0.001], and -0.20[-0.42,0.03], for boys and girls, respectively). Additionally, we found that prenatal mercury was negatively associated with Tanner stage >1 in boys. Finally, we found significant genetic interactions for some single nucleotide polymorphisms in the BDNF gene. In conclusion, pre and postnatal exposure to mercury seems to affect children's sexual development and BDNF may play a role in this association, but further research would be needed.
https://doi.org/10.1016/j.envres.2022.113620

Prenatal bisphenol A exposure in relation to behavioral outcomes in girls aged 4-5 and modification by socio-demographic factors in The Infant Development and Environment Study (TIDES),
IBROCI E., S. W. THURSTON, E. S. BARRETT, N. R. BUSH, R. H. N. NGUYEN, S. SATHYANARAYANA, A. REICHENBERG, B. R. COLLETT, S. H. SWAN and S. F. EVANS,
Neurotoxicology 91 (Jul 2022): 262-268,
Bisphenol A (BPA) is a polymer used in the production of polycarbonate plastics and epoxy resins. An estrogen mimic, prenatal BPA exposure has been associated with several behavioral outcomes in children; however, the impact of maternal demographic and economic factors on associations between BPA and child behavioral outcomes have not been examined. The objective of this study was to examine associations between prenatal maternal urinary BPA and behavior in 4-5 year old girls, and to assess whether socio-demographic factors modify this relationship. Mothers enrolled in The Infant Development and Environment Study (TIDES) provided a single spot urine at enrollment (median gestational age 11 weeks) and completed the Behavior Assessment System for Children-2 (BASC-2) and Social Responsiveness Scale-2 (SRS-2) when their daughters were 4-5 years of age. Mother-daughter pairs with complete phthalate, BASC-2, SRS-2, and covariate data were included in this analysis (N = 244). BPA was detectable in 93 % of urine samples. We used multivariable linear regression analyses to estimate associations between maternal urinary log10-transformed BPA concentration and BASC-2 subscale and composite scores and SRS-2 Total Score. To examine the role of socioeconomic and demographic factors associated with study site, we stratified by TIDES center, comparing those enrolled at University of Rochester Medical Center (URMC), a predominately lower socioeconomic population, and those enrolled elsewhere: University of Washington, University of Minnesota, and University of California San Francisco, whose populations share similar higher socioeconomic demographic characteristics. Across all centers, no associations were seen between BPA and BASC-2 or SRS-2 scores. When stratifying by center, BPA was significantly associated with greater social impairment as measured by the SRS-2 Total Score (beta-coefficient [95 % confidence intervals]: 5.1 [1.0, 9.2]) in URMC participants (N = 61). In non-URMC participants (N = 183), BPA was significantly associated with lower BASC-2 Internalizing composite (-3.3 [-6.7, 0.0]) and Depression subscale

scores (-3.4 [-6.7, 0.0]) while no associations were seen between BPA and SRS-2 scores. Our findings suggest that sociodemographic factors may modify the impacts of maternal prenatal BPA on developmental endpoints. https://doi.org/10.1016/j.neuro.2022.05.018

Prenatal Environmental Exposure to Persistent Organic Pollutants and Reproductive Hormone Profile and Pubertal Development in Dutch Adolescents,
BERGHUIS S. A., A. F. BOS, H. GROEN, W. H. A. DE JONG, A. C. M. KOBOLD, L. WAGENMAKERS-HUIZINGA, P. J. J. SAUER and G. BOCCA,
International Journal of Environmental Research and Public Health 19, no. 15 (Aug 2022),
Persistent organic pollutants (POPs), such as polychlorinated biphenyls (PCBs), may interfere with hormonal processes. Knowledge about the effects of prenatal exposure to PCBs and their hydroxylated metabolites (OH-PCBs) on pubertal development is limited. Therefore, the aim of the current study was to determine whether prenatal environmental PCB and OH-PCB exposure are associated with reproductive hormone levels and pubertal characteristics in 13- to 15-year-old children. In this Dutch observational cohort study, 194 mother-infant pairs were included (1998-2002). Maternal pregnancy serum levels of PCBs, OH-PCBs, and other POPs were measured. At follow-up (2014-2016), we measured serum or plasma levels of reproductive hormones in their children. We assessed Tanner stages and testicular volume (by clinician or standardized self-assessment), and participants completed questionnaires on pubertal onset. In total, 101 adolescents (14.4 +/- 0.8 years; 53.7% of invited) participated, and 55 were boys. In boys, higher prenatal PCB levels were associated with higher testosterone levels, higher pubic hair stage, larger testicular volume, and younger age at onset of growth spurt and voice break. In girls, higher prenatal PCB levels were associated with higher stages for breast development. In conclusion, higher prenatal PCB exposure could be associated with more advanced pubertal development in 13- to 15-year-old children. https://doi.org/10.3390/ijerph19159423

Prenatal exposure to mixtures of phthalates and phenols and body mass index and blood pressure in Spanish preadolescents,
GUIL-OUMRAIT N., G. CANO-SANCHO, P. MONTAZERI, N. STRATAKIS, C. WAREMBOURG, M. J. LOPEZ-ESPINOSA, J. VIOQUE, L. SANTA-MARINA, A. JIMENO-ROMERO, R. VENTURA, N. MONFORT, M. VRIJHEID and M. CASAS,
Environment International 169 (Nov 2022),
Background: Pregnant women are simultaneously exposed to several non-persistent endocrine-disrupting chem-icals, which may influence the risk of childhood obesity and cardiovascular diseases later in life. Previous prospective studies have mostly examined single-chemical effects, with inconsistent findings. We assessed the association between prenatal exposure to phthalates and phenols, individually and as a mixture, and body mass index (BMI) and blood pressure (BP) in preadolescents. Methods: We used data from the Spanish INMA birth cohort study (n = 1,015), where the 1st and 3rd-trimester maternal urinary concentrations of eight phthalate metabolites and six phenols were quantified. At 11 years of age, we calculated BMI z-scores and measured systolic and diastolic BP. We estimated individual chemical effects with linear mixed models and joint effects of the chemical mixture with hierarchical Bayesian kernel machine regression (BKMR). Analyses were stratified by sex and by puberty status. Results: In single-exposure models, benzophenone-3 (BP3) was nonmonotonically associated with higher BMI z -score (e.g. Quartile (Q) 3: beta = 0.23 [95% CI = 0.03, 0.44] vs Q1) and higher diastolic BP (Q2: beta = 1.27 [0.00, 2.53] mmHg vs Q1). Methyl paraben (MEPA) was associated with lower systolic BP (Q4: beta =-1.67 [-3.31,-0.04] mmHg vs Q1). No consistent associations were observed for the other compounds. Results from the BKMR confirmed the single-exposure results and showed similar patterns of associations, with BP3 having the highest importance in the mixture models, especially among preadolescents who reached puberty status. No overall mixture effect was found, except for a tendency of higher BMI z-score and lower systolic BP in girls. Conclusions: Prenatal exposure to UV-filter BP3 may be associated with higher BMI and diastolic BP during preadolescence, but there is little evidence for an overall phthalate and phenol mixture effect. https://doi.org/10.1016/j.envint.2022.107527

Prenatal exposure to organophosphate esters is associated with decreased anogenital distance in offspring,
LUAN M., H. LIANG, Y. F. CHEN, D. CHEN, H. L. JI, H. X. CHEN, M. H. MIAO and W. YUAN,
Science of the Total Environment 856 (Jan 2023),

Background: Evidence from in vitro and rodent studies suggests that organophosphate esters (OPEs) may disrupt sex ste-roid hormone homeostasis, but no human studies, to date, have examined the effects of in utero exposure to OPEs on offspring reproductive development.Objective: Anogenital distance (AGD) is a sensitive biomarker of fetal hormonal milieu and has been used to assess re-productive toxicity. We evaluated the longitudinal effects of prenatal exposure to OPEs on the AGD of offspring from birth to 4 years.Methods: Based on Shanghai-Minhang Birth Cohort Study, pregnant women provided urine samples at a gestational age of 12-16 weeks, which were analyzed for eight OPE metabolites. AGD was measured in offspring at birth and 0.5, 1, and 4 years of age. We used generalized estimating equations (GEE) and Bayesian kernel machine regression (BKMR) models to estimate the associations of prenatal exposure to individual OPE metabolites and OPE mixtures with AGD stratified by sex.Results: A total of 733 mother-infant pairs were analyzed. Prenatal exposure to diphenyl phosphate and bis-(2-ethylhexyl) phosphate was associated with decreased AGD in boys in GEE models. Bis-(1-chloro-2-propyl) phosphate (BCIPP) showed a similar but marginally significant effect. Prenatal exposure to most OPE metabolites was associated with decreased AGD in girls, with the most profound association observed for bis (2-butoxyethyl) phosphate (BBOEP) and alkyl-OPEs. The OPE mixture was also inversely associated with AGD in both sexes. The single-exposure effects of BKMR models were largely consistent with those observed in the GEE models. In addition, alkyl-OPEs, particularly BBOEP, contributed the most to the decreased AGD in girls, while BCIPP contributed the most to the decreased AGD in boys.Conclusions: This study provides the first human evidence that prenatal exposure to OPEs is associated with decreased AGD in offspring. The magnitude of these effects may vary depending on the structure of OPEs.
https://doi.org/10.1016/j.scitotenv.2022.159050

Prenatal exposure to phthalates and phenols and preclinical vascular health during early adolescence,
MONTAZERI P., S. FOSSATI, C. WAREMBOURG, M. CASAS, D. B. P. CLEMENTE, R. GARCIA-ESTEBAN, T. S. NAWROT and M. VRIJHEID,
International Journal of Hygiene and Environmental Health 240 (Mar 2022),
Background and aim: Exposure to endocrine-disrupting chemicals may increase cardiovascular risk from early life, but studies in children have shown inconsistent results, most focused on analysis of single chemicals, and none included measures of micro-vascularization as early preclinical markers. This study aimed to evaluate the association between prenatal exposure to phthalates and phenols and macro- and microvascular health during early adolescence. Methods: Using data from a Spanish birth cohort (n = 416), prenatal exposure to eight phthalate metabolites and seven phenols (bisphenol A, four parabens, benzophenone-3, triclosan) were assessed using first and/or third trimester spot-urine concentrations. Macrovascular health (systolic and diastolic blood pressure (SBP and DBP, mmHg), pulse wave velocity (PWV, m/s)) and microvascular health (central retinal artery/vein equivalent (CRAE/CRVE, mu m)), were measured at 11 years old. Linear regression models assessed associations for individual chemicals and Bayesian weighted quantile sum regression (BWQS) evaluated the overall association of the phthalate and phenol mixture with cardiovascular health. Results: In single exposure models, bisphenol-A was associated with decreased PWV (beta per doubling of exposure = -0.06; 95% CI: -0.10, -0.01). Mono-iso-butyl phthalate was associated with an increase in CRAE (beta = -1.89; 95% CI: 0.34, 3.44). Methyl- and butyl-parabens were associated with a decrease in CRVE (beta = 0-.71; 95% CI: -1.41, -0.01) and (beta = -0.96; 95% CI: -1.57, -0.35), respectively. No statistically significant associations were observed between any of the exposures and SBP or DBP. BWQS models showed no evidence of associations between the phthalate and phenol mixture and any of the outcomes. Conclusions: Our results provide little evidence to suggest that prenatal exposure to phthalates and phenols is associated with macro- or microvascular health during early adolescence, except a few associations with certain compounds. Errors in exposure measurement and reduced variability in cardiovascular measures at this early age limit our ability to draw strong conclusions.
https://doi.org/10.1016/j.ijheh.2021.113909

Prenatal exposure to polybrominated diphenyl ethers and BMI Z-scores from 5 to 14 years,
KUPSCO A., A. SJODIN, W. COWELL, R. JONES, S. OBERFIELD, S. WANG, L. A. HOEPNER, D. GALLAGHER, A. A. BACCARELLI, J. GOLDSMITH, A. G. RUNDLE and J. B. HERBSTMAN,
Environmental Health 21, no. 1 (Sep 2022),
Background Polybrominated diphenyl ethers (PBDEs) are flame-retardant compounds widely used in household products until phase out in 2004. PBDEs are endocrine disruptors and are suggested to influence signaling related to weight control. Prenatal exposures to PBDEs may alter childhood adiposity, yet few studies have examined these associations in human populations. Methods Data were collected from a birth cohort of

Dominican and African American mother-child pairs from New York City recruited from 1998 to 2006. PBDE congeners BDE-47, - 99, - 100, and - 153 were measured in cord plasma (ng/mu L) and dichotomized into low (< 80th percentile) and high (>80th percentile) exposure categories. Height and weight were collected at ages 5, 7, 9, 11, and an ancillary visit from 8 to 14 years (n = 289). Mixed-effects models with random intercepts for participant were used to assess associations between concentrations of individual PBDE congeners or the PBDE sum and child BMI z-scores (BMIz). To assess associations between PBDEs and the change in BMIz over time, models including interactions between PBDE categories and child age and (child age)(2) were fit. Quantile g-computation was used to investigate associations between BMIz and the total PBDE mixture. Models were adjusted for baseline maternal covariates: ethnicity, age, education, parity, partnership status, and receipt of public assistance, and child covariates: child sex and cord cholesterol and triglycerides. Results The prevalence of children with obesity at age 5 was 24.2% and increased to 30% at age 11. Neither cord levels of individual PBDEs nor the total PBDE mixture were associated with overall BMIz in childhood. The changes in BMIz across childhood were not different between children with low or high PBDEs. Results were similar when adjusting for postnatal PBDE exposures. Conclusions Prenatal PBDE exposures were not associated with child growth trajectories in a cohort of Dominican and African American children. https://doi.org/10.1186/s12940-022-00893-5

Prenatal single and combined exposure to phthalates associated with girls' BMI trajectory in the first six years,
GAO H., M. L. GENG, H. GAN, K. HUANG, C. ZHANG, B. B. ZHU, L. SUN, X. L. WU, P. ZHU, F. B. TAO, MA and A. E. A. B. COHORT,
Ecotoxicology and Environmental Safety 241 (Aug 2022),
Evidence of the influence of prenatal phthalate exposure on childhood longitudinal obesity markers is limited. Nested on the Ma'anshan birth cohort study, 990 mother-daughter pairs were included. Seven phthalate metabolites were determined in urine collected in each trimester. Each child underwent a physical examination from birth to 6 years of age twelve times. Latent class growth models were used to identify three trajectories of girls' body mass index (BMI). Logistic regression, quantile g-computation and Bayesian kernel machine regression models analyzed the relationships of prenatal exposure to individual and mixed phthalates with girls' body mass index (BMI) trajectory. Compared to the "lowest trajectory " class, prenatal average concentrations of mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP, ORcrude = 2.095, 95 % CI = 1.014-4.328) and di(2-ethylhexyl) phthalate (DEHP, ORcrude = 2.336, 95 % CI = 1.022-5.338) during pregnancy were associated with an increased probability of being in the "highest trajectory " class. The average concentration of DEHP (ORcrude = 1.879, 95 % CI = 1.002-3.522) was associated with an increased probability of being in the "moderate trajectory " class. Stratified analyses by trimester of pregnancy mainly showed that third-trimester exposure to monoethyl phthalate (MEP, ORadjusted = 1.584, 95 % CI = 1.094-2.292), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP, ORadjusted = 2.885, 95 % CI = 1.367-6.088), MEHHP (ORadjusted = 2.425, 95 % CI = 1.335-4.407), DEHP (ORadjusted = 2.632, 95 % CI = 1.334-5.193) and high molecular weight phthalate (ORadjusted = 2.437, 95 % CI = 1.239-4.792) was associated with an increased probability of being in the "highest trajectory " class. However, the mixture of phthalates was not significantly related to the girl's BMI trajectory. In conclusion, in utero exposure to phthalates, including MEP and DEHP metabolites (MEHHP and MEOHP), was significantly associated with early childhood high BMI trajectories in girls. The third trimester of pregnancy seemed to be the window of vulnerability to phthalate exposure for girls' high BMI trajectory at periods of prenatal development. No evidence supported a significant relationship between combined exposure to phthalate metabolites and girls' high BMI trajectory. https://doi.org/10.1016/j.ecoenv.2022.113837

