Bulletin de veille
Perturbateurs Endocriniens
N°28 - Novembre-Décembre 2024

Objectif : cette veille bibliographique à 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.

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Exposition professionnelle

Epidemiology and Risk Factors for Testicular Cancer: A Systematic Review

Tateo V, Thompson ZJ, Gilbert SM, Cortessis VK, Daneshmand S, Masterson TA, et al. *Eur Urol*. 2024 Nov 13.

BACKGROUND AND OBJECTIVE: Testicular germ cell tumors (TGCTs) are globally rare, although incidence significantly varies across global geographic regions and ethnicities. Recent decades have seen an unexplained increase in incidence. This review investigates the changing epidemiology of TGCT and identifies key risk factors. METHODS: A systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 statement was conducted. After screening and risk-of-bias assessment, 53 reports on significant and updated topics on TGCT epidemiology and risk factors were included for narrative synthesis. Of these, 26 were selected for quantitative synthesis.

KEY FINDINGS AND LIMITATIONS: Projections suggest a continued increase in global TGCT incidence, even in populations with historically low incidence. Genetic predisposition, particularly single-nucleotide polymorphisms, accounts for approximately 44% of TGCT heritability. In utero exposure to endocrine-disrupting chemicals, cryptorchidism, infertility, high height, behavioral factors such as marijuana consumption, and environmental or occupational exposures to potentially harmful substances are associated with higher TGCT risk, with variable strength of evidence. Meta-analyses confirmed a significant association between prenatal/early-life risk factors and TGCT incidence (odds ratio 1.44). Limitations include constrained evidence quality, heterogeneity in study types, and a limited volume of data supporting each topic. CONCLUSIONS AND CLINICAL IMPLICATIONS: TGCT pathogenesis is influenced by genetic predisposition and exposures during early life. The rising incidence may reflect socioeconomic changes and migration patterns, which determine variation in population exposure to risk factors. TGCT epidemiology remains controversial and requires further research and the implementation of optimal screening programs considering the rising incidence and consequent impact on global health and socioeconomic systems. ADVANCING PRACTICE: What does this study add? . Lien vers l'article

A critical review of a hidden epidemic: examining the occupational and environmental risk factors of chronic kidney disease of unknown etiology (CKDu)
Bradley, M., Land, D., Thompson, D. A. and Cwiertny, D. M., *Environmental Science-Advances*, 2024 Nov 2024.

The global burden of chronic kidney disease (CKD) in terms of mortality and disability-adjusted life years has increased, and this trend is expected to worsen over the next few decades. The primary cause of CKD is known to be due to hypertension and diabetes, however, over the last three decades, a form of CKD has been described in people without any known risk factors. These cases can be described as chronic kidney disease of an unknown etiology (CKDu). Cases of CKDu are rising primarily among rural agricultural communities in affected regions and occur mostly among young male farmers. There is no agreement on whether CKDu in these emerging clusters represents a single disease or a group of different diseases. As such, hypothesized causes of CKDu development include chronic occupational heat stress and dehydration, as well as exposure to environmental contaminants and agrochemicals, such as heavy metals and pesticides. The purpose of this critical review is to bring together the current literature on proposed CKDu etiologies, specifically those related to work in the agricultural sector. This review examines what is known about these occupational and environmental factors and their potential impact on the widespread epidemics of CKDu. https://doi.org/10.1039/d4va00304g

Breast Cancer-Related Chemical Exposures in Firefighters
Cardona, B., Rodgers, K. M., Trowbridge, J., Buren, H. and Rudel, R. A., *Toxics*, Oct 2024, Vol. 12, no. 10.

To fill a research gap on firefighter exposures and breast cancer risk, and guide exposure reduction, we aimed to identify firefighter occupational exposures linked to breast cancer. We conducted a systematic search and review to identify firefighter chemical exposures and then identified the subset that was associated with breast cancer. To do this, we compared the firefighter exposures with chemicals that have been shown to increase breast cancer risk in epidemiological studies or increase mammary gland tumors in experimental toxicology studies. For each exposure, we assigned a strength of evidence for the association with firefighter occupation and for the association with breast cancer risk. We identified twelve chemicals or chemical groups that were both linked to breast cancer and were firefighter occupational exposures, including polycyclic aromatic hydrocarbons, volatile aromatics, per- and polyfluoroalkyl substances, persistent organohalogens, and halogenated organophosphate flame retardants. Many of these were found at elevated levels in firefighting

environments and were statistically significantly higher in firefighters after firefighting or when compared to the general population. Common exposure sources included combustion byproducts, diesel fuel and exhaust, firefighting foams, and flame retardants. Our findings highlight breast-cancer-related chemical exposures in the firefighting profession to guide equitable worker's compensation policies and exposure reduction. https://doi.org/10.3390/toxics12100707

An inhalation exposure assessment of Hexafluoroisobutylene in pregnant rats
Gao, Y. C., Gao, T., Gao, J. H., Liu, Z. Y., Sun, C., Xie, X., Yang, Z., Wu, C. Y., Zou, C., Wang, M. Y., Guo, W. W., Fan, P., Deng, H., Shao, D. Y., Qian, A. R. and Hu, L. F., *Ecotoxicology and Environmental Safety*, Nov 2024, Vol. 287.

Hexafluoroisobutylene (HFIB) is an important compound widely used in semiconductor lithography materials, refrigerants, fluorine coatings, and pharmaceutical intermediates in the fluorination industry. Owing to its toxicity, the occupational exposure in the workplace, especially for pregnant woman is the concern and there is still lack of the data of HFIB toxicity on pregnancy and fetal development. Here, for the first time, we investigated the effects of HFIB on pregnant rats and fetal development. The pregnant rats were exposed to different doses of HFIB (0 ppm, 27.2 ppm, 53.5 ppm, 105.6 ppm) via whole-body inhalation for the period of organogenesis, which from implantation (gestation day 5) to the day prior to scheduled caesarean section (gestation day 19). The results showed that the pregnant rats exposed to 105.6 ppm HFIB displayed systemic toxicity, including a decrease in body weight and food consumption, as well as tracheal inflammation, pulmonary interstitial inflammation and renal tubular swelling. Moreover, reduced fetal and placental weights, delayed ossification, and a reduced number of ossification centers were observed in fetuses delivered by pregnant rats exposed to 105.6 ppm. These effects were attributed to severe maternal weight loss. In addition, it would be useful to note that no whole-body, visceral or skeletal congenital malformations were observed. However, HFIB exposure at 53.5 ppm showed no significant adverse effects on pregnant rats and fetuses. These findings demonstrate that 105.6 ppm HFIB is a toxic concentration, while 53.5 ppm HFIB is the no-observed-adverse-effect concentration (NOAEC) for both pregnancy and fetal development. This study for the first time to provide evidence for the health risk of HFIB exposure on pregnancy and fetal development. https://doi.org/10.1016/j.ecoenv.2024.117273

One-Year Impact of Occupational Exposure to Polycyclic Aromatic Hydrocarbons on Sperm Quality
Pena-Garcia, M. V., Moyano-Gallego, M. J., Gómez-Melero, S., Molero-Payán, R., Rodríguez-Cantalejo, F. and Caballero-Villarraso, J., *Antioxidants*, Oct 2024, Vol. 13, no. 10.

Background: Polycyclic aromatic hydrocarbons (PAHs) have toxic potential, especially as carcinogens, neurotoxins, and endocrine disruptors. The objective of this study is to know the impact of exposure to PAHs on the reproductive health of male workers who operate in solar thermal plants. Methods: Case-control study. A total of 61 men were included: 32 workers exposed to PAH at a solar thermal plant and 29 unexposed people. Seminal quality was studied both at the cellular level (quantity and quality of sperm) and at the biochemical level (magnitudes of oxidative stress in seminal plasma). Results: In exposure to PAHs, a significantly higher seminal leukocyte infiltration was observed, as well as lower activity in seminal plasma of superoxide dismutase (SOD) and a reduced glutathione/oxidised glutathione (GSH/GSSG) ratio. The oxidative stress parameters of seminal plasma did not show a relationship with sperm cellularity, neither in those exposed nor in those not exposed to PAH. Conclusion: One year of exposure to PAH in a solar thermal plant does not have a negative impact on the sperm cellularity of the worker, either quantitatively (sperm count) or qualitatively (motility, vitality, morphology, or cellular DNA fragmentation). However, PAH exposure

is associated with lower antioxidant capacity and higher leukocyte infiltration in seminal plasma. https://doi.org/10.3390/antiox13101181

Male reproductive hormone disorders among copper smelter workers
Samir, A. M., Korany, A. M., Foaad, H. and Manawil, M., *Toxicology and Industrial Health*, 2024, Vol. 40, no. 1-2, p. 52-58.

Male workers in copper smelting are exposed to copper, lead, and arsenic. This study aimed to assess the effects of combined exposure to these metals on male reproductive hormone levels and assesses malondialdehyde (MDA) as an oxidative stress parameter. The study was conducted on 40 copper smelter workers compared with 40 non-exposed workers. Laboratory investigations included levels of serum copper, blood lead, serum arsenic, follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, and MDA. Levels of copper, arsenic, lead, FSH, and LH were significantly increased compared to controls. However, a statistically significant decrease in the mean value of testosterone was found among exposed workers. Positive correlations between serum copper and both serum FSH and MDA levels were statistically significant as were correlations between serum arsenic and MDA levels. Testosterone levels showed significant negative correlations with both copper and arsenic among exposed workers. A linear regression model of copper, arsenic, and lead levels as independent variables with FSH, LH, and testosterone as dependent variables revealed a significant negative association between serum copper and testosterone levels. The current study concluded that combined exposure to copper, arsenic, and lead in secondary copper smelters had a negative impact on male reproductive hormone levels that may be mediated by oxidative stress. https://doi.org/10.1177/07482337231215864

Per- And Poly-Fluoroalkyl Substances (PFAS) Exposure and Risk of Breast, and Female Genital Cancers: A Systematic Review and Meta-Analysis
Seyyedsalehi, M. S., Kappil, E. M., Zhang, S. R., Zheng, T. Z. and Boffetta, P., *Medicina Del Lavoro*, 2024, Vol. 115, no. 6.

Background: PFASs, synthetic chemicals, can be encountered by humans through occupational or environmental exposure, and some reports suggest that they can disrupt endocrine and hormonal activities. In this comprehensive review and meta-analysis, we explored the connection between exposure to PFASs and the risks of breast and female genital cancers. Methods: We systematically reviewed the literature from IARC Monographs, ATSDR documents, and PubMed (as of January 2024) for cohort, case-control, and ecological studies on PFAS exposure and breast or female genital cancers. Four reviewers independently screened studies, and data extraction included study design, patient characteristics, and ejfect size measures. The quality of studies was assessed using the modified version of the Newcastle-Ottawa Scale (NOS). Forest plots of relative risks (RR) were constructed for breast and female genital cancer. Meta-analyses were conducted using random-ejfects models, stratified analyses, dose-response assessments, and publication bias evaluation. Results: The meta-analysis included 24 studies, comprising 10 cohort, 13 case-control, and one ecological study. The summary relative risk (RR) of breast cancer for PFOA exposure was 1.08 (95% CI = 0.97-1.20; n=21), and for PFOS was 1.00 (95% CI = 0.85-1.18; n=12). The RR for ovarian cancer and PFAS was 1.07 (95% CI = 1.04-1.09; n=12). The stratification by quality score, year of publication, and exposure source did not reveal any dijferences. However, analysis by geographical region (p=0.01) and study design (p=0.03) did show dijferences, particularly in terms of incidence. Stratified analyses of the dose-response relationship did not reveal a trend in the risk of breast cancer or female genital cancers, and no publication bias was found for either cancer type. No results were available for cervical and endometrial cancers. Conclusion: In summary, our results suggest an association between PFAS exposure and ovarian cancer and a possible ejfect on breast cancer incidence in some

specific groups. However, bias and confounding cannot be excluded and prevent conclusions regarding causality. https://doi.org/10.23749/mdl.v115i6.16330

Occupational exposure to pesticides affects systemic cytokine profile and correlates with poor clinical prognosis in young women with breast cancer
Silva, R., Fagundes, T. R., Coradi, C., Pires, B. R. B., Berne, M. P., Smaniotto, L. L., De Almeida, R. F., Rech, D. and Panis, C., *Immunopharmacology and Immunotoxicology*, Jan 2025, Vol. 47, no. 1, p. 34-41.

Objective: Aging is one of the main risk factors for breast cancer. However, the impact of environmental risk factors, such as pesticide exposure, on the clinical outcomes of patients with breast cancer, depending on disease onset, remains unclear. Material and Methods: This study analyzed clinicopathological data from 188 women with breast cancer, who were either occupationally or domestically exposed to pesticides, or not exposed, according to their age at disease onset (early onset <= 50 years and late onset >50 years). Additionally, interleukin 4 (IL-4), interleukin 17A (IL-17A), and interleukin 12 (IL-12) levels were measured in plasma samples, and clinicopathological data were assessed. Results: In the late-onset group, a greater frequency of low-grade tumors was detected in the exposed patients compared to the unexposed group (23.14 vs. 45.45%, p = 0.0181). A higher frequency of high-risk stratification for recurrence and death was found in early-onset patients when comparing exposed and unexposed groups (10.0 vs. 30.0%, p = 0.0488). Regarding the molecular subtypes of breast cancer, patients in the late-onset group showed a higher frequency of triple-negative tumors than unexposed women with the same disease onset (20.0 vs. 40.63%, p < 0.0001). IL-12 levels were significantly lower in exposed patients in the early-onset group compared to unexposed patients in the same group. Early-onset patients showed a principal component that positively correlated with pesticide exposure, IL-1 beta, IL-17A, and IL-4, while late-onset patients showed negative correlations between pesticide exposure and IL-12, IL-4, and IL-17A. Discussion and Conclusions: These findings suggest that pesticide exposure induces an inflammaging-like state in younger women, contributing to an increased risk of developing more severe disease. https://doi.org/10.1080/08923973.2024.2430665

Occupational exposure to low-level lithium and thyroid dysfunction
Won, Y. L., Lee, H., Choi, J., Park, Y. and Lee, S. G., *Toxicology Letters*, Sep 2024, Vol. 399, p. S342-S342.

Lithium is the main ingredient in the most preferred medications to treat bipolar disorder. The most common side effects of overdosing on lithium drugs include weight gain, polyuria and tremor[1]. Long-term use of lithium may cause hypothyroidism[2]. The side effects of taking lithium as a medicine are well known, but there is a lack of data on the health effects of long-term occupational exposure to low-level lithium. Blood and urine were collected from 310 male workers at two lithium-handling workplaces and 75 male workers at one non-lithium-handling workplace, and lithium in urine and thyroid stimulating hormone, free T4, and T3 in blood were analyzed. Logistic regression analysis was performed on urinary lithium concentration based on the median, and thyroid hormone concentration divided into whether it exceeded the reference value or not. The average age of study participants was 34.3 years, and the average period of current work performance was 26.4 months. The average urinary lithium concentration of workers at two workplaces that handled lithium and one workplace that did not handle lithium was 146.1, 55.3, and 28.5 µg/L, respectively. The average thyroid stimulating hormone concentrations were 2.21, 1.55, and 1.57 mIU/L, respectively, and the rates exceeding the reference value (0.27~4.20) were 18.2% (30/165), 8.3% (12/145), and 4.0% (3/75), respectively. Free T4 and T3 showed no significant differences between workplaces. Based on the median urinary lithium concentration, the odds ratio for exceeding the thyroid stimulating

hormone reference value was 2.4. There were 45 workers who exceeded the thyroid stimulating hormone reference value, and 42 (93.3%) were workers in industries that handle lithium, and the rate of exceeding the reference value was highest in the group with high urinary lithium concentration. Subclinical Hypothyroidism cannot be diagnosed based on a single increase in thyroid stimulating hormone concentration. However, we cannot rule out the possibility that the increase in thyroid stimulating hormone concentration in the study subjects was due to lithium inhaled during work. Additional observations are needed to clearly determine the relationship between long-term occupational exposure to low-level lithium and thyroid function.
https://doi.org/10.1016/j.toxlet.2024.07.815

Occupational Exposure to 50 ppm Isoflurane Impairs Sperm Parameters in Mice
Zanin, M., Varela, A. S., Jr., Acosta, I. B., Da Silva, E. A., Dode, M. E. B., Gehrcke, M. I., Braz, M. G. and Corcini, C. D., *Journal of Occupational and Environmental Medicine*, Dec 2024, Vol. 66, no. 12, p. 978-986.

The aims of the study are to assess the effect of occupational exposure to isoflurane on the sperm quality of mice and to investigate whether cessation of exposure can restore seminal quality. Mice were exposed to 50 ppm of isoflurane for 5 hours per day over a 30-day period. Following this exposure, they were euthanized at predetermined postexposure intervals, and their sperm samples were analyzed for kinetics and viability parameters. Occupational exposure to isoflurane can adversely affect sperm at 50 ppm, a concentration deemed safe by international occupational health conventions in some countries. These effects are marked by oxidative stress, mitochondrial dysfunction, and genomic damage, alongside alterations in sperm kinetics and acrosomal integrity. Furthermore, cessation of exposure does not guarantee restoration of cellular quality. Isoflurane at 50 ppm, previously deemed safe by some countries, impairs sperm kinetics and viability, potentially directing the spermatogenic process toward infertility and apoptosis.
https://doi.org/10.1097/jom.0000000000003218

Epidémiologie

Linking EDC-laden food consumption and modern lifestyle habits with preeclampsia: A non-animal approach to identifying early diagnostic biomarkers through biochemical alterations
Balu, U. R., Vasantharekha, R., Paromita, C., Ali, K., Mudgal, G., Kesari, K. K. and Seetharaman, B., *Food and Chemical Toxicology*, Dec 2024, Vol. 194.

Preeclampsia (PE), a pregnancy complication characterized by new-onset hypertension with or without proteinuria and/or end-organ damage, and it may be influenced by exposure to endocrine-disrupting chemicals present in processed foods and modern lifestyles. This study explores the potential link using a non-animal approach to identify early diagnostic biomarkers for preeclampsia. Seventy pregnant women aged 21-41 years participated, and completed questionnaires assessing socio-demographic factors, Suboptimal Health Status Questionnaire scores for fatigue, digestive, cardiovascular, immune, and mental health issues, and exposure to endocrine-disrupting chemicals from processed food consumption and daily product use. Peripheral blood samples were analyzed for hormone profiles, complete blood count, and liver function tests (LFT). Statistical analysis revealed that mothers above 27 years old, with a Body Mass Index exceeding 32.59 Kg/m2, and a Mean Arterial Pressure of 108.5 mmHg exhibited a potential obesogenic effect on preeclampsia development. Socio-demographic factors like, lower economic class, housewife status, primiparous pregnancy, non-graduate education, and rural residence were significantly associated with results. Analysis of biochemical parameters revealed that serum creatinine, blood urea, total protein, platelet count,

blood urea nitrogen, bilirubin profile, LFT profile, and thyroid profile showed potential detrimental effects on kidney, liver, muscle, and thyroid function in preeclampsia patients. Notably, PC, serum urea, bilirubin, total protein, serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase (ALP), and thyroid stimulating hormone (TSH) levels were significantly associated with preeclampsia in individuals reporting higher exposure to endocrine disrupting chemicals (EDCs). Minor biochemical alterations were also observed with dairy product consumption. SHS-25 analysis indicated a significant increase in fatigue, and digestive, cardiovascular, immune, and mental health-related issues in patients. Probably, biochemical alterations due to EDC exposure from processed foods and modern lifestyle habits contribute to organ dysfunction in preeclampsia. Identifying these potential biomarkers may pave the way for the development of non-invasive, early diagnostic tools for improved preeclampsia management. This research emphasizes the importance of non-animal testing methods for assessing EDC-related health risks in pregnancy and contributes to the advancement of early PE diagnosis strategies. https://doi.org/10.1016/j.fct.2024.115073

Adolescent urinary concentrations of phthalate metabolites and indices of overweight and cardiovascular risk in Dutch adolescents
Berghuis, S. A., Bocca, G., Bos, A. F., Van Faassen, M., Foreman, A. B., Van Vliet-Ostaptchouk, J. V. and Sauer, P. J. J., *Environment International*, Dec 2024, Vol. 194.

Phthalates have been linked to cardiovascular risk factors. Exposure to chemicals with endocrine disrupting properties during the pubertal period can interfere with normal endocrine processes. This study aims to determine whether adolescent urinary concentrations of phthalate metabolites are associated with indices of overweight and cardiovascular risk in 13-15-year-old children. In this Dutch observational cross-sectional cohort study, 101 adolescents were included (mean age 14.4 +/- 0.8 years), 55 were boys. The concentrations of 13 phthalate metabolites were measured in morning urine samples. Levels of cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, fasting insulin, fasting glucose, leptin, and adiponectin were measured. The children's height, weight, waist circumference, hip circumference, and blood pressure were measured. Higher urinary mono-ethyl phthalate concentrations were associated with higher BMI and a larger hip circumference. In girls, higher urinary mono-hydroxy-iso-nonyl phthalate concentrations were associated with higher levels of lipids and obesogenic traits. In boys, higher concentrations of urinary phthalate metabolites were associated with lower LDL-C. The results of this explorative study suggest that higher levels of phthalate metabolites are associated with higher levels of lipids and obesogenic traits in 13-15-year-old girls. https://doi.org/10.1016/j.envint.2024.109167

Can lifestyle changes significantly improve male fertility: A narrative review?
Bocu, K., Boeri, L., Mahmutoglu, A. M. and Vogiatzi, P., *Arab Journal of Urology*, 2024 Nov 2024.

