Bulletin de veille Perturbateurs Endocriniens N°26 - Juillet Août 2024

Objectif : cette veille bibliographique a pour objectif la surveillance de l'actualité et de la littérature scientifique sur les perturbateurs endocriniens. Cette veille est axée sur les aspects suivants : l'exposition, la toxicité, l'évaluation, la prévention, l'épidémiologie et l'actualité.

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

Biochemical study of the effect of lead exposure in nonobese gasoline station workers and risk of hyperglycemia: A retrospective case-control study,
NUMAN A. T., N. K. JAWAD and H. A. FAWZI, *Medicine* 103, no. 32 (Aug 2024),
Evaluate the relationship between blood lead (Pb) levels and other biomedical markers and the risk of diabetes in gasoline station workers. The participants were separated into 2 groups: group A consisted of 26 workers from gasoline filling stations, while group B comprised 26 healthy individuals. Serum levels of malondialdehyde, IL-1 beta, visfatin, insulin, fasting blood sugar, and vitamin D were assessed. Mean Pb level was significantly higher in group A compared to group B (almost 2.9 times higher levels) (14.43 +/- 1.01 vs 5.01 +/- 1.41, mu g/dL). The levels of visfatin (23.19 +/- 0.96 vs 3.88 +/- 0.58, ng/mL), insulin (22.14 +/- 1.31 vs 11.26 +/- 0.75, mU/L), fasting blood sugar (118.4 +/- 26.1 vs 82.7 +/- 9.2, gm/dL), malondialdehyde (6.40 +/- 0.27 vs 1.62 +/- 0.21, nmol/mL), and IL-1 beta

(330.25 +/- 10.34 vs 12.35 +/- 1.43, pg/mL) were significantly higher in group A, meanwhile; vitamin D (11.99 +/- 1.55 vs 35.41 +/- 3.16, ng/mL) were significantly lower in group A. A positive association exists between blood Pb levels and increased inflammatory markers. Lead exposure increases serum insulin and fasting blood sugar, which suggests that it is diabetogenic and that increased inflammation is a possible cause. https://doi.org/10.1097/md.0000000000039152

Low levels of potentially toxic elements in workers are associated with self-reported health outcomes,
SALLES F. J., F. A. DIAZ-QUIJANO, M. S. LUZ, G. A. DE ALMEIDA, N. AKIBA, A. P. DE OLIVEIRA, A. D. ELIAS, M. M. ROGERO and K. P. K. OLYMPIO, *Science of the Total Environment* 947 (Oct 2024),
Occupational exposure to toxic elements can adversely affect health. The current study evaluated blood concentrations of potentially toxic elements (PTE) including As, Cd, Cr, Cu, Hg, Mn, Ni, Pb, Sb, Sn, and Zn in formal and informal workers. Additionally, the study investigated the associations between blood PTE concentrations and reported health outcomes in the study population. The exposed group included women engaged in informal jewelry welding within their homes in Limeira, Sao Paulo state, Brazil (n = 36) and men who worked at a steel company in Volta Redonda, Rio de Janeiro state, Brazil (n = 22). The control group comprised residents of the same neighborhoods as the workers but without occupational exposure to chemicals (n = 28 in Limeira; n = 27 in Volta Redonda). Triple Quadrupole Inductively Coupled Plasma Mass Spectrometry (TQ ICP-MS) was used to determine PTE concentrations in blood samples. Glycemia, insulin, and lipid profile tests were performed. All participants completed questionnaires on household risk and reported morbidity. The blood concentrations of Cd, As, and Pb, as well as glycemia, were higher in informal workers than in control subjects. No significant differences were observed between formal workers and control subjects. A robust Poisson regression model, adjusted for variables suggested by a Directed Acyclic Graph, disclosed associations of blood lead and arsenic concentrations with the prevalence of neurological manifestations in Limeira. Blood lead levels > 2.6 mu g dL(-1) were associated with 2.3 times the prevalence of self-reported neurological manifestations (95 % CI: 1.17-4.58; p = 0.02) than lower blood lead concentrations. Furthermore, a positive association between blood cadmium concentrations and glycemia was observed. Informal occupational exposure to these elements may indicate an increased risk of developing diseases. Monitoring exposure and implementing interventions to reduce PTE exposure in the work environment represent significant steps toward prevention. https://doi.org/10.1016/j.scitotenv.2024.174510

Occupational exposure to pesticides and health in farmers Cienega, Jalisco, Mexico,
SÁNCHEZ E. D. T., C. A. F. GUTIÉRREZ, J. H. T. JASSO, E. R. URIBE and J. S. FLORES, *Revista Bio Ciencias* 11 (2024),
Farmers are more vulnerable to pesticide poisoning. La Ci énega, Jalisco, has high agricultural productivity and high pesticide use. However, there are no previous studies evaluating the health effects on farmers. This study aimed to describe the consequences of pesticide occupational exposure on the health of farmers in La Ci énega de Jalisco area. A total of 121 surveys were applied to farmers with chronic exposure (2019 to 2022) on pesticide use incidents. The survey consisted of 64 dichotomous qualitative-type items and was validated by Cronbach's alpha coefficient, with a value of 0.6880. The most frequent symptoms were dizziness (66.7 % and 36.9 %) and headache (58.3 % and 48.8 %). The most frequent diseases were hypercholesterolemia (34.3 % and 26.7 %), hypertension (31.4 % and 36 %), and type 2 diabetes mellitus (22.9 % and 14.7 %). Glucose levels below 200 mg/dL were found in 92.08 % of the farmers. 63.89 % of the participants consumed food during pesticide application. Dizziness (p p = 0.027)) and burning skin (p p = 0.003)) were associated with gender, indicating that gender may be a condition related to pesticide poisoning symptoms https://doi.org/10.15741/revbio.11.e1612

Recommendations for the reference concentration of cadmium exposure based on a physiologically based toxicokinetic model integrated with a human respiratory tract model,
TANG Y. L., T. LYU, H. B. CAO, W. ZHANG, R. D. ZHANG, S. Q. LIU, T. Q. GUO, X. ZHOU and Y. X. JIANG, *Journal of Hazardous Materials* 477 (Sep 2024),
Cadmium (Cd) poses a significant threat to human health. However, chronic toxicity parameters for inhalation exposure are lacking, especially for noncritical systemic toxic effects. A physiologically based toxicokinetic (PBTK) model can be used to extrapolate toxicity parameters across various exposure routes. We combined a PBTK model with a human respiratory tract (HRT) model, which is applicable to the general population and capable of simulating the deposition and clearance processes of various airborne Cd compounds in the respiratory tract. Monte Carlo analysis was used to simulate the distribution of sensitive parameters to reflect individual variability. Validation based on datasets from general and occupational populations showed that the improved model had acceptable or better predictive performance, outperforming the original model with a 14.45 % decrease in the root mean square error (RMSE). Using this PBTK-HRT model, we extrapolated toxicity parameters from oral exposure to inhalation exposure for four systemic toxic effects with dose-response relationships but no known inhalation toxicity parameters, and ultimately recommended reference concentrations (RfCs) for four diseases (chronic kidney disease: 0.01 mu g/m3, osteoporosis: 0.01 mu g/m3, stroke: 0.04 mu g/m3, diabetes mellitus: 0.13 mu g/m3), contributing to a comprehensive assessment of the health risks of Cd inhalation exposure. Environmental Implication: Cadmium (Cd), a heavy metal, can cause lung cancer, chronic kidney disease, and osteoporosis and pose a significant threat to human health. We combined a physiologically based toxicokinetic (PBTK) model with a human respiratory tract (HRT) model to achieve better predictive performance and wider applicability; this model was subsequently employed for route-to-route extrapolation of toxicity parameters. Additionally, for the first time, we focused on multiple subchronic and chronic systemic toxic effects in addition to critical effects and derived their reference concentrations (RfCs), which can be used to assess the health risk of Cd inhalation exposure more comprehensively and accurately. https://doi.org/10.1016/j.jhazmat.2024.135323

Risk of Gynecological and Breast Cancers in Workers Exposed to Diesel Exhaust: A Systematic Review and Meta-Analysis of Cohort Studies,
D'AGOSTINI M., G. COLLATUZZO, F. TEGLIA and P. BOFFETTA, *Medicina Del Lavoro* 115, no. 3 (2024),
Background: This study aimed to explore the association between occupational exposure to diesel exhaust (DE) and gynaecological and breast cancers. Methods: A systematic review was performed to identify cohort studies reporting results on the association between occupational exposure to DE and risk of gynaecological and breast cancers. STROBE guidelines and PECOS criteria were followed. We identified 6 studies for breast cancer (BC), 4 for cervical cancer (CC), 4 for endometrial cancer (EC) and 7 for ovarian cancer (OC). Random-effects meta-analyses were conducted on the relationship between DE exposure and BC, CC, EC, and OC risk; 95% Confidence Intervals (CI) and prediction intervals (PI) were reported. We investigated between-study heterogeneity and potential publication bias using Egger's test. Results: No associations were observed between occupational DE exposure and risk of BC [RR=0.93; CI: 0.77-1.13; PI:0.50-1.73, I2=80.31% (CI: 21.72-95.05%)], EC [RR=0.89; CI: 0.75-1.05; PI:0. 61-1.30, I2=0.78% (CI: 0-85.57%)], and OC [RR=1.08; CI: 0.89-1.32, PI: 0.76-1.56, I2=11.87% (CI: 0-74.42%)]. A weak association was observed for CC [RR=1.41; CI: 1.17-1.17; PI:0.85-2.30, I2=6.44% (CI: 0-86.40%)]. No between-study heterogeneity or publication bias was detected. Conclusions: This study identified an association between DE exposure and CC, which was not adjusted for potential confounders. No evidence of an association was found with BC, EC, and OC. https://doi.org/10.23749/mdl.v115i3.15568

Epidémiologie

Association between polychlorinated biphenyl (PCB) and dioxin with metabolic syndrome (METS): a systematic review and meta-analysis,
GOON M., S. ZULKIFLI, S. S. A. SOHEIMI, S. A. RAHIM, N. ABD LATIP, N. HASHIM, N. D. KERISNAN, N. YAHAYA, A. MOHAMED and S. KADIR, *Scientific Reports* 14, no. 1 (Aug 2024),
Polychlorinated biphenyls (PCBs) and dioxin are persistent endocrine disrupting chemicals (EDCs) and have been associated with an increased risk of metabolic syndrome (MetS). The aim of this systematic review and meta-analysis was to assess the associations of PCBs and dioxin with MetS and its risk factors, including obesity, hypertriglyceridaemia (HTG), hypertension (HTN) and diabetes mellitus (DM). We searched three electronic databases for epidemiological studies concerning PCBs and dioxin with MetS published up to the end of 2023. Meta-analysis was performed for MetS itself and each of the MetS risks based on a random-effects meta-analysis model, and odds ratios (ORs) with 95% confidence intervals (CIs) were obtained. Publication bias was assessed based on Egger's test. Eleven studies were included from three databases up to 2023. There were 40,528 participants aged 18-89, where 18-100% of them were males, included in our meta-analysis. The meta-analysis results showed a strong association between PCB exposure and DM (OR = 3.593, 95% CI 2.566, 5.031), while most of the risk factors for MetS, including obesity (OR = 1.875, 95% CI 0.883, 3.979), HTN (OR = 1.335, 95% CI 0.902, 1.976) and HTG (OR = 1.611, 95% CI 0.981, 2.643), were weakly associated with PCB. Furthermore, both PCBs (OR = 1.162, 95% CI 0.994, 1.357) and dioxin (OR = 2.742, 95% CI 1.936, 3.883) were found to be weakly and strongly associated with MetS, respectively. Meta-regression analysis showed that DM in the Asian population is associated with PCB exposure, while HTG in the Northern American population is associated with PCB exposure. Our meta-analysis has demonstrated a strong relationship between DM and PCBs, while the relationship between PCBs with MetS and other risk factors is less pronounced. Additionally, MetS is weakly associated with dioxin exposure. To improve primary care outcomes, healthcare providers should consider incorporating the assessment of patients' risk of exposure to PCBs and dioxins into their evaluation procedures for more targeted medical interventions. https://doi.org/10.1038/s41598-024-68369-9

Association between Volatile Organic Compound Exposure and Sex Hormones in Adolescents: The Mediating Role of Serum Albumin,
LIAN X. Y., J. H. GUO, Y. Q. WANG, S. G. WANG and J. LI, *Toxics* 12, no. 6 (Jun 2024),
The associations between VOCs and sex hormones in adolescents remain unclear, and the role of serum albumin in these associations deserves to be explored. We conducted cross-sectional analyses using generalized linear models (GLMs), weighted quantile sum (WQS) regression, and mediation analysis, based on data from 584 adolescents from the National Health and Nutrition Examination Survey (NHANES). The GLM analyses revealed that seven kinds of mVOCs potentially affected sex hormone levels. According to the WQS regression results, 2-aminothiazoline-4-carboxylic acid (ATCA) was the major contributor to the significant associations of mixed mVOC exposure with testosterone, estradiol, and free androgen index in males; N-acetyl-S-(N-methylcarbamoyl)-L-cysteine (AMCC) was the major contributor to the significant associations of mixed mVOC exposure with sex hormone-binding globulin in males; and N-acetyl-S-(benzyl)-L-cysteine (BMA) was the major contributor to the significant associations of mixed mVOC exposure with the ratio of testosterone to estradiol in females. Moreover, serum albumin could mediate up to 9.2% of the associations between mixed exposure to mVOCs and sex hormones. Our findings could provide a reference for studies on the mechanisms underlying the effects of VOCs on sex hormones in adolescents and emphasize the necessity of reducing exposure to ATCA, AMCC, BMA, and their parent compounds. https://doi.org/10.3390/toxics12060438