The relationship between exposure to phthalate metabolites and adult-onset hypogonadism,
LIU Z. H., L. C. YANG, P. SONG, J. H. CHEN, Z. F. PENG and Q. DONG,
Frontiers in Endocrinology 13 (Aug 2022),
ObjectiveAdult-onset hypogonadism (AOH) is a common disease for males >40 years old and is closely associated with age-related comorbidities. Phthalates are compounds widely used in a number of products with endocrine-disrupting effects. However, little is known about the association between exposure to phthalates and the risk of AOH. Thus, we conducted this study to explore the potential association using the 2013-2016 National Health and Nutrition Examination Survey (NHANES) data. MethodData on AOH and urinary phthalate metabolites were collected, and univariable and multivariable logistic regression analyses were adapted to evaluate the association. The concentrations of each metabolite were calculated and grouped according to their

quartiles for the final analysis. ResultFinally, we found that the odds ratio (OR) increased with increased concentrations of di-(2-ethylhexyl) phthalate (DEHP) metabolites, including mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono(2-ethyl-5-oxohexyl) phthalate (MEOHP). Simultaneously, a significant dose-dependent effect was also observed. The OR for the fourth quartile was highest among all three groups. Specifically, the ORs for the third quartile and fourth quartile were 1.774 and 1.858, respectively, in the MECPP group. For the MEHHP group, the OR increased from 1.580 for the second quartile to 1.814 for the fourth quartile. Similarly, the OR for the higher three quartiles varied from 1.424 to 1.715 in the MEOHP group. ConclusionThis study first revealed that there was a positive association between exposure to DEHP metabolites and the risk of AOH. These findings add limited evidence to study this topic, while further studies are needed to explain the potential molecular mechanisms. https://doi.org/10.3389/fendo.2022.991497

Relationship of individual and mixed prenatal phthalate exposure with placental structure and efficiency in the prospective Ma'anshan Birth Cohort Study,
GAO H., M. L. GENG, K. HUANG, B. B. ZHU, C. ZHANG, H. GAN, J. TONG, X. L. WU, C. Y. HU, S. Y. ZHANG, P. ZHU, Q. N. WANG and F. B. TAO,
Science of the Total Environment 838 (Sep 2022),
Background: Few studies have investigated the associations between prenatal phthalate exposure and placental structure and function with inconsistent conclusions. Methods: Nested on the Ma'anshan Birth Cohort study, 2723 women provided spot urine samples during the first, second and third trimesters of pregnancy to analyze six phthalate metabolites. The outcomes of interest were placental weight, efficiency (birth weight/placental weight), chorionic disc area and disc eccentricity. The relationships of prenatal exposure to a single phthalatewith placental measures were analyzed. The associations between prenatal phthalate mixture exposure and placental measures were also evaluated. Results: Most phthalate metabolites were significantly associated with placental weight, efficiency and chorionic disc area during the whole gestation and in each trimester of pregnancy, with different directions of relationships. Sensitivity analyses revealed similar findings, indicating the robustness of the statistical results. Furthermore, inverted Ushaped nonlinear relationships of prenatal exposure to some phthalate metabolites with placental weight, efficiency and chorionic plate area were observed. However, quantile g-computation mixture models did not reveal any association between maternal combined exposure to the total phthalate metabolites and placental measures. Conclusions: Maternal exposure to most phthalates and their metabolites was associated with placental weight, efficiency and chorionic plate area in both a linear manner and an inverted U-shaped nonlinear manner. However, the mixture of multiple phthalate metabolites was not observed to be associated with any placental measure.
https://doi.org/10.1016/j.scitotenv.2022.156498

Serum concentrations of persistent organic pollutants mixture during pregnancy and anogenital distance in 8-year-old children from the INMA-Asturias cohort,
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Environmental Research 213 (Oct 2022),
Background: During pregnancy, women are commonly exposed to several endocrine-disrupting chemicals, including persistent organic pollutants (POPs). These compounds can transfer to the fetus through the placenta. Prenatal POP exposure is related to altered fetal genital and reproductive tract development. However, the relationship between exposure to POP mixtures and anogenital distance (AGD) is poorly investigated. This study investigated the association between prenatal exposure to POP mixtures and AGD in 8-year-old children. Methods: Data were collected from the INMA-Asturias cohort. Maternal serum POP concentrations were measured during the first trimester of pregnancy. Anoscrotal distance (AGDAS) and anopenile distance (AGDAP) in males and anofourchetal distance (AGD(AF)) and anoclitoral distance (AGD(AC)) in females were recorded in 362 8-years-olds. Conventional linear regression, and the novel weighted quantile sum regression (WQSR) and Bayesian kernel machine regression (BKMR) models were applied to assess the relationships between AGD and POPs exposure stratified by sex. Results: Among males, in the linear regression, b-hexachlorocyclohexane, PCB138, PCB153, and PCB180 were inversely associated with the anogenital index (AGI)AS (-0.06 mm/kg (95% confidence interval [CI]: -0.11,-0.02),-0.07 mm/kg (95% CI: -0.14,-0.01),-0.07 mm/kg (95% CI: -0.13,-0.01), and-0.08 mm/kg (95% CI: -0.14,-0.02), respectively). Among females, polybrominated diphenyl ether (PBDE)47 and PBDE154 were positively associated with increased AGIAF (0.02 mm/kg (95% CI: 0.00, 0.03) and 0.09 mm/kg (95% CI: 0.01, 0.17), respectively). BKMR confirmed these associations. WQSR found a negative combined effect

of the POP mixture on AGD, and PCB138, PCB153, and PCB180 (weighted 0.18, 0.13, and 0.09, respectively) were identified as the most impacting chemicals. In females, WQSR found a positive combined effect and determined PBDE47 (weighted 0.35) as the most impacting. Conclusions: Maternal exposure to a POP mixture was negatively associated with AGD in male children and positively associated with AGD in female children, thus providing evidence of the adverse effects of POPs on genital development. https://doi.org/10.1016/j.envres.2022.113607

Sex Differences between Urinary Phthalate Metabolites and Metabolic Syndrome in Adults: A Cross-Sectional Taiwan Biobank Study,
SHIH Y. L., C. J. HSIEH, T. Y. LEE, P. H. LIAO, H. T. WU and C. Y. LIU,
International Journal of Environmental Research and Public Health 19, no. 16 (Aug 2022),
Background: Phthalates are widely used in consumer products, food packaging, and personal care products, so exposure is widespread. Several studies have investigated the association of phthalate exposure with obesity, insulin resistance, and hypertension. However, little is known about the associations of phthalate exposure with sex, age, and menopausal status in metabolic syndrome (MetS). The purpose of this study was to investigate the association between 11 urinary phthalate metabolite concentrations and metabolic syndrome in adults. Methods: We conducted a cross-sectional analysis of 1337 adults aged 30-70 years from the Taiwan Biobank 2016-2020. Prevalence odds ratios (POR) and 95% confidence intervals (CIs) were calculated using logistic regression and stratified by sex, age, and menopausal status. Results: Participants with MetS comprised 16.38%. Higher concentrations of MEP metabolites were associated with more than two- to three-fold increased odds of MetS in males and males >= 50 years (adj. POR Q3 vs. Q1 = 2.13, 95% CI: 1.01, 4.50; p = 0.047 and adj. POR Q2 vs. Q1 = 3.11, 95% CI: 0.13, 8.63; p = 0.029). When assessed by menopausal status, postmenopausal females with higher n-ary sumation DEHP concentrations had more than nine-fold higher odds of MetS compared with postmenopausal females with the lowest n-ary sumation DEHP concentrations (adj. POR Q3 vs. Q1 = 9.58, 95% CI: 1.18, 77.75; p = 0.034). Conclusions: The findings suggest differential associations between certain phthalate metabolites and MetS by sex, age, and menopausal status. https://doi.org/10.3390/ijerph191610458

Sex-specific associations between maternal exposure to parabens, phenols and phthalates during pregnancy and birth size outcomes in offspring,
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Science of the Total Environment 836 (Aug 2022),
Current evidence on the effects of prenatal exposure to endocrine disrupting chemicals on birth size remains largely inconclusive. We aimed to investigate sex-specific associations between maternal exposure to parabens, phenols and phthalates during pregnancy and birth weight, length and head/abdominal circumferences. We performed a prospective study of 88 pregnant women who underwent amniocentesis in the period 2012 to 2014. Maternal urine samples were collected during pregnancy in weeks 12 to 36 (median: 18 weeks). The concentrations of parabens, phenols and individual phthalate diester metabolites were analyzed by isotope-diluted liquid chromatography-tandem mass spectrometry and osmolality adjusted. Linear regression models estimated the associations between urinary levels of selected compounds (tertile(T2-T3)(medium/high) versus T1(low) exposure) and birth size, stratified by offspring sex. A total of three parabens, two phenols, four individual phthalate metabolites and four sums of diester metabolites were detectable above limits of detection in at least 60% of urine samples. Overall, we observed few statistically significant associations, but medium/high exposure to bisphenol A (BPA) in male offspring was associated with statistically significant lower birth size across most outcomes [birth weight: -428 g (95% CI -756 to -99.4); birth length: -1.76 cm (95% CI -3.28 to -0.25); abdominal circumference: -1.97 cm (95% CI -3.55 to -0.39)]. Similarly, medium/high exposure to methyl paraben (MeP) in male offspring was associated with lower birth weight (-661 g, 95% CI -1251 to -70.7) and length (-3.11 cm, 95% CI -5.76 to -0.46) compared to low exposure. None of these associations were statistically significant in female offspring. Across all compounds, individual exposures were associated with more negative estimates of birth weight for male than for female offspring. Our study indicates that prenatal exposure to BPA and MeP may negatively affect birth size outcomes, with a possible sex effect. Given the small sample size, these findings need to be replicated in future larger studies. https://doi.org/10.1016/j.scitotenv.2022.155565

Urinary Biomarkers of Polycyclic Aromatic Hydrocarbons and Timing of Pubertal Development: The California PAH Study,
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Epidemiology 33, no. 6 (Nov 2022): 777-787,
Background: Polycyclic aromatic hydrocarbons (PAHs) are endocrine-disrupting chemicals. Few studies have evaluated the association between pubertal development in girls and PAH exposures quantified by urinary biomarkers. Methods: We examined associations of urinary PAH metabolites with pubertal development in 358 girls 6-16 years of age from the San Francisco Bay Area enrolled in a prospective cohort from 2011 to 2013 and followed until 2020. Using baseline data, we assessed associations of urinary PAH metabolites with pubertal development stage. In prospective analyses limited to girls who at baseline had not yet started breast (N = 176) or pubic hair (N = 179) development or menstruation (N = 267), we used multivariable Cox proportional hazards regression to assess associations of urinary PAH metabolites with the onset of breast and pubic hair development, menstruation, and pubertal tempo (interval between the onset of breast development and menstruation). Results: We detected PAH metabolites in >98% of girls. In cross-sectional analyses using baseline data, PAH metabolites were not associated with the pubertal development stage. In prospective analyses, higher concentrations (>= median) of some PAH metabolites were associated with two-fold higher odds of earlier breast development (2-hydroxy naphthalene, 1-hydroxy phenanthrene, summed hydroxy phenanthrenes) or pubic hair development (1-hydroxy naphthalene) among girls overweight at baseline (body mass index-for-age percentile >= 85) compared with nonoverweight girls with lower metabolites concentrations. PAH metabolites were not associated with age at menarche or pubertal tempo. Conclusions: PAH exposures were widespread in our sample. Our results support the hypothesis that, in overweight girls, PAHs impact the timing of pubertal development, an important risk factor for breast cancer. https://doi.org/10.1097/ede.0000000000001535

Urinary concentration of endocrine-disrupting phthalates and breast cancer risk in Indian women: A case-control study with a focus on mutations in phthalate-responsive genes,
DAS A. M., A. GOGIA, M. GARG, A. ELAIYARAJA, P. ARAMBAM, S. MATHUR, R. BABU-RAJENDRAN, S. V. S. DEO, L. KUMAR, B. C. DAS and R. JANARDHANAN,
Cancer Epidemiology 79 (Aug 2022),
https://doi.org/10.1016/j.canep.2022.102188

Urinary concentration of endocrine-disrupting phthalates and breast cancer risk in Indian women: A case-control study with a focus on mutations in phthalate-responsive genes,
DAS A. M., A. GOGIA, M. GARG, A. ELAIYARAJA, P. ARAMBAM, S. MATHUR, R. BABU-RAJENDRAN, S. V. S. DEO, L. KUMAR, B. C. DAS and R. JANARDHANAN,
Cancer Epidemiology 79 (Aug 2022),
Background: Phthalates are known endocrine-disrupting chemicals used indiscriminately as constituents in consumer products including food processing, and packaging, cosmetics, personal care and household items. Although, few studies have assessed the risk of breast cancer on exposure to phthalates, their association with breast cancer risk in Indian women have not yet been evaluated. Methods: We conducted a case-control study involving 171 participants. Urinary concentrations of six phthalate dieters; DMP (Dimethyl phthalate), DEP (Diethyl phthalate), DBP (Dibutyl phthalate), BBP (benzyl butyl phthalate), DEHP (Di-2-ethyl-hexyl phthalate), DINOP (Di-n-octyl phthalate) were estimated by GC-MS and geometric means were calculated. Univariate and multivariable logistic regression was performed to assess breast cancer risk on exposure to phthalates. Genes responsive to phthalates were identified through literature search and matched with NGS data, and gene-enrichment analysis was performed. Results: Significant associations were observed between urinary phthalate concentrations and increased risk of breast cancer for di-butyl phthalate (OR=1.5, 95% CI; 1.06, 2.11, p = 0.002) and di-2-ethyl-hexyl phthalate (>median vs <= median; OR=2.97, 95% CI; 1.18, 7.47, p = 0.005) in multivariable analyses. We also found several phthalate-responsive gene mutations in paired breast tumor tissues, which include PTPRD (76.19%), AR (42.86%), CYP1A1 (42.86%), CYP19A1 (23.81%), AHRR (19.05%), PIK3CA (19.05%), CYP1B1 (9.52%), RB1 (9.52%) and MMP9 (9.52%). Gene-enrichment analysis revealed that these genes form a major part of ER/PR, PPAR and HIF-1 alpha-TGF-beta signaling cascades involved in breast cancer Conclusion: Although the sample size is small, in this first case-control study from India, DBP and DEHP were found to be associated with increased risk of invasive breast cancer and tumor tissues revealed mutations in several phthalate-responsive genes. It is, therefore suggested that human biomonitoring in India and larger studies evaluating the early life genetic and epigenetic alterations on phthalates exposure are required to establish their role in breast carcinogenesis. https://doi.org/10.1016/j.canep.2022.102188

Urinary concentrations of polycyclic aromatic hydrocarbon and phthalate metabolite mixtures in relation to semen quality among men attending an infertility clinic,
DENG Y. L., P. YANG, Y. X. WANG, C. LIU, Q. LUO, T. SHI, J. Y. ZENG, T. T. LU, P. P. CHEN, Y. MIAO, M. ZHANG, F. P. CUI, W. Q. LU and Q. ZENG,
Environmental Science and Pollution Research 29, no. 54 (Nov 2022): 81749-81759,
Previous studies have reported that exposure to phthalates and polycyclic aromatic hydrocarbons (PAHs) is individually associated with altered semen quality, but no human studies have evaluated their joint effects of exposure mixtures, a more real-world scenario. We aimed to explore urinary metabolite mixtures of phthalates and PAHs in associations with semen quality. Repeated spot-urine samples gathered from 695 men attending a fertility clinic were analyzed for urinary metabolites of eight phthalates and ten monohydroxylated-PAHs (OH-PAHs). Principal component analysis (PCA)-multivariable linear regression (MLR) model, quantile g-computation (qg-comp), and Bayesian kernel machine regression (BKMR) were applied to estimate the associations of urinary mixtures of phthalate and OH-PAH metabolites with semen quality. The overall effects of urinary mixtures of phthalate and PAH metabolites on semen quality were not statistically significant. However, hydroxynaphthalene (OHNa) factor identified from PCA was monotonically associated with decreased total sperm count and sperm concentration, whereas di(2-ethylhexyl) phthalate (DEHP) factor was non-monotonically related to increased progressive sperm motility and total sperm motility. Qg-comp and BKMR models confirmed these findings and identified 2-OHNa and 2-OHFlu as the primary negative contributors, whereas MEOHP and MEHP as the primary positive contributors. Our findings suggest that exposure to mixtures of naphthalene and DEHP is associated with altered semen quality. The finding is warranted to confirm in further well-designed epidemiological studies.
https://doi.org/10.1007/s11356-022-21525-y