Male infertility is increasingly recognized as a significant global health concern, with lifestyle factors being critical contributors to declining male fertility rates. This narrative review comprehensively analyzes the impact of various lifestyle choices, including diet, physical activity, substance use, stress, sleep, weight management, sexual habits, and environmental and occupational exposures on male reproductive health. The review examines the biological and ecological mechanisms through which these lifestyle factors affect spermatogenesis and sperm quality. Furthermore, it discusses potential interventions, such as dietary modifications, weight management strategies, substance cessation programs, stress reduction techniques, and workplace policy changes to improve male fertility outcomes. Emphasis is placed on the role of oxidative stress, hormonal regulation, and DNA integrity in mediating the effects of these lifestyle factors. While lifestyle modifications can significantly enhance male reproductive health, the available evidence highlights the need for more rigorous

research to establish solid guidelines and interventions for mitigating male infertility. https://doi.org/10.1080/20905998.2024.2421626

Associations of endocrine disrupting chemicals with renal function in older individuals
Chen, J. Y., Wang, Y., Zhao, Z. X., Deng, Y., Wang, T. Y., Xiang, Y. T., Wang, Y. T., Chen, J. M. and He, M., *Hygiene and Environmental Health Advances*, Sep 2024, Vol. 11.

Background: Since the twentieth century, endocrine-disrupting substances (EDCs) such as phthalates and organophosphates have been utilised in various goods. The long-term usage of these products may have negative effects on people's health. Most EDCs are metabolized through kidneys, but there are few research investigating renal damage from exposure to EDCs in the elderly. This study aims to examine the effects of EDCs exposure on renal function in the elderly population. Methods: In this cross-sectional study, a total of 200 elder from a community in northeast China were enrolled. All subjects were investigated by questionnaire, physical examination, and biological sample collection. Estimated glomerular filtration rate (eGFR) was used to classify renal function group. Lasso regression was used to screen out the EDCs related to renal function. After covariate adjustment, binary logistic regression was used to analyze the relationship between decreased renal function and EDCs. Weighted quantile sum (WQS) regression was used to assess the association of combined-EDCs with decreased renal function, subgroup analyses were performed to identify potentially sensitive populations to the effects of EDCs on decreased renal function. Results: Binary logistic regression showed that 3,5-di-tert-butyl-4-hydroxybenzoic acid (BHT-COOH), Mono(3carboxypropyl) phthalate (MCPP), and Methyl paraben (MeP) were negatively associated with decreased renal function, with odds ratio (OR) and 95% confidence intervals of 0.591 (0.366, 0.954), 0.990 (0.981, 0.999) and 0.997 (0.995, 0.999), respectively. WQS regression found DPP (Weights = 22.5%) to have the greatest effect on decreased renal function in the elderly. Moreover, significant potential interactions were observed among MEHP&MOcP with hypertension on decreased renal function (Pinteraction = 0.014), as well as BPS and MEHP&MocP with Overweight/obesity on decreased renal function (Pinteraction = 0.032, 0.024). Conclusions: BHT-COOH, MCPP, and MeP were negatively associated with decreased renal function in the elderly. Elders with hypertension and who are overweight /obesity may be more sensitive to EDCs. https://doi.org/10.1016/j.heha.2024.100098

Gestational phthalate exposure and behavioral problems in preschool-aged children with increased likelihood of autism spectrum disorder
Choi, J. W., Bennett, D. H., Calafat, A. M., Tancredi, D. J., Miller, M., Schmidt, R. J. and Shin, H. M., *International Journal of Hygiene and Environmental Health*, Jan 2025, Vol. 263.

Background: Experimental studies have shown associations between gestational phthalate exposure and behavioral problems among offspring; however, epidemiological evidence is still mixed. This study aims to investigate whether gestational phthalate exposure is associated with behavioral problems in preschool-aged children. Methods: Participants include 178 mother-child pairs from MARBLES (Markers of Autism Risk in Babies - Learning Early Signs), a cohort with high familial likelihood of autism spectrum disorder (ASD). We quantified 14 phthalate metabolites in multiple maternal urine samples collected during the 2nd and 3rd trimesters. Preschool behavior problems were assessed using the Child Behavioral Checklist (CBCL), a standardized instrument for evaluating behavior problems of children aged 1.5-5 years. To examine associations of CBCL scores with both individual phthalate biomarker concentrations and their mixture, we used negative binomial regression and weighted quantile sum regression. Results: Overall, maternal phthalate biomarker concentrations were not associated with child behavior problems. Monoisobutyl phthalate (MiBP) concentrations were inversely associated with child anxious/depressed symptoms and somatic complaints. Mono-hydroxy-isobutyl phthalate (MHiBP) and monobenzyl phthalate (MBzP) were also

inversely associated with somatic complaints. When assessing trimester-specific associations, more behavior problems were associated with the 2nd trimester biomarker concentrations: mono(3-carboxypropyl) phthalate (MCPP) and monocarboxyisononyl phthalate (MCNP) were positively associated with somatic complaints. All associations became non-significant after false discovery rate correction. No association between a mixture of phthalates and CBCL scores was found. Conclusions: Our study observed no clear evidence of gestational phthalate exposure on child behavior problems. However, our findings based on the biomonitoring assessment of multiple samples per participant could improve our understanding of gestational phthalate exposure in association with behavior problems in preschool-aged children. https://doi.org/10.1016/j.ijheh.2024.114483

Effects of fine particulate matter mass and chemical components on oxidative DNA damage in human early placenta

Chu, M. Y., Yang, J. N., Gong, C., Li, X. S., Wang, M. Y., Han, B., Huo, Y., Wang, J. M., Bai, Z. P. and Zhang, Y. J., *Environmental Research*, Dec 2024, Vol. 263.

The effects of chemical components of ambient fine particulate matter (PM2.5) 2.5) on human early maternal-fetal interface are unknown. We estimated the associations of PM 2.5 and component exposures with placental villi 8hydroxy-2 '-deoxyguanosine '-deoxyguanosine (8-OHdG) in 142 normal early pregnancy (NEP) and 142 early pregnancy loss (EPL) from December 2017 to December 2022. We used datasets accessed from the Tracking Air Pollution in China platform to estimate maternal daily PM 2.5 and component exposures. Effect of average PM 2.5 and component exposures during the post-conception period (i.e., from ovulation to villi collection) on the concentration of villi 8-OHdG were analyzed using multivariable linear regression models. Distributed lag and cumulative effects of PM 2.5 and component exposures during the periovulatory period and within ten days before villi collection on villi 8-OHdG were analyzed using distributed lag non-linear models combined with multivariable linear regression models. Per interquartile range increase in average PM2.5, 2.5 , black carbon (BC), and organic matter (OM) exposures during the post-conception period increased villi 8-OHdG in all subjects (/I = 34.48% [95% CI : 9.33%, 65.42%], /I = 35.73% [95% CI : 9.08%, 68.89%], and /I = 54.71% [95% CI : 21.56%, 96.91%], respectively), and in EPL (/I = 63.37% [95% CI : 16.00%, 130.10%], /I = 47.43% [95% CI : 4.30%, 108.39%], and /I = 72.32% [95% CI : 18.20%, 151.21%], respectively), but not in NEP. Specific weekly lag effects of PM2.5, 2.5 , BC, and OM exposures during the periovulatory period increased villi 8-OHdG in all subjects. Ten-day cumulative and lag effects of PM2.5, 2.5 , BC, and OM increased villi 8-OHdG in all subjects and EPL, but not in NEP; and the effects of OM were robust after adjusting for BC, ammonium, nitrate, or sulfate in two-pollutant models. In conclusion, placental oxidative DNA damage in early pregnancy was associated with maternal exposure to PM2.5, 2.5 , especially its chemical components BC and OM. https://doi.org/10.1016/j.envres.2024.120136

Dietary bisphenols exposure as an influencing factor of body mass index

Gálvez-Ontiveros, Y., Monteagudo, C., Giles-Mancilla, M., Muros, J. J., Almazán, V., Martínez-Burgos, M. A., Samaniego-Sánchez, C., Salcedo-Bellido, I., Rivas, A. and Zafra-Gómez, A., *Environmental Health*, Oct 2024, Vol. 23, no. 1.

Background Over the past three decades, there has been a significant increase in the prevalence and incidence of overweight and obesity worldwide. The obesogen hypothesis suggests that certain external agents may affect pathways related to fat accumulation and energy balance by stimulating fat cell differentiation and proliferation. Previous research has indicated that exposure to bisphenol A (BPA) and some of its analogues may influence fat accumulation by promoting the transformation of preadipocytes into adipocytes. This study aimed to assess the possible contribution of dietary bisphenol exposure to the odds of developing overweight and obesity in a sample of Spanish children

according to sex. Methods Dietary and anthropometric data were collected from 179 controls and 124 cases schoolchildren aged 3-12 years. Dietary exposure to BPA and bisphenol S (BPS) was assessed using a food consumption frequency questionnaire. Logistic regression models were used to assess the influence of dietary exposure to bisphenols on overweight and obesity stratified by sex. Results For females, cases had significantly higher exposure to BPA from meat and eggs compared to controls (median = 319.55, interquartile range (IQR) = 176.39-381.01 vs 231.79 (IQR) = 162.11-350.19, p-value = 0.046). Diet quality was higher for controls (6.21 (2.14) vs 4.80 (2.24) p < 0.001) among males independently of a high or low exposure to bisphenols. However, higher diet quality was observed for female controls with an high exposure of total bisphenols (6.79 (2.04) vs 5.33 (2.02) p = 0.031). Females exposed to high levels of BPA from meat and eggs had higher likelihood of being overweight and obese (adjusted Odds Ratio = 2.70, 95% confidence interval = 1.00 - 7.32). However, no consistent associations were found in males. Conclusions High BPA levels from meat and eggs were positively associated with overweight and obesity in females. The dietary intake of BPA in the schoolchildren in the present study was much higher than the acceptable daily intake established by EFSA for the last year. https://doi.org/10.1186/s12940-024-01134-7

Environmental exposures and fecundability: The Norwegian Mother, Father, and Child Cohort study

Grindstad, T., Håberg, S. E., Basso, O., Hanevik, H. I., Caspersen, I. H., Arge, L. A., Ramlau-Hansen, C. H., Myrskyla, M. and Magnus, M. C., *International Journal of Hygiene and Environmental Health*, Jan 2025, Vol. 263.

Previous studies have linked certain environmental exposures to reduced fecundability, influencing exposure recommendations. We continue to encounter numerous environmental exposures in our everyday lives, and further evidence is needed regarding their effects on fecundability. We evaluated associations between various self-reported environmental exposures and fecundability, measured as time to pregnancy, in 64,942 women and 53,219 men participating in the Norwegian Mother, Father, and Child Cohort study (MoBa). Women reported on 17, and men on 19, environmental exposures, including heavy metals, pesticides, paints, and radiation. Fecundability ratios (FR) were estimated using log-binomial regression, comparing likelihood of conception during a given menstrual cycle between exposed versus unexposed participants. About 50 % of women and 75 % of men reported minimum one environmental exposure. Exposure to any pesticide (FR 0.94 [95 % CI 0.91-0.98]), and frequent exposure to photographic chemicals (FR 0.84 [95 % CI: 0.73-0.96]), was associated with decreased fecundability in women. We also observed a tendency of a slightly higher fecundability among women and men exposed to disinfectants (FR 1.02 [95 % CI: 1.00-1.04] and 1.03 [95 % CI: 1.00-1.06], respectively). Our results suggests that exposure to pesticides and photographic chemicals could affect women's fecundability. https://doi.org/10.1016/j.ijheh.2024.114492

Relationship between per-fluoroalkyl and polyfluoroalkyl substance exposure and insulin resistance in nondiabetic adults: Evidence from NHANES 2003-2018

Jia, P., Yu, X. W., Jin, Y. X., Wang, X., Yang, A. L., Zhang, L., Jing, X. R., Kang, W. W., Zhao, G. H. and Gao, B., *Ecotoxicology and Environmental Safety*, Nov 2024, Vol. 287.

Background: Studies have linked per- and polyfluoroalkyl substances (PFAS) to chronic metabolic diseases. However, the relationship between PFAS exposure and insulin resistance (IR), a key pathophysiological basis of these metabolic diseases, in nondiabetic individuals have yet to be determined. Methods: This study analyzed data from 3909 participants (aged >= 20) from the NHANES 2003-2018 to investigate the associations between serum levels of seven PFAS and and IR indicators, including including HOMA-IR, HOMA-(3, fasting insulin, QUICKI, and TyG index. Linear and logistic regression models were used, along with a restricted cubic spline to assess dose-response.

Weighted quantile sum (WQS) regression and quantile gcomputation (qgcomp) models were used to assess the association between mixed PFAS exposure and IR. Results: Linear regression revealed that elevated exposure to PFOS [(3 (95 % CI): 0.04 (0.02, 0.06)], PFOA [0.04 (0.01, 0.06)], and Me_PFOSA_AcOH [0.04 (0.02, 0.06)] was associated with a higher TyG index in adults. Notably, Me_PFOSA_AcOH was negatively associated with IR when assessed by HOMA-IR >2.6 [OR (95 % CI): 0.88 (0.79, 0.98)], although this was not supported by linear regression findings. When IR was defined by a TyG index >8.6, exposure to the highest quartiles of PFOS, PFOA, and Me_PFOSA_AcOH was associated with an increased risk of IR by 63 %, 42 %, and 85 %, respectively [1.63 (1.21, 2.20); 1.42 (1.06, 1.92); 1.85 (1.37, 2.50)]. PFOS, PFOA, and Me_PFOSA_AcOH demonstrated a nonlinear dose-response relationship with IR risk. The WQS and qgcomp models revealed significant positive correlations with the TyG index. Conclusion: Mixed PFAS exposure in US nondiabetic adults was positively associated with IR, as indicated by the TyG index, particularly for PFOS, PFOA, and Me_PFOSA_AcOH. Further research is needed to establish causality, and reinforcing environmental risk mitigation strategies to reduce PFAS exposure is recommended. https://doi.org/10.1016/j.ecoenv.2024.117260

Urinary mycoestrogens and gestational weight gain in the UPSIDE pregnancy cohort
Kinkade, C. W., Rivera-Núñez, Z., Brinker, A., Buckley, B., Waysack, O., Kautz, A., Meng, Y., Strickland, P. O., Block, R., Groth, S. W., O'connor, T. G., Aleksunes, L. M. and Barrett, E. S., *Environmental Health*, Nov 2024, Vol. 23, no. 1.

Background Zearalenone (ZEN), a secondary metabolite of Fusarium fungi, is one of the most common mycotoxins in global food supplies such as cereal grains and processed food. ZEN and its metabolites are commonly referred to as mycoestrogens, due to their ability to directly bind nuclear estrogen receptors alpha (ER-alpha) and beta (ER-beta). Zeranol, a synthetic mycoestrogen, is administered to U.S. cattle as a growth promoter. Despite widespread human exposure and ample evidence of adverse reproductive impacts in vitro and in vivo, there has been little epidemiological research on the health impacts of ZEN exposure during pregnancy. The objective of our study was to examine associations between ZEN and gestational weight gain (GWG). Methods Urine samples were collected in each trimester from pregnant participants in the UPSIDE cohort (n = 286, Rochester, NY, USA). High performance liquid chromatography and high-resolution tandem mass spectrometry were used to quantify concentrations of ZEN as well as & sum;mycoestrogens (composite sum of ZEN metabolites; ng/ml). Maternal weights at clinical visits were abstracted from medical records. We fitted longitudinal models of specific-gravity adjusted, log-transformed ZEN and & sum;mycoestrogens in relation to total GWG (kilograms) and GWG rate (kilograms/week). We additionally examined risk of excessive GWG (in relation to Institute of Medicine guidelines) and considered effect modification by fetal sex. Results ZEN and & sum;mycoestrogens were detected in > 93% and > 95% of samples, respectively. Mycoestrogen concentrations were positively associated with total GWG (ZEN beta:0.50 kg; 95%CI: 0.13, 0.87) and GWG rate (ZEN beta:0.20 kg/week; 95%CI: 0.01, 0.03). Associations tended to be stronger among participants carrying male (versus female) fetuses and results were robust to adjustment for diet. Conclusions Mycoestrogen exposure during pregnancy may contribute to greater GWG. Future research is needed to understand potential influences on downstream maternal and offspring health. https://doi.org/10.1186/s12940-024-01141-8

Combined effects and potential mechanisms of phthalate metabolites on serum sex hormones among reproductive-aged women: An integrated epidemiology and computational toxicology study
Li, X. Q., Zheng, N., Zhang, W. H., Yu, Y., Li, Y. Y., Sun, S. Y., Ji, Y. N. and Wang, S. J., *Ecotoxicology and Environmental Safety*, Dec 2024, Vol. 288.

The reproductive age is a crucial stage for women to bear offspring. However, reproductive-aged women are simultaneously exposed to various phthalates, which may pose a threat to their reproductive health. This study employed generalized linear regression and weighted quantile sum (WQS) regression to explore the associations between monoesters of phthalates (MPAEs) and sex hormones in 913 reproductive-aged women in the National Health and Nutrition Examination Survey. Key risk factors driving hormone disruption were identified based on the weights of the WQS models. Interaction models were used to unravel the synergistic or antagonistic effects between MPAEs. The potential toxicological targets of MPAEs interfering with sex hormone-binding globulin (SHBG) levels were revealed based on prior knowledge and molecular docking of hepatocyte nuclear factor 4 alpha (HNF4 alpha). Compared with the first quartile, mono-benzyl phthalate (MBZP) in the second quartile exhibited a decrease in total testosterone (TT) and TT/E2 (estradiol) ratio. Mono-2-ethyl-5-carboxypentyl phthalate (MECPP) in the fourth quartile showed a decrease in SHBG and TT/E2. Additionally, mono-(carboxyoctyl) phthalate and mono-(carboxynonyl) phthalate (MCNP) were negatively associated with SHBG. Each unit increase in the WQS index of MPAE mixtures was associated with 6.73 % lower SHBG levels (95 %CI: - 12.80 %, -0.24 %) with mono-(3-carboxypropyl) phthalate, MCNP, MBZP, and MECPP identified as major risk factors. Interaction analyses revealed that the effects of high-risk MPAEs on SHBG were predominantly antagonistic. Molecular docking suggested that MPAEs might compete to bind tryptophan residues of HNF4 alpha. This study provides key information to help develop the most effective phthalate interventions and improve the reproductive health of reproductive-aged women. https://doi.org/10.1016/j.ecoenv.2024.117353

Endocrine disruptors and bladder function: the role of phthalates in overactive bladder
Liu, L., Li, X., Hao, X. X., Xu, Z. N., Wang, Q. H., Ren, C. Z., Li, M. W. and Liu, X. Q., *Frontiers in Public Health*, Dec 2024, Vol. 12.

Phthalates, widely used as plasticizers, are pervasive environmental contaminants and endocrine disruptors. Their potential role in overactive bladder (OAB) pathogenesis is underexplored, necessitating further investigation into their impact on OAB using large-scale epidemiological data. This study utilized data from the National Health and Nutrition Examination Survey (NHANES) spanning from 2011 to 2018. A weighted multivariable logistic regression model was employed to examine the relationship between urinary phthalate concentrations and OAB. Subgroup analyses were conducted to explore differences in associations across various subgroups. Restricted cubic spline (RCS) analysis was used to investigate the potential non-linear relationship between urinary phthalate concentrations and OAB. Additionally, Bayesian Kernel Machine Regression (BKMR) analysis was performed to explore the overall effects and interactions of phthalate mixtures. In the multivariable logistic regression model fully adjusted for confounding variables, higher concentrations of MBzP and MiBP were associated with an increased risk of OAB, particularly in the highest tertiles (MBzP: OR = 1.401, 95% CI: 1.108-1.771; MiBP: OR = 1.050, 95% CI: 1.045-1.056). Subgroup analysis found that subgroup characteristics did not have a significant moderating effect on the association between phthalates and OAB. RCS analysis revealed a linear relationship between both MBzP and MiBP and OAB. BKMR analysis confirmed a positive overall effect of phthalate mixtures on OAB risk, with MBzP identified as the major contributing factor. In our study cohort, a positive correlation between urinary phthalate concentrations and OAB was observed, necessitating further research to validate and refine this conclusion. https://doi.org/10.3389/fpubh.2024.1493794

Inhaled toxins: A threat to male reproductive health
Mohammadzadeh, M., Khoshakhlagh, A. H., Calderón-Garcidueñas, L., Maya, W. D. C. and Cai, T. M. S., *Ecotoxicology and Environmental Safety*, Nov 2024, Vol. 286.