Association of prenatal exposure to phthalates and synthetic phenols with pubertal development in three European cohorts,
FREIRE C., F. CASTIELLO, I. BABARRO, A. ANGUITA-RUIZ, M. CASAS, M. VRIJHEID, B. SARZO, A. BENEITO, M. KADAWATHAGEDARA, C. PHILIPPAT, C. THOMSEN, A. K. SAKHI and M. J. LOPEZ-ESPINOSA, *International Journal of Hygiene and Environmental Health* 261 (Aug 2024),
Background: There is limited epidemiological evidence on the association of prenatal exposure to phthalates and synthetic phenols with altered pubertal timing. Objective: To examine the association of prenatal exposure to phthalates, bisphenol A (BPA), parabens, benzophenone 3 (BP-3), and triclosan (TCS) with pubertal development in girls and boys from three European cohorts. Methods: Urinary metabolites of six different phthalate diesters (DEP, DiBP, DnBP, BBzP, DEHP, and DiNP), BPA, methyl- (MePB), ethyl- (EtPB), propyl- (PrPB), and butyl-paraben (BuPB), BP-3, and TCS were quantified in one or two (1st and 3rd trimester) urine samples collected during pregnancy (1999 - 2008) from mothers in three birth cohorts: INMA (Spain), EDEN (France), and MoBa (Norway). Pubertal development of their children was assessed at a single visit at age 7 -12 years (579 girls, 644 boys) using the parent-reported Pubertal Development Scale (PDS). Mixed-effect Poisson and g-computation and Bayesian Kernel Machine Regression (BKMR) were employed to examine associations of individual and combined prenatal chemical exposure, respectively, with the probability of overall pubertal onset, adrenarche, and gonadarche (stage 2 +) in girls and boys. Effect modification by child body mass index (BMI) was also assessed. Results: Maternal concentrations of the molar sum of DEHP and of DiNP metabolites were associated with a slightly higher probability of having started puberty in boys (relative risk, RR [95% CI] = 1.13 [0.98 -1.30] and 1.20 [1.06 -1.34], respectively, for a two-fold increase in concentrations), with a stronger association for DiNP in boys with overweight or obesity. In contrast, BPA, BuPB, EtPB, and PrPB were associated with a lower probability of pubertal onset, adrenarche, and/or gonadarche in all boys (e.g. overall puberty, BPA: RR [95% CI] = 0.93 [0.85 -1.01] and BuPB: 0.95 [0.90 -1.00], respectively), and the association with BPA was stronger in boys with underweight/normal weight. In girls, MEHP and BPA were associated with delayed gonadarche in those with underweight/normal weight (RR [95% CI] = 0.86 [0.77 -0.95] and 0.90 [0.84 -0.97], respectively). Most of these associations were trimester specific. However, the chemical mixture was not associated with any pubertal outcome in boys or girls. Conclusions: Prenatal exposure to certain phthalates and synthetic phenols such as BPA may impact the pubertal development of boys, and weight status may modify this effect. BPA may also alter the pubertal development of girls. https://doi.org/10.1016/j.ijheh.2024.114418

Associations between mycoestrogen exposure and sex steroid hormone concentrations in maternal serum and cord blood in the UPSIDE pregnancy cohort,
KINKADE C. W., L. M. ALEKSUNES, A. BRINKER, B. BUCKLEY, J. BRUNNER, C. WANG, R. K. MILLER, T. G. O'CONNOR, Z. RIVERA-NÚÑEZ and E. S. BARRETT, *International Journal of Hygiene and Environmental Health* 260 (Jul 2024),
Zearalenone (ZEN) is a fungal-derived toxin found in global food supplies including cereal grains and processed foods, impacting populations worldwide through diet. Because the chemical structure of ZEN and metabolites closely resembles 17 beta- estradiol (E2), they interact with estrogen receptors alpha/beta earning their designation as 'mycoestrogens'. In animal models, gestational exposure to mycoestrogens disrupts estrogen activity and impairs fetal growth. Here, our objective was to evaluate relationships between mycoestrogen exposure and sex steroid hormone concentrations in maternal circulation and cord blood for the first time in humans. In each trimester, pregnant participants in the UPSIDE study (n = 297) provided urine for mycoestrogen analysis and serum for hormone analysis. At birth, placental mycoestrogens and cord steroids were measured. We fitted longitudinal models examining log-transformed mycoestrogen concentrations in relation to log-transformed hormones, adjusting for covariates. Secondarily, multivariable linear models examined associations at each time point (1st, 2nd, 3rd trimesters, delivery). We additionally considered effect

modification by fetal sex. ZEN and its metabolite, alpha-zearalenol (alpha-ZOL), were detected in >93% and >75% of urine samples; >80% of placentas had detectable mycoestrogens. Longitudinal models from the full cohort exhibited few significant associations. In sexstratified analyses, in pregnancies with male fetuses, estrone (E1) and free testosterone (fT) were inversely associated with ZEN (E1 % Delta : -6.68 95%CI: -12.34, -0.65; fT % Delta : -3.22 95%CI: -5.68, -0.70); while alpha-ZOL was positively associated with E2 (% Delta : 5.61 95%CI: -1.54, 9.85) in pregnancies with female fetuses. In analysis with cord hormones, urinary mycoestrogens were inversely associated with androstenedione (% Delta : 9.15 95%CI: 14.64, -3.30) in both sexes, and placental mycoestrogens were positively associated with cord fT (% Delta : 37.13, 95%CI: 4.86, 79.34) amongst male offspring. Findings support the hypothesis that mycoestrogens act as endocrine disruptors in humans, as in animal models and livestock. Additional work is needed to understand impacts on maternal and child health. https://doi.org/10.1016/j.ijheh.2024.114405

Bisphenol-A and pentachlorophenol sodium levels in patients with rosacea,
DEMIRCIOGLU D., N. CINAR, S. D. PEKTAS, T. EDGUNLU, M. UNAL and D. Y. AKSOY, *Cutaneous and Ocular Toxicology* 43, no. 3 (Jul 2024): 232-236,
Background/ objectives: Rosacea is a common chronic inflammatory skin disorder. Endocrinedisrupting chemicals (EDC) are toxic substances, that may gain entry through the skin and subsequently interfere with hormonal and immune functions. Bisphenol A (BPA) and pentachlorophenol sodium (PCS) are two of these EDCs, incriminated in the pathogenesis of certain inflammatory skin disorders. We aimed to test the hypothesis that exposure to BPA and PCS might be involved in the pathogenesis of rosacea. Methods: This prospective cross-sectional study involved 34 patients with rosacea (18F/16 M; mean age 48.5 +/- 11 years) and 34 age and sex-matched healthy controls (20 F/14 M; mean age 48.2 +/- 10.2 years). Main anthropometric measures, fasting plasma glucose (FPG), insulin, HOMA-IR, lipids, C-reactive protein (CRP), BPA, and PCS levels were quantified and recorded. Results: Serum CRP (9.6 +/- 3.4 vs. 3.7 +/- 1.6 mg/L, respectively, p0.05 for all). Serum BPA levels were 55.8 +/- 14.4 and 51.9 +/- 19.2 ng/mL, and PCS levels were 63.3 +/- 45.9 ng/mL and 68.6 +/- 40.8 ng/mL for patients and healthy controls, respectively. There was no significant difference in BPA and PCS levels between the two groups ($p > 0.05$ for both). No significant association was found among HOMAIR, CRP, BPA, and PCS levels ($p > 0.05$ for all). Conclusions: Although the present study fails to provide presumptive evidence for the role of BPA and PCS in rosacea, the question as to other EDCs might be involved in its etiopathogenesis remains. This hypothesis requires confirmation in large-scale future prospective trials. https://doi.org/10.1080/15569527.2024.2383242

Cohort profile: the Environmental Reproductive and Glucose Outcomes (ERGO) Study (Boston, Massachusetts, USA) - a prospective pregnancy cohort study of the impacts of environmental exposures on parental cardiometabolic health,
PRESTON E. V., M. R. QUINN, P. L. WILLIAMS, T. F. MCELRATH, D. E. CANTONWINE, E. W. SEELY, B. J. WYLIE, M. R. HACKER, K. O'BRIEN, F. M. BROWN, C. E. POWE, A. BELLAVIA, Z. F. WANG, K. S. TOMSHO, R. HAUSER, T. JAMES-TODD, R. ENVIRONM and E. S. GLUCOSE OUTCOMES, *Bmj Open* 14, no. 5 (May 2024),
Purpose Pregnancy and the postpartum period are increasingly recognised as sensitive windows for cardiometabolic disease risk. Growing evidence suggests environmental exposures, including endocrine-disrupting chemicals (EDCs), are associated with an increased risk of pregnancy complications that are associated with long-term cardiometabolic risk. However, the impact of perinatal EDC exposure on subsequent cardiometabolic risk post-pregnancy is less understood. The Environmental Reproductive and Glucose Outcomes (ERGO) Study was established to investigate the associations of environmental exposures during the perinatal period with post-pregnancy parental cardiometabolic health. Participants Pregnant individuals aged >= 18 years without pre-existing

diabetes were recruited at <15 weeks of gestation from Boston, Massachusetts area hospitals. Participants completed <= 4 prenatal study visits (median: 12, 19, 26, 36 weeks of gestation) and 1 postpartum visit (median: 9 weeks), during which we collected biospecimens, health histories, demographic and behavioural data, and vitals and anthropometric measurements. Participants completed a postpartum fasting 2-hour 75 g oral glucose tolerance test. Clinical data were abstracted from electronic medical records. Ongoing (as of 2024) extended post-pregnancy follow-up visits occur annually following similar data collection protocols. Findings to date We enrolled 653 unique pregnancies and retained 633 through delivery. Participants had a mean age of 33 years, 10% (n=61) developed gestational diabetes and 8% (n=50) developed pre-eclampsia. Participant pregnancy and postpartum urinary phthalate metabolite concentrations and postpartum glycaemic biomarkers were quantified. To date, studies within ERGO found higher exposure to phthalates and phthalate mixtures, and separately, higher exposure to radioactive ambient particulate matter, were associated with adverse gestational glycaemic outcomes. Additionally, certain personal care products used in pregnancy, notably hair oils, were associated with higher urinary phthalate metabolite concentrations, earlier gestational age at delivery and lower birth weight. Future plans Future work will leverage the longitudinal data collected on pregnancy and cardiometabolic outcomes, environmental exposures, questionnaires, banked biospecimens and paediatric data within the ERGO Study. https://doi.org/10.1136/bmjopen-2023-079782

Endocrine-disrupting effects of bisphenol-A, thiamethoxam, and fipronil in hormone-naïve transmen compared to cis-women,
ÜSTAY Ö., O. ELBASAN, P. EREL, N. S. BULUT and N. YORGUNER, *Hormones-International Journal of Endocrinology and Metabolism* (2024 Jul 2024),
BackgroundCurrent evidence suggests that the etiology of gender dysphoria (GD) is multifactorial: this, however, remains unclear. Endocrine-disrupting chemicals (EDCs) are one of the etiological hypotheses.ObjectivesIn this study, we aimed to evaluate the urinary levels of bisphenol A (BPA), thiamethoxam, and fipronil in hormone-na ïve transmen compared with case-matched cis-women as well as the relation between sex hormone levels and EDCs.MethodsDrug-na ïve transmen diagnosed with GD and who were referred from the psychiatry outpatient clinic to the outpatient clinic of the Department of Endocrinology, Marmara University Hospital, were included in the study. These individuals were assessed for eligibility; 38 drug-na ïve transmen and 22 cis-women were recruited as the control group. After anthropometric evaluation laboratory tests for FSH, LH, total testosterone, and estradiol were carried out, spot urine samples were collected to evaluate the urine metabolic excretion of BPA, thiamethoxam, and fipronil.ResultsWe found that androgens, total testosterone, androstenedione, and DHEAS levels were significantly higher in transmen than in cis-women. Thiamethoxam was considerably higher in cis-women than in transmen, whereas fipronil and BPA levels were similar in both groups. A negative correlation was found between thiamethoxam and testosterone and between thiamethoxam and BPA levels.ConclusionThe available data suggest that the EDCs that we are most exposed to in our lives are not the only factor in GD development. Even transmen who have not taken hormone replacement have high testosterone levels; however, the mechanism has not as yet been elucidated. The challenge is to determine whether this is a factor leading to GD or a condition that develops in common with GD. https://doi.org/10.1007/s42000-024-00574-7

Environmental factors affecting female fertility,
SAKALI A. K., A. BARGIOTA, J. BJEKIC-MACUT, D. MACUT, G. MASTORAKOS and M. PAPAGIANNI, *Endocrine* (2024 Jul 2024),
IntroductionOver the recent years, scientific community has increased its interest on solving problems of female fertility pathology. Many factors acting separately or in combination affect significantly the reproductive life of a woman. This review summarizes current evidence regarding

the direct and/or indirect action of environmental factors and endocrine disrupting chemicals (EDCs; i.e. heavy metals, plasticizers, parabens, industrial chemicals, pesticides, or medications, by-products, anti-bacterial agents, perfluorochemicals) upon assisted and non-assisted female fertility, extracted from in vivo and in vitro animal and human published data. Transgenerational effects which could have been caused epigenetically by the action of EDCs have been raised.MethodsThis narrative review englobes and describes data from in vitro and in vivo animal and human studies with regard to the action of environmental factors, which include EDCs, on female fertility following the questions for narrative reviews of the SANRA (a scale for the quality assessment of narrative review articles). The identification of the studies was done: through the PubMed Central and the PubMed of the MEDLINE, the Google Scholar database and the Cochrane Library database until December 2023 combining appropriate keywords ("specific environmental factors" including "EDCs" AND "specific negative fertility outcomes"); by manual scanning of references from selected articles and reviews focusing on these subjects. It includes references to EDCs-induced transgenerational effects.ResultsFrom the reported evidence emerge negative or positive associations between specific environmental factors or EDCs and infertility outcomes such as infertility indices, disrupted maturation of the oocytes, anovulation, deranged transportation of the embryo and failure of implantation.ConclusionThe revealed adverse outcomes related to female fertility could be attributed to exposure to specific environmental factors such as temperature, climate, radiation, air pollutants, nutrition, toxic substances and EDCs. The recognition of fertility hazards related to the environment will permit the limitation of exposure to them, will improve female fertility and protect the health potential of future generations. https://doi.org/10.1007/s12020-024-03940-y