Urinary phenol concentrations and fecundability and early pregnancy loss,
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Human Reproduction (STUDY QUESTION Are urinary phenol concentrations of methylparaben, propylparaben, butylparaben, triclosan, benzophenone-3, 2,4-dichlorophenol or 2,5-dichlorophenol associated with fecundability and early pregnancy loss? SUMMARY ANSWER 2,5-dichlorophenol concentrations were associated with an increased odds of early pregnancy loss, and higher concentrations of butylparaben and triclosan were associated with an increase in fecundability. WHAT IS KNOWN ALREADY Phenols are chemicals with endocrine-disrupting potential found in everyday products. Despite plausible mechanisms of phenol reproductive toxicity, there are inconsistent results across few epidemiologic studies examining phenol exposure and reproductive function in non-fertility treatment populations. STUDY DESIGN, SIZE, DURATION Specimens and data were from the North Carolina Early Pregnancy Study prospective cohort of 221 women attempting to conceive naturally from 1982 to 1986. This analysis includes data from 221 participants across 706 menstrual cycles, with 135 live births, 15 clinical miscarriages and 48 early pregnancy losses (before 42 days after the last menstrual period). PARTICIPANTS/MATERIALS, SETTING, METHODS Participants collected daily first-morning urine specimens. For each menstrual cycle, aliquots from three daily specimens across the cycle were pooled within individuals and analyzed for phenol concentrations. To assess sample repeatability, we calculated intraclass correlation coefficients (ICCs) for each phenol. We evaluated associations between phenol concentrations from pooled samples and time to pregnancy using discrete-time logistic regression and generalized estimating equations (GEE), and early pregnancy loss using multivariable logistic regression and GEE. MAIN RESULTS AND THE ROLE OF CHANCE ICCs for within-person variability across menstrual cycles in pooled phenol concentrations ranged from 0.42 to 0.75. There was an increased odds of early pregnancy loss with 2,5-dichlorophenol concentrations although the CIs were wide (5th vs 1st quintile odds ratio (OR): 4.79; 95% CI: 1.06, 21.59). There was an increased per-cycle odds of conception at higher concentrations of butylparaben (OR: 1.62; 95% CI: 1.08, 2.44) and triclosan (OR: 1.49; 95% CI: 0.99, 2.26) compared to non-detectable concentrations. No associations were observed between these endpoints and concentrations of other phenols examined. LIMITATIONS, REASONS FOR CAUTION Limitations include the absence of phenol measurements for male partners and a limited sample size, especially for the outcome of early pregnancy loss, which reduced our power to detect associations. WIDER IMPLICATIONS OF THE FINDINGS This study is the first to use repeated pooled measures to summarize phenol exposure and the first to investigate associations with fecundability and early pregnancy loss. Within-person phenol concentration variability underscores the importance of collecting repeated samples for future studies. Exposure misclassification could contribute to differences between the findings of this study and those of other studies, all of which used one urine sample to assess phenol exposure. This study also contributes to the limited

literature probing potential associations between environmental exposures and early pregnancy loss, which is a challenging outcome to study as it typically occurs before a pregnancy is clinically recognized. STUDY FUNDING/COMPETING INTEREST(S) This research was supported by the National Institute of Environmental Health Sciences of the National Institutes of Health (award number F31ES030594), the Intramural Research Program of the National Institutes of Health, the National Institute of Environmental Health Sciences (project numbers ES103333 and ES103086) and a doctoral fellowship at the Yale School of Public Health. The authors declare they have no competing interests to disclose. https://doi.org/10.1093/humrep/deac230

Variability in urinary phthalates, phenols, and parabens across childhood and relation to adolescent breast composition in Chilean girls,
YOON L. S., A. M. BINDER, A. PEREIRA, A. M. CALAFAT, J. SHEPHERD, C. CORVAL and K. B. MICHELS,
Environment International 170 (Dec 2022),
Background: Epidemiologic evidence suggests that environmental factors acting as endocrine disrupting chemicals (EDCs) are associated with mammographic breast density and the risk of breast cancer. Exposure to EDCs during puberty, a period of rapid breast development, may affect susceptibility to breast carcinogenesis.Methods: In a cohort of 366 Chilean adolescents from the Growth and Obesity Cohort Study, we evaluated the relation between urinary concentrations of 15 suspected EDC biomarkers across three pubertal time points (Tanner breast stage 1 (B1), 4 (B4), and 1-year post-menarche) and breast fibroglandular volume (FGV; percent FGV [%FGV] and absolute FGV [aFGV]) and total breast volume (tBV) at 2-years post-menarche. We used linear mixed models to test differences in creatinine-corrected EDC biomarker concentrations at B4 and 1-year post -menarche compared to B1 and calculated intraclass correlation coefficients (ICC) of EDC concentrations across time points to appraise the consistency of measurements. We fit multivariable generalized estimating equations (GEEs) to evaluate windows of susceptibility for the association between log10-transformed EDCs and log10-transformed breast outcomes. GEEs were adjusted for age, body fat percentage, total caloric intake, and maternal education.Results: Urinary EDC biomarker concentrations highly varied across pubertal time points (ICC range 0.01-0.30). For 12 EDCs, biomarker concentrations decreased over time. Triclosan measured at 1-year post-menarche was inversely associated with %FGV at 2-years post-menarche (beta =-0.025, 95 % confidence interval =-0.041,-0.008). Mono(2-ethyl-5-carboxypentyl) phthalate and the sum of di(2-ethylhexyl) phthalate metabolite con-centrations at B4 were positively associated with aFGV and tBV at 2-years post-menarche. No measured phenols were associated with aFGV and tBV, while no measured parabens were associated with %FGV and aFGV. Conclusions: Our study suggests relatively high variability in EDC biomarker concentrations across the peri-pubertal time period. We also found evidence to suggest that there may be pubertal windows of susceptibility to select EDCs for the association with adolescent breast density. https://doi.org/10.1016/j.envint.2022.107586

Toxicité sur l'homme

AOP key event relationship report: Linking androgen receptor antagonism with nipple retention,
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Current Research in Toxicology 3 (2022),
In rat developmental and reproductive toxicity studies, nipple/areola retention (NR) in male offspring is a biomarker for reduced androgen signaling during development. This is because nipples normally regress in male rats in response to androgen signaling during critical stages of development. NR is thus included as a mandatory endpoint in several OECD test guidelines for assessment of chemicals, particularly as a readout for anti -androgenic effects relevant for reproductive toxicity. With the growing interest in developing Adverse Outcome Pathways (AOPs) to aid in chemical risk assessment, a more pragmatic approach has been proposed, whereby essential units of knowledge could be developed independently of complete AOPs, not least emergent key event relationships (KERs). Herein, we have developed a KER linking "androgen receptor antagonism" and "increased areola/nipple retention". The KER is based on a literature review conducted in a transparent semi -systematic manner in peer-reviewed databases with pre-defined inclusion criteria. Twenty-seven papers were included for development of the KER. The results support a qualitative relationship between the two key events (KEs) with a high weight of evidence; i.e., a causal relationship between androgen receptor (AR) antagonism and nipple retention in male rats exists. https://doi.org/10.1016/j.crtox.2022.100085

Association of serum bisphenol A levels with incident overweight and obesity risk and the mediating effect of adiponectin,
BI J., F. WANG, Y. WEI, Y. ZHANG, C. Y. JIA, J. HE, J. Q. YAO, Z. F. ZHANG, Z. Y. LI, P. W. LI and M. A. HE,
Chemosphere 308 (Dec 2022),
Background: Existing cross-sectional studies indicated a positive association of bisphenol A (BPA) with overweight and obesity. However, the relationship and potential mechanisms underlying this association remain to be elucidated in prospective studies.Objective: This study was designed to investigate whether serum BPA is associated with incident overweight and obesity risk, and to further explore whether adiponectin plays a mediating role in the association.Methods: We measured blood BPA and adiponectin in Chinese populations. The association of serum BPA with overweight and obesity risk was evaluated using multivariable logistic regression models. We further examined the mediating effect of adiponectin by causal mediation analysis.Results: Among 796 participants free of overweight and obesity at baseline, 133 individuals developed overweight and obesity during the follow-up period. Compared with those in the lowest quartile of serum BPA, those in the second and third quartiles were positively associated with incident overweight and obesity risk adjusting for covariates (all P-values < 0.05), whereas this association was not observed in the fourth quartile. Further spline analysis showed an inverted U-shaped dose-response relationship (Pnon-linear = 0.04). Furthermore, each unit of serum log10-transformed BPA levels was associated with higher changes in waist-to-height ratio and body roundness index (all P-values < 0.05). Mediation analysis indicated significant indirect effects of adiponectin on the associations of BPA with overweight and obesity prevalence (mediation proportion: 46.08%; P = 0.02), and BMI levels (mediation proportion: 30.32%; P = 0.03).Conclusion: Serum BPA displayed a positive association with incident overweight and obesity risk in a non -monotonic pattern, and adiponectin might mediate the association. Further mechanistic studies are warranted.
https://doi.org/10.1016/j.chemosphere.2022.136287

Bisphenol A as a Factor in the Mosaic of Autoimmunity,
LAZUROVA Z., I. LAZUROVA and Y. SHOENFELD,
Endocrine Metabolic & Immune Disorders-Drug Targets 22, no. 7 (2022): 728-737,
The population worldwide is largely exposed to bisphenol A (BPA), a commonly used plasticizer, that has a similar molecular structure to endogenous estrogens. Therefore, it is able to influence physiological processes in the human body, taking part in pathophysiology of various endocrinopathies, as well as, cardiovascular, neurological and oncological diseases. BPA has been found to affect the immune system, leading to the development of autoimmunity and allergies, too. In the last few decades, the prevalence of autoimmune diseases has significantly increased that could be explained by a rising exposure of the population to environmental factors, such as BPA. BPA has been found to play a role in the pathogenesis of systemic autoimmune diseases and also organ-specific autoimmunity (thyroid autoimmunity, diabetes mellitus type 1, myocarditis, inflammatory bowel disease, multiple sclerosis, encephalomyelitis etc), but the results of some studies still remain controversial, so further research is needed.
https://doi.org/10.2174/1871530321666210516000042

Bisphenol S Increases Cell Number and Stimulates Migration of Endometrial Epithelial Cells,
BENJAMIN K., C. M. MARQUEZ, M. MORTA, E. M. REYES, L. ARAGONES and M. VELARDE,
Journal of the Asean Federation of Endocrine Societies (Objective. To determine whether bisphenol S (BPS), a common substitute for bisphenol A (BPA), induces cell proliferation and migration in human endometrial epithelial cells (Ishikawa) and adult mouse uterine tissues. Methodology. Human endometrial Ishikawa cells were exposed to low doses of BPS (1 nM and 100 nM) for 72 hours. Cell proliferation was assessed through the viability assays MTT and CellTiter-Glo (R). Wound healing assays were also used to evaluate the migration potential of the cell line. The expression of genes related to proliferation and migration was also determined. Similarly, adult mice were exposed to BPS at a dose of 30 mg/kg body weight/day for 21 days, after which, the uterus was sent for histopathologic assessment. Results. BPS increased cell number and stimulated migration in Ishikawa cells, in association with the upregulation of estrogen receptor beta (ESR2) and vimentin (VIM). In addition, mice exposed to BPS showed a significantly higher mean number of endometrial glands within the endometrium. Conclusion. Overall, in vitro and in vivo results obtained in this study showed that BPS could significantly promote endometrial epithelial cell proliferation and migration, a phenotype also observed with

BPA exposure. Hence, the use of BPS in BPA-free products must be reassessed, as it may pose adverse reproductive health effects to humans. https://doi.org/10.15605/jafes.037.S7

Bisphenols A, F, S and AF trigger apoptosis and/or endoplasmic reticulum stress in human endometrial stromal cells,
FERREIRA R., C. AMARAL, G. CORREIA-DA-SILVA, M. ALMADA, M. BORGES, S. C. CUNHA, J. O. FERNANDES and N. TEIXEIRA,
Toxicology 478 (Aug 2022),
Disruption of non-differentiated endometrial stromal cells could have noxious consequences in female reproduction, impairing endometrial remodelling and implantation. Following the classification of bisphenol A (BPA) as an endocrine disrupting chemical, it started to be gradually withdrawn from the market, being substituted by structural analogues, whose effects in human health are not fully understood. This work used a telomerase-immortalized human endometrial stromal cell line (St-T1b) to study the effects of BPA and its three most commercialized structural analogues (ranked: bisphenols S, F and AF) on endometrial stromal cells to understand their effects on female reproductive function. Bisphenols showed dissimilar effects. All four compounds generated endoplasmic reticulum (ER) stress. In addition, bisphenols A, F and AF induced apoptosis through different mechanisms, with bisphenol AF causing cell cycle arrest at G(2)/M phase. Bisphenol AF decreased mitochondrial transmembrane potential and bisphenols A, F and AF produced oxidative stress. https://doi.org/10.1016/j.tox.2022.153282

Bone Disruption and Environmental Pollutants,
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Endocrine Metabolic & Immune Disorders-Drug Targets 22, no. 7 (2022): 704-715,
Background: Endocrine Disrupting Chemicals (EDCs) are ubiquitous and may significantly contribute to environmental pollution and contamination in humans and wildlife. Ecological pollutants could interfere with bone homeostasis through different mechanisms, including hormonal imbalance, direct osteoblast toxicity, and enhancement of osteoclasts activity, leading to either osteopenia or osteoporosis. Among these chemicals, bisphenols, dioxins, polycyclic aromatic hydrocarbons, polychlorobiphenyls, poly- and perfluoroalkyl, phthalates, parabens, organotins, and cadmium may play a role in the bone disruption. Methods: Authors searched PubMed/MEDLINE, ISI-web of knowledge, and Google scholar databases for medical subject headings terms and free-text words related to the classes mentioned above of chemicals and bone metabolism and remodeling for better clarifying and understanding the main mechanisms of bone disruption. Results: Several EDCs act as xeno-estrogens. Considering that estrogens play a significant role in regulating bone remodeling, most of these chemicals generate hormonal imbalance with possible detrimental consequences on bone tissue structure and its mechanical and non-mechanical properties. Discussion: Much evidence about bone disruptors was obtained from in vitro studies or animal models with equivocal results. Besides, a few data have been acquired from humans, and most of these data focused on the impact of EDCs on bone mineral density without considering their influence on long-term fracture risk. Moreover, humans may be exposed to a mixture of EDCs, and the final effect on bone metabolism might be attributable to either synergistic or antagonist effects. Age of first exposure, cumulative exposure over time, and the usually observed non-monotonic dose-response curve for EDCs should be considered as other essential variables influencing bone metabolism's final effect. Conclusion: Given these variables, observational studies are needed to analyze this issue for ecological purposes better and preserve bone health. https://doi.org/10.2174/1871530321666210118163538

Chemical Effects on Breast Development, Function, and Cancer Risk: Existing Knowledge and New Opportunities,
KAY J. E., B. CARDONA, R. A. RUDEL, L. N. VANDENBERG, A. M. SOTO, S. CHRISTIANSEN, L. S. BIRNBAUM and S. E. FENTON,
Current Environmental Health Reports (Population studies show worrisome trends towards earlier breast development, difficulty in breastfeeding, and increasing rates of breast cancer in young women. Multiple epidemiological studies have linked these outcomes with chemical exposures, and experimental studies have shown that many of these chemicals generate similar effects in rodents, often by disrupting hormonal regulation. These endocrine-disrupting chemicals (EDCs) can alter the progression of mammary gland (MG)

development, impair the ability to nourish offspring via lactation, increase mammary tissue density, and increase the propensity to develop cancer. However, current toxicological approaches to measuring the effects of chemical exposures on the MG are often inadequate to detect these effects, impairing our ability to identify exposures harmful to the breast and limiting opportunities for prevention. This paper describes key adverse outcomes for the MG, including impaired lactation, altered pubertal development, altered morphology (such as increased mammographic density), and cancer. It also summarizes evidence from humans and rodent models for exposures associated with these effects. We also review current toxicological practices for evaluating MG effects, highlight limitations of current methods, summarize debates related to how effects are interpreted in risk assessment, and make recommendations to strengthen assessment approaches. Increasing the rigor of MG assessment would improve our ability to identify chemicals of concern, regulate those chemicals based on their effects, and prevent exposures and associated adverse health effects. https://doi.org/10.1007/s40572-022-00376-2

Comparing the effects of bisphenol A, C, and F on bovine theca cells in vitro,
TYNER M. D. W., M. O. MALONEY, B. J. B. KELLEY and C. M. H. COMBELLES,
Reproductive Toxicology 111 (Aug 2022): 27-33,
Endocrine disrupting chemicals (EDCs) target aspects of hormone activity. Tightly coordinated crosstalk between two somatic cells of the ovary, granulosa and theca cells, governs steroid hormone production and plays a critical role in reproduction. It is thus pertinent to understand the impact of EDCs on granulosa and theca cells. Bisphenol A (BPA), a well-known EDC, is widely used in the manufacturing of consumer products with humans routinely exposed. Strong evidence of the adverse effects of BPA on the female reproductive system has emerged and as a result, manufacturers have begun replacing BPA with other bisphenols, such as BPC and BPF. The safety of these analogs is currently unclear and should be investigated independently. Although much is known about the impact of BPA on granulosa cells, similar study of theca cells has been neglected. Further, there is a lack of studies on the impact of BPC and BPF on the female reproductive system. To fill these gaps, the present study compared the effect of BPA, BPC, and BPF on the viability and steroid production of theca cells from bovine, a clinically relevant model for human reproduction. We show that BPC is more detrimental to theca cell viability and progesterone production compared to BPA. Surprisingly, we also found that BPF induces an increase in progesterone production compared to a decrease with BPA and BPC. To determine safety for the reproductive system, we conclude that a major shift away from BPA to bisphenol analogs should be investigated more thoroughly. https://doi.org/10.1016/j.reprotox.2022.05.003