Exposure to air pollutants is known to be an important risk factor in reducing semen quality in men across the world. Poor semen quality results in decline in the global fertility rate and significant personal stress, dysfunctional sexual relationships, and psychosocial problems. Continuous monitoring and effective efforts to reduce air pollution in industries and the environment and making positive changes in daily lifestyle can prevent adverse effects on semen quality and reduce the high prevalence of men infertility. This review aims to summarize studies associating pollutant concentrations of polycyclic aromatic hydrocarbons (PAHs), formaldehyde (FA), and BTEX (benzene, toluene, ethyl-benzene, and xylene) on semen quality. In this systematic review, Scopus, PubMed and Web of Science databases were searched until November 13, 2022. The PECO statement was formulated to clarify the research question, and articles that did not satisfy the criteria outlined in this statement were excluded. Generally, 497 articles were obtained through searching databases, and after the investigations, 26 articles that met the entry criteria were extracted and finally considered in the systematic review. The results showed that occupational and environmental exposures to PAHs, formaldehyde, and BTEX were associated with increased metabolite concentration of toxic pollutants in body fluids. These toxin-associated pollutants directly or indirectly cause detrimental effects on sperm motility, vitality, DNA fragmentation, and morphology. There is evidence on the impact of PAHs, formaldehyde, and BTEX pollutants on the reduction of semen quality. Therefore, proving the relationship between air pollutants and testicular function in semen quality can play an effective role in macro policies and adopting stricter laws to reduce the emission of air pollutants and promote a healthy lifestyle to improve reproductive health in young men. https://doi.org/10.1016/j.ecoenv.2024.117178

Exploring the role of genetic variability and exposure to bisphenols and parabens on excess body weight in Spanish children

Ramírez, V., Gálvez-Ontiveros, Y., De Bobadillae, V. a. F., González-Palaciosa, P., Salcedo-Bellido, I., Samaniego-Sánchez, C., Alvarez-Cuberob, M. J., Martínez-Gonzálezbh, L. J., Zafra-Gómez, A. and Rivas, A., *Ecotoxicology and Environmental Safety*, Nov 2024, Vol. 286.

Gene-environment interaction studies are emerging as a promising tool to shed light on the reasons for the rapid increase in excess body weight (overweight and obesity). We aimed to investigate the influence of several polymorphisms on excess weight in Spanish children according to a short- and long-term exposure to bisphenols and parabens, combining individual approach with the joint effect of them. This case-control study included 144 controls and 98 cases children aged 3-12 years. Thirty SNPs in genes involved in obesity-related pathways, xenobiotic metabolism and hormone systems were genotyped using the GSA microchip technology and qPCRs with Taqman (R) probes. Levels of bisphenols and parabens in urine and hair were used to assess short- and long-term exposure, respectively, via UHPLC-MS/MS system. LEPR rs9436303 was identified as a relevant risk variant for excess weight (ORDom:AAvsAG+GG=2.65, p<0.001), and this effect persisted across exposure-stratified models. For long-term exposure, GPX1 rs1050450 was associated with increased excess weight at low single paraben exposure (ORGvsA=2.00, p=0.028, p-interaction=0.016), whereas LEPR rs1137101 exhibited a protective function at high co-exposure (ORDom:AAvsAG+GG=0.17, p=0.007, p-interaction=0.043). ESR2 rs3020450 (ORDom:GGvsAG+AA=5.17, p=0.020, p-interaction=0.028) and CYP2C19 rs4244285 (ORDom:GGvsAG+AA=3.54, p=0.039, p-interaction=0.285) were identified as predisposing variants at low and high co-exposure, respectively. In short-term exposure, higher odds were observed for INSIG2 rs7566605 at high bisphenol exposure (ORCvsG=2.97, p=0.035, p-interaction=0.017) and for GSTP1 rs1695 at low levels (ORDom:AAvsAG+GG=5.38, p=0.016, p-interaction=0.016). At low and medium co-exposure, SH2B1 rs7498665 (ORAvsG=0.17, p=0.015, p-interaction=0.085) and MC4R rs17782313 (ORAvsG=0.10, p=0.023, p-interaction=0.045) displayed a protective effect, whereas ESR2 rs3020450 maintained its contributing role (ORGvsA=3.12, p=0.030, p-interaction=0.010). Our findings demonstrate for the first time that understanding the genetic

variation in excess weight and how the level of exposure to bisphenols and parabens might interact with it, is crucial for a more in-depth comprehension of the complex polygenic and multifactorial aetiology of overweight and obesity. https://doi.org/10.1016/j.ecoenv.2024.117206

Prenatal exposure to endocrine disrupting chemicals and the association with behavioural difficulties in 7-year-old children in the SELMA study
Stratmann, M., Özel, F., Marinopoulou, M., Lindh, C., Kiviranta, H., Gennings, C. and Bornehag, C. G., *Journal of Exposure Science and Environmental Epidemiology*, 2024 Dec 2024.

Endocrine disrupting chemicals (EDCs) can cross the placenta and thereby expose the fetus, which may lead to developmental consequences. It is still unclear which chemicals are of concern regarding neurodevelopment and specifically behaviour, when being exposed to a mixture. The objective is to determine associations between prenatal exposure to EDCs and behavioural difficulties. Furthermore, we investigated sex-specific associations and determined chemicals of concern in significant regressions. Associations between prenatal exposure to EDCs (both as single compounds and their mixtures) and behavioural outcomes using the Strengths and Difficulties Questionnaire (SDQ) were estimated in 607 mother-child pairs in the Swedish Environmental Longitudinal, Mother and Child, Asthma and Allergy (SELMA) study. Levels for chemical compounds were measured in either urine or serum (median of 10 weeks of gestation). Associations were estimated for the total SDQ score (quasipoisson regression) and a 90th percentile cut-off (logistic regression). Exposure for EDC mixtures (phenols, phthalates, PFAS and persistent chlorinated) was studied using weighted quantile sum (WQS) regression with deciles and with and without repeated holdout validation techniques. The models were adjusted for selected covariates. The odds for behavioural difficulties increased in girls with higher chemical exposures (OR 1.77, 95% CI 1.67, 1.87) using the full sample and borderline for the validation set (OR 1.31, 95% CI 0.93, 1.85) with 94/100 positive betas in the 100 repeated holdout validations. Chemicals of concern for girls are mostly short-lived chemicals and more specifically plasticizers. No pattern of significant associations was detected for boys. There is an indication of increased behavioural difficulties for girls in the SELMA population with higher exposure to mixtures of EDCs. Using the repeated holdout validation techniques, the inference is more stable, reproducible and generalisable. Prenatal exposure to mixtures of environmental chemicals should be considered when assessing the safety of chemicals. Growing evidence points towards a "mixture effect" where different environmental chemicals might act jointly where individual compounds may be below a level of concern, but the combination may have an effect on human health. We are constantly exposed to a complicated mixture pattern that is individual for every person as this mixture depends on personal choices of lifestyle, diet and housing to name a few. Our study suggests that prenatal exposure to EDCs might adversely affect the behaviour of children and especially girls. Hence, risk assessment needs to improve and sex-specific mechanisms should be included in assessments. https://doi.org/10.1038/s41370-024-00739-x

Prenatal Perfluoroalkyl Substance Exposure in Association with Global Histone Post-Translational Methylation in 2-Year-Old Children
Tsai, W. J., Hsieh, W. S., Chen, P. C. and Liu, C. Y., *Toxics*, Dec 2024, Vol. 12, no. 12.

Perfluoroalkyl substances (PFASs) have elimination half-lives in years in humans and are persistent in the environment. PFASs can cross the placenta and impact fetal development. Exposure to PFASs may lead to adverse effects through epigenetic mechanisms. This study aimed to investigate whether prenatal exposure to perfluorooctyl sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluoroundecanoic acid (PFUA) was associated with global histone methylation level changes among the 130 2-year-old children followed-up in a birth cohort study in Taiwan. PFOS, PFOA, PFNA, and PFUA were measured by UHPLC/MS/MS in cord blood. Global

histone methylation levels were measured from the blood leukocytes of 2-year-old children by Western blotting. Multivariable regression analyses were applied to adjust for potential confounding effects. Among the 2-year-old children, an IQR increase in the natural log-transformed PFUA exposure was associated with an increased H3K4me3 level by 2.76-fold (95%CI = (0.79, 4.73), p = 0.007). PFOA and PFNA exposures was associated with a decreased H3K27me3 level by 2.35-fold (95%CI = (-4.29, -0.41), p = 0.01) and 2.01-fold (95%CI = (-4.00, -0.03), p = 0.04), respectively. Our findings suggest that prenatal PFAS exposure affected histone post-translational modifications.
https://doi.org/10.3390/toxics12120876

Associations of maternal and paternal preconception and maternal pregnancy urinary phthalate biomarker and bisphenol A concentrations with offspring autistic behaviors: The PEACE study
Uldbjerg, C. S., Leader, J., Minguez-Alarcon, L., Chagnon, O., Dadd, R., Ford, J., Fleury, E., Williams, P., Juul, A., Bellinger, D. C., Calafat, A. M., Hauser, R. and Braun, J. M., *Environmental Research*, Dec 2024, Vol. 263.

Background: Environmental chemical exposures in utero may play a role in autism development. While preconception risk factors for autism are increasingly being investigated, little is known about the influence of chemical exposures during the preconception period, particularly for paternal exposures. Methods: In 195 children from the Preconception Environmental exposures And Childhood health Effects (PEACE) cohort born to parents recruited from a fertility clinic in Boston, Massachusetts between 2004 and 2017, we quantified concentrations of 11 phthalate metabolites and bisphenol A (BPA) in urine samples collected from mothers and fathers before conception and mothers throughout pregnancy. When children were 6-15 years old, parents completed the Social Responsiveness Scale (SRS) questionnaire assessing autistic behaviors. We used linear mixed effect models to estimate covariate-adjusted associations of phthalate biomarker and BPA concentrations, separately for maternal preconception (n = 179), paternal preconception (n = 121), and maternal pregnancy (n = 177), with SRS T-scores, based on age and gender, in offspring. We used quantile g-computation models for mixture analyses and evaluated modification by selected dietary factors. Results: The mean SRS T-score was 47.7 (+/- 7.4), lower than the normative mean of 50. In adjusted models for individual biomarkers or mixtures, few associations were observed and estimates were generally negative (e.g., lower SRS T-scores) and imprecise. We observed associations of higher mono-isobutyl phthalate (MiBP) concentrations measured in maternal preconception and paternal preconception periods with lower SRS T-scores (I3maternal_precon = -1.6, 95% CI -2.7; -0.4; I3paternal_precon = -2.9, 95% CI -4.6; -1.2) for each loge increase. In a subset of participants with maternal preconception nutrition information, we generally observed stronger inverse associations with higher folate and iron intake, particularly for folate intake and MiBP concentrations.
https://doi.org/10.1016/j.envres.2024.120253

Pesticide exposure and oxidative stress generation are linked to poor prognosis outcomes in breast cancer women carrying the allelic variant rs7438135 in the UGT2B7 gene
Vacario, B. G. L., Da Silva, I. M., Machado, M. G., Orrutéa, J. F. G., Campos, A. G. H., Matos, R. O., Federige, A. C. L., Koizumi, B. Y., Leite, M. B., Komori, I. M. S., Jaques, H. D., Rech, D., Guembarovski, R. L., Amarante, M. K., Serpeloni, J. M. and Panis, C., *Journal of Biochemical and Molecular Toxicology*, Nov 2024, Vol. 38, no. 11.

Pesticide exposure is a risk factor for the development of several diseases, including breast cancer (BC). The enzyme UGT2B7 participate in detoxification of pesticides and the presence rs7438135 (G > A) variant in your gene increases its glucuronidation potential, contributing to oxidative stress metabolites neutralization. Here we investigated the impact of occupational pesticide exposure on

the systemic oxidative stress generation from 228 women with BC depending on their UGT2B7 rs7438135 (G > A) status. q-PCR investigated the presence of the rs7438135 variant, and oxidative stress markers (lipid peroxidation levels, total antioxidant capacity-TRAP, and nitric oxide metabolites-NOx) were measured in plasma. Pesticide exposure induced significant augment in the systemic lipid peroxidation in the presence of the variant for several clinicopathological conditions, including tumors with high proliferation index (ki67) and with high aggressiveness. NOx was augmented in high ki67, positive progesterone receptors, high-grade and triple-negative/Luminal B tumors, and low-risk stratified patients. TRAP was depleted in young patients at menopause and those with triple-negative/Luminal B tumors, as well as those stratified as at low risk for death and recurrence. These findings showed that the presence of the variant was not able to protect from pesticide-induced oxidative stress generation in BC patients. https://doi.org/10.1002/jbt.70013

Gestational organophosphate esters (OPEs) and executive function in adolescence: The HOME Study

Vuong, A. M., Percy, Z., Yang, W. L., Godbole, A. M., Ospina, M., Calafat, A. M., Cecil, K. M., Lanphear, B. P., Braun, J. M., Yolton, K. and Chen, A. M., *Environmental Research*, Dec 2024, Vol. 263.

Background: Evidence from toxicological studies indicate organophosphate esters (OPEs) are neurotoxic, but few epidemiological studies investigated associations between gestational OPEs and executive function. Objective: To examine the associations between gestational concentrations of OPE urinary metabolites and executive function at 12 years. Methods: We used data from 223 mother-adolescent dyads from the Health Outcomes of Measures of the Environment (HOME) Study. Women provided spot urine samples at 16 weeks gestation, 26 weeks gestation, and at delivery for quantification of bis(1,3-dichloro-2-propyl) phosphate, bis-2-chloroethyl phosphate (BCEP), diphenyl phosphate (DPHP), and di-n-butyl phosphate (DNBP). Executive function was assessed at age 12 years using the parent- and self-report Behavior Rating Inventory of Executive Function (BRIEF2). Covariate-adjusted associations between specific gravity-corrected OPEs and BRIEF2 scores were estimated using multiple informant models. Bayesian Kernel Machine Regression (BKMR) was used to assess the impact of all OPEs simultaneously. Results: Parent- and self-report BRIEF2 indices and composite scores were weakly to moderately correlated (rs = 0.32-0.41). A natural-log unit increase in BCEP at 26 weeks was associated with approximately a 1-point increase on the self-report Cognitive Regulation Index [CRI] (95% CI 0.4, 2.3), the Emotion Regulation Index [ERI] (95% CI 0.3, 2.2), and the Global Executive Composite [GEC] (95% CI 0.4, 2.2), indicating poorer performance. Higher DPHP at 16 weeks was associated with lower parent-report GEC score (beta =-1.1, 95% CI-2.3,-0.003). BKMR identified BCEP and DNBP at 26 weeks as important contributors to CRI and ERI, respectively. Conclusion: OPE metabolites during gestational development, particularly BCEP, may influence adolescent executive function. However, since the FDR p-values failed to reach statistical significance, additional studies would benefit from using larger cohorts.
https://doi.org/10.1016/j.envres.2024.120239

Associations between phenols, parabens, and phthalates and depressive symptoms: The role of inflammatory markers and bioinformatic insights

Wu, L. L., Zhang, J. R., Xin, Y., Ma, J. X., Chen, T., Nie, J. S. and Niu, P. Y., *Ecotoxicology and Environmental Safety*, Nov 2024, Vol. 286.

Phenols, parabens, and phthalates are commonly found in consumer products, yet there is limited research on their individual and combined effects on depressive symptoms, particularly regarding the role of inflammation in these associations. This study aimed to evaluate these effects and explore potential molecular mechanisms, with a focus on inflammation as a mediator. We conducted a cross-sectional analysis involving 2766 adult participants from the National Health and Nutrition

Examination Survey (NHANES) 2013-2016. Urine samples were analyzed for 15 chemicals, including 3 phenols, 2 parabens, and 10 phthalates. Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9). Statistical analyses included linear regression, restricted cubic splines, Bayesian Kernel Machine Regression and quantile g-computation models to investigate the relationships between chemical exposures and depressive symptoms. Additionally, mediation analysis was employed to explore the potential role of inflammation (immune cells, CRP, NLR) in these associations. The underlying molecular mechanisms were analyzed using bioinformatic approaches. Notably, BPA, MECPP, MEHHP, MiBP and MBP were found to be positively associated with depressive symptoms among females. Besides, BPA was the most significant positive contributor to the effect in the context of the chemical mixture, while the overall mixture effect was relatively weak. Furthermore, WBC were found to mediate a marginal portion (4 %) of the potential effects of MBP on depressive symptoms. The 15 genes identified are primarily involved in neurotransmission, mood regulation, and stress response. Further research is needed to elucidate the mechanisms underlying the observed associations. https://doi.org/10.1016/j.ecoenv.2024.117191

Ethylene oxide exposure increases impaired glucose metabolism in the US general population: a national cross-sectional study

Zhao, Y. Q., Liu, D. L., Pan, X. G. and Tan, Y. Y., *Environmental Health and Preventive Medicine*, 2024, Vol. 29.

Background: Current experimental evidence supports that ethylene oxide (EO) exposure-related pathophysiologies may affect glucose metabolism, but few population-based studies have explored the potential links. Methods: This study used cross-sectional data from 15560 participants in the National Health and Nutrition Examination Survey (NHANES) from 2017 to 2020. EO exposure levels were calculated by testing hemoglobin adducts of EO (HbEO) via a modified Edman reaction. We focused on the association of EO exposure with prediabetes and diabetes as well as indicators of impaired glucose metabolism and further analyzed the potential pathogenic mechanisms. Statistics included logistic regression, generalized additive model fitting, penalized spline method, two-piecewise linear regression, recursive algorithm, mediation analysis, and Pearson's Results: EO exposure was associated with changes in glucose metabolic indicators and increased prevalence of prediabetes and diabetes, showing age-consistency and being more pronounced in obese and non-smoking populations. For each one pmol/g Hb, one SD, or two-fold SD increase in log2-HbEO, the risk of prediabetes increased by 12%, 16%, and 33%, with an increased risk of diabetes by 18%, 26%, and 61%, respectively. Dose-response curves revealed that this positive correlation was approximately linear with prediabetes and "J" shaped with diabetes. When log2-HbEO > 8.03 pmol/g Hb, the risk of diabetes would be further increased. Pearson's correlation revealed that EO exposure was associated with reduced fasting insulin and elevated HbA1c in the prediabetic stage. While in the diabetes stage, EO exposure was correlated with elevated fasting glucose, HbA1c, and HOMA-IR, suggesting an exacerbation of diabetes progression by EO exposure. A potential mechanism that the early stages of impaired glucose metabolism may be initiated by EO-related inflammation and oxidative stress damaging pancreatic cent-cells, resulting in decreased insulin secretion. These speculations were partially supported by mediation analysis and mediators' Pearson analysis. Conclusion: Elevated ethylene oxide exposure increases the incidence of impaired glucose metabolism in the general U.S. population and a potential intervention may be to effectively suppress inflammation and oxidative stress imbalances. https://doi.org/10.1265/ehpm.24-00199

Toxicité sur l'homme

Nonylphenol and Cetyl Alcohol Polyethoxylates Disrupt Thyroid Hormone Receptor Signaling to Disrupt Metabolic Health,
Bérubé, R., Murray, B., Kocarek, T. A., Gurdziel, K. and Kassotis, C. D., *Endocrinology*, Nov 2024, Vol. 165, no. 12.

Surfactants are molecules with both hydrophobic and hydrophilic structural groups that adsorb at the air-water or oil-water interface and serve to decrease the surface tension. Surfactants combine to form micelles that surround and break down or remove oils, making them ideal for detergents and cleaners. Two of the most important classes of nonionic surfactants are alkylphenol ethoxylates (APEOs) and alcohol ethoxylates (AEOs). APEOs and AEOs are high production-volume chemicals that are used for many industrial and residential purposes, including laundry detergents, hard-surface cleaners, paints, and pesticide adjuvants. Commensurate with better appreciation of the toxicity of APEOs and the base alkylphenols, use of AEOs has increased, and both sets of compounds are now ubiquitous environmental contaminants. We recently demonstrated that diverse APEOs and AEOs induce triglyceride accumulation and/or preadipocyte proliferation in vitro. Both sets of contaminants have also been demonstrated as obesogenic and metabolism-disrupting in a developmental exposure zebrafish model. While these metabolic health effects are consistent across models and species, the mechanisms underlying these effects are less clear. This study sought to evaluate causal mechanisms through reporter gene assays, relative binding affinity assays, coexposure experiments, and use of both human cell and zebrafish models. We report that antagonism of thyroid hormone receptor signaling appears to mediate at least a portion of the polyethoxylate-induced metabolic health effects. These results suggest further evaluation is needed, given the ubiquitous environmental presence of these thyroid-disrupting contaminants and reproducible effects in human cell models and vertebrate animals. https://doi.org/10.1210/endocr/bqae149

Evaluating the performance of multi-omics integration: a thyroid toxicity case study,
Canzler, S., Schubert, K., Rolle-Kampczyk, U. E., Wang, Z. P., Schreiber, S., Seitz, H., Mockly, S., Kamp, H., Haake, V., Huisinga, M., Bergen, M. V., Buesen, R. and Hackermüller, J., *Archives of Toxicology*, 2024 Oct 2024.

Multi-omics data integration has been repeatedly discussed as the way forward to more comprehensively cover the molecular responses of cells or organisms to chemical exposure in systems toxicology and regulatory risk assessment. In Canzler et al. (Arch Toxicol 94(2):371-388. https://doi.org/10.1007/s00204-020-02656-y), we reviewed the state of the art in applying multi-omics approaches in toxicological research and chemical risk assessment. We developed best practices for the experimental design of multi-omics studies, omics data acquisition, and subsequent omics data integration. We found that multi-omics data sets for toxicological research questions were generally rare, with no data sets comprising more than two omics layers adhering to these best practices. Due to these limitations, we could not fully assess the benefits of different data integration approaches or quantitatively evaluate the contribution of various omics layers for toxicological research questions. Here, we report on a multi-omics study on thyroid toxicity that we conducted in compliance with these best practices. We induced direct and indirect thyroid toxicity through Propylthiouracil (PTU) and Phenytoin, respectively, in a 28-day plus 14-day recovery oral rat toxicity study. We collected clinical and histopathological data and six omics layers, including the long and short transcriptome, proteome, phosphoproteome, and metabolome from plasma, thyroid, and liver. We demonstrate that the multi-omics approach is superior to single-omics in detecting responses at the regulatory pathway level. We also show how combining omics data with clinical and histopathological parameters facilitates the interpretation of the data. Furthermore, we illustrate

how multi-omics integration can hint at the involvement of non-coding RNAs in post-transcriptional regulation. Also, we show that multi-omics facilitates grouping, and we assess how much information individual and combinations of omics layers contribute to this approach. https://doi.org/10.1007/s00204-024-03876-2

Bisphenol A and its metabolites promote white adipogenesis and impair brown adipogenesis in vitro,
Chen, M. Y., Yang, S. J., Yang, D. and Guo, X. B., *Toxicology*, Dec 2024, Vol. 509.