Etude de l'effet perturbateur endocrinien d'isoflavones végétales, approches clinique et mécanistique. Réduction de ces substances dans l'alimentation humaine. Thèse Médecine humaine et pathologie. Université de Bordeaux,
BENSAADA S., (2024/06/24 2024),
La consommation de soja, connait une croissance notable en France. Cependant, le soja contient des isoflavones (IFs), des composés phytochimiques aux effets perturbateurs endocriniens à des doses élevées. Cette thèse s'attache à évaluer les risques associés aux IFs et à l'Entérolactone (ENL), autre phyto-estrogène notable, et à proposer des solutions favorisant une consommation de soja sûre.Objectifs :(1) Évaluer l'exposition des Français·es aux IFs et valider de nouveaux outils d'estimation.(2) Étudier les effets endocriniens des IFs et de l'ENL chez l'humain, en se focalisant sur le lupus érythémateux disséminé (LED) et le cancer du sein triple négatif.(3) Développer des techniques pour réduire les teneurs en IFs des aliments à base de soja.Méthodologie :(1) Exposition aux IFs et à l'ENL :-Analyses d'aliments et validation de questionnaires alimentaires spécifiques pour évaluer la consommation de soja et l'exposition aux IFs et aux lignanes en France.-Dosages des IFs dans les fluides biologiques (sang, urine) et les cheveux.(2) Effets endocriniens des IFs et de l'ENL :- Étude cas-témoin sur le LED, comparant l'exposition aux IFs et à l'ENL de patientes et de volontaires saines-Études in vitro de l'effet des IFs sur la prolifération de cellules de cancer du sein triple négatif, ainsi que des interactions des IFs avec le récepteur des estrogènes GPER.(3) Réduction des teneurs en IFs:-Développement de procédés (pré)industriels pour réduire les IFs des fèves de soja.-Étude des recettes traditionnelles asiatiques de soja et de leurs effets sur la réduction des IFs.Résultats :(1) Exposition aux IFs et à l'ENL :-L'exposition aux IFs en France est significative, même chez les non-consommateur·ices de soja, à cause du "soja caché" présent dans les aliments ultra-transformés.- Les questionnaires alimentaires sont validés et les IFs et l'ENL sont dosés avec succès dans les cheveux.(2) Effets endocriniens des IFs et ENL :-Les résultats préliminaires suggèrent une association entre l'ENL et une réduction du risque de LED mais l'effectif limité de l'étude ne permet pas de conclure sur l'impact des IFs.-Les IFs et leurs conjugués circulants pourraient induire la prolifération des cellules cancéreuses du sein triple négatives, via une interaction avec le GPER.(3) Réduction des teneurs en IFs :- Des rinçages industriels permettent de réduire les IFs des fèves de

soja de 50%.-Les recettes traditionnelles asiatiques et les rinçages domestiques réduisent significativement les IFs des aliments à base de soja. Discussion :La consommation de soja nécessite une vigilance particulière en raison des effets endocriniens des IFs. Des recherches complémentaires sont nécessaires pour comprendre ces effets et proposer des recommandations pour une consommation sûre du soja.Conclusion :Si la consommation de soja, traditionnelle en Asie et présentant un intérêt nutritionnel certain, elle soulève des questions quant à ses répercussions sur la santé humaine à cause de la présence d'IFs estrogéniques et antithyroïdiennes. Cette thèse apporte des éléments de réponse sur l'exposition aux IFs en France, leurs effets potentiels sur le LED et les cancers du sein triple négatifs, et propose des solutions pour réduire les teneurs en IFs des aliments à base de soja. https://theses.hal.science/tel-04677864/document

Exposure to Synthetic Endocrine-Disrupting Chemicals in Relation to Maternal and Fetal Sex Steroid Hormones: A Scoping Review,
HANSEL M. C., A. M. ROSENBERG, C. W. KINKADE, C. CAPURRO, Z. RIVERA-NÚÑEZ and E. S. BARRETT, *Current Environmental Health Reports* 11, no. 3 (Sep 2024): 356-379,
Purpose of ReviewMany synthetic endocrine-disrupting chemicals (EDCs) are ubiquitous in the environment and highly detected among pregnant people. These chemicals may disrupt maternal and/or fetal sex steroid hormones, which are critical to pregnancy maintenance and fetal development. Here, we review the epidemiological literature examining prenatal exposure to common synthetic EDCs in relation to maternal and fetal sex steroid hormones.Recent FindingsWe performed a literature search using PubMed, SCOPUS, and Embase, ultimately identifying 29 articles for full review. Phenols, parabens, and persistent organic pollutants generally showed inverse associations with androgens, estrogens, and progesterone. Phthalates and per-and polyfluoroalkyl substances tended to be inversely associated with progesterone, while evidence regarding androgens and estrogens was mixed. Inconsistent, but noteworthy, differences by fetal sex and timing of exposure/outcome were observed.SummaryOverall, the literature suggests EDCs may disrupt maternal and fetal sex steroid activity, though findings are mixed. Given the pervasive, high-volume production of these synthetic chemicals and the critical functions sex steroid hormones play during gestation, additional research is warranted. https://doi.org/10.1007/s40572-024-00455-6

Fetal and Infancy Exposure to Phenols, Parabens, and Phthalates and Anthropometric Measurements up to 36 Months, in the Longitudinal SEPAGES Cohort,
OUIDIR M., A. H. CISSÉ, J. BOTTON, S. LYON-CAEN, C. THOMSEN, A. K. SAKHI, A. SABAREDZOVIC, S. BAYAT, R. SLAMA, B. HEUDE and C. PHILIPPAT, *Environmental Health Perspectives* 132, no. 5 (May 2024),
B ACKGROUND : Endocrine -disrupting chemicals may play a role in adiposity development during childhood. Until now literature in this scope su ffers from methodologic limitations in exposure assessment using one or few urine samples and missing assessment during the infancy period. O BJECTIVES : We investigated the associations between early -life exposure to quickly metabolized chemicals and post -natal growth, relying on repeated within -subject urine collections over pregnancy and infancy. M ETHODS : We studied the associations of four phenols, four parabens, seven phthalates, and one nonphthalate plasticizer from weekly pooled urine samples collected from the mother during second and third trimesters (median 18 and 34 gestational weeks, respectively) and infant at 2 and 12 months of age, and child growth until 36 months. We relied on repeated measures of height, weight and head circumference from study visits and the child health booklet to predict growth outcomes at 3 and 36 months using the Jenss-Bayley nonlinear mixed model. We assessed associations with individual chemicals using adjusted linear regression and mixtures of chemicals using a Bayesian kernel machine regression model. R ESULTS : The unipollutant analysis revealed few associations. Bisphenol S (BPS) at second trimester was positively associated with all infant growth parameters at 3 and 36 months, with similar patterns between exposure at third

trimester and all infant growth parameters at 3 months. Mono - n -butyl phthalate (MnBP) at 12 months was positively associated with body mass index (BMI), weight, and head circumference at 36 months. Mixture analysis revealed positive associations between exposure at 12 months and BMI and weight at 36 months, with MnBP showing the highest e ffect size within the mixture. C ONCLUSIONS : This study suggests that exposure in early infancy may be associated with increased weight and BMI in early childhood, which are risk factors of obesity in later life. Furthermore, this study highlighted the impact of BPS, a compound replacing bisphenol A, which has never been studied in this context. https://doi.org/10.1289/EHP13644

Impact of antenatal exposure to a mixture of persistent organic pollutants on intellectual development,
BARREA C., P. DUFOUR, P. CATHERINE, C. CHARLIER, F. BREVERS, L. ROUSSELLE and A. S. PARENT, *International Journal of Hygiene and Environmental Health* 261 (Aug 2024),
Objective: Strong experimental evidence exists that several endocrine disrupting chemicals (EDCs) have neurobehavioral toxicity. However, evidence of associations between prenatal exposure and child's cognitive development is inconsistent. Moreover, toxicants are generally analyzed one by one without considering aggregate effects. We examined here the impact of a prenatal exposure to a mixture of persistent organic pollutants (POPs) on intellectual abilities in preschool children, and compared their effects to those described in the literature. Methods: Sixty-two children were included in a longitudinal cohort. Four organochlorine pesticides, four polychlorinated biphenyls (PCBs) and seven perfluorinated compounds (PFCs) were measured in cord blood. Intellectual abilities were assessed at 6 years of age using the Wechsler Preschool and Primary Scale of Intelligence 4th ed. (WPPSI-IV). We examined the associations between a mixture of POPs and cognitive performances using principal components approach (PCA) and weighted quantile sum (WQS) regression taking sex difference into account. Results: No negative correlation was found when analyses were performed on boys and girls together. In sexstratified analyses, lower scores in full scale intelligence quotient (FSIQ) and fluid reasoning index (FRI) were observed in boys most exposed to a mixture of POPs. Increase of the WQS index was also associated with lower verbal comprehension index (VCI) scores in girls only. No other negative correlation was found using both WQS and PCA models. Conclusion: Our study suggests deleterious associations between antenatal exposure to a mixture of POPs and sexspecific cognitive level, clarifying some trends described in the literature. https://doi.org/10.1016/j.ijheh.2024.114422

Influence of Genetic Polymorphisms on Cognitive Function According to Dietary Exposure to Bisphenols in a Sample of Spanish Schoolchildren,
RAMÍREZ V., P. GONZÁLEZ-PALACIOS, P. J. GONZÁLEZ-DOMENECH, S. JAIMEZ-PÉREZ, M. A. BACA, L. RODRIGO, M. J. ÁLVAREZ-CUBERO, C. MONTEAGUDO, L. J. MARTÍNEZ-GONZÁLEZ and A. RIVAS, *Nutrients* 16, no. 16 (Aug 10 2024),
BACKGROUND: Neurodevelopmental disorders (NDDs) like intellectual disability (ID) are highly heritable, but the environment plays an important role. For example, endocrine disrupting chemicals (EDCs), including bisphenol A (BPA) and its analogues, have been termed neuroendocrine disruptors. This study aimed to evaluate the influence of different genetic polymorphisms (SNPs) on cognitive function in Spanish schoolchildren according to dietary bisphenol exposure. METHODS: A total of 102 children aged 6-12 years old were included. Ten SNPs in genes involved in brain development, synaptic plasticity, and neurotransmission (BDNF, NTRK2, HTR2A, MTHFR, OXTR, SLC6A2, and SNAP25) were genotyped. Then, dietary exposure to bisphenols (BPA plus BPS) was estimated and cognitive functions were assessed using the WISC-V Spanish form. RESULTS: BDNF rs11030101-T and SNAP25 rs363039-A allele carriers scored better on the fluid reasoning domain, except for those inheriting the BDNF rs6265-A allele, who had lower scores. Secondly, relevant SNP-bisphenol interactions existed in verbal comprehension (NTRK2 rs10868235 (p-int = 0.043)), working memory

(HTR2A rs7997012 (p-int = 0.002), MTHFR rs1801133 (p-int = 0.026), and OXTR rs53576 (p-int = 0.030)) and fluid reasoning (SLC6A2 rs998424 (p-int = 0.004)). CONCLUSIONS: Our findings provide the first proof that exploring the synergistic or additive effects between genetic variability and bisphenol exposure on cognitive function could lead to a better understanding of the multifactorial and polygenic aetiology of NDDs. https://doi.org/10.3390/nu16162639

Prenatal endocrine-disrupting chemicals exposure and impact on offspring neurodevelopment: A systematic review and meta-analysis,
YANG Z. Y., J. ZHANG, M. B. WANG, X. WANG, H. H. LIU, F. ZHANG and H. FAN, *Neurotoxicology* 103 (Jul 2024): 335-357,
Purpose: Considering that endocrine disruptors have certain effects on fetal growth, we conducted a systematic review of epidemiological literature to elucidate the correlation between exposure to endocrine-disrupting chemicals during pregnancy and the neurodevelopment of offspring. Method: We systematically explored PubMed, Web of Science, and CINAHL databases from inception to April 4, 2023. References from pertinent studies were reviewed, and data regarding the link between maternal prenatal EDC exposure and offspring neurological development were compiled. A domain-based approach was used to evaluate studies of neurodevelopmental effects in children <= 3 years old by two reviewers, including cognition, motor, behavior, language, and non-verbal ability. Results: A comprehensive search yielded 45,373 articles, from which 48 articles, involving 26,005 mother-child pairs, met the criteria and were subsequently included in our analysis. The results revealed that EDC exposure during pregnancy had a significant impact on offspring neurobehavior development, especially in cognition, motor, and language. Our findings indicated adverse associations between prenatal exposure to metals and offspring cognition (before 12 months: (3 coefficient: -0.28; 95% CI, -0.50 to -0.06; 1-3 years old: (3 coefficient: -0.55; 95 % CI: -1.08 to -0.02). Furthermore, metals ((3 coefficient: -0.71; 95 % CI: -1.23 to -0.19) and phthalates ((3 coefficient: -0.69; 95 % CI: -1.05 to -0.33) exposure exhibited detrimental effects on motor development from1-3 years old, while poly-fluoroalkyl substances were linked to the disruption of offspring language development ((3 coefficient: -1.01; 95 % CI: -1.90 to -0.11) within this timeframe. Additionally, exposure to EDCs during pregnancy had a negative impact on cognition development among girls from 12 to 36 months of age ((3 coefficient: -0.53; 95% CI: -1.01 to -0.06). Conclusion: Prenatal exposure to EDCs, especially metals, phthalates and, poly-fluoroalkyl substances, was associated with disrupting the development of offspring neurobehavior in the short and long term. Additionally, cognitive development showed gender differences due to prenatal endocrine-disrupting chemicals exposure. https://doi.org/10.1016/j.neuro.2024.07.006