The Congenital and Acquired Mechanisms Implicated in the Etiology of Central Precocious Puberty,
BRITO V. N., A. P. M. CANTON, C. E. SERAPHIM, A. P. ABREU, D. B. MACEDO, B. B. MENDONCA, U. B. KAISER, J. ARGENTE and A. C. LATRONICO,
Endocrine Reviews (The etiology of central precocious puberty (CPP) is multiple and heterogeneous, including congenital and acquired causes that can be associated with structural or functional brain alterations. All causes of CPP culminate in the premature pulsatile secretion of hypothalamic GnRH and, consequently, in the premature reactivation of hypothalamic-pituitary-gonadal axis. The activation of excitatory factors or suppression of inhibitory factors during childhood represent the 2 major mechanisms of CPP, revealing a delicate balance of these opposing neuronal pathways. Hypothalamic hamartoma (HH) is the most well-known congenital cause of CPP with central nervous system abnormalities. Several mechanisms by which hamartoma causes CPP have been proposed, including an anatomical connection to the anterior hypothalamus, autonomous neuroendocrine activity in GnRH neurons, trophic factors secreted by HH, and mechanical pressure applied to the hypothalamus. The importance of genetic and/or epigenetic factors in the underlying mechanisms of CPP has grown significantly in the last decade, as demonstrated by the evidence of genetic abnormalities in hypothalamic structural lesions (eg, hamartomas, gliomas), syndromic disorders associated with CPP (Temple, Prader-Willi, Silver-Russell, and Rett syndromes), and isolated CPP from monogenic defects (MKRN3 and DLK1 loss-of-function mutations). Genetic and epigenetic discoveries involving the etiology of CPP have had influence on the diagnosis and familial counseling providing bases for potential prevention of premature sexual development and new treatment targets in the future. Global preventive actions inducing healthy lifestyle habits and less exposure to endocrine-disrupting chemicals during the lifespan are desirable because they are potentially associated with CPP. https://doi.org/10.1210/endrev/bnac020

The Current Findings on the Impact of Prenatal BPA Exposure on Metabolic Parameters: In Vivo and Epidemiological Evidence,
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Nutrients 14, no. 13 (Jul 2022),
Metabolic syndrome (MS) is a multifactorial disease entity and is not fully understood. Growing evidence suggests that early exposure to bisphenol A (BPA) is a significant risk factor for the development of metabolic diseases. BPA is a monomer used in the manufacturing of polycarbonate plastics, thermal receipt paper, and epoxy resins. Owing to its widespread use, BPA has been detected in human fluids and tissues, including blood, placental breast milk, and follicular fluid. In the present review, we aimed to review the impact of prenatal exposure to different doses of BPA on metabolic parameters as determined by in vivo and epidemiological studies. The PubMed, Scopus, and Web of Science electronic databases were searched to identify articles published during a period of 15 years from 2006 to 2021, and 29 studies met the criteria. Most studies demonstrated that prenatal exposure to low BPA concentrations correlated with alterations in metabolic parameters in childhood and an increased risk of metabolic diseases, such as obesity and type 2 diabetes mellitus (T2DM), in adulthood. Therefore, prenatal exposure to low doses of BPA may be associated with an increased risk of obesity and T2DM in a sex-specific manner. https://doi.org/10.3390/nu14132766

Developmental exposure to indoor flame retardants and hypothalamic molecular signatures: Sex-dependent reprogramming of lipid homeostasis,
KOZLOVA E. V., M. E. DENYS, J. BENEDUM, M. C. VALDEZ, D. ENRIQUEZ, A. E. BISHAY, B. D. CHINTHIRLA, E. TRUONG, J. M. KRUM, N. V. DIPATRIZIO, P. DEOL, M. MARTINS-GREEN and M. C. CURRAS-COLLAZO,
Frontiers in Endocrinology 13 (Sep 2022),
Polybrominated diphenyl ethers (PBDEs) are a class of flame-retardant organohalogen pollutants that act as endocrine/neuroendocrine disrupting chemicals (EDCs). In humans, exposure to brominated flame retardants (BFR) or other environmentally persistent organic pollutants (POPs) such as polychlorinated biphenyls (PCBs) and novel organophosphate flame retardants has been associated with increasing trends of diabetes and metabolic disease. However, the effects of PBDEs on metabolic processes and their associated sex-dependent features are poorly understood. The metabolic-disrupting effects of perinatal exposure to industrial penta-PBDE mixture, DE-71, on male and female progeny of C57BL/6N mouse dams were examined in adulthood. Dams were exposed to environmentally relevant doses of PBDEs daily for 10 weeks (p.o.): 0.1 (L-DE-71) and 0.4 mg/kg/d (H-DE-71) and offspring parameters were compared to corn oil vehicle controls (VEH/CON). The following lipid metabolism indices were measured: plasma cholesterol, triglycerides, adiponectin, leptin, and liver lipids. L-DE-71 female offspring were particularly affected, showing hypercholesterolemia, elevated liver lipids and fasting plasma leptin as compared to same-sex VEH/CON, while L- and H-DE-71 male F1 only showed reduced plasma adiponectin. Using the quantitative Folch method, we found that mean liver lipid content was significantly elevated in L-DE-71 female offspring compared to controls. Oil Red O staining revealed fatty liver in female offspring and dams. General measures of adiposity, body weight, white and brown adipose tissue (BAT), and lean and fat mass were weighed or measured using EchoMRI. DE-71 did not produce abnormal adiposity, but decreased BAT depots in L-DE-71 females and males relative to same-sex VEH/CON. To begin to address potential central mechanisms of deregulated lipid metabolism, we used RT-qPCR to quantitate expression of hypothalamic genes in energy-regulating circuits that control lipid homeostasis. Both doses of DE-71 sex-dependently downregulated hypothalamic expression of Lepr, Stat3, Mc4r, Agrp, Gshr in female offspring while H-DE-71 downregulated Npy in exposed females relative to VEH/CON. In contrast, exposed male offspring displayed upregulated Stat3 and Mc4r. Intestinal barrier integrity was measured using FITC-dextran since it can lead to systemic inflammation that leads to liver damage and metabolic disease, but was not affected by DE-71 exposure. These findings indicate that maternal transfer of PBDEs disproportionately endangers female offspring to lipid metabolic reprogramming that may exaggerate risk for adult metabolic disease.
https://doi.org/10.3389/fendo.2022.997304

Effect of exposure to endocrine disrupting chemicals in obesity and neurodevelopment: The genetic and microbiota link,
RAMIREZ V., P. GONZALEZ-PALACIOS, M. A. BACA, P. J. GONZALEZ-DOMENECH, M. FERNANDEZ-CABEZAS, M. J. ALVAREZ-CUBERO, L. RODRIGO and A. RIVAS,
Science of the Total Environment 852 (Dec 2022),
Current evidence highlights the importance of the genetic component in obesity and neurodevelopmental

disorders (attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and intellectual disability (ID)), given that these diseases have reported an elevated heritability. Additionally, environmental stressors, such as endo-crine disrupting chemicals (EDCs) have been classified as obesogens, neuroendocrine disruptors, and microbiota disrupting chemicals (MDCs). For this reason, the importance of this work lies in examining two possible biological mechanistic pathways linking obesity and neurodevelopmental/behavioural disorders: EDCs - gene and EDCs - micro -biota interactions. First, we summarise the shared mechanisms of action of EDCs and the common genetic profile in the bidirectional link between obesity and neurodevelopment. In relation to interaction models, evidence from the re-viewed studies reveals significant interactions between pesticides/heavy metals and gene polymorphisms of detoxify-ing and neurotransmission systems and metal homeostasis on cognitive development, ASD and ADHD symptomatology. Nonetheless, available literature about obesity is quite limited. Importantly, EDCs have been found to induce gut microbiota changes through gut-brain-microbiota axis conferring susceptibility to obesity and neurodevelopmental disorders. In view of the lack of studies assessing the impact of EDCs - gene interactions and EDCs - mediated dysbiosis jointly in obesity and neurodevelopment, we support considering genetics, EDCs exposure, and microbiota as interactive factors rather than individual contributors to the risk for developing obesity and neurodevelopmental disabilities at the same time. https://doi.org/10.1016/j.scitotenv.2022.158219

Effects of Di-2-Ethylhexyl Phthalate on Central Nervous System Functions: A Narrative Review,
SAFARPOUR S., M. GHASEMI-KASMAN, S. SAFARPOUR and Y. M. DARBAN,
Current Neuropharmacology 20, no. 4 (2022): 766-776,
Background: Phthalates are widely used in the plastics industry. Di-2-Ethylhexyl Phthalate (DEHP) is one of the most important phthalate metabolites that disrupt the function of endocrine glands. Exposure to DEHP causes numerous effects on animals, humans, and the environment. Low doses of DEHP increase neurotoxicity in the nervous system that has arisen deep concerns due to the widespread nature of DEHP exposure and its high absorption during brain development. Objective: In this review article, we evaluated the impacts of DEHP exposure from birth to adulthood on neurobehavioral damages. Then, the possible mechanisms of DEHP-induced neurobehavioral impairment were discussed. Methodology: Peer-reviewed articles were extracted through Embase, PubMed, and Google Scholar till the year 2021. Results: The results showed that exposure to DEHP during pregnancy and infancy leads to memory loss and irreversible nervous system damage. Conclusion: Overall, it seems that increased levels of oxidative stress and inflammatory mediators possess a pivotal role in DEHP-induced neurobehavioral impairment. https://doi.org/10.2174/1570159x19666210713122517

Effects of Organochlorine Pesticide Residues in Maternal Body on Infants,
QI S. Y., X. L. XU, W. Z. MA, S. L. DENG, Z. X. LIAN and K. YU,
Frontiers in Endocrinology 13 (Jun 2022),
https://doi.org/10.3389/fendo.2022.890307

Effects of Organochlorine Pesticide Residues in Maternal Body on Infants,
QI S. Y., X. L. XU, W. Z. MA, S. L. DENG, Z. X. LIAN and K. YU,
Frontiers in Endocrinology 13 (Jun 2022),
There are many organochlorine pollutants in the environment, which can be directly or indirectly exposed to by mothers, and as estrogen endocrine disruptors can cause damage to the lactation capacity of the mammary gland. In addition, because breast milk contains a lot of nutrients, it is the most important food source for new-born babies. If mothers are exposed to organochlorine pesticides (OCPs), the lipophilic organochlorine contaminants can accumulate in breast milk fat and be passed to the infant through breast milk. Therefore, it is necessary to investigate organochlorine contaminants in human milk to estimate the health risks of these contaminants to breastfed infants. In addition, toxic substances in the mother can also be passed to the fetus through the placenta, which is also something we need to pay attention to. This article introduces several types of OCPs, such as dichlorodiphenyltrichloroethane (DDT), methoxychlor (MXC), hexachlorocyclohexane (HCH), endosulfan, chlordane, heptachlorand and hexachlorobenzene (HCB), mainly expounds their effects on women's lactation ability and infant health, and provides reference for maternal and infant health. In addition, some measures and methods for the control of organochlorine pollutants are also described here.
https://doi.org/10.3389/fendo.2022.890307

ENDOCRINE DISRUPTING CHEMICALS AND OBESITY: THE EVOLVING STORY OF OBESOGENS,
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Acta Endocrinologica-Bucharest 17, no. 4 (Oct-Dec 2021): 503-508,
Increase in obesity pandemic all over the world consequently leads to the investigation of possible causes. In addition to the traditional explanation using the so-called caloric model, the field of endocrine disruptors (EDs), especially subgroup called obesogens, offered more light on the pathogenetic mechanisms involved. After the Second World War a correlation between an increased production of exogenous pollutants and actual obesity epidemic was suggested. "Obesogen hypothesis" implies that molecules called obesogens inadequately stimulate the development of adipose cells and lipid accumulation in existing adipose cells, as well as change metabolic balance or hormonal control of appetite and satiety, leading to an increase in body fat mass. The list of obesogens includes some industrial chemicals, biocides, pharmaceuticals, pollutants, and smoke. EDs from the group of obesogens may exert their effects by the impairment in the programming development of adipocytes, by an increase in energetic depot in the adipose tissue, and by influencing neuroendocrine control of appetite and satiety. Increased scientific evidence on obesogens and their mechanisms of action may help to prevent obesity and mitigate deleterious effects of the environment on human life and development. New translational studies are needed to explain the possible mechanism proposed.
https://doi.org/10.4183/aeb.2021.503

Endocrine Disruptors and Obesity: An Overview,
MURRO I., G. LISCO, C. DI NOIA, L. LAMPIGNANO, R. ZUPO, V. A. GIAGULLI, E. GUASTAMACCHIA, V. TRIGGIANI and G. DE PERGOLA,
Endocrine Metabolic & Immune Disorders-Drug Targets 22, no. 8 (2022): 798-806,
Obesity is a growing pandemic. Endocrine-disrupting chemicals are widespread in the environment. In this perspective, the authors examine the issue related to the exposure to several chemicals with endocrine-disrupting properties as promoting factors to obesity. Data show that Phthalates, Bisphenol compounds, Persistent Organic Pollutants (POPs), solvents, and personal care products can modify metabolic properties in a dose-response and sex-specific manner. Phthalates and bisphenol compounds increase body mass index, waist circumference, waist to height ratio, and the sum of skinfold thicknesses in women and not in men. Low-dose exposure to Persistent Organic Pollutants is strongly associated with increased body mass index in men and decreased this parameter in women. The mechanism through which these compounds act on anthropometric parameters is not entirely understood. Several studies suggest a possible interference in gonadotropin secretion and the thyroid axis. These inspire a decrease in both total and free testosterone levels in men and FT3 and FT4 levels in women, particularly after a pregnancy. The impact of endocrine disruptor chemicals on adipose tissue inflammation and future cardio-metabolic disorders remains to be elucidated. Therefore, studies involving both healthy and obese individuals are needed to unambiguously confirm results from in vitro and animal models.
https://doi.org/10.2174/1871530322666220328122300

Endocrine-disrupting chemicals affect Sertoli TM4 cell functionality through dysregulation of gap junctional intercellular communication in vitro,
YAWER A., E. SYCHROVA, J. RASKA, P. BABICA and I. SOVADINOVA,
Food and Chemical Toxicology 164 (Jun 2022),
The frequencies of adverse outcomes associated with male reproductive health, including infertility and testicular cancer, are increasing. These adverse trends are partially attributed to increased exposure to environmental agents such as endocrine-disrupting chemicals (EDCs). This study addresses effects on EDCs on adjacent prepubertal Sertoli TM4 cells, specifically on 1) testicular gap junctional intercellular communication (GJIC), one of the hallmarks of non-genotoxic carcinogenicity, 2) GJIC building blocks connexins (Cx), and 3) mitogen-activated protein kinases MAPKs. We selected eight representatives of EDCs: organochlorine chemicals such as pesticides dichlorodiphenyltrichlomethane, lindane, methoxychlor, and vinclozolin, industrial chemicals bisphenol A and 2,2',4,4',5,5'-hexachlorobiphenyl, and components of personal care products, triclocarban and triclosan. EDCs rapidly dysregulated GJIC in Sertoli TM4 cells mainly via MAPK p38 and/or Erk1/2 pathways by the intermediate hyper- or de-phosphorylation of Cx43 (Ser368, Ser282) and translocation of Cx43 from the plasma membrane, suggesting disturbed intracellular trafficking of Cx43 protein. Surprisingly, EDCs did not rapidly activate MAPK Erk1/2 or p38; on the contrary, TCC and TCS decreased their activity (phosphorylation). Our results indicate that EDCs might disrupt testicular homeostasis and development via testicular GJIC,

junctional and non-junctional functions of Cx43 and MAPK-signaling pathways in Sertoli cells. https://doi.org/10.1016/j.fct.2022.113004

Endometrial Cells Acutely Exposed to Phthalates In Vitro Do Not Phenocopy Endometriosis,
GONZALEZ-MARTIN R., A. PALOMAR, Y. MEDINA-LAVER, A. QUINONERO and F. DOMINGUEZ,
International Journal of Molecular Sciences 23, no. 19 (Oct 2022),
Environmental factors that have been linked to an increased endometriosis risk include exposure to di-(2-ethylhexyl)-phthalate (DEHP), an endocrine disruptor. This study aims to investigate whether DEHP in vitro exposure in primary endometrial stromal cells (EnSC), primary endometrial epithelial cells (EnEC), and the human endometrial adenocarcinoma cell line Ishikawa properly mimics alterations described in the eutopic endometrium of women with endometriosis. Primary EnSC and EnEC, isolated from six fertile egg donors, and Ishikawa cells were exposed to DEHP (0.1, 1, and 10 mu M) and were assessed for viability, endometriosis markers (IL-6, VEGF-A, HOXA10, EZH2, and LSD1), steroid receptor gene expressions (ER-1, ER-2, PR-T, PR-B, and PGRMC1), and invasive capacity. Viability after 72 h of DEHP exposure was not significantly affected. None of the endometriosis markers studied were altered after acute DEHP exposure, nor was the expression of steroid receptors. The invasive capacity of EnSC was significantly increased after 10 mu M of DEHP exposure. In conclusion, acute DEHP exposure in primary endometrial cells does not fully phenocopy the changes in the viability, expression of markers, or steroidal receptors described in endometriosis. However, the significant increase in EnSC invasiveness observed after DEHP exposure could be a link between DEHP exposure and increased endometriosis likelihood. https://doi.org/10.3390/ijms231911041