Bisphenol A (BPA), an obesogen, can disrupt adipogenesis in vitro, but these studies did not distinguish adipocytes as white or brown. BPA can be metabolized into BPA-glucuronide (BPA-G) and BPA-sulfate (BPA-S). These metabolites are not completely inactive in the body, but the related studies remain limited. In this study, preadipocytes isolated from mouse white and brown adipose tissues were treated with 0.1, 1, and 10 mu M of BPA and its metabolites for 6 days, which are equivalent to the exposure level of general and occupational populations, to investigate and compare the effects of BPA and its metabolites on white and brown adipogenesis. The results showed that BPA and BPA-G increased lipid accumulation during white adipogenesis, whereas only BPA induced this same effect during brown adipogenesis. Moreover, BPA and its metabolites upregulated the expression of pan-adipogenic markers, such as peroxisome proliferator-activated receptor gamma (PPAR gamma), during white adipogenesis, whereas they downregulated that of PPAR gamma during brown adipogenesis. Additionally, BPA also inhibited the mRNA and protein expression of brown fat-specific markers (e.g., PPAR gamma coactivator 1-1alpha (PGC1-alpha) and uncoupling protein 1 (UCP1)), and mitochondrial activity during brown adipogenesis, and BPA-G also reduced the mRNA expression levels of Pgc1-alpha and Ucp1. These findings indicated that BPA induced different effects on white and brown adipogenesis, enhancing the former and hindering the latter. Despite less potent than BPA, BPA-G and BPA-S might also affect white and brown adipogenesis. This research provides in-depth insights into the obesogenic effects of BPA and the biological activities of its metabolites. https://doi.org/10.1016/j.tox.2024.153995

The impact of bisphenol AF on skeletal muscle function and differentiation in vitro,
Cui, M. Y., Tzioufa, F., Bruton, J., Westerblad, H. and Kos, V. M., *Toxicology in Vitro*, Mar 2025, Vol. 103.

Various environmental chemicals have been identified as contributors to metabolic diseases. Bisphenol AF (BPAF), a substitute for bisphenol A, has been associated with changes in glucose metabolism and incidence of type 2 diabetes mellitus in humans. However, its mode of action remains unclear. Considering that skeletal muscle is the primary tissue for glucose utilization and the development of insulin resistance, yet largely neglected in toxicological assessments, we investigated the impact of BPAF on skeletal muscle function and differentiation. We examined the effects of BPAF (0.01-10 mu M) on glucose uptake, response to insulin, production of reactive oxygen species (ROS), intracellular calcium, and myocyte differentiation, during hyperglycemia, insulin stimulation, and muscle contraction. We used the rat myoblast cell line L6 differentiated into myotubes, and murine primary isolated muscle fibers. In myotubes and contracting adult fibers, BPAF increased mitochondrial ROS. Basal glucose uptake was increased in myotubes while cells' ability to respond to insulin was decreased. Additionally, in developing myotubes, differentiation markers were downregulated with BPAF, along with impaired formation of tube structures. These effects were primarily observed at 10 mu M concentration, which is markedly higher than reported human exposure concentrations. The results provide an insight into potential hazards associated with BPAF in terms of metabolic disruption in skeletal muscle. The developed in vitro methods show promise for

future usage in assessments of new chemicals and their mixtures. https://doi.org/10.1016/j.tiv.2024.105975

The Influence of Environmental Exposure to Xenoestrogens on the Risk of Cancer Development, Gachowska, M., Dabrowska, A., Wilczynski, B., Kuznicki, J., Sauer, N., Szlasa, W., Kobierzycki, C., Lapinska, Z. and Kulbacka, J., *International Journal of Molecular Sciences*, Nov 2024, Vol. 25, no. 22.

Xenoestrogens (XEs) are a group of exogenous substances that may interfere with the functioning of the endocrine system. They may mimic the function of estrogens, and their sources are plants, water or dust, plastic, chemical agents, and some drugs. Thus, people are highly exposed to their actions. Together with the development of industry, the number of XEs in our environment increases. They interact directly with estrogen receptors, disrupting the transmission of cellular signals. It is proven that XEs exhibit clinical application in e.g., menopause hormone therapy, but some studies observed that intense exposure to XEs leads to the progression of various cancers. Moreover, these substances exhibit the ability to cross the placental barrier, therefore, prenatal exposure may disturb fetus development. Due to the wide range of effects resulting from the biological activity of these substances, there is a need for this knowledge to be systematized. This review aims to comprehensively assess the environmental sources of XEs and their role in increasing cancer risk, focusing on current evidence of their biological and pathological impacts. https://doi.org/10.3390/ijms252212363

Effects of Bisphenol A on the Risk of Developing Obesity, García, M. G., Picó, Y. and Morales-Suárez-Varela, M., *Nutrients*, Nov 2024, Vol. 16, no. 21.

Background: Every year the global incidence of obesity increases considerably and among the factors that favor it is bisphenol A (BPA), an endocrine disruptor widely used in plastics and omnipresent in many everyday objects. Methods: A total of 19 studies published between 2018 and 2023 that addressed the relationship between BPA exposure and obesity were included in this review in order to better understand its behavior and mechanisms of action. Results: The studies reviewed conclude that BPA is an obesogen that alters the function of hormonal receptors, promotes metabolic syndrome, affects certain genes, etc., leading to a greater risk of developing obesity. With important emphasis on the ability to cause epigenetic changes, thus transmitting the effects to offspring when exposure has occurred during critical stages of development such as during gestation or the perinatal period. Conclusions: There is sufficient evidence to show that BPA is a risk factor in the development of obesity. Even so, further research is necessary to exhaustively understand the causal relationship between the two in order to develop prevention measures and avoid possible future adverse effects. https://doi.org/10.3390/nu16213740

Environmental triggers and future risk of developing autoimmune diseases: Molecular mechanism and network toxicology analysis of bisphenol A, Hong, Y. G., Wang, D. Q., Lin, Y. F., Yang, Q. R., Wang, Y., Xie, Y. Y., Shu, W. Y., Gao, S. and Hua, C. Y., *Ecotoxicology and Environmental Safety*, Dec 2024, Vol. 288.

Bisphenol A (BPA), a chemical compound in plastics and resins, widely exist in people's production and life which have great potential to damage human and animal health. It has been proved that BPA could affect human immune function and promote the occurrence and development of autoimmune diseases (ADs). However, the mechanism and pathophysiology remain unknown. Therefore, this study aims to advance network toxicology strategies to efficiently investigate the putative toxicity and underlying molecular mechanisms of environmental pollutants, focusing on ADs induced by BPA exposure. Leveraging databases including ChEMBL, STITCH, SwissTargetPrediction, GeneCards, and

OMIM, we identified potential targets associated with BPA exposure and ADs, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), Hashimoto's thyroiditis (HT), inflammatory bowel disease (IBD), and type 1 diabetes (T1D). Subsequent refinement using STRING and Cytoscape software highlighted core targets respectively, and Metascape was utilized for enrichment analysis. Gene expression data from the GEO database revealed the upregulation or downregulation of these targets across these ADs. Molecular docking performed with Autodock confirmed robust binding between BPA and core targets, notably PPARG, CTNNB1, ESR1, EGFR, SRC, and CCND1. These findings suggest that BPA exposure may serve as an environmental trigger in the development of autoimmunity, underscoring potential environmental risk factors for the onset of autoimmune conditions. https://doi.org/10.1016/j.ecoenv.2024.117352

Impact of Real-life Environmental Exposures on Reproduction: Endocrine-disrupting chemicals, reproductive aging, and menopause,
Inman, Z. C. and Flaws, J. A., *Reproduction*, Nov 2024, Vol. 168, no. 5.

Menopause marks the end of a woman's reproductive lifetime and can have a significant effect on a woman's quality of life. Menopause naturally occurs at 51 years of age on average, but recent literature suggests that endocrine-disrupting chemicals (EDCs) in our environment can accelerate reproductive aging, causing women to reach menopause at earlier ages. This is concerning as menopause can significantly alter a woman's quality of life and is associated with increased risks of conditions such as depression, osteoporosis, and cardiovascular disease. EDC exposures have also been associated with more intense menopausal symptoms, making the menopausal transition more difficult for some women. This review highlights the associations between EDC exposure, early menopause, and reproductive aging, using both epidemiological and experimental studies. https://doi.org/10.1530/rep-24-0113

The effects of bisphenol A and its analogs on steroidogenesis in MA-10 Leydig cells and KGN granulosa cells,
Iskandarani, L., Romanelli, S., Hales, B. F. and Robaire, B., *Biology of Reproduction*, 2024 Nov 2024.

Bisphenols are a family of chemicals used in the manufacture of consumer products containing polycarbonate plastics and epoxy resins. Studies have shown that exposure to bisphenol A (BPA) may disrupt steroidogenesis and induce adverse effects on male and female reproduction, but little is known about BPA replacements. We determined the effects of six bisphenols on the steroidogenic function of MA-10 Leydig cells and KGN granulosa cells by measuring the levels of progesterone and estradiol produced by these cells as well as the expression of transcripts involved in steroid and cholesterol biosynthesis. MA-10 and KGN cells were exposed for 48 h to one of six bisphenols (0.01-50 mu M): BPA, bisphenol F, bisphenol S, bisphenol AF, bisphenol M, or bisphenol TMC, under both basal and dibutyryl cAMP (Bu(2)cAMP)-stimulated conditions. In MA-10 cells, most bisphenols increased the Bu(2)cAMP-stimulated production of progesterone. In KGN cells, there was a general decrease in progesterone production, while estradiol levels were increased following exposure to many bisphenols. Quantitative real-time polymerase chain reaction analyses revealed that all six bisphenols (>= 1 mu M) upregulated the expression of STAR, a cholesterol transporter, in both cell lines after stimulation. Key transcripts directly involved in steroid and cholesterol biosynthesis were significantly altered in a cell line, chemical, and concentration-dependent manner. Thus, BPA and five of its analogs can disrupt steroid production in two steroidogenic cell lines and alter the levels of transcripts involved in this process. Importantly, BPA replacements do not appear to have fewer effects than BPA. Bisphenol A and its structural analogs affect progesterone and estradiol production and differentially alter the expression of genes involved in steroidogenesis and cholesterol

biosynthesis in MA-10 mouse Leydig cells and KGN human granulosa cells. [GRAPHICS] . https://doi.org/10.1093/biolre/ioae165

Expositions environnementales et modifications de l'épigénome dans la période des 1000 premiers jours de vie,
Johanna, L., Lucile, B., Paulina, J., Chloé, M., Claire, P., Ariane, G., Aurélie, N., *médecine/sciences*, 2025, Vol. 40, no. 12, p. 947-954.

Les expositions environnementales précoces peuvent influencer le développement et la santé de l'enfant à long terme. Des modifications épigénétiques pourraient partiellement expliquer ces effets, et leur identification conduire à des progrès significatifs dans la compréhension des mécanismes impliqués. Dans cette revue, nous présentons les données récentes en épidémiologie épigénétique et environnementale pendant la période des 1 000 premiers jours de vie concernant plusieurs expositions très courantes, dont le tabac, les phénols et les phtalates, les polluants de l'air, la température ambiante et la végétation. https://doi.org/10.1051/medsci/2024178

Heavy metals: toxicity and human health effects,
Jomova, K., Alomar, S. Y., Nepovimova, E., Kuca, K. and Valko, M., *Archives of Toxicology*, 2024 Nov 2024.

Heavy metals are naturally occurring components of the Earth's crust and persistent environmental pollutants. Human exposure to heavy metals occurs via various pathways, including inhalation of air/dust particles, ingesting contaminated water or soil, or through the food chain. Their bioaccumulation may lead to diverse toxic effects affecting different body tissues and organ systems. The toxicity of heavy metals depends on the properties of the given metal, dose, route, duration of exposure (acute or chronic), and extent of bioaccumulation. The detrimental impacts of heavy metals on human health are largely linked to their capacity to interfere with antioxidant defense mechanisms, primarily through their interaction with intracellular glutathione (GSH) or sulfhydryl groups (R-SH) of antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), glutathione reductase (GR), and other enzyme systems. Although arsenic (As) is believed to bind directly to critical thiols, alternative hydrogen peroxide production processes have also been postulated. Heavy metals are known to interfere with signaling pathways and affect a variety of cellular processes, including cell growth, proliferation, survival, metabolism, and apoptosis. For example, cadmium can affect the BLC-2 family of proteins involved in mitochondrial death via the overexpression of antiapoptotic Bcl-2 and the suppression of proapoptotic (BAX, BAK) mechanisms, thus increasing the resistance of various cells to undergo malignant transformation. Nuclear factor erythroid 2-related factor 2 (Nrf2) is an important regulator of antioxidant enzymes, the level of oxidative stress, and cellular resistance to oxidants and has been shown to act as a double-edged sword in response to arsenic-induced oxidative stress. Another mechanism of significant health threats and heavy metal (e.g., Pb) toxicity involves the substitution of essential metals (e.g., calcium (Ca), copper (Cu), and iron (Fe)) with structurally similar heavy metals (e.g., cadmium (Cd) and lead (Pb)) in the metal-binding sites of proteins. Displaced essential redox metals (copper, iron, manganese) from their natural metal-binding sites can catalyze the decomposition of hydrogen peroxide via the Fenton reaction and generate damaging ROS such as hydroxyl radicals, causing damage to lipids, proteins, and DNA. Conversely, some heavy metals, such as cadmium, can suppress the synthesis of nitric oxide radical (NO<middle dot>), manifested by altered vasorelaxation and, consequently, blood pressure regulation. Pb-induced oxidative stress has been shown to be indirectly responsible for the depletion of nitric oxide due to its interaction with superoxide radical (O2<middle dot>-), resulting in the formation of a potent biological oxidant, peroxynitrite (ONOO-). This review comprehensively discusses the mechanisms of heavy metal toxicity and their health effects. Aluminum

(Al), cadmium (Cd), arsenic (As), mercury (Hg), lead (Pb), and chromium (Cr) and their roles in the development of gastrointestinal, pulmonary, kidney, reproductive, neurodegenerative (Alzheimer's and Parkinson's diseases), cardiovascular, and cancer (e.g. renal, lung, skin, stomach) diseases are discussed. A short account is devoted to the detoxification of heavy metals by chelation via the use of ethylenediaminetetraacetic acid (EDTA), dimercaprol (BAL), 2,3-dimercaptosuccinic acid (DMSA), 2,3-dimercapto-1-propane sulfonic acid (DMPS), and penicillamine chelators. https://doi.org/10.1007/s00204-024-03903-2

Comparative study of cytotoxic Signaling pathways in H1299 cells exposed to alternative Bisphenols: BPA, BPF, and BPS,
Kim, J. Y., Shin, G. S., An, M. J., Lee, H. M., Jo, A. R., Park, Y., Kim, J., Hwangbo, Y., Kim, C. H. and Kim, J. W., *Toxicology Research*, Dec 2024, Vol. 13, no. 6.

Bisphenols are prevalent in food, plastics, consumer goods, and industrial products. Bisphenol A (BPA) and its substitutes, bisphenol F (BPF) and bisphenol S (BPS), are known to act as estrogen mimics, leading to reproductive disorders, disruptions in fat metabolism, and abnormalities in brain development. Despite numerous studies exploring the adverse effects of bisphenols both in vitro and in vivo, the molecular mechanisms by which these compounds affect lung cells remain poorly understood. This study aims to compare the effects of BPA, BPF, and BPS on the physiological behavior of human nonsmall cell lung cancer (NSCLC) cells. Human non-small cell lung cancer (NSCLC) H1299 cells were treated with various concentration of BPA, BPF and BPS during different exposure time. Cellular physiology for viability and cell cycle was assessed by the staining with apoptotic cell makers such as active Caspase-3 and cyclins antibodies. Toxicological effect was quantitatively counted by using flow-cytometry analysis. Our findings indicate that BPA induces apoptosis by increasing active Caspase-3 levels in H1299 cells, whereas BPF and BPS do not promote late apoptosis. Additionally, BPA was found to upregulate cyclin B1, causing cell cycle arrest at the G0/G1 phase and leading to apoptotic cell death through Caspase-3 activation. These results demonstrate that BPA, BPF, and BPS differentially impact cell viability, cell cycle progression, and cell death in human NSCLC cells. https://doi.org/10.1093/toxres/tfae200

Deciphering the Liaison Between Fine Particulate Matter Pollution, Oxidative Stress, and Prostate Cancer: Where Are We Now?
Lee, C. W., Chiang, Y. C., Vo, T. T. T., Lin, Z. C., Chi, M. C., Fang, M. L., Peng, K. T., Tsai, M. H. and Lee, I. T., *Antioxidants (Basel)*, Dec 10 2024, Vol. 13, no. 12.

Prostate cancer (PCa), a highly prevalent cancer in men worldwide, is projected to rise in the coming years. As emerging data indicate the carcinogenic effects of fine particulate matter (PM2.5) in lung cancer and other site-specific cancers, there is an urgent need to evaluate the relationship between this environmental risk factor and PCa as a potential target for intervention. The present review provides up-to-date evidence about the impact of airborne PM2.5 pollution on the initiation and progression of PCa. Examining the composition and characteristics of PM2.5 reveals its ability to induce toxic effects, inflammatory injuries, and oxidative damages. Additionally, PM2.5 can attach to endocrine-disrupting chemicals implicated in prostatic carcinogenesis. Considering the potential significance of oxidative stress in the risk of the disease, our review underlines the protective strategies, such as antioxidant-based approaches, for individuals exposed to increased PM2.5 levels. Moreover, the findings call for further research to understand the associations and mechanisms linking PM2.5 exposure to PCa risk as well as to suggest appropriate measures by policymakers, scientific researchers, and healthcare professionals in order to address this global health issue. https://doi.org/10.3390/antiox13121505

Adverse outcome pathway for the neurotoxicity of Per- and polyfluoroalkyl substances: A systematic review,
Li, S. P., Qin, S. J., Zeng, H. X., Chou, W. C., Oudin, A., Kanninen, K. M., Jalava, P., Dong, G. H. and Zeng, X. W., *Eco-Environment & Health*, Dec 2024, Vol. 3, no. 4, p. 476-493.

Per- and polyfluoroalkyl substances (PFAS) are endocrine disruptors with unambiguous neurotoxic effects. However, due to variability in experimental models, population characteristics, and molecular endpoints, the elucidation of mechanisms underlying PFAS-induced neurotoxicity remains incomplete. In this review, we utilized the adverse outcome pathway (AOP) framework, a comprehensive tool for evaluating toxicity across multiple biological levels (molecular, cellular, tissue and organ, individual, and population), to elucidate the mechanisms of neurotoxicity induced by PFAS. Based on 271 studies, the reactive oxygen species (ROS) generation emerged as the molecular initiating event 1 (MIE1). Subsequent key events (KEs) at the cellular level include oxidative stress, neuroinflammation, apoptosis, altered Ca2+ signal transduction, glutamate and dopamine signaling dyshomeostasis, and reduction of cholinergic and serotonin. These KEs culminate in synaptic dysfunction at organ and tissue levels. Further insights were offered into MIE2 and upstream KEs associated with altered thyroid hormone levels, contributing to synaptic dysfunction and hypomyelination at the organ and tissue levels. The inhibition of Na+/Isymporter (NIS) was identified as the MIE2, initiating a cascade of KEs at the cellular level, including altered thyroid hormone synthesis, thyroid hormone transporters, thyroid hormone metabolism, and binding with thyroid hormone receptors. All KEs ultimately result in adverse outcomes (AOs), including cognition and memory impairment, autism spectrum disorders, attention deficit hyperactivity disorders, and neuromotor development impairment. To our knowledge, this review represents the first comprehensive and systematic AOP analysis delineating the intricate mechanisms responsible for PFAS-induced neurotoxic effects, providing valuable insights for risk assessments and mitigation strategies against PFAS-related health hazards. https://doi.org/10.1016/j.eehl.2024.08.002

Adipose tissue as target of environmental toxicants: focus on mitochondrial dysfunction and oxidative inflammation in metabolic dysfunction-associated steatotic liver disease,
Lolescu, B. A., Furdui-Linta, A. V., Ilie, C. A., Sturza, A., Zara, F., Muntean, D. M., Blidisel, A. and Cretu, O. M., *Molecular and Cellular Biochemistry*, 2024 Dec 2024.