Prenatal exposure to polycyclic aromatic hydrocarbons and phthalate acid esters and gestational diabetes mellitus: A prospective cohort study,
GUO M. H., Y. W. FANG, M. L. PENG, C. HE, J. CHEN, B. R. SUN, C. Y. LIU, Y. Z. ZHOU, H. P. ZHANG and K. ZHAO, *International Journal of Hygiene and Environmental Health* 261 (Aug 2024),
Background: Polycyclic aromatic hydrocarbons and phthalate acid esters (PAHs & PAEs), known as endocrine disrupting chemicals (EDCs), widely exist in daily life and industrial production. Previous studies have suggested that PAHs & PAEs may modify the intrauterine homeostasis and have adverse effects on fetal development. However, epidemiological evidence on the associations between PAHs & PAEs and gestational diabetes mellitus (GDM) is still limited. Objective: To investigate the effects of prenatal PAHs &PAEs exposure on the risk of GDM and hyperglycemia in pregnant women. Methods: The study population was a total of 725 pregnant women from a prospective birth cohort study conducted from December 2019 to December 2021. Blood glucose levels were collected by the hospital information system. Urinary PAHs & PAEs concentrations were determined by gas chromatography tandem mass spectrometry. The Poisson regression in a generalized linear model (GLM), multiple linear regression, quantile-based g-computation method (qgcomp), and Bayesian

kernel machine regression (BKMR) were applied to explore and verify the individual and overall effects of PAHs & PAEs on glucose homeostasis. Potential confounders were adjusted in all statistical models. Results: A total of 179 (24.69%) women were diagnosed with GDM. The Poisson regression suggested that a lnunit increment of 4-OHPHE (4-hydroxyphenanthrene) (adjusted Risk Ratio (aRR) = 1.13; 1.02-1.26) was associated with the increased GDM risk. Mixed-exposure models showed similar results. We additionally found that MBZP (mono-benzyl phthalate) (aRR = 1.19; 1.02-1.39) was positively related to GDM risk in qgcomp model. Although neither model demonstrated that 2-OHNAP (2-hydroxynaphthalene) and 9-OHFLU (9hydroxyfluorene) increased the risk of GDM, 2-OHNAP and 9-OHFLU exposure significantly increased blood glucose levels. BKMR model further confirmed that overall effects of PAHs & PAEs were significantly associated with the gestational hyperglycemia and GDM risk. Conclusions: Our study presents that environmental exposure to PAHs & PAEs was positively associated with gestational glucose levels and the risks of developing GDM. In particular, 2-OHNAP, 9-OHFLU, 4-OHPHE and MBZP may serve as important surveillance markers to prevent the development of GDM. https://doi.org/10.1016/j.ijheh.2024.114419

Reduced ovarian cholesterol and steroid biosynthesis along with increased inflammation are associated with high DEHP metabolite levels in human ovarian follicular fluids,
VARIK I., R. ZOU, A. BELLAVIA, K. ROSENBERG, Y. SJUNNESSON, I. HALLBERG, J. HOLTE, V. LENTERS, M. VAN DUURSEN, M. PEDERSEN, T. SVINGEN, R. VERMEULEN, A. SALUMETS, P. DAMDIMOPOULOU and A. VELTHUT-MEIKAS, *Environment International* 191 (2024/09/01/ 2024): 108960,
The plasticizer di(2-ethylhexyl) phthalate (DEHP) is known to have endocrine-disrupting properties mediated by its many metabolites that form upon exposure in biological systems. In a previous study, we reported an inverse association between DEHP metabolites in the human ovarian follicular fluid (FF) and the responsiveness of the follicles to controlled ovarian stimulation during in vitro fertilization (IVF) treatments. Here, we explored this association further through molecular analysis of the ovarian FF samples. Ninety-six IVF patients from Swedish (N = 48) and Estonian (N = 48) infertility clinics were selected from the previous cohort (N = 333) based on the molar sum of DEHP metabolites in their FF samples to arrive at "high" (mean 7.7 ± SD 2.3 nM, N = 48) and "low" (0.8 ± 0.4 nM, N = 48) exposure groups. Extracellular miRNA levels and concentrations of 15 steroid hormones were measured across FF samples. In addition, FF somatic cells, available for the Estonian patients, were used for RNA sequencing. Differential expression (DE) and interactions between miRNA and mRNA networks revealed that the expression levels of genes in the cholesterol biosynthesis and steroidogenesis pathways were significantly decreased in the high compared to the low DEHP group. In addition, the DE miRNAs were predicted to target key enzymes within these pathways (FDR < 0.05). A decreased 17-OH-progesterone to progesterone ratio was observed in the FF of the high DEHP group ($p < 0.05$). Additionally, the expression levels of genes associated with inflammatory processes were elevated in the FF somatic cells, and a computational cell-type deconvolution analysis suggested an increased immune cell infiltration into the high DEHP follicles ($p < 0.05$). In conclusion, elevated DEHP levels in FF were associated with a significantly altered follicular milieu within human ovaries, involving a pro-inflammatory environment and reduced cholesterol metabolism, including steroid synthesis. These results contribute to our understanding of the molecular mechanisms of female reprotoxic effects of DEHP.
https://doi.org/10.1016/j.envint.2024.108960

The triple exposure nexus of microplastic particles, plastic-associated chemicals, and environmental pollutants from a human health perspective,
ALIJAGIC A., D. SULJEVIC, M. FOCAK, J. SULEJMANOVIC, E. SEHOVIC, E. SÄRNDAHL and M. ENGWALL, *Environment International* 188 (Jun 2024),
The presence of microplastics (MPs) is increasing at a dramatic rate globally, posing risks for exposure and subsequent potential adverse effects on human health. Apart from being physical objects, MP

particles contain thousands of plastic-associated chemicals (i.e., monomers, chemical additives, and non-intentionally added substances) captured within the polymer matrix. These chemicals are often migrating from MPs and can be found in various environmental matrices and human food chains; increasing the risks for exposure and health effects. In addition to the physical and chemical attributes of MPs, plastic surfaces effectively bind exogenous chemicals, including environmental pollutants (e.g., heavy metals, persistent organic pollutants). Therefore, MPs can act as vectors of environmental pollution across air, drinking water, and food, further amplifying health risks posed by MP exposure. Critically, fragmentation of plastics in the environment increases the risk for interactions with cells, increases the presence of available surfaces to leach plastic-associated chemicals, and adsorb and transfer environmental pollutants. Hence, this review proposes the so-called triple exposure nexus approach to comprehensively map existing knowledge on interconnected health effects of MP particles, plastic-associated chemicals, and environmental pollutants. Based on the available data, there is a large knowledge gap in regard to the interactions and cumulative health effects of the triple exposure nexus. Each component of the triple nexus is known to induce genotoxicity, inflammation, and endocrine disruption, but knowledge about long-term and inter-individual health effects is lacking. Furthermore, MPs are not readily excreted from organisms after ingestion and they have been found accumulated in human blood, cardiac tissue, placenta, etc. Even though the number of studies on MPs-associated health impacts is increasing rapidly, this review underscores that there is a pressing necessity to achieve an integrated assessment of MPs' effects on human health in order to address existing and future knowledge gaps. https://doi.org/10.1016/j.envint.2024.108736

Xenoestrogen concentration in women with endometriosis or leiomyomas: A case-control study, VALDES-DEVESA V., D. SANZ-ROSA, I. J. THUISSARD-VASALLO, C. ANDREU-VÁZQUEZ and R. S. DE LA CUESTA, *Plos One* 19, no. 6 (Jun 2024),

Background Xenoestrogens are synthetic or naturally occurring chemicals capable of altering the endocrine system of humans and animals owing to their molecular similarity to endogenous hormones. There is limited data regarding their effects on women<acute accent>s health. Chronic exposure to xenoestrogens can promote the development of estrogen-related diseases.Objectives To examine xenoestrogen concentration (TEXB-alpha) differences between women with leiomyomas or endometriosis and control women, and to study the relationship between the clinical and sociodemographic characteristics of these patients and their xenoestrogen levels.Methods Prospective case-control study. We selected 221 women who underwent surgery at Quironsalud Madrid University Hospital between 2017 and 2021. The cases included 117 patients: 74 women who underwent surgery for uterine leiomyomas, 21 with endometriosis, and 22 with both pathologies. The control group comprised 104 healthy women who underwent surgical procedures for other reasons. TEXB-alpha was determined in the omental fat of all patients. Using a questionnaire and reviewing the patients' medical records, we collected sociodemographic data and other relevant variables.Results A significant majority of study participants (68.8%) had detectable levels of xenoestrogens. We found no association between TEXB-alpha levels in omental fat and the presence of myomas or endometriosis. In the case group, women living or working in Madrid Community exhibited, on average, 3.12 Eeq pM/g higher levels of TEXB-alpha compared to those working in other areas (p = 0.030). Women who referred to the use of estrogen-containing hormonal contraceptives had, on average, 3.02 Eeq pM/g higher levels of TEXB-alpha than those who had never used them (p = 0.022).Conclusions This study found no association between omental xenoestrogen levels and leiomyomas or endometriosis. However, their presence in most participants and their association with highly polluted areas emphasizes the importance of limiting environmental exposure to these substances. We also identified an association between hormonal contraceptive use and xenoestrogen concentration. https://doi.org/10.1371/journal.pone.0304766

Toxicité sur l'homme

Antifungal climbazole alters androgenic pathways in mammalian cells,
NDIAYE D., M. PERCEAU, M. LORCIN, F. DENIS and L. GATÉ, *Toxicology in Vitro* 99 (2024/08/01/ 2024): 105854,
Among antifungal agents used in pharmaceuticals and personal care products, the synthetic azole climbazole (CBZ; 1-(4-Chlorophenoxy)-1-(imidazol-1-yl)-3,3-dimethylbutan-2-one) acts on the fungus Malassezia. Despite concerns surrounding its effects on health, based on alterations to reproduction and steroidogenesis found in fish, little is known about its mechanism of action as an endocrine disrupting chemical (EDC) in mammalian cells. In this study, using OECD test guidelines, we investigated the effects of CBZ (i) in H295R cells, on the production of estradiol and testosterone, as well as intermediate metabolites in steroidogenesis pathway, and (ii) in HeLa9903 and AR-EcoScreen cell lines, on the transactivation of estrogen and androgen receptors. Our results are the first evidence in H295R cells, that CBZ treatment (from 0.3 µM) decreased secreted levels of testosterone and estradiol. This was associated with reduced 17α-hydroxypregnenolone and 17α-hydroxyprogesterone levels. The altered levels of these metabolites were associated with a decrease in cytochrome P450 17α-hydroxylase/17,20-lyase (Cyp17A1) activity without any effect on its protein level. CBZ was also found to exert antagonistic effects toward androgen and estrogen α receptors. These results give insights into the toxicological mechanism of action of CBZ. Many azoles share structural similarities; therefore, caution should be adopted due to their potential toxicity. https://doi.org/10.1016/j.tiv.2024.105854

AOP-based framework for predicting the joint action mode of di-(2-ethylhexyl) phthalate and bisphenol A co-exposure on autism spectrum disorder,
CUI K. L., L. D. LI, K. LI, W. S. XIAO and Q. WANG, *Neurotoxicology* 104 (Sep 2024): 75-84,
Autism spectrum disorder (ASD), also known as autism, is a common, highly hereditary and heterogeneous neurodevelopmental disorder. The global prevalence of ASD among children continues to rise significantly, which is partially attributed to environmental pollution. It has been reported that pre- or post-natal exposure to di-(2-ethylhexyl) phthalate (DEHP) or bisphenol A (BPA), two prevalent environmental endocrine disruptors, increases the risk of ASD in offspring. Yet, the joint action mode linking DEHP and BPA with ASD is incompletely understood. This study aims to unravel the joint action mode of DEHP and BPA co-exposure on the development of ASD. An adverse outcome pathway (AOP) framework was employed to integrate data from multiple public database and construct chemical-gene-phenotype-disease networks (CGPDN) for DEHP- and BPA-related ASD. Topological analysis and comprehensive literature exploration of the CGPDN were performed to build the AOP. By analysis of shared key events (KEs) or phenotypes within the AOP or the CGPDN, we uncovered two AOPs, decreased N-methyl-D-aspartate receptor (NMDAR) and estrogen antagonism that were likely linked to ASD, both with moderate confidence. Our analysis further predicted that the joint action mode of DEHP and BPA related ASD was possibly an additive or synergistic action. Thus, we propose that the co-exposure to BPA and DEHP perhaps additively or synergistically increases the risk of ASD. https://doi.org/10.1016/j.neuro.2024.07.012

Bisphenol A (BPA) and neurological disorders: An overview,
HYUN S. A. and M. KA, *International Journal of Biochemistry & Cell Biology* 173 (Aug 2024),
The human body is commonly exposed to bisphenol A (BPA), which is widely used in consumer and industrial products. BPA is an endocrine -disrupting chemical that has adverse effects on human health. In particular, many studies have shown that BPA can cause various neurological disorders by affecting brain development and neural function during prenatal, infancy, childhood, and adulthood exposure. In this review, we discussed the correlation between BPA and neurological disorders based on molecular cell biology, neurophysiology, and behavioral studies of the effects of BPA on brain

development and function. Recent studies, both animal and epidemiological, strongly indicate that BPA significantly impacts brain development and function. It hinders neural processes, such as proliferation, migration, and differentiation during development, affecting synaptic formation and activity. As a result, BPA is implicated in neurodevelopmental and neuropsychiatric disorders like autism spectrum disorder (ASD), attention -deficit hyperactivity disorder (ADHD), and schizophrenia. https://doi.org/10.1016/j.biocel.2024.106614