Environmental Contamination and Chronic Exposure to Endocrine-Disrupting Phthalates: An Overlooked and Emerging Determinant for Hormone-Sensitive Cancers,
DAS A. M., A. GOGIA, R. JANARDHANAN, R. BABU-RAJENDRAN and B. C. DAS,
Journal of the Indian Institute of Science 102, no. 2 (Apr 2022): 731-742,
Despite several modifiable and non-modifiable risk factors of hormone-associated cancers have been established, less heed has been paid to chemicals, those having the potential to thwart the body's normal detox system and affect the endocrine-hormonal pathways. Phthalates are endocrine-disrupting chemicals, most widely manufactured and used indiscriminately in several industries, including processed, ultra-processed and packaged food, single-use plastics, household and personal care/cosmetic products including diapers and electronics. The general population is regularly being exposed to phthalates on contact with these products, especially women and children are most vulnerable. It is therefore highly crucial to monitor and evaluate the biological burden of plasticizing phthalates in humans and understand the potential mechanisms of etiological link between pervasive exposure to phthalates and development of chronic diseases such as cancer through epigenetic and/or genetic alterations. It is also important to identify sustainable and scalable interventions for increasing public awareness, and restricting chronic phthalate exposure to individual and the population at large through relevant policy legislations, particularly in low-income and middle-income countries, such as India. https://doi.org/10.1007/s41745-022-00319-8

Environmental disruptors and testicular cancer,
FAJA F., S. ESTEVES, F. PALLOTTI, G. CICOLANI, S. DI CHIANO, E. D. PAOLI, A. LENZI, F. LOMBARDO and D. PAOLI,
Endocrine 78, no. 3 (Dec 2022): 429-435,
Purpose Testicular cancer (TC) is the most common malignancy among young adult males. The etiology is multifactorial, and both environmental and genetic factors play an essential role in the origin and development of this tumor. In particular, exposure to environmental endocrine disruptors (EEDs), resulting from industrialization and urbanization, seems crucial both in pre-and postnatal life. However, the lack of long-term studies on a wide caseload and the difficulty in evaluating their toxic effects in vivo make it challenging to establish a causal link. This review aims to discuss the main human epidemiological studies currently available in the literature to define a possible association between these chemicals and TC. Methods A comprehensive Medline/PubMed and Embase search was performed, selecting all relevant, peer-reviewed papers in English published from 2002 to January 2022. Other relevant papers were selected from the reference lists. Results To date, literature evidence is limited due to the scarcity and heterogeneity of human studies and shows controversial data, highlighting the complexity of the topic. However, most human epidemiological studies seem to point toward a correlation between EEDs exposure and TC. Conclusion Although the molecular mechanisms

are not yet fully understood, the role of EEDs in TC onset is plausible, but several factors, such as the individual genetic background, the exposure time, and the complex mechanism of action of these chemicals, do not allow defining the causal link with certainty and make further studies necessary to investigate this complex topic. https://doi.org/10.1007/s12020-022-03171-z

Hormonal regulation of mammary gland development and lactation,
HANNAN F. M., T. ELAJNAF, L. N. VANDENBERG, S. H. KENNEDY and R. V. THAKKER,
Nature Reviews Endocrinology (Lactation is critical to infant short-term and long-term health and protects mothers from breast cancer, ovarian cancer and type 2 diabetes mellitus. The mammary gland is a dynamic organ, regulated by the coordinated actions of reproductive and metabolic hormones. These hormones promote gland development from puberty onwards and induce the formation of a branched, epithelial, milk-secreting organ by the end of pregnancy. Progesterone withdrawal following placental delivery initiates lactation, which is maintained by increased pituitary secretion of prolactin and oxytocin, and stimulated by infant suckling. After weaning, local cytokine production and decreased prolactin secretion trigger large-scale mammary cell loss, leading to gland involution. Here, we review advances in the molecular endocrinology of mammary gland development and milk synthesis. We discuss the hormonal functions of the mammary gland, including parathyroid hormone-related peptide secretion that stimulates maternal calcium mobilization for milk synthesis. We also consider the hormonal composition of human milk and its associated effects on infant health and development. Finally, we highlight endocrine and metabolic diseases that cause lactation insufficiency, for example, monogenic disorders of prolactin and prolactin receptor mutations, maternal obesity and diabetes mellitus, interventions during labour and delivery, and exposure to endocrine-disrupting chemicals such as polyfluoroalkyl substances in consumer products and other oestrogenic compounds.
https://doi.org/10.1038/s41574-022-00742-y

Implications of endocrine-disrupting chemicals on polycystic ovarian syndrome: A comprehensive review,
JALA A., B. VARGHESE, G. KAUR, K. RAJENDIRAN, R. DUTTA, R. ADELA and R. M. BORKAR,
Environmental Science and Pollution Research 29, no. 39 (Aug 2022): 58484-58513,
Polycystic ovarian syndrome (PCOS) is a complex multifactorial disorder of unknown pathogenesis in which genetic and environmental factors contribute synergistically to its phenotypic expressions. Endocrine-disrupting chemicals (EDCs), a group of widespread pollutants freely available in the environment and consumer products, can interfere with normal endocrine signals. Extensive evidence has shown that EDCs, environmental contributors to PCOS, can frequently induce ovarian and metabolic abnormalities at low doses. The current research on environmental EDCs suggests that there may be link between EDC exposure and PCOS, which calls for more human bio-monitoring of EDCs using highly sophisticated analytical techniques for the identification and quantification and to discover the underlying pathophysiology of the disease. This review briefly elaborated on the general etiology of PCOS and listed various epidemiological and experimental data from human and animal studies correlating EDCs and PCOS. This review also provides insights into various analytical tools and sample preparation techniques for biomonitoring studies for PCOS risk assessment. Furthermore, we highlight the role of metabolomics in disease-specific biomarker discovery and its use in clinical practice. It also suggests the way forward to integrate biomonitoring studies and metabolomics to underpin the role of EDCs in PCOS pathophysiology. https://doi.org/10.1007/s11356-022-21612-0

Increased gut serotonin production in response to bisphenol A structural analogs may contribute to their obesogenic effects,
BARRA N. G., Y. H. KWON, K. M. MORRISON, G. R. STEINBERG, M. G. WADE, W. I. KHAN, M. M. VIJAYAN, J. D. SCHERTZER and A. C. HOLLOWAY,
American Journal of Physiology-Endocrinology and Metabolism 323, no. 1 (Jul 2022): E80-E91,
Obesogens are synthetic, environmental chemicals that can disrupt endocrine control of metabolism and contribute to the risk of obesity and metabolic disease. Bisphenol A (BPA) is one of the most studied obesogens. There is considerable evidence that BPA exposure is associated with weight gain, increased adiposity, poor blood glucose control, and nonalcoholic fatty liver disease in animal models and human populations. Increased usage of structural analogs of BPA has occurred in response to legislation banning their use in some commercial products. However, BPA analogs may also cause some of the same metabolic impairments because of common mechanisms of action. One key effector that is altered by BPA and its analogs is serotonin, however, it is

unknown if BPA-induced changes in peripheral serotonin pathways underlie metabolic perturbations seen with BPA exposure. Upon ingestion, BPA and its analogs act as endocrine-disrupting chemicals in the gastrointestinal tract to influence serotonin production by the gut, where over 95% of serotonin is produced. The purpose of this review is to evaluate how BPA and its analogs alter gut serotonin regulation and then discuss how disruption of serotonergic networks influences host metabolism. We also provide evidence that BPA and its analogs enhance serotonin production in gut enterochromaffin cells. Taken together, we propose that BPA and many BPA analogs represent endocrine-disrupting chemicals that can influence host metabolism through the endogenous production of gut-derived factors, such as serotonin. https://doi.org/10.1152/ajpendo.00049.2022

Low Doses of PFOA Promote Prostate and Breast Cancer Cells Growth through Different Pathways,
CHARAZAC A., C. HINAULT, B. DOLFI, S. HAUTIER, C. D. LE BUTOR, F. BOST and N. CHEVALIER,
International Journal of Molecular Sciences 23, no. 14 (Jul 2022),
Endocrine Disrupting Compounds (EDCs) are found in everyday products. Widely distributed throughout the environment, persistent organic pollutants (POPs) are a specific class of EDCs that can accumulate in adipose tissue. Many of them induce adverse effects on human health-such as obesity, fertility disorders and cancers-by perturbing hormone effects. We previously identified many compounds with EDC activity in the circulation of obese patients who underwent bariatric surgery. Herein, we analyzed the effects of four of them (aldrin, BDE28, PFOA and PCB153) on two cancer cell lines of hormone-sensitive organs (prostate and breast). Each cell line was exposed to serial dilutions of EDCs from 10(-6) M to 10(-12) M; cytotoxicity and proliferation were monitored using the IncuCyte (R) technology. We showed that none of these EDCs induce cytotoxicity and that PFOA and PCB153, only at very low doses (10(-12) M), increase the proliferation of DU145 (prostate cancer) and MCF7 (breast cancer) cells, while the same effects are observed with high concentrations (10(-6) M) for aldrin or BDE28. Regarding the mechanistic aspects, PFOA uses two different signaling pathways between the two lines (the Akt/mTORC1 and PlexinD1 in MCF7 and DU145, respectively). Thus, our study demonstrates that even at picomolar (10(-12) M) concentrations PFOA and PCB153 increase the proliferation of prostate and breast cancer cell lines and can be considered possible carcinogens. https://doi.org/10.3390/ijms23147900

Mémoire. Perturbateurs endocriniens et cancer : les bisphénols pourraient-ils avoir un impact sur l'initiation et la progression du cancer de la vessie?,
E. P.,
Université de Laval (octobre 2022),
Les bisphénols sont des composés synthétiques utilisés dans la synthèse des plastiques. Ils ont la capacité de se lier à plusieurs récepteurs cellulaires, dont certains récepteurs hormonaux, ce qui leur confère des propriétés de perturbateurs endocriniens. Certains de ces récepteurs hormonaux sont, entre autres, présents au niveau de l'urothélium de la vessie. De plus en plus d'études ont démontré que l'exposition aux bisphénols est associée à la progression tumorale, surtout pour les cancers hormono-dépendants tels que le cancer de la prostate. La vessie n'est pas considérée comme un tissu hormono-sensible, mais des études ont démontré le rôle des récepteurs hormonaux dans l'initiation et la progression de cancer de la vessie. Étant donné la présence de ces composés dans l'urine chez l'humain, nous avions pour objectif de déterminer si l'exposition chronique aux bisphénols pourrait avoir un impact sur l'initiation et la progression du cancer de la vessie. Ainsi, nous avons exposé des cellules urothéliales saines, des cellules cancéreuses non-invasives et cancéreuses invasives de vessie, des fibroblastes vésicaux et des fibroblastes associés au cancer à des concentrations physiologiques de bisphénols. Nous avons ensuite caractérisé l'impact de cette exposition sur le métabolisme énergétique et l'activité physiologique des cellules. Nous avons observé que les cellules urothéliales et stromales saines présentaient une diminution de ces caractéristiques par rapport aux contrôles, tandis que ces paramètres chez les cellules cancéreuses et les fibroblastes associés au cancer étaient augmentés. Ainsi, l'exposition chronique aux bisphénols semble favoriser la progression des cancers de vessie non-invasifs en cancers invasifs. Ce projet de recherche a permis d'apporter des informations novatrices sur l'impact de perturbateurs endocriniens sur le développement du cancer de la vessie. http://hdl.handle.net/20.500.11794/102929

The Mixture of Bisphenol-A and Its Substitutes Bisphenol-S and Bisphenol-F Exerts Obesogenic Activity on Human Adipose-Derived Stem Cells,
REINA-PEREZ I., A. OLIVAS-MARTINEZ, V. MUSTIELES, E. SALAMANCA-FERNANDEZ, J. M. MOLINA-MOLINA, N. OLEA and M. F. FERNANDEZ,

Toxics 10, no. 6 (Jun 2022),
Bisphenol A (BPA) and its substitutes, bisphenol F (BPF) and S (BPS), have previously shown in vitro obesogenic activity. This study was designed to investigate their combined effect on the adipogenic differentiation of human adipose-derived stem cells (hASCs). Cells were exposed for 14 days to an equimolar mixture of bisphenols (MIX) (range 10 nM-10 mu M). Oil Red staining was used to measure intracellular lipid accumulation, quantitative real-time polymerase chain reaction (qRT-PCR) to study gene expression of adipogenic markers (PPAR gamma, C/EBP alpha, LPL, and FABP4), and Western Blot to determine their corresponding proteins. The MIX promoted intracellular lipid accumulation in a dose-dependent manner with a maximal response at 10 mu M. Co-incubation with pure antiestrogen (ICI 182,780) inhibited lipid accumulation, suggesting that the effect was mediated by the estrogen receptor. The MIX also significantly altered the expression of PPAR gamma, C/EBP alpha, LPL, and FABP4 markers, observing a non-monotonic (U-shaped) dose-response, with maximal gene expression at 10 nM and 10 mu M and lesser expression at 1 mu M. This pattern was not observed when bisphenols were tested individually. Exposure to MIX (1-10 mu M) also increased all encoded proteins except for FABP4, which showed no changes. Evaluation of the combined effect of relevant chemical mixtures is needed rather than single chemical testing. https://doi.org/10.3390/toxics10060287

Molecular consequences of the exposure to toxic substances for the endocrine system of females,
KOWALCZYK A., M. WRZECINSKA, E. CZERNIAWSKA-PIATKOWSKA, J. P. ARAUJO and P. CWYNAR,
Biomedicine & Pharmacotherapy 155 (Nov 2022),
Endocrine-disrupting chemicals (EDCs) are common in the environment and in everyday products such as cosmetics, plastic food packaging, and medicines. These substances are toxic in small doses (even in the order of micrograms) and enter the body through the skin, digestive or respiratory system. Numerous studies confirm the negative impact of EDCs on living organisms. They disrupt endocrine functions, contributing to the development of neoplastic and neurological diseases, as well as problems with the circulatory system and reproduction. EDCs affect humans and animals by modulating epigenetic processes that can lead to disturbances in gene expression or failure and even death. They also affect steroid hormones by binding to their receptors as well as interfering with synthesis and secretion of hormones. Prenatal exposure may be related to the impact of EDCs on offspring, resulting in effects of these substances on the ovaries and leading to the reduction of fertility through distur-bances in the function of steroid receptors or problems with steroidogenesis and gametogenesis. Current liter-ature indicates the need to continue research on the effects of EDCs on the female reproductive system. The aim of this review was to identify the effects of endocrine-disrupting chemicals on the female reproductive system and their genetic effects based on recent literature.
https://doi.org/10.1016/j.biopha.2022.113730

Mono-(2-ethyl-5-hydroxyhexyl) phthalate promotes uterine leiomyoma cell survival through tryptophan-kynurenine-AHR pathway activation,
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Proceedings of the National Academy of Sciences 119, no. 47 (2022): e2208886119,
Uterine leiomyoma is the most common tumor in women and causes severe morbidity in 15 to 30% of reproductive-age women. Epidemiological studies consistently indicate a correlation between leiomyoma development and exposure to endocrine-disrupting chemical phthalates, especially di-(2-ethylhexyl) phthalate (DEHP); however, the underlying mechanisms are unknown. Here, among the most commonly encountered phthalate metabolites, we found the strongest association between the urine levels of mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), the principal DEHP metabolite, and the risk of uterine leiomyoma diagnosis (n = 712 patients). The treatment of primary leiomyoma and smooth muscle cells (n = 29) with various mixtures of phthalate metabolites, at concentrations equivalent to those detected in urine samples, significantly increased cell viability and decreased apoptosis. MEHHP had the strongest effects on both cell viability and apoptosis. MEHHP increased cellular tryptophan and kynurenine levels strikingly and induced the expression of the tryptophan transporters SLC7A5 and SLC7A8, as well as, tryptophan 2,3-dioxygenase (TDO2), the key enzyme catalyzing the conversion of tryptophan to kynurenine that is the endogenous ligand of aryl hydrocarbon receptor (AHR). MEHHP stimulated nuclear localization of AHR and up-regulated the expression of CYP1A1 and CYP1B1, two prototype targets of AHR. siRNA knockdown or pharmacological inhibition of SLC7A5/SLC7A8, TDO2, or AHR abolished MEHHP-mediated effects on leiomyoma cell survival. These findings indicate that MEHHP promotes leiomyoma cell survival by activating the tryptophan-kynurenine-AHR pathway. This study pinpoints MEHHP exposure as a high-risk factor for leiomyoma growth, uncovers a mechanism by which

exposure to environmental phthalate impacts leiomyoma pathogenesis, and may lead to the development of novel druggable targets. https://doi.org/doi:10.1073/pnas.2208886119