Obesity, diabetes, and their cardiovascular and hepatic comorbidities are alarming public health issues of the twenty-first century, which share mitochondrial dysfunction, oxidative stress, and chronic inflammation as common pathophysiological mechanisms. An increasing body of evidence links the combined exposure to multiple environmental toxicants with the occurrence and severity of metabolic diseases. Endocrine disruptors (EDs) are ubiquitous chemicals or mixtures with persistent deleterious effects on the living organisms beyond the endocrine system impairment; in particular, those known as metabolism-disrupting chemicals (MDCs), increase the risk of the metabolic pathologies in adult organism or its progeny. Being largely lipophilic, MDCs mainly target the adipose tissue and elicit mitochondrial dysfunction by interfering with mitochondrial bioenergetics, biogenesis, dynamics and/or other functions. Plastics, when broken down into micro- and nano-plastics (MNPs), have been detected in several human tissues, including the liver. The harmful interplay between inflammatory and redox processes, which mutually interact in a positive feed-back loop, hence the term oxidative inflammation ("OxInflammation"), occurs both at systemic and organ level. In both liver and adipose tissue, oxinflammation contributes to the progression of the metabolic dysfunction-associated steatotic liver disease (MASLD). Moreover, it has been reported that individuals with MASLD may be more susceptible to the harmful effects of toxicants (mainly, those related to mitochondria) and that chronic exposure to EDs/MDCs or MNPs may play a role in the development of the disease. While liver has been systematically investigated as major target organ for ambient chemicals, surprisingly, less

information is available in the literature with respect to the adipose tissue. In this narrative review, we delve into the current literature on the most studied environmental toxicants (bisphenols, polychlorinated biphenyls, phthalates, tolylfluanid and tributyltin, per-fluoroalkyl and polyfluoroalkyl substances, heavy metals and MNPs), summarize their deleterious effects on adipose tissue, and address the role of dysregulated mitochondria and oxinflammation, particularly in the setting of MASLD. https://doi.org/10.1007/s11010-024-05165-z

Epigenetic transgenerational inheritance of toxicant exposure-specific non-coding RNA in sperm, Mcswiggin, H., Magalhaes, R., Nilsson, E. E., Yan, W. and Skinner, M. K., *Environmental Epigenetics*, Nov 2024, Vol. 10, no. 1.

Environmentally induced epigenetic transgenerational inheritance of phenotypic variation and disease susceptibility requires the germ cell (sperm or egg) transmission of integrated epigenetic mechanisms involving DNA methylation, histone modifcations, and noncoding RNA (ncRNA) actions. Previous studies have demonstrated that transgenerational exposure and disease-specifc differential DNA methylation regions (DMRs) in sperm are observed and that ncRNA-mediated DNA methylation occurs. The current study was designed to determine if transgenerational exposure-specifc ncRNAs exist in sperm. Specifcally, toxicants with distinct mechanisms of action including the fungicide vinclozolin (anti-androgenic), pesticide dichlorodiphenyltrichloroethane (estrogenic), herbicide atrazine (endocrine disruptor at cyclic adenosine monophosphate level), and hydrocarbon mixture jet fuel (JP8) (aryl hydrocarbon receptor disruptor) were used to promote transgenerational disease phenotypes in F3 generation outbred rats. New aliquots of sperm, previously collected and used for DNA methylation analyses, were used in the current study for ncRNA sequencing analyses of nuclear RNA. Signifcant changes in transgenerational sperm ncRNA were observed for each transgenerational exposure lineage. The majority of ncRNA was small noncoding RNAs including piwi-interacting RNA, tRNA-derived small RNAs, microRNAs, rRNA-derived small RNA, as well as long ncRNAs. Although there was some overlap among the different classes of ncRNA across the different exposures, the majority of differentially expressed ncRNAs were exposure-specifc with no overlapping ncRNA between the four different exposure lineages in the transgenerational F3 generation sperm nuclear ncRNAs. The ncRNA chromosomal locations and gene associations were identifed for a small number of differential expressed ncRNA. Interestingly, an overlap analysis between the transgenerational sperm DMRs and ncRNA chromosomal locations demonstrated small populations of overlapping ncRNA, but a large population of nonoverlapping ncRNAs. Observations suggest that transgenerational sperm ncRNAs have both exposure-specifc populations within the different classes of ncRNA, as well as some common populations of ncRNAs among the different exposures. The lack of co-localization of many of the ncRNAs with previously identifed transgenerational DMRs suggests a distal integration of the different epigenetic mechanisms. The potential use of ncRNA analyses for transgenerational toxicant exposure assessment appears feasible https://doi.org/10.1093/eep/dvae014

Delineating lipidomic landscapes in human and mouse ovaries: Spatial signatures and chemically-induced alterations via MALDI mass spectrometry imaging Spatial ovarian lipidomics, Pascuali, N., Tobias, F., Valyi-Nagy, K., Salih, S. and Veiga-Lopez, A., *Environment International*, Dec 2024, Vol. 194.

This study addresses the critical gap in understanding the ovarian lipidome's abundance, distribution, and vulnerability to environmental disruptors, a largely unexplored field. Leveraging the capabilities of matrixassisted laser desorption ionization mass spectrometry imaging (MALDI MSI), we embarked on a novel exploration of the ovarian lipidome in both mouse and human healthy tissues. Our findings revealed that the obesogenic chemical tributyltin (TBT), at environmentally relevant exposures, exerts

a profound and region-specific impact on the mouse ovarian lipidome. TBT exposure predominantly affects lipid species in antral follicles and oocytes, suggesting a targeted disruption of lipid homeostasis in these biologically relevant regions. Our comprehensive approach, integrating advanced lipidomic techniques and bioinformatic analyses, documented the disruptive effects of TBT, an environmental chemical, on the ovarian lipid landscape. Similar to mice, our research also unveiled distinct spatial lipidomic signatures corresponding to specific ovarian compartments in a healthy human ovary that may also be vulnerable to disruption by chemical exposures. Findings from this study not only underscore the vulnerability of the ovarian lipidome to environmental factors but also lay the groundwork for unraveling the molecular pathways underlying ovarian toxicity mediated through lipid dysregulation. https://doi.org/10.1016/j.envint.2024.109174

Parabens effects on female reproductive health - Review of evidence from epidemiological and rodent-based studies,
Pulcastro, H. and Ziv-Gal, A., *Reproductive Toxicology*, Sep 2024, Vol. 128.

Parabens have been used as antimicrobial preservatives since the 1920s. The prevalent use of parabens increases their detection in the environment and in women's biological samples including reproductive tissues. Recent studies suggest parabens may alter endocrine function and thus female reproductive health may be affected. In this literature review, we summarize findings on parabens and female reproduction while focusing on epidemiological and rodent-based studies. The topics reviewed include paraben effects on cyclicity, pregnancy, newborn and pubertal development, reproductive hormones, and ovarian and uterine specific outcomes. Overall, the scientific literature on paraben effects on female reproduction is limited and with some conflicting results. Yet, some epidemiological and/or rodent-based experimental studies report significant findings in relation to paraben effects on cyclicity, fertility, gestation length, birth weight, postnatal development and pubertal onset, hormone levels, and hormone signaling in reproductive tissues. Future epidemiological and experimental studies are needed to better understand paraben effects on female reproduction while focusing on human related exposures including mixtures, physiologic concentrations of parabens, and multi-generational studies. https://doi.org/10.1016/j.reprotox.2024.108636

In Vitro Investigation of Biological and Toxic Effects of 4-Octylphenol on Human Cells,
Romanelli, A. M., Montefusco, A., Sposito, S., Scafuri, B., Caputo, I. and Paolella, G., *International Journal of Molecular Sciences*, Dec 2024, Vol. 25, no. 23.

Alkylphenols are byproducts of anthropogenic activities that widely contaminate waters, soils and air; among them, the most represented are 4-nonylphenol (4-NP) and 4-octylphenol (4-OP). These compounds tend to bioaccumulate in animal and plant tissues and also represent a risk to human health. Indeed, humans are constantly exposed to alkylphenols through ingestion of contaminated water and food, inhalation and dermal absorption. In the present work, we characterized the cytotoxic ability of 4-OP towards several human cell lines, representing the potential main targets in the human body, also comparing its effect with that of 4-NP and of a mixture of both 4-OP and 4-NP in a range of concentrations between 1 and 100 mu M. Viability assays demonstrated that each cell type had a peculiar sensitivity to 4-OP and that, in some cases, a combination of the two alkylphenols displayed a higher cytotoxic activity with respect to the single compound. Then, we focused our attention on a liver cell line (HepG2) in which we observed that 4-OP increased cell death and also caused interference with protective physiological cell processes, such as the unfolded protein response, autophagy and the antioxidant response. Finally, our experimental data were compared and correlated with ADMET properties originating from an in silico analysis. Altogether, our findings

highlight a possible contribution of this pollutant to deregulation of the normal homeostasis in human liver cells. https://doi.org/10.3390/ijms252313032

Endocrine-Disrupting Chemicals, Hypothalamic Inflammation and Reproductive Outcomes: A Review of the Literature,
Stathori, G., Hatziagapiou, K., Mastorakos, G., Vlahos, N. F., Charmandari, E. and Valsamakis, G., *International Journal of Molecular Sciences*, Nov 2024, Vol. 25, no. 21.

Endocrine-disrupting chemicals (EDCs) are environmental and industrial agents that interfere with hormonal functions. EDC exposure is linked to various endocrine diseases, especially in reproduction, although the mechanisms remain unclear and effects vary among individuals. Neuroinflammation, particularly hypothalamic inflammation, is an emerging research area with implications for endocrine-related diseases like obesity. The hypothalamus plays a crucial role in regulating reproduction, and its inflammation can adversely affect reproductive health. EDCs can cross the blood-brain barrier, potentially causing hypothalamic inflammation and disrupting the reproductive axis. This review examines the existing literature on EDC-mediated hypothalamic inflammation. Our findings suggest that exposure to 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD), polychlorinated biphenyl (PCB), tributyltin (TBT), phthalates, bisphenol A (BPA), and chlorpyrifos (CPF) in animals is linked to hypothalamic inflammation, specifically affecting the hypothalamic centers of the gonadotropic axis. To our knowledge, this is the first comprehensive review on this topic, indicating hypothalamic inflammation as a possible mediator between EDC exposure and reproductive dysfunction. Further human studies are needed to develop effective prevention and treatment strategies against EDC exposure. https://doi.org/10.3390/ijms252111344

The impact of persistent organic pollutants on fertility: exposure to the environmental toxicant 2,3,7,8-tetrachlorodibenzo-p-dioxin alters reproductive tract immune responses,
Stephens, V. R., Horner, K. B., Avila, W. M., Spicer, S. K., Chinni, R., Bernabe, E. B., Hinton, A. O., Jr., Damo, S. M., Eastman, A. J., Mccallister, M. M., Osteen, K. G. and Gaddy, J. A., *Frontiers in Immunology*, Dec 2024, Vol. 15.

Exposure to environmental contaminants can result in profound effects on the host immune system. One class of environmental toxicants, known as dioxins, are persistent environmental contaminants termed "forever chemicals". The archetype toxicant from this group of chemicals is 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD), an immunotoxicant that activates the aryl-hydrocarbon receptor pathway leading to a variety of changes in immune cell responses. Immune cell functions are crucial to the development and maintenance of healthy reproduction. Immune cells facilitate tolerance between at the maternal-fetal interface between the parent and the semi-allogenic fetus and help defend the gravid reproductive tract from infectious assault. Epidemiological studies reveal that exposure to environmental contaminants (such as TCDD) are linked to adverse reproductive health outcomes including endometriosis, placental inflammation, and preterm birth. However, little is known about the molecular mechanisms that underpin how environmental toxicant exposures impact immune functions at the maternal-fetal interface or within the reproductive tract in general. This review presents the most recent published work that studies interactions between dioxin or TCDD exposure, the host immune system, and reproduction. https://doi.org/10.3389/fimmu.2024.1497405

Neuroendocrine and Developmental Impacts of Early Life Exposure to EDCs,
Streifer, M., Thompson, L. M., Mendez, S. A. and Gore, A. C., *Journal of the Endocrine Society*, Dec 2024, Vol. 9, no. 1.

Polychlorinated biphenyls (PCBs) pose a global challenge to environmental and human health. Although toxic and carcinogenic at higher exposure levels, at lower concentrations they can act as endocrine-disrupting chemicals. Individuals are more vulnerable to endocrine-disrupting effects of PCB exposures during the perinatal period, when the neuroendocrine system is developing, although assessing the full impact of PCB exposure is difficult because of the often-latent onset of adverse effects. The goal of this study was to determine developmental effects of an estrogenic PCB mixture, Aroclor 1221 (A1221), on KNDy and kisspeptin neuron numbers in the hypothalamic arcuate nucleus and anteroventral periventricular nucleus (AVPV), together with measures of hypothalamic-pituitary-gonadal hormones and postnatal development. We conducted RNAscope of kisspeptin, prodynorphin, neurokinin B, and estrogen receptor alpha genes in the P30 hypothalamus. Early-life PCBs caused small but significant changes in development (body weight and anogenital index) but had no effect on puberty. We found sex-specific effects of treatment on serum LH, FSH, and estradiol in a sex- and developmental age-dependent manner. RNAscope results revealed increased prodynorphin in the AVPV of male rats, but no effects on kisspeptin or neurokinin B in AVPV or arcuate nucleus. An unexpected species difference was found: we were unable to detect prodynorphin coexpression with kisspeptin within KNDy neurons in rats, unlike mice, sheep, and primates. These data show that early-life PCBs can induce developmental and hormonal changes that together with other reports showing latent effects on behavior and the hypothalamic-pituitary-gonadal axis, indicate adverse endocrine and neurobehavioral outcomes. https://doi.org/10.1210/jendso/bvae195

Endocrine disruptor chemicals exposure and female fertility declining: from pathophysiology to epigenetic risks,
Tricotteaux-Zarqaoui, S., Lahimer, M., Abou Diwan, M., Corona, A., Candela, P., Cabry, R., Bach, V., Khorsi-Cauet, H. and Benkhalifa, M., *Frontiers in Public Health*, Dec 2024, Vol. 12.

Over the last decades, human infertility has become a major concern in public health, with severe societal and health consequences. Growing evidence shows that endocrine disruptors chemicals (EDCs) have been considered as risk factors of infertility. Their presence in our everyday life has become ubiquitous because of their universal use in food and beverage containers, personal care products, cosmetics, phytosanitary products. Exposure to these products has an impact on human reproductive health. Recent studies suggest that women are more exposed to EDCs than men due to higher chemical products use. The aim of this review is to understand the possible link between reproductive disorders and EDCs such as phthalates, bisphenol, dioxins, and pesticides. In women, the loss of endocrine balance leads to altered oocyte maturation, competency, anovulation and uterine disorders, endometriosis, premature ovarian insufficiency (POI) or embryonic defect and decreases the in vitro fertilization outcomes. In this review, we consider EDCs effects on the women's reproductive system, embryogenesis, with a focus on associated reproductive pathologies. https://doi.org/10.3389/fpubh.2024.1466967

Evaluating the combined estrogenic effects of plant growth regulators via electrochemical and E-Screen methods,
Wang, X. J., Zhao, Z. J., Qi, S. L., Li, Z., Wang, Z., Zhou, S., Cui, J. W., Li, J. L. and Wu, D. M., *Rsc Advances*, Nov 2024, Vol. 14, no. 49, p. 36745-36753.

The study shows that plant growth regulators (PGRs) have estrogenic effects, which may disrupt the normal physiological functions of endogenous estrogen in organisms. This study used electrochemical methods to investigate the electrochemical behavior and estrogenic effects of PGRs gibberellic acid (GA3), ethylene (ETH), and naphthalene acetic acid (NAA) on estrogen-free human breast cancer cells (MCF-7) cells when exposed individually or in combination. The results indicate that GA3, ETH, and NAA, whether used alone or in combination, exhibit estrogenic effects on MCF-7 cells. The accuracy

of the electrochemical method was validated against the E-Screen method, with consistent results between the two methods. Analysis of the combined estrogenic effects of PGRs detected by electrochemical and E-Screen methods revealed antagonistic effects for GA3/ETH, synergistic effects for GA3/NAA, additive effects for NAA/ETH, and synergistic effects for GA3/ETH/NAA. The combined estrogenic effects of PGRs at environmental actual concentration ratios detected by the electrochemical method were consistent with the results of the E-Screen method. This study successfully established a simple, fast, sensitive, and low-cost electrochemical detection method for the combined estrogenic effects of PGRs, providing a new approach for detecting such effects. https://doi.org/10.1039/d4ra06838f

Impact of Endocrine-Disrupting Chemicals, Climate, and Air Pollution on Pregnancy Outcomes: A Scoping Review,
Wesley, S. R., Gallo, M., Apata, T., Van Dis, J. and Hollenbach, S. J., *Seminars in Reproductive Medicine*, 2024 Dec 2024.

Environmental pollutants, including endocrine-disrupting chemicals (EDCs), air pollution, and climate change, are increasingly recognized for their potential impact on pregnancy outcomes. EDCs, found in pesticides, industrial chemicals, and personal care products, are associated with preterm birth and fetal growth restriction, primarily through hormonal interference. Air pollution, notably PM 2.5 , NO 2 , and O 3 , has been linked to increased rates of preterm birth, low birth weight, and stillbirth. Climate factors, such as extreme heat, elevate risks of pregnancy loss and preterm birth, with significant impacts on vulnerable populations across diverse socioeconomic and geographic regions. These exposures contribute to adverse pregnancy outcomes through mechanisms involving oxidative stress, inflammation, and endocrine disruption. The interplay among these environmental factors underscores the need for integrated, longitudinal studies to understand their combined effects on pregnancy outcomes better. Future research should focus on region-specific impacts, cumulative exposure, and policy-driven interventions to mitigate these environmental risks, especially in vulnerable populations disproportionately affected by these hazards. This scoping review synthesizes recent findings from 2019 to 2024 to highlight these associations and identify research gaps. https://doi.org/10.1055/s-0044-1800961

Interference Mechanisms of Endocrine System and Other Systems of Endocrine-Disrupting Chemicals in Cosmetics-In Vitro Studies,
Zhang, Y. X., Tu, L. H., Chen, J. and Zhou, L. H., *International Journal of Endocrinology*, Dec 2024, Vol. 2024.

Endocrine-disrupting chemicals (EDCs), found in various cosmetic products, interfere with the normal functioning of the endocrine system, impacting hormone regulation and posing risks to human health. Common cosmetic EDCs, such as ultraviolet (UV) filters, parabens, and triclosan, can enter the human body through different routes, including skin absorption. Their presence has been linked to adverse effects on reproduction, immune function, and development. High-throughput in vitro assays, using various human cell lines, were employed to assess the effects of common cosmetic EDCs such as ethylhexyl methoxycinnamate (EHMC), benzophenone-3 (BP-3), homosalate, and parabens. Despite ongoing regulatory efforts, gaps persist in understanding their long-term impacts, particularly when they are present as mixtures or degradation products in the environment. This study focuses on recent in vitro research to investigate the mechanisms through which cosmetic-related EDCs disrupt the endocrine system and other physiological systems. The in vitro findings highlight the broader systemic impact of these chemicals, extending beyond the endocrine system to include immune, reproductive, and cardiovascular effects. This research underscores the importance of developing safer cosmetic

formulations and enhancing public health protection, emphasizing the need for stricter regulations. https://doi.org/10.1155/ije/2564389

Environmentally-relevant doses of bisphenol A and S exposure in utero disrupt germ cell programming across generations resolved by single nucleus multi-omics,
Zhao, L., Shi, M., Winuthayanon, S., Maclean, J. A., 2nd and Hayashi, K., *bioRxiv*, Dec 10 2024.

BACKGROUND: Exposure to endocrine-disrupting chemicals (EDCs), such as bisphenol A (BPA), disrupts reproduction across generations. Germ cell epigenetic alterations are proposed to bridge transgenerational reproductive defects resulting from EDCs. Previously, we have shown that prenatal exposure to environmentally relevant doses of BPA or its substitute, BPS, caused transgenerationally maintained reproductive impairments associated with neonatal spermatogonial epigenetic changes in male mice. While epigenetic alterations in germ cells can lead to transgenerational phenotypic variations, the mechanisms sustaining these changes across generations remain unclear. OBJECTIVES: This study aimed to systematically elucidate the mechanism of transgenerational inherence by prenatal BPA and BPS exposure in the murine germline from F1 to F3 generations at both transcriptomic and epigenetic levels. METHODS: BPA or BPS with doses of 0 (vehicle control), 0.5, 50, or 1000 µg/kg/b.w./day was orally administered to pregnant CD-1 females (F0) from gestational day 7 to birth. Sperm counts and motility were examined in F1, F2, and F3 adult males. THY1(+) germ cells on postnatal day 6 from F1, F2, and F3 males at a dose of 50 µg/kg/b.w./day were used for analysis by single-nucleus (sn) multi-omics (paired snRNA-seq and snATAC-seq on the same nucleus). RESULTS: Prenatal exposure to BPA and BPS with 0.5, 50, and 1000 µg/kg/b.w./day reduced sperm counts in mice across F1 to F3 generations. In the F1 neonatal germ cells, ancestral BPA or BPS exposure with 50 µg/kg/b.w./day resulted in increased differentially expressed genes (DEGs) associated with spermatogonial differentiation. It also disrupted the balance between maintaining the undifferentiated and differentiating spermatogonial populations. Differentially accessible peaks (DAPs) by snATAC-seq were primarily located in the promoter regions, with elevated activity of key transcription factors, including SP1, SP4, and DMRT1. Throughout F1-F3 generations, biological processes related to mitosis/meiosis and metabolic pathways were substantially up-regulated in BPA- or BPS-exposed groups. While the quantities of DEGs and DAPs were similar in F1 and F2 spermatogonia, with both showing a significant reduction in F3. Notably, approximately 80% of DAPs in F1 and F2 spermatogonia overlapped with histone post-translational modifications linked to transcription activation, such as H3K4me1/2/3 and H3K27ac. Although BPA exerted more potent effects on gene expression in F1 spermatogonia, BPS induced longer-lasting effects on spermatogonial differentiation across F1 to F3 males. Interestingly, DMRT1 motif activity was persistently elevated across all three generations following ancestral BPA or BPS exposure. DISCUSSION: Our work provides the first systematic analyses for understanding the transgenerational dynamics of gene expression and chromatin landscape following prenatal exposure to BPA or BPS in neonatal spermatogonia. These results suggest that prenatal exposure to environmentally relevant doses of BPA or BPS alters chromatin accessibility and transcription factor motif activities, consequently contributing to disrupted transcriptional levels in neonatal germ cells, and some are sustained to F3 generations, ultimately leading to the reduction of sperm counts in adults. https://doi.org/10.1101/2024.12.05.627072

Effect of 2,5-hexanedione on rat ovarian granulosa cell apoptosis involves endoplasmic reticulum stress-dependent m-TOR signaling pathway,
Zhu, L. M., Yang, Y., Tan, J. S., Lin, Y. B., Qing, J. Q., Li, X. and Zeng, L. F., *Journal of Toxicology and Environmental Health-Part a-Current Issues*, 2024 Dec 2024.