Cytotoxicity by endocrine disruptors through effects on ER Ca²⁺ transporters, aberrations in Ca²⁺ signalling pathways and ER stress,
MICHELANGELI F., N. A. MOHAMMED, B. JONES, M. TAIRU and F. AL-MOUSA, *Febs Open Bio* (2024 Aug 2024),
Concerns regarding man-made organic chemicals pervading our ecosystem and having adverse and detrimental effects upon organisms, including man, have now been studied for several decades. Since the 1970s, some environmental pollutants were identified as having endocrine disrupting affects. These endocrine disrupting chemicals (EDC) were initially shown to have estrogenic or anti-estrogenic properties and some were also shown to bind to a variety of hormone receptors. However, since the 1990s it has also been identified that many of these EDC additionally, have the ability of causing abnormal alterations in Ca2+ signalling pathways (also commonly involved in hormone signalling), leading to exaggerated elevations in cytosolic [Ca2+] levels, that is known to cause activation of a number of cell death pathways. The major emphasis of this review is to present a personal perspective of the evidence for some types of EDC, specifically alkylphenols and brominated flame retardants (BFRs), causing direct effects on Ca2+ transporters (mainly the SERCA Ca2+ ATPases), culminating in acute cytotoxicity and cell death. Evidence is also presented to indicate that this Ca(2+)ATPase inhibition, which leads to abnormally elevated cytosolic [Ca2+], as well as a decreased luminal ER [Ca2+], which triggers the ER stress response, are both involved in acute cytotoxicity. https://doi.org/10.1002/2211-5463.13880

Di-(2-ethylhexyl) phthalate promotes benign prostatic hyperplasia through KIF11-Wnt/ll-catenin signaling pathway,
SONG P., D. LV, L. C. YANG, J. ZHOU, X. YAN, Z. H. LIU, K. MA, Y. F. YU, X. Y. LIU and Q. DONG, *Ecotoxicology and Environmental Safety* 281 (Aug 2024),
Di-(2-ethylhexyl) phthalate (DEHP) might led to chronic and long-term effects on human organs due to its widespread use and bioaccumulation. Despite some cohorts reporting an association between DEHP exposure and BPH, its underlying mechanisms have not been investigated. Our findings indicate that exposure to DEHP or MEHP (main metabolites of DEHP in the human body) leads to increased prostate weights, elevated prostate index, and notable epithelial thickening in rats. It has been observed to promote BPH-1 cell proliferation with effects ranging from low to high concentrations. Transcriptome sequencing analysis of rat prostate tissues identified KIF11 as the key hub gene. KIF11 is highly expressed after DEHP/MEHP exposure, and knocking down of KIF11 inhibits the MEHP-induced promotion of cell proliferation. Exposure to MEHP has been observed to increase the expression of p-GSK-3ll and elevate the levels of ll-catenin, thereby activating the Wnt/ll-catenin signaling pathway. Knocking down of KIF11 significantly inhibits these effects. Histone H3 at Lysine 27 acetylation (H3K27ac) is implicated in the upregulation of KIF11 expression, as evidenced by the addition of the acetylation inhibitor C646. In summary, our findings established that DEHP exposure could promote BPH through H3K27ac regulated KIF11/Wnt/ll-catenin signaling pathway. https://doi.org/10.1016/j.ecoenv.2024.116602

Differences in endocrine and reproductive responses to substance exposure across generations: highlighting the importance of complementary findings,
BICHLMAIER I., *Archives of Toxicology* (2024/07/18 2024),
This article analyzes the results from 112 Extended One-Generation Reproductive Toxicity studies. The objective was to determine if test animals show consistent endocrine and reproductive effects within the same and across different generations and life stages. The analysis, grounded in a comprehensive Binary Matrix, included 530 observed effects and 193 unique, statistically significant associations. Associations' strength was quantified using Jaccard (J) coefficients to measure effect co-occurrence in the same study. Associated effects co-occur infrequently across the whole dataset (median J = 0.231). However, specific patterns emerged: associations of same effects across generations exhibited a higher strength (median J = 0.400) compared to associations of different effects (median J = 0.222). Notably, associations with effects observed in both the parental animals of the adult first filial generation (P1) and developing second filial generations (dF2) demonstrated J coefficients (with medians ranging from 0.300 to 0.430) that were approximately twofold higher than those of other associations. Consistently, equivalent life stage associations across generations revealed statistically significant higher association strengths for the P1 and dF2 generations (medians of 0.375 and 0.333, respectively) compared to other generations (medians of 0.200 and 0.174), possibly due to longer exposure duration and altered cross-talk between pregnant P1 dam and its conceptus. Overall, it is concluded that co-occurrence of associated effects in the same study is rather infrequent and that associations with effects in P1 and dF2 are stronger than all other associations. In general, the findings underscore the importance of independently analyzing each effect per generation due to the generally low co-occurrence rates of associated effects, challenging traditional expectations of generational continuity in toxic effects. https://doi.org/10.1007/s00204-024-03813-3

The Effect of Various Environmental Pollutants on the Reproductive Health in Children: A Brief Review of the Literature,
YESILDEMIR O. and M. N. CELIK, *Current Nutrition Reports* 13, no. 3 (Sep 2024): 382-392,
Purpose of ReviewEnvironmental pollutants in air, water, soil, and food are a significant concern due to their potential adverse effects on fetuses, newborns, babies, and children. These chemicals, which pass to fetuses and babies through trans-placental transfer, breast milk, infant formula, dermal transfer, and non-nutritive ingestion, can cause health problems during childhood. This review aims to discuss how exposure to various environmental pollutants in early life stages can disrupt reproductive health in children.Recent FindingsEnvironmental pollutants can affect Leydig cell proliferation and differentiation, decreasing testosterone production throughout life. This may result in cryptorchidism, hypospadias, impaired semen parameters, and reduced fertility. Although many studies on female reproductive health cannot be interpreted to support causal relationships, exposure to pollutants during critical windows may subsequently induce female reproductive diseases, including early or delayed puberty, polycystic ovary syndrome, endometriosis, and cancers.SummaryThere is growing evidence that fetal and early-life exposure to environmental pollutants could affect reproductive health in childhood. Although diet is thought to be the primary route by which humans are exposed to various pollutants, there are no adopted nutritional interventions to reduce the harmful effects of pollutants on children's health. Therefore, understanding the impact of environmental contaminants on various health outcomes may inform the design of future human nutritional studies. https://doi.org/10.1007/s13668-024-00557-5

Elucidating the mechanisms and mitigation strategies for six-phthalate-induced toxicity in male germ cells,
KIM S. M., Y. H. KIM, G. U. HAN, S. G. KIM, B. J. KIM, S. H. MOON, S. H. SHIN and B. Y. RYU, *Frontiers in Cell and Developmental Biology* 12 (Jul 2024),
Phthalate esters (PAEs) are primary plasticizers and endocrine-disrupting chemicals (EDCs) that are extensively used in numerous everyday consumer products. Although the adverse effects of single PAEs have been studied, our understanding of the effect of multiple phthalate exposure on male germ cell vitality remains limited. Therefore, this study aimed to investigate the collective effects of a mixture of PAEs (MP) comprising diethyl-, bis (2-ethylhexyl)-, dibutyl-, diisononyl-, diisobutyl-, and benzyl butyl-phthalates in the proportions of 35, 21, 15, 15, 8, and 5%, respectively, on differentiated male germ cells using GC-1 spermatogonia (spg) cells. As a mixture, MP substantially hindered GC-1 spg cell proliferation at 3.13 mu g/mL, with a half-maximal inhibitory concentration of 16.9 mu g/mL. Treatment with 25 mu g/mL MP significantly induced reactive oxygen species generation and promoted apoptosis. Furthermore, MP activated autophagy and suppressed phosphorylation of phosphoinositide 3-kinase, protein kinase B, and mammalian target of rapamycin (mTOR). The triple inhibitor combination treatment comprising parthenolide, N-acetylcysteine, and 3-methyladenine effectively reversed MP-induced GC-1 spg cell proliferation inhibition, mitigated apoptosis and autophagy, and restored mTOR phosphorylation. This study is the first to elucidate the mechanism underlying MP-induced male germ cell toxicity and the restoration of male germ cell proliferation mediated by chemical inhibitors. Therefore, it provides valuable insights into the existing literature by proposing a combinatorial toxicity mitigation strategy to counteract male germ cell toxicity induced by various EDCs exposure. https://doi.org/10.3389/fcell.2024.1398176

Emerging regulatory roles of noncoding RNAs induced by bisphenol a (BPA) and its alternatives in human diseases,
HE B., H. M. XU, S. W. LI, Y. F. ZHANG and J. W. TIAN, *Environmental Pollution* 357 (Sep 2024),
Bisphenols (BPs), including BPA, BPF, BPS, and BPAF, are synthetic phenolic organic compounds and endocrinedisrupting chemicals. These organics have been broadly utilized to produce epoxy resins, polycarbonate plastics, and other products. Mounting evidence has shown that BPs, especially BPA, may enter into the human body and participate in the development of human diseases mediated by nuclear hormone receptors. Moreover, BPA may negatively affect human health at the epigenetic level through processes such as DNA methylation and histone acetylation. Recent studies have demonstrated that, as part of epigenetics, noncoding RNAs (ncRNAs), including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), and small nucleolar RNAs (snoRNAs), have vital impacts on BP-related diseases, such as reproductive system diseases, nervous system diseases, digestive system diseases, endocrine system diseases, and other diseases. Moreover, based on the bioinformatic analysis, changes in ncRNAs may be relevant to normal activities and functions and BP-induced diseases. Thus, we conducted a meta-analysis to identify more promising ncRNAs as biomarkers and therapeutic targets for BP exposure and relevant human diseases. In this review, we summarize the regulatory functions of ncRNAs induced by BPs in human diseases and latent molecular mechanisms, as well as identify prospective biomarkers and therapeutic targets for BP exposure and upper diseases. https://doi.org/10.1016/j.envpol.2024.124447

Endocrine disruption of adipose physiology: Screening in SGBS cells,
KUCERA J., Z. CHALUPOVA, M. WABITSCH and J. BIENERTOVA-VASKU, *Journal of Applied Toxicology* n/a, no. n/a (Abstract The increasing use of industrial chemicals has raised concerns regarding exposure to endocrine-disrupting chemicals (EDCs), which interfere with developmental, reproductive and metabolic processes. Of particular concern is their interaction with adipose tissue, a vital component of the endocrine system regulating metabolic and hormonal functions. The SGBS (Simpson Golabi Behmel Syndrome) cell line, a well-established human-relevant model for adipocyte

research, closely mimics native adipocytes' properties. It responds to hormonal stimuli, undergoes adipogenesis and has been successfully used to study the impact of EDCs on adipose biology. In this study, we screened human exposure-relevant doses of various EDCs on the SGBS cell line to investigate their effects on viability, lipid accumulation and adipogenesis-related protein expression. Submicromolar doses were generally well tolerated; however, at higher doses, EDCs compromised cell viability, with cadmium chloride (CdCl2) showing the most pronounced effects. Intracellular lipid levels remained unaffected by EDCs, except for tributyltin (TBT), used as a positive control, which induced a significant increase. Analysis of adipogenesis-related protein expression revealed several effects, including downregulation of fatty acid-binding protein 4 (FABP4) by dibutyl phthalate, upregulation by CdCl2 and downregulation of perilipin 1 and FABP4 by perfluorooctanoic acid. Additionally, TBT induced dose-dependent upregulation of C/EBPα, perilipin 1 and FABP4 protein expression. These findings underscore the importance of employing appropriate models to study EDC-adipocyte interactions. Conclusions from this research could guide strategies to reduce the negative impacts of EDC exposure on adipose tissue. https://doi.org/10.1002/jat.4679

Environmental pollutants and male infertility: Effects on CatSper,
HE Y. X., B. H. WANG, J. HUANG, D. L. ZHANG and Y. Y. YUAN, *Ecotoxicology and Environmental Safety* 277 (Jun 2024),
Infertility is a growing health concern among many couples worldwide. Men account for half of infertility cases. CatSper, a sperm-specific Ca2+ channel, is expressed on the cell membrane of mammalian sperm. CatSper plays an important role in male fertility because it facilitates the entry of Ca2+ necessary for the rapid change in sperm motility, thereby allowing it to navigate the hurdles of the female reproductive tract and successfully locate the egg. Many pollutants present in the environment have been shown to affect the functions of CatSper and sperm, which is a matter of capital importance to understanding and solving male infertility issues. Environmental pollutants can act as partial agonists or inhibitors of CatSper or exhibit a synergistic effect. In this article, we briefly describe the structure, functions, and regulatory mechanisms of CatSper, and discuss the body of literature covering the effects of environmental pollutants on CatSper. https://doi.org/10.1016/j.ecoenv.2024.116341

Evaluation of effects of bisphenol analogs AF, S, and F on viability, proliferation, production of selected cancer-related factors, and expression of selected transcripts in Caov-3 human ovarian epithelial cell line,
MLYNARCIKOVA A. B. and S. SCSUKOVA, *Food and Chemical Toxicology* 191 (Sep 2024),
Bisphenol A (BPA) has been a substantial additive in plastics until the reports on its adverse effects have led to its restrictions and replacement. Monitoring studies document the increasing occurrence of bisphenol analogs, however, data on their effects and risks is still insufficient. Based on the indications that BPA might contribute to ovarian cancer pathogenesis, we examined effects of the analogs AF (BPAF), S (BPS) and F (BPF) (10- 9-10- 4 M) on the Caov-3 epithelial cancer cells, including the impact on cell viability, proliferation, oxidative stress, and production and expression of several factors and genes related to ovarian cancer. At environmentally relevant doses, bisphenols did not exert significant effects. At the highest concentration, BPAF caused varied alterations, including decreased cell viability and proliferation, caspase activation, down-regulation of PCNA and BIRC5, elevation of IL8, VEGFA, MYC, PTGS2 and ABCB1 expressions. Only BPA (10-4 M) increased IL-6, IL-8 and VEGFA output by the Caov-3 cells. Each bisphenol induced generation of reactive oxygen species and decreased superoxide dismutase activity at the highest concentration. Although the effects were observed only in the supraphysiological doses, the results indicate that certain bisphenol analogs might affect several ovarian cancer cell characteristics and merit further investigation. https://doi.org/10.1016/j.fct.2024.114889