Multi- and Transgenerational Effects of Environmental Toxicants on Mammalian Reproduction,
REBUZZINI P., G. FABOZZI, D. CIMADOMO, F. M. UBALDI, L. RIENZI, M. ZUCCOTTI and S. GARAGNA,
Cells 11, no. 19 (Oct 2022),
Environmental toxicants (ETs) are an exogenous chemical group diffused in the environment that contaminate food, water, air and soil, and through the food chain, they bioaccumulate into the organisms. In mammals, the exposure to ETs can affect both male and female fertility and their reproductive health through complex alterations that impact both gametogeneses, among other processes. In humans, direct exposure to ETs concurs to the declining of fertility, and its transmission across generations has been recently proposed. However, multi- and transgenerational inheritances of ET reprotoxicity have only been demonstrated in animals. Here, we review recent studies performed on laboratory model animals investigating the effects of ETs, such as BPA, phthalates, pesticides and persistent contaminants, on the reproductive system transmitted through generations. This includes multigenerational effects, where exposure to the compounds cannot be excluded, and transgenerational effects in unexposed animals. Additionally, we report on epigenetic mechanisms, such as DNA methylation, histone tails and noncoding RNAs, which may play a mechanistic role in a nongenetic transmission of environmental information exposure through the germline across generations.
https://doi.org/10.3390/cells11193163

The Putative Adverse Effects of Bisphenol A on Autoimmune Diseases,
SHARIF K., A. KURNICK, L. COPLAN, M. ALEXANDER, A. WATAD, H. AMITAL and Y. SHOENFELD,
Endocrine Metabolic & Immune Disorders-Drug Targets 22, no. 7 (2022): 665-676,
Bisphenol A (BPA) is a monomer that is widely used in the manufacturing of polycarbonate plastics (including storage plastics and baby bottles) and is considered to be one of the most widely used synthetic compounds in the manufacturing industry. Exposure to BPA mainly occurs after oral ingestion and results from leaks into food and water from plastic containers. According to epidemiological data, exposure is widespread and estimated to occur in 90% of individuals. BPA exhibits pleiotropic and estrogen-like effects; thus, it is considered an endocrine-disrupting chemical. A growing body of evidence highlights the role of BPA in modulating immune responses and signaling pathways, which results in a proinflammatory response by enhancing the differential polarization of immune cells and cytokine production profile to one that is consistent with proinflammation. Indeed, epidemiological studies have uncovered associations between several autoimmune diseases and BPA exposure. Data from animal models provided consistent evidence, which highlighted the role of BPA in the pathogenesis, exacerbation, and perpetuation of various autoimmune phenomena including neuroinflammation in the context of multiple sclerosis, colitis in inflammatory bowel disease, nephritis in systemic lupus erythematosus, and insulitis in type 1 diabetes mellitus. Owing to the widespread use of BPA and its effects on immune system dysregulation, a call for careful assessment of patients' risks and public health measures are needed to limit exposure and subsequent deleterious effects. The purpose of this study is to explore the autoimmune triggering mechanisms and present the current literature supporting the role of BPA in the pathogenesis of autoimmune diseases. https://doi.org/10.2174/1871530321666210210154309

Testicular toxicity of bisphenol compounds: Homeostasis disruption of cholesterol/testosterone via PPAR alpha activation,
GAO Z. S., S. H. LIU, L. TAN, X. N. GAO, W. T. FAN, C. C. DING, M. C. LI, Z. H. TANG, X. Z. SHI, Y. LUO and S. Q. SONG,
Science of the Total Environment 836 (Aug 2022),
The widespread application of bisphenols (BPs) has made them ubiquitous in the environment. Although the side effects of bisphenol A (BPA) substitutes have received increasing attention, studies on their reproductive toxicity remain lacking. In this research, the effects of BPA and its substitutes, including bisphenol S (BPS), bisphenol F (BPF), and bisphenol AF (BPAF), on the male reproductive system were evaluated. Results proved that these BPs disturbed germ cell proliferation, induced germ cell apoptosis, and perturbed sperm physiologies and spermatogenesis, which resulted from the disruption of testosterone (T) biosynthesis in Leydig cells (LCs). Importantly, in vitro and in vivo studies indicated that the exhausted cholesterol in ICs accounted for the reduced T production. Furthermore, the knockdown of peroxisome proliferator-activated receptor alpha (PPAR

alpha) remarkably ameliorated the downregulation of cholesterogenesis-related genes (i.e., Hmgcs1, Hmgcr, and Srebf2), indicating that PPAR alpha played a critical role in BPs-induced testicular dysfunction. Overall, our studies indicated that BPS, BPF, and BPAF could induce testicular toxic effects similar to that of BPA, which were associated with the PPAR alpha pathway. https://doi.org/10.1016/j.scitotenv.2022.155628

Méthodes

Analytical method for the biomonitoring of bisphenols and parabens by liquid chromatography coupled to tandem mass spectrometry in human hair,
ROBIN J., G. BINSON, M. ALBOUY, A. SAUVAGET, P. PIERRE-EUGENE, V. MIGEOT, A. DUPUIS and N. VENISSE,
Ecotoxicology and Environmental Safety 243 (Sep 2022),
Bisphenols and parabens are endocrine disruptors families widely used in daily life. They are known to be linked to numerous pathologies such as reproductive disorders, obesity, breast cancer, hypertension and asthma. Bio-monitoring is an essential tool for assessing population exposure to environmental pollutants. Blood and urine are the main matrices used in human biomonitoring. However, they are not suitable to evaluate long-term exposure to endocrine disruptors with a short elimination half-life such as parabens or phenols. Hair appears to be an interesting alternative matrix allowing a wide window of exposure due to an accumulation of xeno-biotics during hair growth. This study presents the development and validation of a high-performance liquid chromatography coupled to tandem mass spectrometry for the simultaneous determination of bisphenol A, its chlorinated derivatives, bisphenol F, bisphenol S and parabens in human hair. An optimised sample preparation based on acidic hydrolysis followed by liquid-liquid extraction was performed, before an analysis by ultra-high performance liquid chromatography coupled to tandem mass spectrometry in multiple reaction monitoring mode. To validate the method, recognized bioanalytical guidelines were used and calibration and quality control samples were prepared in human hair samples. Linearities were over 0.996 in the whole range of concentrations. Trueness and precision were demonstrated for each target analyte with intra-day and inter-day bias values ranging from 86 % to 118 % and relative standard deviation values ranging from 0 % to 19 %. At the same time, limits of quantification were set at 0.25 ng/g for bisphenol A and parabens, 0.05 ng/g for bisphenols F and S and 0.00625 ng/g for the chlorinated derivatives of bisphenol A. This reliable method was applied to hair samples taken from hospital professionals and allowed the quantification of these endocrine disruptors in this population. Chlorinated derivatives of bisphenol A were quantified here in hair for the first time.
https://doi.org/10.1016/j.ecoenv.2022.113986

High-content imaging analyses of the effects of bisphenols and organophosphate esters on TM4 mouse Sertoli cells(dagger),
RAJKUMAR A., T. LUU, B. F. HALES and B. ROBAIRE,
Biology of Reproduction 107, no. 3 (Sep 2022): 858-868,
The endocrine disruptive effects of bisphenol A (BPA) and brominated flame retardants (BDE-47) have led to restrictions on their use and increased the pressure to identify safe replacements for these chemicals. Although there is evidence that some of these alternatives may be toxic to spermatogonial and Leydig cells, little is known about the toxicity of emerging replacements on Sertoli cells. We used high-content imaging to compare the effects of legacy chemicals, BPA and BDE-47, to their corresponding replacements. TM4 Sertoli cells were exposed for 48 h to each chemical (0.001-100 mu M) followed by cytotoxicity and phenotypic endpoint assessment. The benchmark concentration potency ranking for bisphenols based on cytotoxicity was BPTMC > bisphenol M > BPAF>BPF > BPS > BPA. Human administered equivalent dose (AED) determination ranked BPS as the most potent alternative replacement. The benchmark concentration potency ranking of BDE-47 and organophosphate esters based on cytotoxicity was TDtBPP>BDMPP>TBOEP>TDCPP>TMPP>TPHP>BDE47>IPPP=BPDP=TCPP. Additionally, TM4 cell exposure to BDE-47 increased Calcein intensity (57.9 mu M) and affected lysosomes (21.6 mu M), while exposure to TPHP and TMPP resulted in cellular oxidative stress changes at benchmark concentration values as low as 0.01 and 0.4 mu M, respectively. Overall bioactivity considerations of the chemicals on TM4 via ToxPi analyses and AED modeling further validated emerging replacements as highly potent chemicals in comparison to BPA and BDE-47. These findings demonstrate that many bisphenol and flame retardant replacements are more potent in

Sertoli cells than the legacy chemical they are replacing and that phenotypic parameter assessment is an effective tool in chemical toxicity assessment. In TM4 Sertoli cells, many of the chemicals that are emerging as replacements for BPA and brominated flame retardants show greater toxicity than the chemicals that they are replacing. https://doi.org/10.1093/biolre/ioac101

Identification of endocrine-disrupting chemicals targeting the genes and pathways of genital anomalies in males,
ZHOU X., X. ZHANG, X. ZHOU, G. ABULIMITI, Y. C. WANG, Q. J. ZHANG, R. CONG, C. J. JI, J. C. LUAN, L. Y. YAO, J. YANG and N. H. SONG,
Ecotoxicology and Environmental Safety 247 (Dec 2022),
Hypospadias and cryptorchidism are the most common congenital malformations in male neonates, both of which are also the important clinical manifestations of testicular dysgenesis syndrome and share a same origin. Many studies have suggested that prenatal exposure to endocrine-disrupting chemicals (EDCs) is associated with hypospadias and cryptorchidism development. However, the consistent mechanisms remain unclear. To identify the key EDCs, genes and biological networks related to the development of hypospadias and cryptorchidism respectively and commonly, we conduct the present study and found a new method for predicting the correlation between the interactive genes of hypospadias/cryptorchidism and chemicals. Transcriptome profiles were ob-tained from the Comparative Toxicogenomics Database (CTD). Gene ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways enrichment analyses and protein-protein interaction (PPI) network were applied for integrative analyses. The rat model and molecular docking were applied to furtherly verifying the findings of the integrative analyses. Besides the highly related genes, most enriched pathways and chemicals for hypospadias and cryptorchidism respectively, we found hypospadias and cryptorchidism share many same highly associated EDCs (e.g., dibutyl phthalate) and genes (e.g., androgen receptor and estrogen receptor 1) through comparing highly related chemicals or genes of hypospadias and cryptorchidism respectively. GO and KEGG analysis showed that these same interactive genes were mainly enriched in steroidogenesis, response to steroid hormone and nuclear receptor activity. PPI network analysis identified 15 biological hub genes. Fur-therly, hypospadias and cryptorchidism were induced by prenatal dibutyl phthalate exposure. Decreased serum testosterone level, downregulation of nuclear androgen-dependent and upregulation of cytoplasmic estrogen -dependent pathways may lead to hypospadias and cryptorchidism. This study proposed a new method for pre-dicting the correlation between the interactive genes of hypospadias/cryptorchidism and chemicals and found that hypospadias and cryptorchidism share many same highly associated EDCs and genes. https://doi.org/10.1016/j.ecoenv.2022.114241

Improved method for the determination of endocrine-disrupting chemicals in urine of school-age children using microliquid-liquid extraction and UHPLC-MS/MS,
MOSCOSO-RUIZ I., Y. GALVEZ-ONTIVEROS, M. GILES-MANCILLA, M. D. GOMEZ-REGALADO, A. RIVAS and A. ZAFRA-GOMEZ,
Analytical and Bioanalytical Chemistry 414, no. 22 (Sep 2022): 6681-6694,
The presence of endocrine-disrupting chemicals in our daily life is increasing every day and, by extension, human exposure and the consequences thereof. Among these substances are bisphenols and parabens. Urine is used to analyze the exposure. The determination of 12 bisphenol homologues and 6 parabens is proposed. A procedure based on a method previously developed by our research group in 2014 is improved. The extraction yield is higher, because the new protocol is 5 times more efficient. Also, a comparison between calibration with pure standards and matrix calibration, to calculate the matrix effect, was also made. A high grade of matrix effect for all analytes was observed. In terms of validation, the limits of detection (LOD) were between 0.03 and 0.3 ng mL(-1) and limits of quantification (LOQ) 0.1 to 1.0 ng mL(-1), respectively, and the recovery is higher than 86.4% and lower than 113.6%, with a RSD lower than 13.5% in all cases. A methodology for accurate and sensitive quantification of bisphenol homologues together with parabens in human urine using UHPLC-MS/MS was developed. The method was successfully applied to 30 urine samples from children.
https://doi.org/10.1007/s00216-022-04231-z

Placental model as an important tool to study maternal-fetal interface,
GONCALVES B. M., J. B. GRACELI, P. B. DA ROCHA, H. P. TILLI, E. M. VIEIRA, M. T. DE SIBIO, V. V. PEGHINELLI, I. C. DEPRA, L. S. MATHIAS, R. M. C. OLIMPIO, V. C. BELIK and C. R. NOGUEIRA,

Reproductive Toxicology 112 (Sep 2022): 7-13,
The placenta is a temporary organ that plays critical roles at the maternal-fetal interface. Normal development and function of the placenta is dependent on hormonal signaling pathways that make the placenta a target of endocrine disrupting chemical (EDC) action. Studies showing association between prenatal exposure, hormone disruption, and reproductive damage indicate that EDCs are developmentally toxic and can impact future generations. In this context, new placental models (trophoblast-derived cell lines, organotypic or 3D cell models, and physiologically based kinetic models) have been developed in order to create new approach methodology (NAM) to assess and even prevent such disastrous toxic harm in future generations. With the widespread discouragement of conducting animal studies, it has become irrefutable to develop in vitro models that can serve as a substitute for in vivo models. The goal of this review is to discuss the newest in vitro models to understand the maternal -fetal interface and predict placental development, physiology, and dysfunction generated by failures in molecular hormone control mechanisms, which, consequently, may change epigenetic programming to increase suscepti-bility to metabolic and other disorders in the offspring. We summarize the latest placental models for devel-opmental toxicology studies, focusing mainly on three-dimensional (3D) culture models. https://doi.org/10.1016/j.reprotox.2022.06.005

Quantitative structure-activity relationship modeling of hydroxylated polychlorinated biphenyls as constitutive androstane receptor agonists,
AKINOLA L. K., A. UZAIRU, G. A. SHALLANGWA and S. E. ABECHI,
Structural Chemistry (Hydroxylated polychlorinated biphenyls (OH-PCBs), a series of toxic chemical compounds produced via biotic and abiotic transformation of polychlorinated biphenyls (PCBs), are known to cause endocrine disruption by interacting inappropriately with human nuclear receptors. Due to occurrence of high numbers of inactive OH-PCB congeners recorded in many experimental toxicity studies, it is pertinent to develop rapid and inexpensive QSAR models that can reliably predict the activities of OH-PCB congeners prior to experimental testing. Using a combination of genetic function approximation and multiple linear regression methods, a local QSAR model, consisting of six 2D descriptors (MATS1s, VE3_DzZ, VE1_Dzp, SpMin8_Bhv, SpMax5_Bhi, topoRadius) and two 3D descriptors (RDF95u, RDF45m), was developed from a training set of 44 OH-PCBs. Statistical parameters for fitting (R-2 = 0.8902, R-adj( )2= 0.8651, s= 0.2840), cross-validation (Q(LOO)(2) = 0.8201, RMSECV = 0.3242), and Y-randomization (cR(p)(2) = 0.8019) obtained for the developed QSAR model indicate that the model is reliable, robust, and provides good fit to the data in the training set. The results of external validation carried out on 20 OH-PCBs in the test set also indicate that the developed QSAR model possessed good external predictivity and can be used to predict the agonistic activities of untested OH-PCB congeners to constitutive androstane receptor. https://doi.org/10.1007/s11224-022-01992-2

Rapid and reagent-free bioassay using autobioluminescent yeasts to detect agonistic and antagonistic activities of bisphenols against rat androgen receptor and progesterone receptor,
HUANG Y., W. ZHANG, C. D. ZHANG, N. CUI, Z. M. XIAO, R. G. WANG and X. O. SU,
Journal of Steroid Biochemistry and Molecular Biology 222 (Sep 2022),
Bisphenol A (BPA) and its analogues have been classified as endocrine disruptors via binding to nuclear receptors. Two novel bioassays, BLYrARS and BLYrPRS, were developed for rapid detection of agonistic and antagonistic activities of BPA and five of its analogues binding rat androgen receptor (rAR) and rat progesterone receptor (rPR). The reporter bioassay was based on two autonomously bioluminescent strains of the yeast Saccharomyces cerevisiae, recombined with a bacterial luciferase reporter gene cassette (lux) that can produce autofluorescence, regulated by the corresponding hormone response element acting as the responsive promoter. The bioluminescent signal is autonomous and continuous without cell lysis or addition of exogenous reagents. The AR agonist R1881 could be detected at 4 h with a half-maximal effective concentration (EC50) of ~9.4 nM. The PR agonist progesterone could be determined at 4 h with an EC50 of ~2.74 nM. None of the sixteen bisphenols presented agonistic activities against rAR and rPR. However, thirteen BPs were rAR antagonists and eleven BPs acted as rPR antagonists with different potency. The BLYrARS and BLYrPRS bioassay characterized by automated signal acquisition without additional manipulations or cost can be applied for simple and rapid detection of agonistic and antagonistic activities of BPs and other compounds acting as agonists or antagonists of rAR and rPR. Based on data derived by use of this bioassay endocrine-disrupting activities of some BPA analogues are more potent than BPA. https://doi.org/10.1016/j.jsbmb.2022.106151