Occupational exposure to N-hexane/2,5-hexanedione (2,5-HD) was found to adversely affect reproductive functions in females. However, there are few studies regarding the mechanisms underlying reproductive system damage initiated by 2,5-HD. Several studies demonstrated that 2,5-HD exerts hormonal dysfunctions in females by promoting apoptosis using rat ovarian granulosa cells (GCs) as a model. The endoplasmic reticulum (ER) plays a key role in cellular processes such as protein folding and modification, Ca2+ storage, and lipid synthesis, which are known to involve the activation of stress (ERS)-dependent m-TOR signaling pathway. Thus, the aim of this study was to examine the effects of 2,5-HD on ER and the associated activation of stress (ERS)-dependent m-TOR signaling pathway resulting in consequent apoptosis of ovarian GCs. Data demonstrated that after intraperitoneal treatment with 100, 200, or 400 mg/kg 2,5-HD for 6 consecutive weeks, 5 times per week, a decrease in body weight, ovarian weight, and relative ovary weight was found. Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay showed that 2,5-HD promoted apoptosis of ovarian GCs, which involved enhanced relative protein expression levels of m-TOR/p-mTOR. Our findings demonstrated that 2,5-HD (1) elevated expression levels of pro-apoptosis-related genes Bax and Caspase 3, (2) decreased expression levels of the anti-apoptosis gene Bcl-2, and (3) activated the protein expression of glucose-regulatory protein 78 (GRP78), inositol-requiring enzyme-1 (IRE1), and c-Jun terminal kinase (JNK) associated with increased apoptosis. Evidence indicates that chronic exposure to 2,5-HD induced apoptosis of ovarian GCs, and the possible mechanism underlying this effect involves the ERS-dependent m-TOR signaling pathway. https://doi.org/10.1080/15287394.2024.2438832

Endocrine disrupting effects on morphological synaptic plasticity,
Zsarnovszky, A., Alymbaeva, D., Jocsak, G., Szabo, C., Schilling-Tóth, B. M. and Kiss, D. S., *Frontiers in Neuroendocrinology*, Oct 2024, Vol. 75.

Neural regulation of the homeostasis depends on healthy synaptic function. Adaptation of synaptic functions to physiological needs manifests in various forms of synaptic plasticity (SP), regulated by the normal hormonal regulatory circuits. During the past several decades, the hormonal regulation of animal and human organisms have become targets of thousands of chemicals that have the potential to act as agonists or antagonists of the endogenous hormones. As the action mechanism of these endocrine disrupting chemicals (EDCs) came into the focus of research, a growing number of studies suggest that one of the regulatory avenues of hormones, the morphological form of SP, may well be a neural mechanism affected by EDCs. The present review discusses known and potential effects of some of the best known EDCs on morphological synaptic plasticity (MSP). We highlight molecular mechanisms altered by EDCs and indicate the growing need for more research in this area of neuroendocrinology. https://doi.org/10.1016/j.yfrne.2024.101157

Méthodes

Comparison of fish and mammalian adipogenesis in vitro: Implications for regulating endocrine disruptors,
Dang, Z. C., *Critical Reviews in Environmental Science and Technology*, 2024 Nov 2024.

Adipogenesis, the process by which preadipocytes differentiate into mature fat cells, is closely associated with the development of obesity and metabolic syndrome. Identifying and classifying chemicals interfering with adipogenesis are needed for both human health and the environment. However, challenges remain in testing and interpreting data on chemical-induced adipogenesis. This study reviewed available in vitro fish adipogenesis assays, summarized the effects of chemicals on fish adipogenesis, and compared chemical-induced adipogenesis results between mammalian and

fish assays. Primary fish adipocyte cultures have been developed for eight species of freshwater and seawater fish, with significant variation in culture media, particularly in adipogenic cocktails used. While lipid mixtures can enhance adipogenesis, they may not affect the commitment of multipotent progenitor cells to adipocyte linage and may not always be necessary for fish adipocyte cultures. Differences in chemical-induced adipogenesis between mammalian and fish assays may result not from species differences, but from variations in culture conditions, such as the composition of adipogenic cocktails and lipid mixtures, which can obscure the effects of chemicals on adipogenesis. There is a need for standardized adipogenesis assays, and developing OECD test guidelines is essential for their regulatory use. Fish adipogenesis assays can detect mechanisms of endocrine disruption that may not be apparent in mammalian cells, providing insights into mechanisms of action relevant to both human health and the environment. It is crucial to integrate adipogenesis data into the regulatory frameworks by expanding data requirements to include adipogenesis assays and developing reliability criteria for assessing adipogenesis studies. https://doi.org/10.1080/10643389.2024.2426815

Transcriptomic characterization of 2D and 3D human induced pluripotent stem cell-based in vitro models as New Approach Methodologies for developmental neurotoxicity testing,
Lislien, M., Kuchovska, E., Kapr, J., Duale, N., Andersen, J. M., Dirven, H., Myhre, O., Fritsche, E., Koch, K. and Wojewodzic, M. W., *Toxicology*, Jan 2025, Vol. 510.

The safety and developmental neurotoxicity (DNT) potential of chemicals remain critically understudied due to limitations of current in vivo testing guidelines, which are low throughput, resource-intensive, and hindered by species differences that limit their relevance to human health. To address these issues, robust New Approach Methodologies (NAMs) using deeply characterized cell models are essential. This study presents the comprehensive transcriptomic characterization of two advanced human-induced pluripotent stem cell (hiPSC)-derived models: a 2D adherent and a 3D neurosphere model of human neural progenitor cells (hiNPCs) differentiated up to 21 days. Using high-throughput RNA sequencing, we compared gene expression profiles of 2D and 3D models at three developmental stages (3, 14, and 21 days of differentiation). Both models exhibit maturation towards post-mitotic neurons, with the 3D model maturing faster and showing a higher prevalence of GABAergic neurons, while the 2D model is enriched with glutamatergic neurons. Both models demonstrate broad applicability domains, including excitatory and inhibitory neurons, astrocytes, and key endocrine and especially the understudied cholinergic receptors. Comparison with human fetal brain samples confirms their physiological relevance. This study provides novel in-depth applicability insights into the temporal and dimensional aspects of hiPSC-derived neural models for DNT testing. The complementary use of these two models is highlighted: the 2D model excels in synaptogenesis assessment, while the 3D model is particularly suited for neural network formation as observed as well in previous functional studies with these models. This research marks a significant advancement in developing human-relevant, high-throughput DNT assays for regulatory purposes. https://doi.org/10.1016/j.tox.2024.154000

Characterization of Chemical Exposome in A Paired Human Preconception Pilot Study,
Marchiandi, J., Dagnino, S., Zander-Fox, D., Green, M. P. and Clarke, B. O., *Environmental Science & Technology*, Nov 2024, Vol. 58, no. 46, p. 20352-20365.

Parental preconception exposure to synthetic chemicals may have critical influences on fertility and reproduction. Here, we present a robust LC-MS/MS method covering up to 95 diverse xenobiotics in human urine, serum, seminal and follicular fluids to support exposome-wide assessment in reproductive health outcomes. Extraction recoveries of validated analytes ranged from 62% to 137%

and limits of quantification from 0.01 to 6.0 ng/mL in all biofluids. We applied the validated method to a preconception cohort of Australian couples (n = 30) receiving fertility treatment. In total, 36 and 38 xenobiotics were detected across the paired biofluids of males and females, respectively, including PFAS, parabens, organic UV-filters, plastic additives, antimicrobials, and other industrial chemicals. Results showed 39% of analytes in males and 37% in females were equally detected in paired serum, urine, and reproductive fluids. The first detection of the sunscreen ingredient avobenzone and the industrial chemical 4-nitrophenol in follicular and seminal fluids suggests it can cross both blood-follicle/testis barriers, indicating potential risks for fertility. Further, the blood-follicle transfer of perfluorobutanoic acid, PFOA, PFHxS, PFOS, and oxybenzone corroborate that serum concentrations can be reliable proxies for assessing exposure within the ovarian microenvironment. In conclusion, we observed significant preconception exposure to multiple endocrine disruptors in couples and identified potential xenobiotics relevant to male and female fertility impairments. https://doi.org/10.1021/acs.est.4c04356

Analyzing high-throughput assay data to advance the rapid screening of environmental chemicals for human reproductive toxicity,
Varshavsky, J. R., Lam, J., Cooper, C., Allard, P., Fung, J., Oke, A., Kumar, R., Robinson, J. F. and Woodruff, T. J., *Reproductive Toxicology*, Jan 2025, Vol. 131.

While high-throughput (HTP) assays have been proposed as platforms to rapidly assess reproductive toxicity, there is currently a lack of established assays that specifically address germline development/function and fertility. We assessed the applicability domains of yeast (S. cerevisiae) and nematode (C. elegans) HTP assays in toxicity screening of 124 environmental chemicals, determining their agreement in identifying toxicants and their concordance with reproductive toxicity in vivo. We integrated data generated in the two models and compared results using a streamlined, semi-automated benchmark dose (BMD) modeling approach. We then extracted and modeled relevant mammalian in vivo data available for the matching chemicals included in the Toxicological Reference Database (ToxRefDB). We ranked potencies of common compounds using the BMD and evaluated correlation between the datasets using Pearson and Spearman correlation coefficients. We found moderate to good correlation across the three data sets, with r = 0.48 (95 % CI: 0.28-1.00, p<0.001) and rs = 0.40 (p=0.002) for the parametric and rank order correlations between the HTP BMDs; r = 0.95 (95 % CI: 0.76-1.00, p=0.0005) and rs = 0.89 (p=0.006) between the yeast assay and ToxRefDB BMDs; and r = 0.81 (95 % CI: 0.28-1.00, p=0.014) and rs = 0.75 (p=0.033) between the worm assay and ToxRefDB BMDs. Our findings underscore the potential of these HTP assays to identify environmental chemicals that exhibit reproductive toxicity. Integrating these HTP datasets into mammalian in vivo prediction models using machine learning methods could further enhance their predictive value in future rapid screening efforts. https://doi.org/10.1016/j.reprotox.2024.108725

Quantifying EDC Emissions from Consumer Products: A Novel Rapid Method and Its Application for Systematic Evaluation of Health Impacts,
Wu, Y. L., Li, H. W., Fan, Y. J., Hubal, E. a. C., Little, J. C., Eichler, C. M. A., Bi, C. Y., Song, Z. D., Qiu, S. L. and Xu, Y., *Environmental Science & Technology*, Dec 2024, Vol. 58, no. 51, p. 22700-22713.

Endocrine-disrupting chemicals (EDCs) are widely used in consumer products and have been associated with adverse public health outcomes and significant economic costs. We developed a rapid chamber method for measuring EDC emissions from consumer products, significantly reducing the time to reach steady state from weeks or months to minutes or hours. Using this method, we quantified EDC emissions from a wide range of products, determined the emission-control parameters, and established their relationship with the EDC content (W f) and physicochemical properties. By incorporating W f data from consumer product databases and applying stochastic

models, we systematically estimated emissions for 400 EDC-product combinations and assessed the associated exposure and disease burden for the U.S. population. Our results suggest that more than 60% of these combinations could result in carcinogenic disability-adjusted life years (DALYs) above the acceptable threshold. The overall disease burden caused by EDCs in consumer products can be substantial, with DALYs exceeding those associated with other pollutants, such as particulate matter, in a worst-case scenario. This study provides a valuable tool for prioritizing hazardous EDCs in consumer products, evaluating safer alternatives, and formulating effective intervention strategies, thereby supporting policymakers and manufacturers in making informed, sustainable decisions. https://doi.org/10.1021/acs.est.4c09466

Employment of a Newly Defined In Vitro Fertilization Protocol to Determine the Cytoskeletal Machinery, DNA Damage, and Subsequent DNA Repair Resulting from Endocrine Disruption by Hexavalent Chromium in Rat Metaphase II Oocytes,
Wuri, L., Zarutskie, P. W., Arosh, J. A. and Banu, S. K., *Current Protocols*, Dec 2024, Vol. 4, no. 12.

These protocols describe a detailed method to determine the DNA damage and F-actin and microtubule defects of metaphase II oocytes caused by hexavalent chromium, Cr(VI), an endocrine disrupting chemical (EDC). The protocol provides systematic steps to determine protein expression encoded by pluripotency proteins such as Oct4, Nanog, and Cdx2 during early embryonic development. Occupational or environmental exposure to EDCs has significantly increased infertility in both men and women. The urinary concentration of the EDC bisphenol A in patients undergoing in vitro fertilization (IVF) is directly related to decreased implantation rates and the number of metaphase II oocytes recovered. This protocol outlines crucial steps in assessing the structure of F-actin and microtubules, DNA damage, and repair mechanisms in metaphase II oocytes as well as pluripotency protein markers of early-stage embryos. IVF techniques to achieve fertility goals in both humans and animals are of paramount importance. The interplay between F-actin and microtubules is crucial for bipolar spindle assembly and correct partitioning of the nuclear genome in mammalian oocyte meiosis. EDCs induce DNA damage and impair DNA repair mechanisms, compromising oocyte quality. In human IVF, this results in failure to implant, early miscarriage, and live births with congenital disorders, thus decreasing success rates and increasing poor outcomes. The application of IVF protocols in rats to understand EDC-mediated defects in the cytoskeletal network of metaphase II oocytes is not well established. We present a newly defined rat IVF protocol and demonstrate outcomes using these protocols to determine the adverse effects of Cr(VI) on metaphase II oocytes. Basic Protocol 1 includes steps to superovulate rats, dissect ampullae, retrieve oocytes/eggs, perform immunofluorescence staining of cytoskeletal machinery (microtubules and F-actin), and assess expression of the DNA double-strand break marker gamma-H2AX and the DNA repair protein RAD51 in control and Cr(VI)-exposed rats. Basic Protocol 2 describes methods for detecting the pluripotency proteins Oct4, Nanog, and Cdx2 during early embryonic development in control rats. (c) 2024 Wiley Periodicals LLC.Basic Protocol 1: In vivo EDC treatment of rats and immunostaining of treated oocytesBasic Protocol 2: In vitro fertilization and immunostaining of early-stage embryos https://doi.org/10.1002/cpz1.70060

The associations between exposure to mixed environmental endocrine disruptors and sex steroid hormones in men: a comparison of different statistical models,
Zhao, S. H., Dong, J. L. and Luo, Z. Y., *Scientific Reports*, Nov 2024, Vol. 14, no. 1.

In recent years, worldwide fertility rates have continued to decrease. Humans are frequently exposed to a combination of environmental endocrine disruptors, which can cause male reproductive disorders. The study employed three distinct analytical models to examine the correlation between exposure to a combination of 25 chemicals and sex steroid hormone levels in adult males. This

involved evaluating 12 chemicals and their metabolites from personal care and consumer products, as well as 13 metabolites linked to phthalates and plasticisers. The study analysed 25 chemicals and 3 measured sex steroid hormone outcomes, as well as two calculated hormonal outcomes (free androgen index, TT/E2 ratio) in 1262 adult men who participated in the National Health and Nutrition Examination Survey (NHANES) 2013-2016 in the United States. The study employed several statistical methods to estimate the relationships between single chemicals or chemical blends and sex hormones. These methods included linear regression, weighted quantile sum (WQS) regression, and Bayesian kernel machine (BKMR) regression. The results of the linear regression analysis indicate that chemical exposure has a negative correlation with E2, TT, and FAI, and a positive correlation with SHBG and TT/E2. The mixture effect analyses using the WQS and BKMR models further confirmed that BP3, MECPP, and MECOP were the most highly weighted chemical mixtures. The analyses also suggested that there were differences in the effects of different concentrations of EDCs on sex steroid hormones. Exposure to environmental endocrine-disrupting chemicals (EDCs) has been found to have a negative correlation with estradiol and total testosterone, as well as FAI. Conversely, this exposure has been found to have a positive correlation with sex hormone binding globulin and the TT/E2 ratio. The study also revealed differences in the effects of different concentrations of EDCs. https://doi.org/10.1038/s41598-024-76972-z

Agenda, actualité, politique, et évaluation de l'exposition

EDLists - List Updates,
EDLists (décembre 2024),
More information about the substances has been added to the lists: New status text, reason for removal of substances, enable clicking on all the substances etc.
List I
Triphenyl phosphate (TPP) added: Identified as a SVHC (ED ENV)
Metribuzin added: EFSA ED proposal has now been legally adopted
More substances added that belong to the group entry 4-Nonylphenol, branched and linear, ethoxylated (SVHC - ED ENV)
2-[2-(nonylphenoxy)ethoxy]ethanol
Poly(oxy-1,2-ethanediyl), α-(nonylphenyl)-ω-hydroxy-, branched
2-(nonylphenoxy)ethanol
20-(isononylphenoxy)-3,6,9,12,15,18-hexaoxaicosan-1-ol
44-(nonylphenoxy)-3,6,9,12,15,18,21,24,27,30,33,36,39,42-tetradecaoxatetratetracontanol
2-(isononylphenoxy)ethanol
3,6,9,12-Tetraoxatetradecan-1-ol, 14-(4-nonylphenoxy)-, branched
3,6,9,12,15,18,21,24,27-Nonaoxanonacosan-1-ol, 29-(isononylphenoxy)-
3,6,9,12,15-Pentaoxaheptadecan-1-ol, 17-(nonylphenoxy)-
29-(nonylphenoxy)-3,6,9,12,15,18,21,24,27-nonaoxanonacosanol
20-(nonylphenoxy)-3,6,9,12,15,18-hexaoxaicosan-1-ol
List II
Triphenyl phosphate (TPP) removed: Added to list I (SVHC). SCCS evaluation also finalised.
Bis(dibutyldithiocarbamato-S,S')copper removed: Suspended from Corap
EDDHMAFEK removed: Substance evaluation concluded
Fludioxonil added: Concluded ED in EFSA opinion. Not yet legally adopted.
Flufenacet added: Concluded ED in EFSA opinion. Not yet legally adopted.
Medetomidine added: Concluded ED in BPC opinion. Not yet legally adopted.
Metribuzin removed: EFSA ED proposal legally adopted. Added to list I
Daidzein and genistein removed: SCCS evaluations finalized

1-isopropyl-2,2-dimethyltrimethylene diisobutyrate added: ED HH CLH intention submitted
Tris[2-chloro-1-(chloromethyl)ethyl] phosphate added: ED HH CLH intention submitted
3-aminopropyldimethylamine added: ED HH CLH intention submitted
List III
Lithium carbonate, lithium chloride and lithium hydroxide added by France (ED HH)
Tris(4-nonylphenyl, branched) phosphite added by France (ED ENV). This concern addresses the group of substances "Tris(4-nonylphenyl, branched and linear) phosphite (TNPP)".' https://edlists.org/list-updates

Draft Community Rolling Action Plan (CoRAP) update for years 2025-2027,
ECHA (décembre 2024),
The draft is for an annual update of the CoRAP and covers the three subsequent years 2025-2027. It contains substances suspected of posing a risk to human health or the environment. The draft CoRAP contains 31 substances, including 13 new substances compared to the current CoRAP 2024-2026; 8 substances are being planned for evaluation in 2025, including two groups of 2 substances, 15 substances for evaluation in 2026 and 5 substances for evaluation in 2027. https://echa.europa.eu/documents/10162/879660/draft_corap_update_2025-2027_en.pdf/bcc2e3fa-f6a4-5d49-851a-7c14163b3f15?#msdynttrid=UnO6VPeb1UlqnmmSa25pLo_Au7Xy_u4XyMkkpfY5mfo

Candidate Liste : update of one entry,
ECHA (janvier 2025),
Tris(4-nonylphenyl, branched and linear) phosphite has endocrine disrupting properties affecting the environment and is used in polymers, adhesives, sealants and coatings. The entry for this substance is updated to reflect that it is an endocrine disrupter to the environment both due to its intrinsic properties and when it contains ≥ 0.1% w/w of 4-nonylphenol, branched and linear (4-NP). https://echa.europa.eu/fr/-/echa-adds-five-hazardous-chemicals-to-the-candidate-list-and-updates-one-entry

Perturbateurs endocriniens, comment supprimer ou réduire l'exposition ?,
Prévention BTP, 2024.