IMPACT OF REAL-LIFE ENVIRONMENTAL EXPOSURES ON REPRODUCTION: Biosolids and male reproduction,
BELLINGHAM M. and N. EVANS, *Reproduction* 168, no. 2 (Aug 2024),
Over the past 50 years, there has been a concerning decline in male reproductive health and an increase in male infertility which is now recognised as a major health concern globally. While male infertility can be linked to some genetic and lifestyle factors, these do not fully explain the rate of declining male reproductive health. Increasing evidence from human and animal studies suggests that exposure to chemicals found ubiquitously in the environment may in part play a role. Many studies on chemical exposure, however, have assessed the effects of exposure to individual environmental chemicals (ECs), usually at levels not relevant to everyday human exposure. There is a need for study models which reflect the 'real-life' nature of EC exposure. One such model is the biosolids-treated pasture (BTP) sheep model which utilises biosolids application to agricultural land to examine the effects of exposure to low-level mixtures of chemicals. Biosolids are the by-product of the treatment of wastewater from industrial and domestic sources and so their composition is reflective of the ECs to which humans are exposed. Over the last 20 years, the BTP sheep model has published multiple effects on offspring physiology including consistent effects on the male reproductive system in fetal, neonatal, juvenile, and adult offspring. This review focuses on the evidence from these studies which strongly suggests that low-level EC exposure during gestation can alter several components of the male reproductive system and highlights the BTP model as a more relevant model to study real-life EC exposure effects. https://doi.org/10.1530/rep-24-0119

Impacts of Acrylamide on testis and spermatozoa,
SEIFY M., N. ABEDPOUR, S. F. TALEBI, V. HAZARI, M. MEHRARA, Y. KOOHESTANIDEHAGHI, H. SHOOREI and R. K. BHANDARI, *Molecular Biology Reports* 51, no. 1 (Dec 2024),
Acrylamide (ACR) is an industrial chemical used to produce polyacrylamide, a synthetic polymer with a wide range of applications. Depending on the dosage, its presence in occupational and environmental sources poses potential health risks to humans and animals. ACR can be formed in starchy foods cooked at high temperatures. Its effects on human sperm are not well understood. Animal studies indicate that ACR induces toxicity in the male reproductive system through oxidative stress mechanisms. Exposure to ACR alters the normal structure of testicular tubules, leading to congestion, interstitial edema, degeneration of spermatogenic cells, formation of abnormal spermatid giant cells, and necrosis and apoptosis. It also disrupts the balance of important biomarkers such as malondialdehyde, nitric oxide, superoxide dismutase, catalase, and glutathione. ACR has a negative impact on mitochondrial function, antioxidant enzymes, ATP production, and sperm membrane integrity, resulting in decreased sperm quality. Furthermore, it interferes with the expression of steroidogenic genes associated with testosterone biosynthesis. This review explores the detrimental effects of ACR on sperm and testicular function and discusses the potential role of antioxidants in mitigating the adverse effects of ACR on male reproduction. https://doi.org/10.1007/s11033-024-09677-1

In vitro assessment of thyroid peroxidase inhibition by chemical exposure: comparison of cell models and detection methods,
LIU R., J. NOVÁK and K. HILSCHEROVÁ, *Archives of Toxicology* 98, no. 8 (2024/08/01 2024): 2631-2645,
Disruption of the thyroid hormone (TH) system is connected with diverse adverse health outcomes in wildlife and humans. It is crucial to develop and validate suitable in vitro assays capable of measuring the disruption of the thyroid hormone (TH) system. These assays are also essential to comply with the 3R principles, aiming to replace the ex vivo tests often utilised in the chemical assessment. We compared the two commonly used assays applicable for high throughput screening [Luminol and Amplex UltraRed (AUR)] for the assessment of inhibition of thyroid peroxidase (TPO, a

crucial enzyme in TH synthesis) using several cell lines and 21 compounds from different use categories. As the investigated cell lines derived from human and rat thyroid showed low or undetectable TPO expression, we developed a series of novel cell lines overexpressing human TPO protein. The HEK-TPOA7 model was prioritised for further research based on the high and stable TPO gene and protein expression. Notably, the Luminol assay detected significant peroxidase activity and signal inhibition even in Nthy-ori 3-1 and HEK293T cell lines without TPO expression, revealing its lack of specificity. Conversely, the AUR assay was specific to TPO activity. Nevertheless, despite the different specificity, both assays identified similar peroxidation inhibitors. Over half of the tested chemicals with diverse structures and from different use groups caused TPO inhibition, including some widespread environmental contaminants suggesting a potential impact of environmental chemicals on TH synthesis. Furthermore, in silico SeqAPASS analysis confirmed the high similarity of human TPO across mammals and other vertebrate classes, suggesting the applicability of HEK-TPOA7 model findings to other vertebrates. https://doi.org/10.1007/s00204-024-03766-7

Modulation of adipogenesis and lipogenesis by indomethacin and pantoprazole,
ENTEZARI B., H. AKBABA and H. GURER-ORHAN, *Toxicology in Vitro* 100 (Oct 2024),
Endocrine disruptors are suggested to act as potential "obesogens" by interacting with various metabolic processes in adipose tissue. Besides industrial chemicals that are blamed for acting as endocrine disruptors as well as obesogens, pharmaceuticals can also cause obesogenic effects as unintended adverse effects. However, limited studies evaluated the obesogenic adverse effects of pharmaceuticals. Based on this information, the present study aimed to investigate the possible in vitro adipogenic/lipogenic potential of indomethacin and pantoprazole that are prescribed during pregnancy. Their effects on lipid accumulation, adiponectin level, glycerol-3-phosphate dehydrogenase (G3PDH) activity, and expression of adipogenic genes and proteins were investigated in 3 T3L1 cell line. The range of concentrations of the pharmaceuticals was selected according to their Cmax values. Lipid accumulation was increased dependently with indomethacin dose and with pantoprazole at its highest concentration. Both pharmaceuticals also increased adiponectin levels, which was thought to play a role in stimulating the adipogenesis pathway. Moreover, both pharmaceuticals altered the gene and/or protein expression of some adipogenic/lipogenic transcriptional factors, which may lead to disruption of metabolic pathways during the fetal period. In conclusion, indomethacin and pantoprazole may have obesogenic effects through different mechanisms and their potential to cause obesity should be investigated by further in vivo and epidemiological studies. https://doi.org/10.1016/j.tiv.2024.105895

Phthalates and reproduction functions of woman: Real effects or myths?,
TOUHOUCHE S., A. GUENIFED, N. D. YAKER and A. KHELFI, *Toxicologie Analytique Et Clinique* 36, no. 2 (Jun 2024): 109-130,
Background. - Phthalates are omnipresent plasticizers in the environment. The multiplicity of sources of exposure to these chemical pollutants makes the human body susceptible to contamination through multiple routes. Serious health problems can then appear, in particular on the reproductive function. Objective. - This review aims to compile as much recent evidence as possible on the effects of phthalates on female reproductive functions in order to elucidate the mechanism of action of these substances on this organism. Method. - Different scientific databases (Sciencedirect, PubMed and Springer) were used to gather the most reliable and relevant studies on the multiple effects caused by phthalate exposure. Results. - Some phthalates seem to induce significant disturbances in the reproductive function of women starting with puberty where studies have shown opposite effects (early or delayed puberty in adolescents). Furthermore, the ovary seems to be a potential target for phthalates since common contact, even at low doses, with these pollutants can induce follicular apoptosis and therefore premature ovarian failure (POF) or even infertility. Pregnancy, a period even more sensitive to any exogenous substance, seems to be affected by these components.

Miscarriages or premature births have been observed in women who have been exposed to these substances and effects on offspring have also been noted. Conclusion. - Additional studies are essential to understand the deleterious effects of phthalates on human health and to deepen current knowledge regarding their mechanism of action in the body. (c) 2023 Socie<acute accent>te<acute accent> Franc,aise , aise de Toxicologie Analytique. Published by Elsevier Masson SAS. All rights reserved. https://doi.org/10.1016/j.toxac.2023.10.001

Regrettable Substitutes and the Brain: What Animal Models and Human Studies Tell Us about the Neurodevelopmental Effects of Bisphenol, Per- and Polyfluoroalkyl Substances, and Phthalate Replacements,
MORALES-GRAHL E., E. N. HILZ and A. C. GORE, *International Journal of Molecular Sciences* 25, no. 13 (Jul 2024),
In recent decades, emerging evidence has identified endocrine and neurologic health concerns related to exposure to endocrine-disrupting chemicals (EDCs), including bisphenol A (BPA), certain per- and polyfluoroalkyl compounds (PFASs), and phthalates. This has resulted in consumer pressure to remove these chemicals from the market, especially in food-contact materials and personal care products, driving their replacement with structurally or functionally similar substitutes. However, these "new-generation" chemicals may be just as or more harmful than their predecessors and some have not received adequate testing. This review discusses the research on early-life exposures to new-generation bisphenols, PFASs, and phthalates and their links to neurodevelopmental and behavioral alterations in zebrafish, rodents, and humans. As a whole, the evidence suggests that BPA alternatives, especially BPAF, and newer PFASs, such as GenX, can have significant effects on neurodevelopment. The need for further research, especially regarding phthalate replacements and bio-based alternatives, is briefly discussed. https://doi.org/10.3390/ijms25136887

Unveiling the intricacies of BPA and BPS: comprehensive insights into its toxic effects using a cutting-edge microphysiological system,
GANZERLA M. D., N. D. INDOLFO, L. C. M. OLIVEIRA, T. R. DORATIOTO, T. M. AVELINO, R. J. DE AZEVEDO, L. B. TOFANI, M. F. TERRA, G. B. ELIAS, I. L. DE SOUSA, M. R. ALBORGUETTI, S. A. ROCCO, K. F. ARROTEIA and A. C. M. FIGUEIRA, *Toxicology in Vitro* 98 (Jun 2024),
Concerns over Bisphenol A (BPA) and its substitute, Bisphenol S (BPS), have led to innovative exploration due to potential adverse health effects. BPS, replacing BPA in some regions to avoid toxic impacts, remains insufficiently studied. Besides this, the organ -on -a -chip technology emerges as a transformative solution in drug discovery and chemiclas toxicity testing, minimizing costs and aligning with ethical standards by reducing reliance on animal models, by integrating diverse tissues and dynamic cell environments enhances precision in predicting organ function. Here, we employ a 3 -organ -on -a -chip microfluidic device with skin, intestine, and liver cultures to assess the effects of BPA and BPS via topical and oral administration. Our evaluation focused on gene markers associated with carcinogenicity, systemic toxicity, and endocrine disruption. BPA exhibited expected absorption profiles, causing liver injury and genetic modulation in related pathways. BPS, a safer alternative, induced adverse effects on gene expression, particularly in topical absorption, with distinct absorption patterns. Our findings underscore the urgency of addressing BPA and BPS toxicity concerns, highlighting the crucial role of organ -on -a -chip technology in understanding associated health risks. The study promotes the organ -on -a -chip methodology as a valuable tool for safe drug development and disease treatments, offering a novel liver toxicity screening alternative to traditional animal tests. This contributes to advancing comprehension of the biological effects of these compounds, fostering improved safety assessments in human health. https://doi.org/10.1016/j.tiv.2024.105849

Méthodes

AOP Report: An Upstream Network for Reduced Androgen Signaling Leading to Altered Gene Expression of Androgen Receptor-Responsive Genes in Target Tissues,
DRASKAU M. K., A. K. ROSENMAI, N. BOUFTAS, H. K. L. JOHANSSON, E. M. PANAGIOTOU, M. L. HOLMER, E. ELMELUND, J. ZILLIACUS, A. BERONIUS, P. DAMDIMOPOLOU, M. VAN DUURSEN and T. SVINGEN, *Environ Toxicol Chem* (Aug 29 2024),
Adverse outcome pathways (AOPs) can aid with chemical risk assessment by providing plausible links between chemical activity at the molecular level and effect outcomes in intact organisms. Because AOPs can be used to infer causality between upstream and downstream events in toxicological pathways, the AOP framework can also facilitate increased uptake of alternative methods and new approach methodologies to help inform hazard identification. However, a prevailing challenge is the limited number of fully developed and endorsed AOPs, primarily due to the substantial amount of work required by AOP developers and reviewers. Consequently, a more pragmatic approach to AOP development has been proposed where smaller units of knowledge are developed and reviewed independent of full AOPs. In this context, we have developed an upstream network comprising key events (KEs) and KE relationships related to decreased androgen signaling, converging at a nodal KE that can branch out to numerous adverse outcomes (AOs) relevant to androgen-sensitive toxicological pathways. Androgen signaling represents an extensively studied pathway for endocrine disruption. It is linked to numerous disease outcomes and can be affected by many different endocrine-disrupting chemicals. Still, pathways related to disrupted androgen signaling remain underrepresented in the AOP-wiki, and endorsed AOPs are lacking. Given the pivotal role of androgen signaling in development and function across vertebrate taxa and life stages of both sexes, this upstream AOP network serves as a foundational element for developing numerous AOPs. By connecting the upstream network with various downstream AOs, encompassing different species, it can also facilitate cross-species extrapolations for hazard and risk assessment of chemicals. Environ Toxicol Chem 2024;00:1-9. © 2024 The Author(s). Environmental Toxicology and Chemistry published by Wiley Periodicals LLC on behalf of SETAC. https://doi.org/10.1002/etc.5972