Rapid and simultaneous determination of multiple endocrine-disrupting chemicals and their metabolites in human serum and urine samples,
LI A. J., F. B. WANG, L. TAO, C. Y. MA, L. BI, M. Y. SONG and G. B. JIANG,
Talanta 248 (Oct 2022),
Bisphenols, parabens, and their metabolites are a group of chemical compounds with a wide range of polarities but similar chemical structures, which presents a challenge for the simultaneous determination of these compounds in complex biological samples. In this study, a rapid and sensitive method for simultaneous quantification of free bisphenol A (BPA), conjugated BPA, bisphenols, and parabens analogs was developed using solid-phase extraction (SPE) tandem liquid-liquid extraction (LLE). We compared the effects of different types of SPE cartridges, diluents, and LLE solvents on the analyte recovery. Utilizing the direct and indirect determination methods (enzyme hydrolysis), we confirmed the accuracy of the direct method for measuring BPA glucuronide and BPA disulfate. The method enabled the analysis of 24 endocrine-disrupting chemicals (EDCs) in one injection through UHPLC-MSMS measurements, with satisfactory recovery (mean: 91.8-98.6% for urine, 80.2%-96.8% for serum) and precision (RSD <15%). The LOD and LOQ values were 0.003 and 0.01 ng/mL for serum, and 0.002 and 0.006 ng/mL for urine samples, respectively. For real sample analysis, the median concentration of analytes in serum and urine samples ranged from 0.04 ng/mL (BPS) to 56.4 ng/mL (4-HB) and 0.11 ng/mL (BPA) to 136 ng/mL (4-HB), respectively. This method provides a new strategy to simultaneously identify compounds with a wide range of polarities from complicated biological matrices.
https://doi.org/10.1016/j.talanta.2022.123639

Agenda, actualité, politique et évaluation de l'exposition

Risques toxicologiques : accéder à l'information pertinente
BIJAOUI A.
TM71. *Références en santé au travail*. 09/2022, 30 p.
Une stratégie de recherche documentaire apparaît nécessaire face au foisonnement des informations relatives aux risques toxicologiques. L'objectif de cet article est de sélectionner les sites et autres supports les plus pertinents et de définir une méthodologie de recherche. Les sites d'organismes officiels ou de sources connues (agences d'État, instituts, bibliothèques...), dont les documents sont datés avec des mises à jour régulières, ont été privilégiés. En effet, une information non validée nécessitera une vérification sur d'autres sources et donc une nouvelle recherche. Les informations trouvées sur Internet peuvent être complétées par la consultation d'ouvrages. **Un focus particulier est fait sur les perturbateurs endocriniens**.
https://www.inrs.fr/media.html?refINRS=TM%2071

The EU chemicals strategy for sustainability: critical reflections on proposed regulatory changes for endocrine disruptors and mixture toxicity,
BATKE M., G. DAMM, H. FOTH, A. FREYBERGER, T. GEBEL, U. GUNDERT-REMY, J. HENGSTLER, A. MANGERICH, F. PARTOSCH, C. RÖHL, T. SCHUPP and K. M. WOLLIN,
Archives of Toxicology 96, no. 4 (2022/04/01 2022): 1133-1135,
https://doi.org/10.1007/s00204-022-03227-z

Projet scientifique : Validation d'une méthode de bioaccessibilité des perturbateurs endocriniens dans la poussière intérieure – BIOACID,
ANR (aout 2022),
Projet financé par l'ANR et soumis par : LERES Laboratoire d'Etude et de Recherche en Environnement et Santé (Barbara Le Bot) / URAFPA UNITÉ DE RECHERCHES ANIMAL ET FONCTIONNALITÉS DES PRODUITS ANIMAUX / CSTB. Résumé du projet : La population passe près de 90 % de son temps en environnement intérieur où elle est exposée à des polluants comme les composés organiques semi-volatils (COSV) qui font aujourd'hui l'objet d'une attention particulière en raison d'effets suspectés sur la santé humaine : ils sont en effet pour la plupart suspectés d'être perturbateurs endocriniens (PE) avec des effets cancérogènes, reprotoxiques, et neurotoxiques. La littérature scientifique montre que l'ingestion de poussière intérieure est une voie d'exposition non négligeable à certains PE. Les enfants, par les contacts sol-main-bouche fréquents, sont particulièrement concernés aussi bien à la maison qu'à l'école. Pour une meilleure évaluation des risques sanitaires associés, une

meilleure connaissance de l'exposition réelle à ces polluants est nécessaire, à commencer par une meilleure connaissance des doses absorbées. À cette fin, il est nécessaire d'évaluer la bioaccessibilité orale des PE, définie comme la fraction de polluant libérée dans le tractus gastro-intestinal et disponible pour l'absorption. Une méthode de mesure in vitro de la bioaccessibilité est préconisée, mais il n'existe à ce jour aucune méthode validée. Dans ce contexte, ce projet propose d'abord de valider, par des tests in vivo chez le porc, une méthode in vitro simplifiée déjà existante, prenant en compte la dynamique de la digestion, puis de la déployer dans des campagnes de mesure sur des échantillons de poussières déjà disponibles, provenant d'écoles et de logements. Une méthode de modélisation de la fraction bioaccessible sera également développée comme alternative pour les molécules adsorbées uniquement en surface des poussières. Ce projet permettra de produire des premiers résultats de concentration bioaccessible pour des phtalates, organophosphates et pyréthrinoïdes dans les poussières intérieures et d'évaluer l'impact de la bioaccessibilité orale en termes de précision sur l'évaluation des risques sanitaires. https://anr.fr/Projet-ANR-21-CE34-0023

Symposium scientifique du CIAPE : 9 décembre 2022 (Québec), en présentiel ou virtuel.,
CIAPE (Centre intersectoriel d'analyse des perturbateurs endocrinien) (2022),
Le Centre intersectoriel d'analyse des perturbateurs endocriniens (CIAPE) est un regroupement de chercheurs.es ayant pour mission d'informer, d'assister et de servir de ressource aux instances gouvernementales, aux organismes à but non lucratif et l'industrie ainsi qu'à la population québécoise et canadienne, afin d'identifier, reconnaître, quantifier et gérer les perturbateurs endocriniens. Basé à l'Institut national de la recherche scientifique (INRS), ce regroupement interdisciplinaire est composé de scientifiques de haut niveau de plusieurs domaines d'activités complémentaires. https://www.ciape-iceda.ca/symposium-aga-2022/

Assessment of human exposure to benzophenone-type UV filters: A review,
MAO J. F., W. X. LI, C. N. ONG, Y. L. HE, M. C. JONG and K. Y. H. GIN,
Environment International 167 (Sep 2022),
To avoid the harmful effects of UV radiation, benzophenone-type UV filters (BPs) are widely used in personal care products and other synthetic products. Biomonitoring studies have shown the presence of BPs in various human biological samples, raising health concerns. However, there is a paucity of data on the global human exposure to this group of contaminants. In this study, we compiled data on the body burden of BPs along with the possible exposure routes and biotransformation pathways. BPs can easily penetrate the skin barrier and thus, they can be absorbed through the skin. In the human body, BPs can undergo Phase I (mainly demethylation and hydroxylation) and Phase II (mainly glucumnidation and sulfation) biotransformations. From a total of 158 studies, most of the studies are related to urine (concentration up to 92.7 mg L-1), followed by those reported in blood (up to 0.9 mg L-1) and milk (up to 0.8 mg L-1). Among BPs, benzophenone-1 and benzophenone-3 are the most commonly detected congeners. The body burden of BPs is associated with various factors, including the country of residence, lifestyle, income, education level, and ethnicity. The presence of BPs in maternal urine (up to 1.1 mg L-1), placenta (up to 9.8 ng g(-1)), and amniotic fluid (up to 15.7 mu g L-1) suggests potential risks of prenatal exposure. In addition, transplacental transfer of BPs is possible, as demonstrated by their presence in maternal serum and cord serum. The possible association of BPs exposure and health effects was discussed. Future human biomonitoring studies and studies on the potential health effects are warranted. Overall, this review provides a summary of the global human exposure to BPs and can serve as supporting evidence to guide usage in order to protect humans from being exposed to BPs. https://doi.org/10.1016/j.envint.2022.107405

Nonylphenol (NP) exposure in Germany between 1991 and 2021: Urinary biomarker analyses in the German Environmental Specimen Bank (ESB),
RINGBECK B., T. WEBER, D. BURY, M. KASPER-SONNENBERG, C. PALMKE, T. BRUNING, H. M. KOCH and M. KOLOSSA-GEHRING,
International Journal of Hygiene and Environmental Health 245 (Aug 2022),
Nonylphenol (NP) is a high production volume chemical with a wide range of uses, e.g. in NP ethoxylates (NPEO). NP and NPEO have become ubiquitous in the environment and are considered of concern due to their general ecotoxicity and endocrine disrupting properties. However, knowledge on human exposure is scarce. In this study, we analyzed novel NP metabolites (OH-NP and oxo-NP) as robust biomarkers of exposure in 24h-urine samples from the German Environmental Specimen Bank (ESB). This enables us to reliably determine the in-dividual NP body burden and to retrospectively evaluate NP exposure over the past 30 years. We analyzed

660 urine samples from eleven sampling years between 1991 and 2021. All samples were from young German adults between 20 and 29 years of age. OH-NP was quantifiable in all samples until 2017. In 2019 and 2021, the frequency of samples above the LOQ dropped to 90% and 77%, respectively. Median OH-NP concentrations significantly decreased from 4.32 mu g/L in 1991 to 0.70 mu g/L in 2021. OH-NP and oxo-NP levels correlated strongly, but oxo-NP concentrations and detections were considerably lower, in line with its known lower metabolic conversion. Reverse dosimetry back-calculated daily intakes (DI) of NP, based on OH-NP, decreased by almost a factor of four from medians of 0.16 mu g/(kg bw*d) in 1991 to 0.04 mu g/(kg bw*d) in 2021, respectively. The major drop took place only after 2012. This came as a surprise, because strict restrictions had been enacted much earlier in the EU, in 2003. All NP DIs were below the provisional tolerable daily intake of 5 mu g/(kg bw*d) from the Danish Environmental Agency. DIs back-calculated from the ESB biomonitoring data agree well with calculations from food. This indicates to contaminated foodstuff as a major source of exposure. The time lag of regulatory restrictions to decreasing human exposure levels, the general lack of knowledge on exposure levels in susceptible populations such as children, and the ongoing worldwide use of NP underline the urgent need to continue monitoring NP exposures in Germany and worldwide. With these novel NP biomarkers, we provide a robust and sensitive tool for exposure and risk assessments, complementing environmental monitoring. https://doi.org/10.1016/j.ijheh.2022.114010

Toxicité sur les animaux

Chronic Exposure to Vinclozolin Induced Fibrosis, Mitochondrial Dysfunction, Oxidative Stress, and Apoptosis in Mice Kidney,
DI PAOLA D., R. D'AMICO, T. GENOVESE, R. SIRACUSA, M. CORDARO, R. CRUPI, A. F. PERITORE, E. GUGLIANDOLO, L. INTERDONATO, D. IMPELLIZZERI, R. FUSCO, S. CUZZOCREA and R. DI PAOLA,
International Journal of Molecular Sciences 23, no. 19 (Oct 2022),
Vinclozolin is one of the most used fungicides in the control of fungi in fruits, vegetables, and ornamental plants. The effects of its exposure on different organs have been described, but information regarding its relevance to vinclozolin-induced nephrotoxicity is largely missing. This study focuses on the potential mechanism of vinclozolin-induced nephrotoxicity. CD1 male mice were administered vinclozolin (100 mg/kg) by oral gavage for 28 days. Vinclozolin administration decreased body weight over the treatment period and at the end of the experiment, increased the ratio of kidney weight to body weight and increased serum urea nitrogen and creatinine contents. Vinclozolin also induced histopathological alterations, including tubular dilatation and necrosis and impaired the integrity of the renal-tubular architecture and kidney fibrosis. The analyses conducted showed that vinclozolin administration altered the mRNA levels of mitochondrial function-related proteins (SIRT3, SIRT1, PGC-1 alpha, TFAM, NRF1, VDAC-1, and Cyt c) and oxidative stress (increased lipid peroxidation and decreased total antioxidative capacity, catalase, and superoxide dismutase activities, glutathione levels, and glutathione peroxidase activity) in the kidneys. Furthermore, vinclozolin induced toxicity that altered Nrf2 signalling and the related proteins (HO-1 and NQO-1). Vinclozolin administration also affected both the extrinsic and intrinsic apoptotic pathways, upregulating the expression of proapoptotic factors (Bax, Caspase 3, and FasL) and downregulating antiapoptotic factor (Bcl-2) levels. This study suggests that vinclozolin induced nephrotoxicity by disrupting the transcription of mitochondrial function-related factors, the Nrf2 signalling pathway, and the extrinsic and intrinsic apoptotic pathways. https://doi.org/10.3390/ijms231911296

Developmental Exposure to Endocrine Disrupter DDT Interferes with Age-Related Involution of Thymus,
YAGLOVA N. V., S. S. OBERNIKHIN, E. S. TSOMARTOVA, V. V. YAGLOV, S. V. NAZIMOVA, D. A. TSOMARTOVA, E. P. TIMOKHINA, E. V. CHERESHNEVA, M. Y. IVANOVA and O. V. PAYUSHINA,
International Journal of Molecular Sciences 23, no. 12 (Jun 2022),
The impact of endocrine-disrupting chemicals on the development and involution of the immune system is a possible reason for the increased incidence of disorders associated with inappropriate immune function. The thymus is a lymphoid and also an endocrine organ, and, accordingly, its development and functioning may be impaired by endocrine disruptors. The aim was to evaluate age-related thymus involution in mature rats exposed to the endocrine disruptor DDT during prenatal and postnatal ontogeny. Methodology included in vivo experiment on male Wistar rats exposed to low doses of DDT during prenatal and postnatal development and morphological assessment of thymic involution, including the immunohistochemical detection of proliferating

thymocytes. The study was carried out at the early stage of involution. Results: DDT-exposed rats exhibited a normal anatomy, and the relative weight of the thymus was within the control ranges. Histological and immunohistochemical examinations revealed increased cellularity of the cortex and the medulla, higher content of lymphoblasts, and more intensive proliferation rate of thymocytes compared to the control. Evaluation of thymic epithelial cells revealed a higher rate of thymic corpuscles formation. Conclusion: The data obtained indicate that endocrine disrupter DDT disturbs postnatal development of the thymus. Low-dose exposure to DDT during ontogeny does not suppress growth rate but violates the developmental program of the thymus by slowing down the onset of age-related involution and maintaining high cell proliferation rate. It may result in excessive formation of thymus-dependent areas in peripheral lymphoid organs and altered immune response. https://doi.org/10.3390/ijms23126678

EFFECT OF DI-(2-ETHYLHEXYL) PHTHALATE (DEHP) EXPOSURE ON MICROARCHITECTURE OF FEMORAL BONE IN MALE LABORATORY MOUSE: PRELIMINARY RESULTS,
SULKOVA E., R. BABOSOVA, B. KOLENA, Z. POLACIKOVA, H. HLISNIKOVA, M. SIDLOVSKA, M. VONDRAKOVA, M. MARTINIAKOVA and I. PETROVICOVA,
Journal of Microbiology Biotechnology and Food Sciences 11, no. 4 (Feb-Mar 2022),
Di-2-ethylhexyl phthalate (DEHP) is a toxic and hazardous endocrine disruptor with adverse effects on animal and human health. However, its impact on bone tissue has not been sufficiently investigated. Therefore, the purpose of our preliminary study was to examine the effects of DEHP on compact bone structure in two 57-days-old male mice. Daily oral administration of DEHP (4.5 mg/kg body weight dissolved in 500 mu l of peanut oil per 15 days) was studied, compared to a control. We observed a significant effect of DEHP exposure on macroscopic bone characteristics. Similarly, we identified differences in qualitative characteristics, such as the presence of resorption lacunae and absence of non-vascular and primary vascular radial bone tissue near the endosteal border, compared to the control. On the contrary, quantitative analysis showed no demonstrable alterations in morphometric parameters. Our preliminary findings support the hypothesis about the negative impact of DEHP on bone tissue. However, further investigation is needed to understand this issue better and more precisely. https://doi.org/10.55251/jmbfs.4435