Les perturbateurs endocriniens ne sont pas faciles à identifier en milieu professionnel. C'est pourtant indispensable pour pouvoir se préserver de leur toxicité. https://doi.org/https://www.preventionbtp.fr/actualites/magazine/sante/perturbateurs-endocriniens-comment-supprimer-ou-reduire-l-exposition_5KydTvnskj7CyAnWTbA27E

Une grande quantité d'aliments non bio présente des traces de substances dangereuses,
Actu Environnement (décembre 2024),
Les aliments d'origine végétale cultivés de manière conventionnelle (donc non biologique), puis vendus (avec l'étiquetage approprié) et consommés en France contiennent encore un taux significatif de résidus de pesticides, en particulier, lesquels sont des substances dangereuses pour la santé. L'association Générations futures en a dressé le constat statistique, ce mardi 17 décembre, à partir des données françaises de l'année 2022 remontées à l'Agence européenne de sécurité alimentaire (Efsa) en 2024. https://www.actu-environnement.com/ae/news/aliments-non-bio-substances-cmr-perturbateur-endocrinien-pfas-pesticides-45269.php4

Le bisphénol A proscrit des contenants alimentaires en Europe au terme d'une longue bataille,
Le Monde, 2025-01-11 2025.

A partir du 20 janvier, le perturbateur endocrinien ne doit plus entrer en contact avec des aliments en Europe. L'UE a mis dix ans pour s'aligner sur la position de la France, qui avait banni la molécule en 2015. https://doi.org/https://www.lemonde.fr/planete/article/2025/01/11/le-bisphenol-a-proscrit-des-contenants-alimentaires-en-europe-au-terme-d-une-longue-bataille_6492963_3244.html

Les perturbateurs endocriniens : quels risques ? quelle prévention ? Symposium INRS-CARSAT Languedoc-Roussillon. Montpellier, 6 juin 2024,
Delepine, A., *Références en santé au travail*, 2024.

TD 321. Article de 7 pages, publié dans le n°180. 12/2024
Ce symposium, organisé par l'INRS et la CARSAT Languedoc-Roussillon, a permis de faire le point des connaissances sur les perturbateurs endocriniens (PE). Le repérage des PE en entreprise est la première étape dans la démarche de prévention des risques qui leur sont associés.
Dans ce contexte, le rôle des services de prévention et de santé au travail (SPST) ainsi que celui des CARSAT est précieux dans l'accompagnement des actions de prévention, notamment pour la substitution des PE et le suivi médical des salariés exposés. Des exemples d'actions menées en entreprise sont également présentés.
https://doi.org/https://www.inrs.fr/media.html?refINRS=TD%20321

Des perturbateurs endocriniens et des PFAS retrouvés dans des emballages alimentaires en fibres végétales,
Vert, 2025.

Les emballages alimentaires à base de fibres végétales peuvent contenir des substances nocives et ne sont pas forcément durables, déplore l'association Consommation logement cadre de vie (CLCV) dans une étude publiée ce mardi. https://doi.org/https://vert.eco/articles/des-substances-nefastes-retrouvees-dans-des-emballages-alimentaires-en-fibres-vegetales

Les Surligneurs,
2025.
La rumeur selon laquelle la prise de paracétamol pendant une grossesse peut « féminiser » les fœtus refait surface sur Instagram. Cette théorie n'a été prouvée par aucune étude scientifique, nous expliquent trois experts, et prospère sur une confusion sur le terme de « féminisation ». https://doi.org/https://www.lessurligneurs.eu/non-aucune-etude-ne-prouve-que-le-paracetamol-feminise-les-petits-garcons/

Contaminant Exposure Profiles Demonstrate Similar Physiological Effects Across Environments Despite Unique Profile Composition in Formosa, Argentina, and Connecticut, USA,
Chaney, C., Mansilla, L., Kubica, M., Pinto-Pacheco, B., Dunn, K., Bertacchi, V., Walker, D. I. and Valeggia, C., *American Journal of Human Biology*, Jan 2025, Vol. 37, no. 1.

Exposure to environmental contaminants is globally universal. However, communities vary in the specific combination of contaminants to which they are exposed, potentially contributing to variation in human health and creating "locally situated biologies." We investigated how environmental exposures differ across environments by comparing exposure profiles between two contexts that differ markedly across political, economic, and sociocultural factors-Namqom, Formosa, Argentina, and New Haven, Connecticut, United States.MethodsWe collected infant urine, maternal urine, and human milk samples from mother-infant dyads in Formosa (n = 13) and New Haven (n = 21). We used untargeted liquid chromatography with high-resolution mass spectrometry (LC-HRMS) to annotate

environmental contaminants and endogenous metabolites in these samples, and we analyzed the data using exposome-wide association studies (EWAS) followed by pathway enrichment.We found statistically significant differences between the chemical exposure profiles of the Argentinian and US mothers, mostly involving pesticides; however, we observed similarities in the infant urine and human milk environmental contaminant profiles, suggesting that the maternal body may buffer infant exposure through human milk. We also found that infants and mothers were exposed to contaminants that were associated with alterations in amino acid and carbohydrate metabolism. Infants additionally showed alterations in vitamin metabolism, including vitamins B1, B3, and B6. Differences in chemical exposure profiles may be related to structural factors. Despite variation in the composition of exposure profiles between the two study sites, environmental contaminant exposure was associated with similar patterns in human physiology when we considered contaminants comprehensively rather than individually, with implications for metabolic and cardiovascular disease risk as well as infant cognitive development. https://doi.org/10.1002/ajhb.24178

Associations of per- and polyfluoroalkyl substances with human milk metabolomic profiles in a rural North American cohort,
Criswell, R. L., Bauer, J. A., Christensen, B. C., Meijer, J., Peterson, L. A., Huset, C. A., Walker, D. I., Karagas, M. R. and Romano, M. E., *Environmental Epidemiology*, Dec 2024, Vol. 8, no. 6.

Per- and polyfluoroalkyl substances (PFAS) are a class of persistent synthetic chemicals that are found in human milk and are associated with negative health effects. Research suggests that PFAS affect both lactation and the human metabolome. We measured perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) in the milk of 425 participants from the New Hampshire Birth Cohort Study using liquid chromatography-tandem mass spectrometry (LC-MS/MS). A nontargeted metabolomics assay was performed using LC with high-resolution MS, and metabolites were identified based on in-house database matching. We observed six metabolic profiles among our milk samples using self-organizing maps, and multinomial logistic regression was used to identify sociodemographic and perinatal predictors of these profiles, including infant sex, parity, participant body mass index, participant age, education, race, smoking status, gestational weight gain, and infant age at time of milk collection.Results:Elevated PFOA was associated with profiles containing higher amounts of triglyceride fatty acids, glycerophospholipids and sphingolipids, and carnitine metabolites, as well as lower amounts of lactose and creatine phosphate. Lower concentrations of milk PFOS were associated with lower levels of fatty acids. Our findings suggest that elevated PFOA in human milk is related to metabolomic profiles consistent with enlarged milk fat globule membranes and altered fatty acid metabolism. Further, our study supports the theory that PFAS share mammary epithelial membrane transport mechanisms with fatty acids and associate with metabolic markers of reduced milk production. https://doi.org/10.1097/ee9.0000000000000352

The ENDOMIX perspective: how everyday chemical mixtures impact human health and reproduction by targeting the immune system,
Gómez-Olarte, S., Mailänder, V., Castro-Neves, J., Stojanovska, V., Schumacher, A., Meyer, N. and Zenclussen, A. C., *Biology of Reproduction*, Oct 2024, Vol. 111, no. 6, p. 1170-1187.

Endocrine-disrupting chemicals are natural and synthetic compounds found ubiquitously in the environment that interfere with the hormonal- immune axis, potentially impacting human health and reproduction. Exposure to endocrine-disrupting chemicals has been associated with numerous health risks, such as neurodevelopmental disorders, metabolic syndrome, thyroid dysfunction, infertility, and cancers. Nevertheless, the current approach to establishing causality between these substances and disease outcomes has limitations. Epidemiological and experimental research on endocrine-disrupting chemicals faces challenges in accurately assessing chemical exposure and interpreting non-

monotonic dose response curves. In addition, most studies have focused on single chemicals or simple mixtures, overlooking complex real-life exposures and mechanistic insights, in particular regarding endocrine-disrupting chemicals' impact on the immune system. The ENDOMIX project, funded by the EU's Horizon Health Program, addresses these challenges by integrating epidemiological, risk assessment, and immunotoxicology methodologies. This systemic approach comprises the triangulation of human cohort, in vitro, and in vivo data to determine the combined effects of chemical mixtures. The present review presents and discusses current literature regarding human reproduction in the context of immunotolerance and chemical disruption mode of action. It further underscores the ENDOMIX perspective to elucidate the impact of endocrine- disrupting chemicals on immune-reproductive health. https://doi.org/10.1093/biolre/ioae142

Consensus on the key characteristics of metabolism disruptors,
La Merrill, M. A., Smith, M. T., Mchale, C. M., Heindel, J. J., Atlas, E., Cave, M. C., Collier, D., Guyton, K. Z., Koliwad, S., Nadal, A., Rhodes, C. J., Sargis, R. M., Zeise, L. and Blumberg, B., *Nature Reviews Endocrinology*, 2024 Nov 2024.

Metabolism-disrupting agents (MDAs) are chemical, infectious or physical agents that increase the risk of metabolic disorders. Examples include pharmaceuticals, such as antidepressants, and environmental agents, such as bisphenol A. Various types of studies can provide evidence to identify MDAs, yet a systematic method is needed to integrate these data to help to identify such hazards. Inspired by work to improve hazard identification of carcinogens using key characteristics (KCs), we developed 12 KCs of MDAs based on our knowledge of processes underlying metabolic diseases and the effects of their causal agents: (1) alters function of the endocrine pancreas; (2) impairs function of adipose tissue; (3) alters nervous system control of metabolic function; (4) promotes insulin resistance; (5) disrupts metabolic signalling pathways; (6) alters development and fate of metabolic cell types; (7) alters energy homeostasis; (8) causes inappropriate nutrient handling and partitioning; (9) promotes chronic inflammation and immune dysregulation in metabolic tissues; (10) disrupts gastrointestinal tract function; (11) induces cellular stress pathways; and (12) disrupts circadian rhythms. In this Consensus Statement, we present the logic that revealed the KCs of MDAs and highlight evidence that supports the identification of KCs. We use chemical, infectious and physical agents as examples to illustrate how the KCs can be used to organize and use mechanistic data to help to identify MDAs. This Consensus Statement uses available mechanistic knowledge on pharmaceutical, chemical, physical and biological agents to identify the key characteristics (KCs) of metabolism-disrupting agents (MDAs). Examples demonstrating the use of these KCs to characterize the toxicity of various agents are provided. Recommendations for assessing how previously untested chemicals might affect specific KCs are also outlined. https://doi.org/10.1038/s41574-024-01059-8

Reproductive toxicology: keeping up with our changing world,
Miller, L. B., Feuz, M. B., Meyer, R. G. and Meyer-Ficca, M. L., *Frontiers in Toxicology*, Oct 2024, Vol. 6.

Reproductive toxicology testing is essential to safeguard public health of current and future generations. Traditional toxicological testing of male reproduction has focused on evaluating substances for acute toxicity to the reproductive system, with fertility assessment as a main endpoint and infertility a main adverse outcome. Newer studies in the last few decades have significantly widened our understanding of what represents an adverse event in reproductive toxicology, and thus changed our perspective of what constitutes a reproductive toxicant, such as endocrine disrupting chemicals that affect fertility and offspring health in an intergenerational manner. Besides infertility or congenital abnormalities, adverse outcomes can present as increased likelihood for various health problems in offspring, including metabolic syndrome, neurodevelopmental problems like autism and

increased cancer predisposition, among others. To enable toxicologic studies to accurately represent the population, toxicologic testing designs need to model changing population characteristics and exposure circumstances. Current trends of increasing importance in human reproduction include increased paternal age, with an associated decline of nicotinamide adenine dinucleotide (NAD), and a higher prevalence of obesity, both of which are factors that toxicological testing study design should account for. In this perspective article, we highlighted some limitations of standard testing protocols, the need for expanding the assessed reproductive endpoint by including genetic and epigenetic sperm parameters, and the potential of recent developments, including mixture testing, novel animal models, in vitro systems like organoids, multigenerational testing protocols, as well as in silico modelling, machine learning and artificial intelligence. https://doi.org/10.3389/ftox.2024.1456687

Study of Endocrine-Disrupting Chemicals in Infant Formulas and Baby Bottles: Data from the European LIFE-MILCH PROJECT,
Nuti, F., Fernandez, F. R., Severi, M., Traversi, R., Fanos, V., Street, M. E., Palanza, P., Rovero, P. and Papini, A. M., *Molecules*, Nov 2024, Vol. 29, no. 22.

Exposure to endocrine-disrupting chemicals (EDCs) is inevitable, and growing scientific evidence indicates that even very low doses can negatively impact human health, particularly during pregnancy and the neonatal period. As part of the European project LIFE18 ENV/IT/00460, this study aims to identify the presence of EDCs in 20 infant formulas (both powdered and liquid) and the release from baby bottles and teats. Particularly, sensitization of young people and future parents towards the potential harmful effects of EDCs could significantly help to reduce exposure. Seven different UPLC-MS/MS methodologies and one ICP-AES were set up to quantify already assessed and suspected EDCs among 85 different chemicals (bisphenols, parabens, PAHs, phthalates, pesticides, herbicides and their main metabolites, PFAS, and metals). Results showed that in 2 out of 14 baby bottles, only anthracene and phenanthrene of the group of PAHs were released (10.68-10.81 ng/mL). Phthalates such as mono-ethyl phthalate (MEP) were found in 9 of 14 samples (0.054-0.140 ng/mL), while mono(2-ethyl-5-oxohexyl) phthalate (MeOHP) appeared in 2 samples (0.870-0.930 ng/mL). In accordance with current EU regulations, other chemicals were not detected in baby bottles and teats. However, bisphenols, parabens, PAHs, phthalates, PFAS, and metals were detected in infant formula, emphasizing the need for continued monitoring and public health interventions. https://doi.org/10.3390/molecules29225434

Awareness and Knowledge of Endocrine-Disrupting Chemicals Among Pregnant Women and New Mothers: A Cross-Sectional Survey Study,
Okman, E. and Yalçin, S. S., *Toxics*, Dec 2024, Vol. 12, no. 12.

Background/Objectives: Endocrine-disrupting chemicals (EDCs) are exogenous substances that interfere with hormone regulation, leading to adverse health outcomes. Despite the wide use of EDCs in daily products like plastics, personal care items, and food packaging, public awareness remains low. Pregnant women and new mothers are particularly vulnerable, as exposure to EDCs during early life stages can have long-term health impacts. This cross-sectional, questionnaire-based study aimed to assess the awareness of EDCs among pregnant women and new mothers at a maternity hospital. Methods: This cross-sectional study was conducted in a tertiary care hospital between January and August 2022. A questionnaire based on the Mutualit és Libres/AIM 2020 survey was used to assess awareness of EDCs among pregnant and postpartum women. The original survey was adapted culturally and linguistically for the Turkish population through translation and expert review. The questionnaire included sections on sociodemographics, habits, knowledge, information sources, healthcare, readiness for change, expectations, and attitudes. Results: The results showed that 59.2% of participants were unfamiliar with EDCs, and many lacked awareness of the associated health risks,

including cancers, infertility, and developmental disorders in children. A significant portion of respondents had never heard of bisphenol A (BPA) or phthalates, while awareness of parabens was relatively higher. Conclusions: The study concluded that increasing awareness of EDCs is essential for fostering informed avoidance behaviors, especially in vulnerable populations like pregnant women and new mothers. Public health campaigns and healthcare provider involvement are crucial for enhancing awareness and reducing the health risks associated with EDCs. https://doi.org/10.3390/toxics12120890

Comparative analysis of the bioaccumulation of bisphenol A in the blood serum and follicular fluid of women living in two areas with different environmental impacts,
Raimondo, S., Chiusano, M. L., Gentile, M., Gentile, T., Cuomo, F., Gentile, R., Danza, D., Siani, L., Crescenzo, C., Palmieri, M., Iaccarino, S., Iaccarino, M., Fortunato, A., Liguori, F., Esposito, A., Zullo, C., Sosa, L., Sosa, L., Ferrara, I., Piscopo, M., Notari, T., Lacatena, R., Gentile, A. and Montano, L., *Frontiers in Endocrinology*, Oct 2024, Vol. 15.

Introduction Bisphenol A (BPA) is a common contaminant widely used in many industrial sectors. Because of its wide use and dispersion, it can be accumulated in living human bodies through both oral assumption and nondietary routes. BPA exhibits hormone-like properties, falling under the class of endocrine disruptors; therefore, it can alter relevant physiological functions. In particular, in women, it can affect folliculogenesis and therefore reproduction, contributing not only to infertility, but also to endometriosis and premature puberty. Methods We conducted a multicenter study on 91 women undergoing a first in vitro fertilization (IVF) treatment in the Campania region (Southern Italy). We investigated the presence and concentration of BPA in serum and follicular fluids to assess the effects of airborne BPA contamination. The analysis was conducted on 32 women living in a low environmental impact (LEI) area, from the Sele Valley River and Cilento region, and 59 women living in a high environmental impact (HEI) area, the so-called "Land of Fires", a highly contaminated territory widely exposed to illegal waste practices. Results A higher average BPA content in both blood serum and follicular fluid was revealed in the HEI group when compared with the LEI group. In addition, we revealed higher average BPA content in blood serum than in folliclular fluid in the HEI area, with opposite average content in the two fluids in the LEI zone. In addition, our results also showed a lack of correlation between BPA content in follicular and serum fluids both in the overall population and in the HEI and LEI groups, with peculiar trends in different subsets of women. Conclusion From our results, we revealed a heterogeneity in the distribution of BPA content between serum and follicular fluid. Further studies are needed to unravel the bioaccumulation mechanisms of BPA in highly polluted and nonpolluted areas. https://doi.org/10.3389/fendo.2024.1392550

Management of phthalates in Canada and beyond: can we do better to protect human health?
Renwick, M. J., Bolling, A. K., Shellington, E., Rider, C. F., Diamond, M. L. and Carlsten, C., *Frontiers in Public Health*, Nov 2024, Vol. 12.

Ortho-phthalates (herein referred to as phthalates) are synthetic chemicals used in thousands of different everyday products and materials. Nearly ubiquitous environmental exposure is reflected by phthalate metabolites in the urine of almost all Canadians. However, phthalate exposure tends to be higher amongst people of low socioeconomic status and ethnic minorities. Substantial evidence shows that certain phthalates cause harm to human health, particularly developing fetuses and children. Governments vary in their approach to assessing and managing risks associated with phthalates. Canada continues to take a more permissive stance on phthalate regulations compared to the EU and some US states. We argue that the recent Canadian national risk assessment on phthalates does not appropriately reflect the growing evidence demonstrating harm to human health from phthalate exposure and does not adequately consider the evidence showing higher exposures faced by

vulnerable populations. Canadians would benefit from adopting a more stringent regulatory approach to phthalates. Specifically, Canada should expand phthalate restrictions to apply to all consumer products, implement sunset dates toward eliminating the use of existing phthalates, and mandate publicly available evidence of no harm for phthalate alternatives. Canadian alignment on phthalate regulations with the EU and a growing number of US states could encourage other countries to follow suit. https://doi.org/10.3389/fpubh.2024.1473222

Exposure of elementary school-aged Brazilian children to bisphenol A: association with demographic, social, and behavioral factors, and a worldwide comparison,
Rocha, P. R. S., Moura, H., Silva, N. G., Neves, F. a. R., Sodré, F. F. and Amato, A. A., *Scientific Reports*, Oct 2024, Vol. 14, no. 1.

Bisphenol A (BPA) is a plasticizer used to synthesize polycarbonate plastics and epoxy resins and is well-known for its endocrine-disrupting action. BPA occurrence in the environment is widespread, and there is a growing concern regarding exposure to this chemical during childhood, given the findings indicating the long-lasting hazards associated with exposure during early life compared to adulthood. We examined urinary BPA concentrations from 319 elementary school-aged Brazilian children, using high-performance liquid chromatography coupled to high-resolution mass spectrometry. We found that urinary BPA was detectable in the majority of children, and that urinary BPA levels were higher among children with lower family income and lower maternal educational levels. BPA levels found herein were compared with those from countries with different regulation policies concerning exposure to BPA. They were similar to those reported from studies conducted in Egypt and Australia. Despite more protective regulatory policies in the European Union, they were similar or lower than those reported in European studies. Our findings indicate that exposure of Brazilian children to BPA is widespread and comparable to or even lower than that of countries with stricter regulatory policies. https://doi.org/10.1038/s41598-024-67267-4

Toxicity as process: tracing a new epigenetic regime of im/perceptibility in environmental toxicology,
Rossmann, S. and Müller, R., *Science as Culture*, 2024 Oct 2024.