Human and fish differences in steroid receptors activation: A review,
TOSO A., C. GAROCHE and P. BALAGUER, *Science of the Total Environment* 948 (Oct 2024),
Steroid receptors (SRs) are transcription factors activated by steroid hormones (SHs) that belong to the nuclear receptors (NRs) superfamily. Several studies have shown that SRs are targets of endocrine disrupting chemicals (EDCs), widespread substances in the environment capable of interfering with the endogenous hormonal pathways and causing adverse health effects in living organisms and/or their progeny. Cell lines with SRs reporter gene are currently used for in vitro screening of large quantities of chemicals with suspected endocrine-disrupting activities. However, most of these cell lines express human SRs and therefore the toxicological data obtained are also extrapolated to non-mammalian species. In parallel, in vivo tests have recently been developed on fish species whose data are also extrapolated to mammalian species. As some species-specific differences in SRs activation by natural and synthetic chemicals have been recently reported, the aim of this review is to summarize those between human and fish SRs, as representatives of mammalian and non-mammalian toxicology, respectively. Overall, this literature study aims to improve inter-species extrapolation of toxicological data on EDCs and to understand which reporter gene cell lines expressing human SRs are relevant for the assessment of effects in fish and whether in vivo tests on fish can be properly used in the assessment of adverse effects on human health. https://doi.org/10.1016/j.scitotenv.2024.174889

Les modifications épigénétiques : potentiels biomarqueurs d'effet d'une exposition professionnelle ? - Article de revue - INRS,
(juin 2024),
Article (HST / Veille et prospective) : L'épigénétique, au-delà de jouer un rôle crucial dans la physiologie humaine, peut aussi être impliquée dans la réponse de l'organisme lors d'une exposition à des agents chimiques, physiques ou biologiques. Une perturbation dans la régulation de l'expression des gènes peut être à l'origine de pathologies invalidantes pour les salariés. Cet article décrit ce qu'est l'épigénétique et donne quelques exemples de perturbations épigénétiques associées à des expositions professionnelles et leurs effets sur la santé, et propose des perspectives en matière de prévention. https://www.inrs.fr/media.html?refINRS=VP%2042

Screening (ant)agonistic activities of xenobiotics on the retinoic acid receptor alpha (RARα) using in vitro and in silico analysis,
SU J. H., X. X. YANG, H. Q. XU, Y. PEI, Q. S. LIU, Q. F. ZHOU and G. B. JIANG, *Science of the Total Environment* 947 (Oct 2024),
Retinoic acid receptors (RARs) are known as crucial endocrine receptors that could mediate a broad diversity of biological processes. However, the data on endocrine disrupting effects of emerging chemicals by targeting RAR (ant)agonism are far from sufficient. Herein, we investigated the RAR alpha agonistic or antagonistic activities for 75 emerging chemicals of concern, and explored their interactions with this receptor. A recombinant two-hybrid yeast assay was used to examine the RAR alpha activities of the test chemicals, wherein 7 showed effects of RAR alpha agonism and 54 exerted potentials of RAR alpha antagonism. The representative chemicals with RAR alpha agonistic activities, i.e. 4-hydroxylphenol (4-HP) and bisphenol AF (BPAF), significantly increased the mRNA levels of CRABP2 and CYP26A1, while 4 select chemicals with RAR alpha antagonistic potentials, including bisphenol A (BPA), tetrabromobisphenol A (TBBPA), 4-tert-octylphenol (4-t-OP), and 4-n-nonylphenol (4-n-NP), conversely decreased the transcriptional levels of the test genes. The in silico molecular docking analysis using 3 different approaches further confirmed the substantial binding between the chemicals with RAR alpha activities and this nuclear receptor protein. This work highlights the promising strategy for screening endocrine-disrupting effects of emerging chemicals of concern by targeting RAR alpha (ant)agonism. https://doi.org/10.1016/j.scitotenv.2024.174717

Actualité, politique et évaluation de l'exposition

Alerte sur les crèmes de protection solaire à usage professionnel à la SNCF !,
Actu (aout 2024),
SUD-Rail a alerté mi-juillet 2024 la direction de SNCF Réseau sur les risques possibles liés à l'utilisation des deux crèmes de protection solaire professionnelles actuellement mis à disposition par l'entreprise à ses salarié-e-s. En effet, certains composants de ces produits, fabriqués industriellement, font aujourd'hui débat, car suspectés à risque pour la santé humaine et avérés à risque pour l'environnement. https://www.actu44.fr/alerte-sur-les-cremes-de-protection-solaire-a-usage-professionnel-a-la-sncf/

The bench to community initiative: community-based participatory research model for translating research discoveries into community solutions,
TAPIA J. L., A. LOPEZ, D. B. TURNER, T. FAIRLEY, T. TOMLIN-HARRIS, M. HAWKINS, P. R. HOLBERT, L. S. TREVIÑO and D. K. TETEH-BROOKS, *Front Public Health* 12 (2024): 1394069,

Community-based participatory research (CBPR) is an effective methodology for translating research findings from academia to community interventions. The Bench to Community Initiative (BCI), a CBPR program, builds on prior research to engage stakeholders across multiple disciplines with the goal of disseminating interventions to reduce breast cancer disparities and improve quality of life of Black communities. METHODS: The BCI program was established to understand sociocultural determinants of personal care product use, evaluate the biological impact of endocrine disrupting chemicals, and develop community interventions. The three pillars of the program include research, outreach and engagement as well as advocacy activities. The research pillar of the BCI includes development of multidisciplinary partnerships to understand the sociocultural and biological determinants of harmful chemical (e.g., endocrine disrupting chemicals) exposures from personal care products and to implement community interventions. The outreach and engagement pillar includes education and translation of research into behavioral practice. The research conducted through the initiative provides the foundation for advocacy engagement with applicable community-based organizations. Essential to the mission of the BCI is the participation of community members and trainees from underrepresented backgrounds who are affected by breast cancer disparities. RESULTS: Two behavioral interventions will be developed building on prior research on environmental exposures with the focus on personal care products including findings from the BCI. In person and virtual education activities include tabling at community events with do-it-yourself product demonstrations, Salon Conversations-a virtual platform used to bring awareness, education, and pilot behavior change interventions, biennial symposiums, and social media engagement. BCI's community advisory board members support activities across the three pillars, while trainees participate in personal and professional activities that enhance their skills in research translation. DISCUSSION: This paper highlights the three pillars of the BCI, lessons learned, testimonies from community advisory board members and trainees on the impact of the initiative, as well as BCI's mission driven approaches to achieving health equity. https://doi.org/10.3389/fpubh.2024.1394069

Consommation. Des gourdes pour enfants "Paris 2024" rappelées à cause d'un perturbateur endocrinien,
Le progrès (20 juillet 2024),
Les autorités appellent à ne plus utiliser les gourdes en question. Elles contiennent trop de Bisphénol A, interdit en France. https://www.leprogres.fr/economie/2024/07/20/des-gourdes-pour-enfants-paris-2024-rappelees-a-cause-d-un-perturbateur-endocrinien

Final newsletter from the ERGO project out now! - ERGO,
Ergo (juillet 2024),
As usual it includes all the latest NEWS and EVENTS from our consortium and our cluster, EURION. Check out our GRAND FINALE INTERACTIVE WORKSHOP! In this final issue, our coordinator Henrik Holbech fills us in on project activities in the final months and focuses on the legacy of ERGO in exciting new projects and initiatives. We also meet researcher Lucia Vergauwen in Belgium, learn more about a group of endocrine disruptors known as POLYBROMINATED DIPHENYL ETHERS (PBDE) and how to make our own EDC-FREE MOISTURISER! https://ergo-project.eu/final-newsletter-from-the-ergo-project-out-now/

Innovative techniques for combating a common enemy forever chemicals: A comprehensive approach to mitigating per- and polyfluoroalkyl substances (PFAS) contamination,
BAYODE A. A., S. S. EMMANUEL, A. O. AKINYEMI, O. T. ORE, S. O. AKPOTU, D. T. KOKO, D. E. MOMODU and E. A. LÓPEZ-MALDONADO, *Environmental Research* 261 (Nov 2024),
The pervasive presence of per and polyfluoroalkyl substances (PFAS), commonly referred to as "forever chemicals," in water systems poses a significant threat to both the environment and public health. PFAS are persistent organic pollutants that are incredibly resistant to degradation and have a

tendency to accumulate in the environment, resulting in long-term contamination issues. This comprehensive review delves into the primary impacts of PFAS on both the environment and human health while also delving into advanced techniques aimed at addressing these concerns. The focus is on exploring the efficacy, practicality, and sustainability of these methods. The review outlines several key methods, such as advanced oxidation processes, novel materials adsorption, bioremediation, membrane filtration, and in-situ chemical oxidation, and evaluates their effectiveness in addressing PFAS contamination. By conducting a comparative analysis of these techniques, the study aims to provide a thorough understanding of current PFAS remediation technologies, as well as offer insights into integrated approaches for managing these persistent pollutants effectively. While acknowledging the high efficiency of adsorption and membrane filtration in reducing persistent organic pollutants due to their relatively low cost, versatility, and wide applicability, the review suggests that the integration of these methods could result in an overall enhancement of removal performance. Additionally, the study emphasizes the need for researcher attention in key areas and underscores the necessity of collaboration between researchers, industry, and regulatory authorities to address this complex challenge. https://doi.org/10.1016/j.envres.2024.119719

Les liens entre exposition des femmes enceintes au bisphénol A et autisme de l'enfant à naître se précisent,
Le Monde (2024-08-21 2024),
Une récente étude a mis au jour un mode d'action du plastifiant sur une enzyme ayant un rôle crucial dans le développement du cerveau des garçons. Les chercheurs ont pu reproduire ce mécanisme sur des animaux de laboratoire. https://www.lemonde.fr/planete/article/2024/08/21/les-liens-entre-exposition-des-femmes-enceintes-au-bisphenol-a-et-autisme-de-l-enfant-a-naitre-se-precisent_6289576_3244.html

Lutte contre les perturbateurs endocriniens : la France progresse mais peut mieux faire,
(11 juillet 2024),
Un rapport ministériel publié lundi évalue cinq ans d'action contre ces substances chimiques capables de modifier notre système hormonal. Un des auteurs appelle les autorités à réguler toute cette famille de produits et invite les industriels à les remplacer par d'autres moins nocifs pour la santé. https://www.liberation.fr/environnement/lutte-contre-les-perturbateurs-endocriniens-la-france-progresse-mais-peut-mieux-faire-20240711_FJABTETMU5BCDOJDB67UZZQN3I/

Perturbateurs endocriniens : comment la recherche aiguillonne la réglementation,
Actu Environnement (30 juillet 2024),
La 2e rencontre scientifique de l'Anses sur les perturbateurs endocriniens a examiné les derniers résultats de recherche sur les conséquences pour les milieux et l'Homme. Elle est également revenue sur le dialogue entre science et réglementation. https://www.actu-environnement.com/ae/news/perturbateurs-endocriniens-recherche-contamination-biodiversite-homme-sante-reglementation-44547.php4

Endocrine disrupting chemicals in children's and their parents' urine: Is the exposure related to the Chinese and Western lifestyle?,
LI N., J. LIU, G. G. YING, J. C. K. LEE, T. F. LEUNG, A. COVACI and W. J. DENG, *International Journal of Hygiene and Environmental Health* 259 (Jun 2024),
Children are known to be more vulnerable to exposure to endocrine-disrupting chemicals (EDCs) compared to adults, but evaluating the exposure pathways can be challenging. This research employed target and non-target analysis (NTA) to examine the exposure characteristics of EDCs in

spot urine samples collected from 46 children's (aged 3-12 years) and their parents in Hong Kong (Chinese/Western lifestyle) and Guangzhou (mainly Chinese lifestyle). The results revealed that the geometric mean concentrations of phthalate esters metabolites (mPAEs) and bisphenols (BPs) in children's urine were 127.3 mu g/gcrea and 2.5 mu g/gcrea in Guangzhou, and 93.7 mu g/gcrea and 2.9 mu g/gcrea in Hong Kong, respectively, which were consistent with global levels. NTA identified a total of 1069 compounds, including 106 EDCs, commonly detected in food, cosmetics, and drugs. Notable regional differences were observed between Guangzhou and Hong Kong with potential sources of EDCs including dietary and cosmetic additives, toys, flooring and dust, as well as differences in lifestyles, diet, and living environment. However, age was found to significantly impact EDC exposure. The quantified EDCs (mPAEs and BPs) posed possible health risks to 60% of the children. Moreover, the presence of caffeine in children's urine, which exhibited higher detection rates in children from Hong Kong (95.6%) and Guangzhou (44.4%), warrants further attention. The sources of EDCs exposure in these regions need to be fully confirmed. https://doi.org/10.1016/j.ijheh.2024.114383

Monitoring human exposure to chemicals: PARC Aligned Studies,
Parc (juin 2024 2024),
As part of PARC, an EU-wide human biomonitoring (HBM) survey is being conducted by aligning national and regional human biomonitoring studies across Europe, building on the work previously done by the Human Biomonitoring Initiative in Europe, HBM4EU ↗. This ambitious project includes participation from 24 countries and focuses on collecting data from three age groups: children (6-11 years), teenagers (12-17 years), and adults (18-39 years). https://www.eu-parc.eu/news/risk-assessment/monitoring-human-exposure-chemicals-parc-aligned-studies

Toxicité sur les animaux

Combining transcriptomics and metabolomics to assess neurodevelopmental alteration caused by in utero exposure of mice to three putative thyroid hormone system disruptors,
ZEKRI Y., R. POULSEN, M. HANSEN, F. FLAMANT and R. GUYOT, *Toxicology* 508 (2024/11/01/ 2024): 153905,
Gestating mice were exposed to three chemicals, tetrabromo-bisphenol A (TBBPA; 2 mg/kg/day), amitrole (25 and 50 mg/kg/day) and pyraclostrobin (0.4 and 2 mg/kg/day) to assess their capacity to act as thyroid hormone disruptors and compromise neurodevelopment. Propyl-thio-uracyl, a known pharmacological inhibitor of thyroid gland secretion, was used at both high and low dose as a reference thyroid hormone system disruptor (1 ppm, 1500 ppm). A combination of plasma metabolomics and striatum transcriptomics revealed the induced change in pups at the postnatal stages. Although the underlying mechanism is unlikely to involve thyroid hormone disruption, these chemicals had a detectable effect on pups' neurodevelopment. https://doi.org/10.1016/j.tox.2024.153905