Effects of Tartrazine on Some Sexual Maturation Parameters in Immature Female Wistar Rats,
MINDANG E. L. N., C. F. AWOUNFACK, D. T. NDINTEH, R. W. M. KRAUSE and D. NJAMEN,
International Journal of Environmental Research and Public Health 19, no. 16 (Aug 2022),
Over the past century, the average age for onset of puberty has declined. Several additives present in our food are thought to contribute significantly to this early puberty which is recognized to also affect people's health in later life. On this basis, the impact of 40-days unique oral administration of the food dye tartrazine (7.5, 27, and 47 mg/kg BW doses) was evaluated on some sexual maturation parameters on immature female Wistar rats. Vaginal opening was evaluated during the treatment period. At the end of the treatments, animals were sacrificed (estrus phase) and the relative weight of reproductive organs, pituitary gonadotrophin and sexual steroids level, cholesterol level in ovaries and folliculogenesis were evaluated. Compared to the control group, animals receiving tartrazine (47 mg/kg BW) showed significantly high percentage of early vaginal opening from day 45 of age, and an increase in the number of totals, primaries, secondaries, and antral follicles; a significant increase in serum estrogen, LH and in uterine epithelial thickness. Our findings suggest that tartrazine considerably disturbs the normal courses of puberty. These results could validate at least in part the global observations on increasingly precocious puberty in girls feeding increasingly with industrially processed foods. https://doi.org/10.3390/ijerph191610410

Influence on the adult male Leydig cell biomarker insulin-like peptide 3 of maternal exposure to estrogenic and anti-androgenic endocrine disrupting compound mixtures: A retrospective study,
IVELL R., A. M. VINGGAARD, H. SOYAMA and R. ANAND-IVELL,
Andrologia (Insulin-like peptide 3 (INSL3) is a peptide biomarker secreted specifically by the mature Leydig cells of the testes. It is constitutive, has low within-individual variance, and effectively measures the functional capacity of Leydig cells to make testosterone. In young adult men there is a large 10-fold range of serum INSL3 concentration, persisting into old age, and implying that later hypogonadal status might be programmed in early life. To determine whether maternal exposure to environmental endocrine disrupting compounds (EDCs) influences adult serum INSL3 concentration, using a retrospective paradigm, INSL3 was measured in young adult

male rats (80-90 days) from the F1 generation of females maternally exposed to varied doses of bisphenol A (BPA), butylparaben, epoxiconazole, and fludioxonil as single compounds, as well as estrogenic and anti-androgenic mixtures of BPA and butylparaben, and di(2-ethylhexyl) phthalate and procymidone respectively. A mixture of BPA and butylparaben significantly reduced circulating INSL3 concentration in adult male progeny. The remaining compounds or mixtures tested, though sufficient to induce other effects in the F1 generation were without significant effect. Maternal exposure to low concentrations of some EDCs may be a contributing factor to the variation in the Leydig cell biomarker INSL3 in young adulthood, though caution is warranted translating results from rats to humans. https://doi.org/10.1111/and.14566

Investigation of combined effects of propyl paraben and methyl paraben on the hypothalamic-pituitary-adrenal axis in male rats,
INKAYA E. N. and N. BARLAS,
Toxicology and Industrial Health 38, no. 10 (Oct 2022): 687-701,
The aim of this study was to investigate the endocrine-disrupting effects of methyl paraben (MeP) and propyl paraben (PrP) mixture on the hypothalamic-pituitary-adrenal axis (HPA). In this study, six experimental groups were designated. These groups included three control groups (control, corn oil control, and positive control (50 mg/kg/day BPA)) and three dose groups (10, 100, and 500 mg/kg/day MeP+PrP). MeP with PrP were mixed in a 1:1 ratio and administered to the 42-day-old male rats by oral gavage for 30 days. At the end of the experiment, adrenocorticotropic hormone (ACTH), corticosterone and aldosterone hormones were analyzed in serum. Effects of MeP+PrP on the adrenal glands were investigated by immunohistochemical staining of 11ss hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2) enzymes involved in the synthesis steps of corticosterone and aldosterone. Also, pituitary and adrenal glands were examined histopathologically. In the histopathological findings, cortical nodule, congestion, and edema were found in the tissues. In the pituitary gland, cytokeratin rings were detected in all MeP+PrP dose groups, supporting the increase of corticosterone and ACTH. Serum corticosterone, aldosterone, and ACTH hormone levels were increased in the 100 mg/kg/day MeP+PrP and BPA groups. Results obtained from immunohistochemical staining showed that increased staining parallelled increased corticosterone and aldosterone hormone levels. In summary, the results showed that exposure to the MeP+PrP mixture caused a significant increase in ACTH and corticosterone. Also, the MeP+PrP mixture caused a significant increase of CYP11B1 and CYP11B2. MeP+PrP exposure disrupts the normal HPA axis.
https://doi.org/10.1177/07482337221117652

Investigation of obesogenic effects of hexachlorobenzene, DDT and DDE in male rats,
AL-OBAIDI Z. A. F., C. S. ERDOGAN, E. SUEMER, H. B. OZGUEN, B. GEMICI, S. SANDAL and B. YILMAZ,
General and Comparative Endocrinology 327 (Oct 2022),
Obesity has become a very important public health problem and is increasing globally. Genetics, individual and environmental factors play roles in the etiology of this complex disorder. Recently, several environmental pol-lutants have been suggested to have obesogenic activities. Peroxisome proliferator activating receptor gamma (PPAR gamma), uncoupling protein-1 (UCP1) and their expression in white adipose tissue (WAT) and brown adipose tissue (BAT) play key roles in adipogenesis. UCP3 and irisin were reported to play roles in non-shivering ther-mogenesis. Our primary aim was to investigate obesogenic effects of hexachlorobenzene (HCB), dichlor-odiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) in rats. In addition, thermoregulatory effects of HCB, DDT and DDE were also investigated by analyzing the levels of Ucp3 and irisin. Thirty-two adult male Sprague-Dawley rats were randomly divided into four groups as control, HCB, DDT and DDE. Animals were administered with organochlorine pesticides (OCPs; 5 mg/kg bw) by oral gavage every other day for five weeks. At the end of the experimental period, the animals were sacrificed, BAT and WAT samples were collected to analyze Ppar gamma, Ucp1 and Ucp3 levels. Moreover, skeletal muscle samples were collected to examine Ucp3 and irisin levels. Serum glucose, cholesterol and triglyceride levels were also determined. Body weight and core temperature of the animals were not significantly affected by any of the OCP administration. Serum glucose, cholesterol and triglyceride levels were similar among the experimental groups. Ppar gamma expression was significantly elevated by HCB administration only in WAT ($p < 0.05$). On the other hand, both Ppar gamma and Ucp1 expressions were diminished in WAT and BAT ($p < 0.01$) by DDT treatment, while in WAT, DDE signifi-cantly decreased Ppar gamma expression without altering its expression in BAT ($p < 0.001$). Ucp3 and irisin levels in skeletal muscle were not altered. Our findings show that both DDT and DDE reduce the browning of WAT by suppressing white adipocytes and thus may have obesogenic activity in male rats without altering thermoreg-ulation. In addition, HCB, DDT and DDE-induced alterations in expression of Ppar gamma

and Ucp1 in WAT implicates differential regulation of adipogenic processes.
https://doi.org/10.1016/j.ygcen.2022.114098

Multigenerational Effects of an Environmentally Relevant Phthalate Mixture on Reproductive Parameters and Ovarian miRNA Expression in Female Rats,
GONSIOROSKI A. V., A. M. AQUINO, L. G. ALONSO-COSTA, L. F. BARBISAN, W. R. SCARANO and J. A. FLAWS,
Toxicological Sciences 189, no. 1 (Aug 2022): 91-106,
Phthalates are endocrine-disrupting chemicals used in many consumer products. Our laboratory previously developed an environmentally relevant phthalate mixture consisting of 6 phthalates and found that it disrupted female fertility in mice. However, it was unknown if maternal exposure to the mixture affects reproductive parameters and ovarian post-transcription in the F1 and F2 generation of female rats. Thus, we tested the hypothesis that maternal exposure to the phthalate mixture affects folliculogenesis, steroidogenesis, and ovarian microRNA (miRNA) in the F1 and F2 generations of female rats. Pregnant female rats were divided into 4 groups and orally dosed daily from gestational day 10 to postnatal day 21 with corn oil (control group), 20 mu g/kg/day, 200 mu g/kg/day, or 200 mg/kg/day of the phthalate mixture. Maternal exposure to the phthalate mixture impaired folliculogenesis in the F1 and F2 generations of female rats and affected steroidogenesis in the F1 generation of female rats compared to control. Further, the phthalate mixture altered ovarian expression of some genes related to the cell cycle and steroidogenesis compared to control in the F1 and F2 generations of female rats. The mixture also increased ovarian expression of rno-mir-184 that is involved with the oocyte maturation process. Collectively, our data show that maternal exposure to the phthalate mixture affects folliculogenesis and steroidogenesis in the F1 and F2 generations of female rats and alters ovarian miRNA expression in the F1 generation of female rats. https://doi.org/10.1093/toxsci/kfac066

Perinatal exposure to tributyltin affects feeding behavior and expression of hypothalamic neuropeptide Y in the paraventricular nucleus of adult mice,
PONTI G., E. BO, B. BONALDO, A. FARINETTI, M. MARRAUDINO, G. PANZICA and S. GOTTI,
Journal of Anatomy (Organotins such as tributyltin chloride (TBT), are highly diffused environmental pollutants, which act as metabolism disrupting chemicals, i.e. may interfere with fat tissue differentiation, as well as with neuroendocrine circuits, thus impairing the control of energetic balance. We have previously demonstrated that adult exposure to TBT altered the expression of neuropeptides in the hypothalamus. In this study, we orally administered daily a solution containing oil, or TBT (0.25, 2.5, or 25 mu g/kg body weight/day) to pregnant females from gestational day 8 until birth, and to their pups from day 0 until post-natal day 21. Our results showed that TBT exposure of female mice during gestation and of pups during lactation permanently altered the feeding efficiency of pups of both sexes and subcutaneous fat distribution in adult males. In addition, the neuropeptide Y system was affected at the level of the paraventricular nucleus, with a decrease in immunoreactivity in both sexes (significant in females for all TBT doses and in males only for intermediate TBT doses), while no effect was observed in other hypothalamic areas (arcuate, ventromedial and dorsomedial nuclei). Metabolic syndrome, as well as obesity and diabetes, which are significant health issues, are considered multifactorial diseases and may be caused by exposure to metabolic disruptors, both in adults and during perinatal life. In addition, our work indicates that TBT doses defined as the tolerably daily intake had a profound and sex-specific long-term effect. https://doi.org/10.1111/joa.13766

Reproductive toxicity of maternal exposure to di(2-ethylhexyl)phthalate and butyl paraben (alone or in association) on both male and female Wistar offspring,
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Journal of Applied Toxicology (Parabens and phthalates are commonly found as contaminants in human fluids and are able to provoke reproductive toxicity, being considered endocrine disruptors. To evaluate the effects of phthalate and paraben, alone or in combination, on reproductive development of the offspring, female pregnant Wistar rats were allocated in six experimental groups: Three control groups (gavage [CG], subcutaneous [CS], and gavage + subcutaneous) received corn oil as vehicle, and the remaining groups were exposed to di(2-ethylhexyl)phthalate (DEHP) (500 mg/kg, gavage), butyl paraben (BP) (100 mg/kg, subcutaneously), or MIX (DEHP + BP), from Gestational Day 12 until Postnatal Day (PND) 21. The following parameters were assessed on the offspring: anogenital distance and weight at PND 1, nipple counting at PND 13, puberty onset, estrous cycle,

weights of reproductive and detoxifying organs, histological evaluation of reproductive organs, and sperm evaluations (counts, morphology, and motility). Female pups from MIX group presented reduced body weight at PND 1, lower AGD, and decreased endometrium thickness. Male animals showed decreased body weight at PND 1 and lower number of Sertoli cells on DEHP and MIX groups, MIX group revealed increase of abnormal seminiferous tubules, DEHP animals presented delayed preputial separation and higher percentage of immotile sperms, and BP males presented diminished number of Leydig cells. In conclusion, the male offspring was more susceptible to DEHP toxicity; even when mixed to paraben, the main negative effects observed seem to be due to antiandrogenic phthalate action. On the other hand, DEHP seems to be necessary to improve the effects of BP on reducing estrogen-dependent and increasing androgen-dependent events. https://doi.org/10.1002/jat.4377

Sex-dependent and long-lasting effects of bisphenol AF exposure on emotional behaviors in mice,
GONG M., H. SONG, Y. DONG, Z. Q. HUAI, Y. L. FU, P. P. YU, B. Y. HUANG, R. YANG, Y. GUO, Q. MENG, Y. GAO, L. SONG, Q. J. GUO, Q. GAO, X. YIN, S. WANG, Y. SHI and H. S. SHI,
Physiology & Behavior 249 (May 2022),
We recently reported that maternal exposure to bisphenol AF (BPAF), an environmental endocrine disruptor (EED), induced significant alterations in emotional behaviors in offspring mice during adolescence in a sex-dependent manner. However, the effects of adult BPAF exposure and the potential long-lasting effects of maternal exposure to BPAF on offspring mice are still unknown. The present study aimed to investigate the neurobehavioral effects of adult and maternal exposure to BPAF, intragastrically (0.4, 4 mg.kg(-1), i.g.), by using a series of classic emotional behavioral tests, mainly referring to depression, anxiety, and memory. The results showed that adult BPAF exposure significantly attenuated anxiety- and depression-like behaviors in adult male mice, while increasing anxiety-like behaviors, promoting novel object recognition memory formation, and impairing contextual fear conditioning memory formation in adult female mice. Maternal exposure to BPAF induced anxiety-like effects and anti-depression-like effects in male offspring mice during adulthood, while maternal BPAF exposure increased anxiety- and depression-like behaviors in female offspring mice during adulthood. Our present findings indicate that BPAF exposure significantly affects emotional behaviors in adult/offspring mice in a sex-dependent manner and that female adult mice are more likely to have adverse consequences to BPAF exposure during adulthood, even during early life stages.
https://doi.org/10.1016/j.physbeh.2022.113747

Sex-specific influence of maternal exposure to bisphenol A on sodium and fluid balance in response to dipsogenic challenges in rats,
NUNEZ P., J. ARGUELLES and C. PERILLAN,
Appetite 176 (Sep 2022),
https://doi.org/10.1016/j.appet.2022.106091

Subchronic exposure to environmentally relevant concentrations of di-(2-ethylhexyl) phthalate differentially affects the colon and ileum in adult female mice,
BASHIR S. T., K. CHIU, E. L. ZHENG, A. MARTINEZ, J. CHIU, K. RAJ, S. STASIAK, N. Z. E. LAI, R. B. ARCANJO, J. A. FLAWS and R. A. NOWAK,
Chemosphere 309 (Dec 2022),
Di(2-ethylhexyl) phthalate (DEHP) is a large-molecular-weight phthalate added to plastics to impart versatile properties. DEHP can be found in medical equipment and devices, food containers, building materials, and children's toys. Although DEHP exposure occurs most commonly by ingesting contaminated foods in the majority of the population, its effects on the gastrointestinal tract have not been well studied. Therefore, we analyzed the effects of subchronic exposure to DEHP on the ileum and colon morphology, gene expression, and immune microenvironment. Adult C57BL/6 female mice were orally dosed with corn oil (control, n = 7) or DEHP (0.02, 0.2, or 30 mg/kg, n = 7/treatment dose) for 30-34 days. Mice were euthanized during diestrus, and colon and ileum tissues were collected for RT-qPCR and immunohistochemistry. Subchronic DEHP exposure in the ileum altered the expression of several immune-mediating factors (Muc1, Lyz1, Cldn1) and cell viability factors (Bcl2 and Aifm1). Similarly, DEHP exposure in the colon impacted the gene expression of factors involved in mediating immune responses (Muc3a, Zo2, Ocln, Il6, and Il17a); and also altered the expression of cell viability factors (Ki67, Bcl2, Cdk4, and Aifm1) as well as a specialized epithelial cell marker (Vil1). Immunohistochemical

analysis of the ileum showed DEHP increased expression of VIL1, CLDN1, and TNF and decreased number of T-cells in the villi. Histological analysis of the colon showed DEHP altered morphology and reduced cell proliferation. Moreover, in the colon, DEHP increased the expression of MUC2, MUC1, VIL1, CLDN1, and TNF. DEHP also increased the number of T-cells and Type 2 immune cells in the colon. These data suggest that subchronic DEHP exposure differentially affects the ileum and colon and alters colonic morphology and the intestinal immune microenvironment. These results have important implications for understanding the effects of DEHP on the gastrointestinal system. https://doi.org/10.1016/j.chemosphere.2022.136680