Induction of insulin resistance in female mice due to prolonged phenanthrene exposure: Unveiling the low-dose effect and potential mechanisms,
FANG L., F. F. KONG, K. L. OU, L. N. HONG, C. G. WANG and X. M. TONG, *Environmental Research* 260 (Nov 2024),
Phenanthrene (Phe) is a commonly occurring polycyclic aromatic hydrocarbon (PAH) found in various food sources and drinking water. Previous studies have shown that long-term exposure to Phe in

male mice leads to insulin resistance in a dose-dependent manner. However, the effect of Phe on glucose homeostasis in female mice remains unknown. To address this knowledge gap, female Kunming mice were exposed to Phe through their drinking water at concentrations of 0.05, 0.5, and 5 ng/mL. After 270 d of exposure, we surprisingly discovered a low-dose effect of Phe on insulin resistance in female mice, which differed from the effect observed in male mice and showed sexual dimorphism. Specifically, insulin resistance was only observed in the 0.05 ng/mL treatment, and this low-dose effect was also reflected in the concentration of Phe in white adipose tissue (WAT). Differences in metabolic enzyme activities in the liver may potentially explain this effect. The observed sexual dimorphism in Phe exposure could be attributed to variations in estrogen (E2) level and estrogen receptor beta (ER beta) expression in WAT. These findings highlight the association between environmental factors and the development of insulin resistance, emphasizing the pathogenic effect of even low doses of Phe. Moreover, sex dependent-effect should be given more attention when studying the toxic effects of environmental pollutants. https://doi.org/10.1016/j.envres.2024.119597

Male autism spectrum disorder is linked to brain aromatase disruption by prenatal BPA in multimodal investigations and 10HDA ameliorates the related mouse phenotype,
SYMEONIDES C., K. VACY, S. THOMSON, S. TANNER, H. K. CHUA, S. DIXIT, T. MANSELL, M. O'HELY, B. NOVAKOVIC, J. B. HERBSTMAN, S. WANG, J. GUO, J. CHIA, N. T. TRAN, S. E. HWANG, K. BRITT, F. CHEN, T. H. KIM, C. A. REID, A. EL-BITAR, G. B. BERNASOCHI, L. M. D. DELBRIDGE, V. R. HARLEY, Y. W. YAP, D. DEWEY, C. J. LOVE, D. BURGNER, M. L. K. TANG, P. D. SLY, R. SAFFERY, J. F. MUELLER, N. RINEHART, B. TONGE, P. VUILLERMIN, F. COLLIER, A.-L. PONSONBY, L. C. HARRISON, S. RANGANATHAN, L. GRAY, A.-L. PONSONBY, W. C. BOON and B. I. S. I. G. THE, *Nature Communications* 15, no. 1 (2024/08/07 2024): 6367,
Male sex, early life chemical exposure and the brain aromatase enzyme have been implicated in autism spectrum disorder (ASD). In the Barwon Infant Study birth cohort (n = 1074), higher prenatal maternal bisphenol A (BPA) levels are associated with higher ASD symptoms at age 2 and diagnosis at age 9 only in males with low aromatase genetic pathway activity scores. Higher prenatal BPA levels are predictive of higher cord blood methylation across the CYP19A1 brain promoter I.f region (P = 0.009) and aromatase gene methylation mediates (P = 0.01) the link between higher prenatal BPA and brain-derived neurotrophic factor methylation, with independent cohort replication. BPA suppressed aromatase expression in vitro and in vivo. Male mice exposed to mid-gestation BPA or with aromatase knockout have ASD-like behaviors with structural and functional brain changes. 10-hydroxy-2-decenoic acid (10HDA), an estrogenic fatty acid alleviated these features and reversed detrimental neurodevelopmental gene expression. Here we demonstrate that prenatal BPA exposure is associated with impaired brain aromatase function and ASD-related behaviors and brain abnormalities in males that may be reversible through postnatal 10HDA intervention. https://doi.org/10.1038/s41467-024-48897-8

Microglial responses to inflammatory challenge in adult rats altered by developmental exposure to polychlorinated biphenyls in a sex-specific manner,
WALKER K. A., S. T. RHODES, D. A. LIBERMAN, A. C. GORE and M. R. BELL, *Neurotoxicology* 104 (Sep 2024): 95-115,
Polychlorinated biphenyls are ubiquitous environmental contaminants linkedc with peripheral immune and neural dysfunction. Neuroimmune signaling is critical to brain development and later health; however, effects of PCBs on neuroimmune processes are largely undescribed. This study extends our previous work in neonatal or adolescent rats by investigating longer-term effects of perinatal PCB exposure on later neuroimmune responses to an inflammatory challenge in adulthood. Male and female Sprague-Dawley rats were exposed to a low-dose, environmentally relevant, mixture of PCBs (Aroclors 1242, 1248, and 1254, 1:1:1, 20 mu g / kg dam BW per gestational day) or

oil control during gestation and via lactation. Upon reaching adulthood, rats were given a mild inflammatory challenge with lipopolysaccharide (LPS, 50 mu g / kg BW, ip) or saline control and then euthanized 3 hours later for gene expression analysis or 24 hours later for immunohistochemical labeling of Iba1+ + microglia. PCB exposure did not alter gene expression or microglial morphology independently, but instead interacted with the LPS challenge in brain region- and sex-specific ways. In the female hypothalamus, PCB exposure blunted LPS responses of neuroimmune and neuromodulatory genes without changing microglial morphology. In the female prefrontal cortex, PCBs shifted Iba1+ + cells from reactive to hyperramified morphology in response to LPS. Conversely, in the male hypothalamus, PCBs shifted cell phenotypes from hyperramified to reactive morphologies in response to LPS. The results highlight the potential for long-lasting effects of environmental contaminants that are differentially revealed over a lifetime, sometimes only after a secondary challenge. These neuroimmune endpoints are possible mechanisms for PCB effects on a range of neural dysfunction in adulthood, including mental health and neurodegenerative disorders. The findings suggest possible interactions with other environmental challenges that also influence neuroimmune systems. https://doi.org/10.1016/j.neuro.2024.07.009

Prenatal arsenic exposure alters EZH2-H3K27me3 occupancy at TNF-α promoter leading to insulin resistance and metabolic syndrome in a mouse model,
KOSHTA K., A. CHAUHAN, S. SINGH and V. SRIVASTAVA, *Environment International* 190 (Aug 2024),
The global prevalence of Metabolic Syndrome (MetS) is continuously rising and exposure to environmental toxicants such as arsenic could be contributing to this rapid surge. In this study, we have assessed the effects of prenatal arsenic exposure on insulin resistance and MetS parameters in a mouse model, and an underlying mechanism was identified. We found that prenatal arsenic exposure promotes insulin resistance and adipocyte dysfunction which leads to the early onset of MetS in male offspring. Primary adipocytes isolated from 20-weekold arsenic-exposed offspring showed hypertrophy, elevated basal lipolysis, and impaired insulin response along with enhanced expression of Tumor necrosis factor-alpha (TNF-alpha). TNF-alpha levels were consistently high at gestational day 15.5 (GD15.5) as well as primary adipocytes of 6-week-old arsenic-exposed male offspring. Along with TNF-alpha, downstream p-JNK1/2 levels were also increased, which led to inhibitory phosphorylation of IRS1and reduced GLUT4 translocation upon insulin stimulation in adipocytes. Insulin response and downstream signaling were restored upon TNF-alpha inhibition, confirming its central role. The persistent overexpression of TNF alpha in adipocytes of arsenic-exposed mice resulted from diminished EZH2 occupancy and reduced H3K27me3 (gene silencing histone marks) at the TNF-alpha promoter. This further led to chromatin relaxation, recruitment of cJun and CBP/p300, formation of an enhanceosome complex, and TNF-alpha expression. Our findings show how prenatal arsenic exposure can epigenetically modulate TNF-alpha expression to promote adipocyte dysfunction and insulin resistance which contributes to the early onset of MetS in offspring. https://doi.org/10.1016/j.envint.2024.108929

Prenatal exposure to an environmentally relevant phthalate mixture alters serum cytokine levels and inflammatory markers in the F1 mouse ovary,
FLETCHER E. J., W. S. STUBBLEFIELD, J. HUFF, R. SANTACRUZ-MÁRQUEZ, M. LAWS, E. BREHM and J. A. FLAWS, *Toxicological Sciences* 201, no. 1 (Jul 2024): 26-37,
Phthalates are used as plasticizers and solvents in consumer products. Virtually 100% of the US population has measurable exposure levels to phthalates, however, the mechanisms by which prenatal exposure to phthalate mixtures affects reproductive health in the offspring remain unclear. Thus, this study tested the hypothesis that prenatal exposure to an environmentally relevant phthalate mixture promotes inflammation in F1 ovarian tissue. Pregnant CD-1 dams were dosed orally with vehicle control (corn oil) or phthalate mixture (20 mu g/kg/d, 200 mu g/kg/d, 200 mg/kg/d, 500 mg/kg/d). Pregnant dams delivered pups naturally and ovaries and sera from the F1 females

were collected at postnatal day (PND) 21, PND 60, 3 mo, and 6 mo. Sera were used to measure levels of C-reactive protein (CRP). Ovaries and sera were used for cytokine array analysis. RNA was isolated from F1 ovaries and used to quantify expression of selected cytokine genes. Prenatal exposure to the mixture significantly increased the levels of CRP at 200 mu g/kg/d on PND 21 compared with controls. The mixture altered 6 immune factors in sera at PND 21 and 33 immune factors in the ovary and sera at 6 mo compared with controls. The mixture increased ovarian expression of cytokines at PND 21 and decreased ovarian expression of cytokines at 6 mo compared with controls. These data suggest that prenatal exposure to a phthalate mixture interferes with the immune response in F1 female mice long after initial exposure. https://doi.org/10.1093/toxsci/kfae084

Quantitative label-free proteomic analysis of mouse ovarian antral follicles following oral exposure to a human-relevant mixture of three phthalates,
MILLER K. L., X. S. LIU, M. G. MCSWAIN, E. J. JAUREGUI, P. R. LANGLAIS and Z. R. CRAIG, *Toxicological Sciences* (2024 Jul 2024),
Dibutyl phthalate (DBP), di-2-ethylhexyl phthalate (DEHP), and benzyl butyl phthalate (BBP) are used in personal and medical care products. In the ovary, antral follicles are essential for steroidogenesis and ovulation. DBP, BBP, and DEHP are known to inhibit mouse antral follicle growth and ovulation in vitro, and associate with decreased antral follicle counts in women. Given that the in vivo effects of a three-phthalate mixture on antral follicles are unknown, we evaluated the effects of a human-relevant mixture of DBP, BBP, and DEHP on ovarian follicles through proteome profiling analysis. Adult CD-1 female mice were fed corn oil (vehicle), or two dose levels of a phthalate mixture based on estimated exposures in general (32 mu g/kg/d; PHT 32) and occupationally exposed (500 mu g/kg/d; PHT 500) populations for 10 d. Antral follicles (>250 mu m) were isolated and subjected to proteome profiling via label-free tandem mass spectrometry. A total of 5,417 antral follicle proteins were detected, of which 194 were differentially abundant between vehicle and PHT 32, and 136 between vehicle and PHT 500. Bioinformatic analysis revealed significantly different responses between the two phthalate doses. Protein abundance differences in the PHT 32 exposure mapped to cytoplasm, mitochondria, and lipid metabolism; whereas those in the PHT 500 exposure mapped to cytoplasm, nucleus, and phosphorylation. When both doses altered proteins mapped to common processes, the associated predicted transcription factors were different. These findings provide novel mechanistic insight into phthalate-associated, ovary-driven reproductive outcomes in women. https://doi.org/10.1093/toxsci/kfae089

Subacute tributyltin exposure alters the development and morphology of mammary glands in association with CYP19A1 expression in female rats,
SILVA N. P., C. S. DA COSTA, K. L. BARBOSA, C. D. JANUARIO, L. N. GAMA-DE-SOUZA, C. BREVES, R. S. FORTUNATO, L. MIRANDA-ALVES, M. DE OLIVEIRA, C. R. NOGUEIRA and J. B. GRACELI, *Reproductive Toxicology* 128 (Sep 2024),
Tributyltin (TBT) is an endocrine-disrupting chemical (EDC) related to reproductive dysfunctions. However, few studies have investigated the effects of TBT exposure on mammary gland development. Thus, we assessed whether subacute TBT exposure causes irregularities in mammary gland development. We administered TBT (100 and 1,000 ng/kg/day for 30 days) to female rats from postnatal day (PND) 25 to PND 55, and mammary gland development, morphology, inflammation, collagen deposition, and protein expression were evaluated. Abnormal mammary gland development was observed in both TBT groups. Specifically, TBT exposure reduced the number of terminal end buds (TEBs), type 1 (AB1) alveolar buds, and type 2 (AB2) alveolar buds. An increase in the lobule and differentiation (DF) 2 score was found in the mammary glands of TBT rats. TBT exposure increased mammary gland blood vessels, mast cell numbers, and collagen deposition. Additionally, both TBT rats exhibited intraductal hyperplasia and TEB-like structures. An increase in estrogen receptor alpha (ER alpha), progesterone receptor (PR), and cytochrome P450 family 19

subfamily A member 1 (CYP19A1) - positive cells was observed in the mammary glands of TBT rats. A strong negative correlation was observed between CYP19A1positive cells and TEB number. In addition, CYP19A1 - positive cells were positively correlated with mammary gland TEB-like structure, ductal hyperplasia, inflammation, and collagen deposition. Thus, these data suggest that TBT exposure impairs mammary gland development through the modulation of CYP19A1 signaling pathways in female rats. https://doi.org/10.1016/j.reprotox.2024.108635