Science and Technology Studies (STS) research has paid considerable attention to how toxicology produces knowledge on toxicity and how this knowledge has changed. For example, modern toxicological approaches of dose-response and threshold levels and genetic/genomic approaches for tracing exposure-induced DNA damage have been found to yield specific notions of toxicity. However, some of the toxicants' latent exposure effects have remained invisible with these two established epistemic perspectives. To tackle this issue, environmental toxicologists have recently turned to environmental epigenetics, offering a promising biomolecular perspective to better understand the role of latent exposure effects on health. Analysing environmental toxicology literature on epigenetics and interviews with key researchers demonstrates how an epigenetic perspective yields a novel notion of toxicity as process. This temporal emphasis foregrounds the idea that bodies are not just exposed to toxicants but dynamically respond to the exposures they experience. In particular, environmental toxicologists draw on a specific combination of an epigenetic theory of toxicity and new but compatible methods and technologies, which establish a new epistemic understanding of toxicity. Characterising these developments as a Regime of Im/Perceptibility shows how novel regimes can emerge in both difference and continuity with prior regimes such as modern and genetic/genomic toxicology. The case study on epigenetic research in environmental toxicology adds to STS scholarship on epistemic developments in scientific fields by illuminating how a new epistemic perspective is successfully adopted while co-existing with established regimes of knowledge production in a given field. https://doi.org/10.1080/09505431.2024.2416667

Estimated human intake of endogenous and exogenous hormones from beef in the United States, Thilakaratne, R., Castorina, R., Solomon, G., Mosburg, M. M., Moeller, B. C., Trott, J. F., Falt, T. D., Villegas-Gomez, A., Dodd, K. W., Thomsen, C., English, P., Yang, X., Khan, A., Bradman, A. and Hovey, R. C., *Journal of Exposure Science and Environmental Epidemiology*, 2024 Nov 2024.

BackgroundEndogenous and exogenous hormones may be present in beef. Human consumption of hormones has been linked to adverse health effects. ObjectiveTo estimate daily intake of hormonal growth promotants (HGP) from beef consumed by the US population. We combined self-reported beef consumption information from a nationally-representative survey with concentrations of 12 HGP measured in 397 samples of retail beef/fat purchased in California. We defined typical, high, and maximum intake scenarios assuming self-reported consumed beef contained the mean, 95th percentile, and maximum concentrations of each HGP, respectively. We estimated distributions of usual (i.e., long-term) daily intake and short-term daily intake (mu g/kg/day). We calculated the hazard quotient (HQ), or ratio of estimated intake to the World Health Organization's acceptable daily intake (ADI) for the HGP.ResultsThe highest estimated HQs were found for melengestrol acetate (MGA). For usual daily intake under the typical intake scenario, no HQ exceeded 0.02 (0.00047 mu g MGA/kg/day). Under the maximum intake scenario, the highest HQ was 0.29 (0.0087 mu g MGA/kg/day), corresponding to the 99th percentile of intake among young boys (ages 1-5). The highest short-term intake estimates for MGA under the maximum intake scenario were the 99th percentile of intake among young girls and boys, which equaled (HQ = 1.00) or exceeded (HQ = 1.29) the ADI for MGA, respectively. ImpactHormonal growth promotants (HGP) are used to increase beef production and have been linked to adverse reproductive effects. We estimated daily intake of MGA and several other HGP using US nationally-representative beef consumption data collected between 2015-2018 and HGP concentrations in retail beef. Estimated intake was highest for young children, but estimates were generally very low compared to current health-based intake limits. However, these limits are typically based on studies in adult animals, and further study of potential adverse effects during sensitive developmental periods, such as in early life, may be warranted to ensure recommended intake limits are health-protective. https://doi.org/10.1038/s41370-024-00727-1

Improving the Health and Environmental Health Literacy of Professionals: Evaluating the Effect of a Virtual Intervention on Phthalate Environmental Health Literacy,
Tomsho, K. S., Quinn, M. R., Wang, Z., Preston, E. V., Adamkiewicz, G., Joseph, N. T., Wylie, B. J. and James-Todd, T., *Int J Environ Res Public Health*, Nov 26 2024, Vol. 21, no. 12.

The American College of Obstetricians and Gynecologists provided updated guidance in 2021, recommending that reproductive health professionals should include discussion of environmental exposures with their patients. However, environmental health is seldom included in medical training, with endocrine-disrupting chemicals, such as phthalates-linked to adverse pregnancy outcomes-being among the least discussed. We developed a one-hour virtual educational intervention to train reproductive health professionals on the routes of phthalate exposure, potential associated health impacts, and suggestions on how to discuss exposure reduction with patients. The intervention was designed to include perspectives from patients, scientists, and clinicians. Using a pre/post/post design, we evaluated the impact of the intervention on reproductive health professionals' phthalate-related reproductive health literacy via a validated environmental health literacy (EHL) scale, their confidence in discussing phthalates, and the frequency of discussions about phthalates with patients. All materials, including the study questionnaires and intervention materials, were administered virtually to reproductive health professionals (n = 203) currently seeing patients working in the United States. After completing the intervention, reproductive health professionals' average EHL increased

(pre-course: 22.3, post-course: 23.7, 2 months post-course: 24.0), as did their confidence in discussing phthalates with their patients (pre-course: 1% (2/203) reported being quite confident, post-course: 64% (131/203) reported being quite confident, and 2 months post course: 86% (174/203) reported being quite confident). Additionally, the reported frequency of discussions about phthalates with patients rose substantially (pre-course: 0% (0/203) reported usually discussing phthalates with patients, and 2 months post-course: 86% (175/203) reported usually discussing phthalates with patients): In line with the recommendations of the American College of Obstetricians and Gynecologists, this online phthalate educational intervention tool increased EHL among reproductive health professionals and shifted clinical care to include discussion about phthalates, a reproductive toxicant. https://doi.org/10.3390/ijerph21121571

Toxicité sur les animaux

Endocrine-disrupting chemical, methylparaben, in environmentally relevant exposure promotes hazardous effects on the hypothalamus-pituitary-thyroid axis,
Azeredo, D. B. C., Sousa Anselmo, D., Falcão Veríssimo, A. C., Souza, L. L., Lisboa, P. C., Soares, P., Santos-Silva, A. P., Graceli, J. B., Carvalho, D. P., Magliano, D. and Miranda-Alves, L., *Mol Cell Endocrinol*, Dec 24 2024, Vol. 598, p. 112444.

Methylparaben (MP) belongs to the paraben class and is widely used as a preservative in personal care products, medicines, and some foods. MP acts as an endocrine disrupting chemical (EDC) on the hypothalamic-pituitary-thyroid (HPT) axis. However, the effects of MP have not yet been completely elucidated, as published results are scarce and controversial. The objective of this work was to evaluate the effects of subacute exposure to MP on the HPT axis of male rats. To achieve this, in this study the animals were divided into four experimental groups: control, MP3, MP30 and MP300 (3, 30 and 300 µg/kg/day, respectively). The rats were gavage for 14 days and sacrificed at the end of MP treatment. Our findings demonstrated that MP can promote important changes in thyroid morphology, including a decrease in follicular area, colloid area, epithelial area, and epithelial height, affecting the homeostasis of the HPT axis, and affecting the expression of genes related to hormonal biosynthesis. Furthermore, changes in interstitial collagen deposition were also demonstrated. Finally, we conclude that exposure to MP can be harmful to health, as it is involved in the dysregulation of the thyroid gland, affecting its morphophysiology, suggesting that even doses considered safe by current legislation can be dangerous and should be reconsidered.
https://doi.org/10.1016/j.mce.2024.112444

Low dose exposure to dioxins alters hepatic energy metabolism and steatotic liver disease development in a sex-specific manner,
Bolatimi, O. E., Hua, Y., Ekuban, F. A., Gripshover, T. C., Ekuban, A., Luulay, B., Watson, W. H., Hardesty, J. E. and Wahlang, B., *Environment International*, Dec 2024, Vol. 194.

"Dioxins" are persistent organic pollutants (POPs) that are continuously present in the environment at appreciable levels and have been associated with increased risk of steatotic liver disease (SLD). However, current understanding of the role of sex and effects of mixtures of dioxins in SLD development is limited. Additionally, there exists debates on the levels of dioxins required to be considered dangerous as emphasis has shifted from high level exposure events to the steady state of lower-level exposures. We therefore investigated sex-dependent effects of low-level exposures to a mixture of dioxins: 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), 2,3,4,7,8Pentachlorodibenzofuran (PeCDF) and Polychlorinated biphenyl 126 (PCB126), in the context of SLD and associated metabolic dysfunction. Male and female C57BL/6J mice were fed a low-fat diet and weekly administered either

vehicle control or TCDD (10 ng/kg), PeCDF (80 ng/kg) and PCB 126 (140 ng/kg) over a two-week period. Female mice generally demonstrated higher hepatic fat content compared to males. However, exposure to dioxins further elevated hepatic cholesterol levels in females, and this was accompanied by increased lipogenic gene expression (Acaca, Fasn) in the liver. In contrast, exposed males but not females displayed higher white adipose tissue weights. Furthermore, TCDD + PeCDF + PCB126 activated the AHR (hepatic Cyp1a1, Cyp1a2 induction); with Cyp1a1 induction observed only in exposed females. Notably, gene expression of hepatic albumin (Alb) was also reduced only in exposed females. Overall, exposure to the low dose dioxin mixture compromised hepatic homeostasis via metabolic perturbations, and hepatic dysregulation was more accelerated in female livers. https://doi.org/10.1016/j.envint.2024.109152

The impact of early life exposure to individual and combined PFAS on learning, memory, and bioaccumulation in C. elegans,
Currie, S. D., Ji, Y. Q., Huang, Q. G., Wang, J. S. and Tang, L. L., *Environmental Pollution*, Dec 2024, Vol. 363.

Per- and Polyfluoroalkyl Substances (PFAS) are a group of water-soluble chemicals used for decades with important industrial and commercial applications. Due to their chemical and thermal stability, persistence in the environment, and widespread human exposure, PFAS become an important concern for public health. In this study, eleven highly prevalent PFAS and a reference mixture were selected according to various drinking water sources. The nematode, Caenorhabditis elegans, were exposed to PFAS at 0.1, 1, 10, 100, and 200 mu M, and the toxic effects on learning & memory along with the bioaccumulation were investigated using a high-throughput screening (HTS) platform. Our results showed that perfluorooctanesulfonic acid (PFOS) and perfluorobutanesulfonic acid (PFBS) exhibited significant inhibitory effects ($p < 0.05$) on learning and memory in both time points at concentrations between 100 and 200 mu mol/L. After 48 h of exposure, every PFAS resulted in an inhibition of learning and memory with a concentration of 200 mu mol/L. Furthermore, the PFOS and PFBS had the highest bioaccumulation levels after 48 h of exposure. These findings provide valuable insight into the developmental adverse effects associated with exposure and the bioaccumulation of both individual and mixtures of PFAS.
https://doi.org/10.1016/j.envpol.2024.125257

Perinatal exposure to environmental chemicals that disrupt thyroid function can perturb testis development,
Draskau, M. K., Strand, I. W., Davila, R. A., Ballegaard, A. S. R., Pedersen, M., Ramhoj, L., Rising, S., Tran, K. M., Axelstad, M., Bowles, J., Rosenmai, A. K., Spiller, C. M. and Svingen, T., *Environmental Pollution*, Dec 2024, Vol. 363.

Thyroid hormones (THs) are essential for normal growth and development. Their role in skeletal and brain development is well established, with congenital hypothyroidism causing stunted growth and severe intellectual disability. THs are also important for the development of other tissues and organs, including the testis. Developmental hypothyroidism can manifest as smaller testes in early postnatal life that later develop into macroorchidism in adulthood due to increased proliferation of Sertoli cells. Effects of hypothyroidism on the testes can be modelled in rodents by exposing developing animals to TH-suppressing pharmaceuticals such as propylthiouracil (PTU) and methimazole (MMI). These drugs act by inhibiting the thyroperoxidase (TPO) enzyme in the thyroid gland, inhibiting the synthesis of THs. It is possible that environmental chemicals that inhibit TPO activity can also cause TH-mediated effects on the developing testis, but the extent to which this occurs is not known. Herein, we characterized the effects of perinatal exposure to the herbicide amitrole together with the antithyroid drug MMI. Pregnant Sprague-Dawley rats were exposed by

oral gavage to two doses of amitrole (25 or 50 mg/kg body weight/day) or MMI (8 or 16 mg/kg body weight/day) from gestational day 7 until birth. After birth, pup exposure was continued by dosing lactating dams from day of delivery until pup day 16. Both chemicals caused a significant reduction in TH levels on day 16. This perinatal hypothyroidism disrupted both germ and Sertoli cell development, resulting in smaller testes and reduced seminiferous tubule diameter in 16day old pups. Notably, fetal male blood progesterone levels were increased after exposure to both amitrole and MMI, whereas the amitrole-exposed animals also displayed increased estradiol levels. Our study raises concerns that exposure to environmental chemicals that happen to disrupt TH production may disrupt TH-dependent testis development, with adverse consequences to human reproductive health. https://doi.org/10.1016/j.envpol.2024.125117

Developmental programming: preconceptional and gestational exposure of sheep to biosolids on offspring ovarian dynamics†,
Halloran, K. M., Zhou, Y. R., Bellingham, M., Lea, R. G., Evans, N. P., Sinclair, K. D., Smith, P. and Padmanabhan, V., *Biology of Reproduction*, 2024 Dec 2024.

Developmental exposure to environmental chemicals perturbs establishment and maintenance of the ovarian reserve across the reproductive lifetime, leading to premature follicle depletion and ovarian aging. Considering humans are exposed to a complex mixture of environmental chemicals, real-life models assessing their cumulative impact on the ovarian reserve are needed. Biosolids are a source of a real-life mixture of environmental chemicals. While earlier studies demonstrated that grazing pregnant sheep on biosolids-treated pastures did not influence establishment of the ovarian reserve in fetal life, its impact on subsequent depletion of ovarian reserve during reproductive life of offspring is unknown. We hypothesized that developmental exposure to biosolids accelerates depletion of ovarian reserve. Ovaries were collected from F1 juveniles (9.5 weeks) and adults (2.5 years) born to F0 ewes grazed on control inorganic fertilizer pastures or biosolids-treated pastures from before conception and throughout gestation. The impact on follicular density, activation rate, and anti-M üllerian hormone (mediator of activation) expression by immunohistochemistry was determined. Activation rate was increased in F1 biosolids-treated pastures juveniles with a corresponding reduction in primordial follicle density. In contrast, activation rate and ovarian reserve were similar between control and F1 biosolids-treated pastures adults. The density of anti-M üllerian hormone-positive antral follicles was lower in biosolids-treated pastures juveniles, whereas anti-M üllerian hormone expression tended to be higher in antral follicles of biosolids-treated pastures adults, consistent with the changes in the ovarian reserve. These findings of detrimental effects of developmental exposure to biosolids during juvenile life that normalizes in adults is supportive of a shift in activation rate likely related to peripubertal hormonal changes. Sentence Maternal preconceptional and gestational exposure to biosolids programs increased activation rate and reduced ovarian reserve in juvenile offspring that is normalized by adult life, which is likely related to changes during peripuberty. https://doi.org/10.1093/biolre/ioae166

Exposure to brominated flame retardants in utero and through lactation delays the development of DMBA-induced mammary cancer: potential effects on subtypes?
Juarez, M. N., Mcdermott, A., Wade, M. G. and Plante, I., *Frontiers in Endocrinology*, Nov 2024, Vol. 15.

Introduction Brominated flame retardants (BFRs) are chemical compounds used to reduce the flammability of various products; some BFRs exhibit endocrine-disrupting properties and can leach into the environment leading to human and wildlife exposure. The mammary gland has specific vulnerability windows during which it is more sensitive to the effects of endocrine disrupting compounds (EDCs), such as the in utero life, puberty and pregnancy. Our previous studies revealed

precocious mammary gland development, disruptions in junctional proteins, and altered proliferation-apoptosis balance during puberty in rats exposed to BFRs in utero and through lactation. Such effects have been associated with increased mammary cancer risk.Objective The current study aimed to determine if in utero and lactational exposure to BFRs renders the mammary gland more susceptible to 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary cancer.Methods Dams were exposed to a BFRs mixture (0. 0.06 or 60 mg/kg/day), and mammary cancer was induced in pups using DMBA at post-natal day 46. Tumors onset and growth were monitored, and tumors were characterized using histology and molecular biology.Results Although BFRs exposure did not significantly affect mammary tumor number or burden, it showed significant delay in mammary tumor onset and growth in BFR-exposed animal. These effects could potentially be due to BFRs' impact on cellular responses, DMBA metabolism, or mammary gland shift of the sensitivity window. Molecular analysis of mammary tumors showed a shift in the ratio of luminal A, luminal B, and (HER2)-enriched tumors, and an increase in triple-negative breast cancer (TNBC) subtypes in BFR-exposed animals. Additionally, BFRs exposure showed lung lesions indicative of inflammation, independent of mammary cancer development.Conclusion Our study highlights the complex relationship between BFRs exposure and mammary cancer risk, emphasizing the need for further investigation into underlying mechanisms and long-term effects of BFRs on mammary gland development and carcinogenesis. https://doi.org/10.3389/fendo.2024.1429142

Maternal exposure to 4-tert-octylphenol causes alterations in the morphology and function of microglia in the offspring mouse brain,
Lee, S. H., Shin, H. S., So, Y. H., Lee, D. H., An, B. S., Lee, G. S. and Jung, E. M., *Journal of Hazardous Materials*, Dec 2024, Vol. 480.

4-tert-Octylphenol (OP), an endocrine disrupting chemical is widely used in the production of industrial products. Prenatal exposure to endocrine-disrupting chemicals negatively affects the brain. However, the influence of OP exposure during neurodevelopment in adult offspring remains unclear. Thus, in the present study, we investigated the effects of maternal OP exposure on brain development in adult offspring by analyzing primary glial cell cultures and mice. Our findings revealed that OP exposure led to a specific increase in the mRNA expression of the ionized calcium-binding adapter molecule 1 (Iba-1) and the proportion of amoeboid microglia in the primary glial cell culture and adult offspring mice. Exposure to OP increased the transcriptional activation of Iba-1 and estrogen response element, which were counteracted by estrogen receptor antagonists ICI 182,780. Moreover, OP exposure increased the nuclear localization of the estrogen receptor. Remarkably, OP exposure decreased the mRNA expression levels of proinflammatory cytokines and genes associated with immune response in the brains of the offspring. OP exposure upregulated actin filament-related genes and altered cytoskeletal gene expression, as demonstrated by microarray analysis. The morphological changes in microglia did not result in an inflammatory response following lipopolysaccharide treatment. Taken together, the effects of OP exposure during neurodevelopment persist into adulthood, resulting in microglial dysfunction mediated by estrogen receptor signaling pathways in the brains of adult offspring mice.
https://doi.org/10.1016/j.jhazmat.2024.136258

Impact of exposure to a mixture of organophosphate esters on the adrenal glands of Sprague Dawley rats,
Li, Z. X., Hales, B. F. and Robaire, B., *Toxicological Sciences*, 2024 Dec 2024.

There is growing evidence that organophosphate esters (OPEs) can act as endocrine-disrupting chemicals. However, only a few studies have assessed the effects of OPE exposure on one of the most important endocrine glands in the body, the adrenal gland. Our aim was to test the effects of a

mixture of OPEs detected in Canadian house dust on adrenal function in Sprague Dawley rats. Adult male and female rats (n = 15 per treatment group) were administered either a vehicle or an OPE mixture (0.048, 1.6, or 48 mg/kg bw/d) for 70 to 72 d via their diet. With OPE exposure, adrenal glands from male adult rats were reduced in weight, whereas those of female rats showed an increase in weight. This led us to investigate whether OPEs induce sex-specific effects on adrenal gland function and the mechanisms involved. Serum levels of two adrenal hormones, aldosterone and corticosterone, were decreased only in male serum samples. Serum levels of renin and adrenocorticotropic hormone, which regulate aldosterone and corticosterone synthesis, respectively, were assessed. Exposure to the OPE mixture decreased renin levels only in males. Serum biochemistry analysis revealed that triglycerides and LDL cholesterol levels were increased in males. Transcriptomic analysis revealed that the top affected pathways in male adrenal glands from all three treatment groups were related to potassium channels, which play a role in regulating aldosterone and corticosterone levels. The most affected pathways in female adrenal glands were related to cholesterol biosynthesis and immune functions. These results show that an environmentally relevant mixture of OPEs affects adrenal function and that these effects are sex specific. https://doi.org/10.1093/toxsci/kfae154

Perfluorooctane sulfonate (PFOS) and benzo a pyrene (BaP) synergistically induce neurotoxicity in C6 rat glioma cells via the activation of neurotransmitter and Cyp1a1-mediated steroid hormone synthesis pathways,
Lu, Y. S., Chen, J., He, X. R., Yang, S. L., Ma, B. J., Yu, J., Qiu, J., Qian, Y. Z. and Xu, Y. Y., *Food and Chemical Toxicology*, Nov 2024, Vol. 193.

Humans are often exposed to complex mixtures of multiple pollutants rather than a single pollutant. However, the combined toxic effects and the molecular mechanism of PFOS and BaP remain poorly understood. In this study, two typical environmental pollutants, perfluorooctane sulfonate acid (PFOS) and benzo [a]pyrene (BaP), were selected to investigate their combined neurotoxic effects on rat C6 glioma cells at environmentally relevant concentrations. The results showed that coexposure to low-dose PFOS and BaP induced greater toxicity (synergistic effect) than did single exposure. PFOS-BaP coexposure had stronger toxic effects on inducing oxidative stress and promoting early apoptosis. Targeted metabolomics confirmed that increased levels of the neurotransmitters 5-hydroxytryptophan, dopamine, tryptophan and serotonin disturb the phenylalanine, tyrosine and tryptophan biosynthesis pathways. Mechanistically, exposure to a low-dose PFOS-BaP binary mixture induces steroid hormone synthesis disorder through the activation of Cyp1a1 and Hsd17b8 (steroid hormone synthesis genes) and Dhcr24 and Dhcr7 (cholesterol synthesis genes). These findings are useful for comprehensively and systematically elucidating the biological safety of PFOS-BaP and its potential threats to human health. https://doi.org/10.1016/j.fct.2024.115058

Multigenerational Consequences of Prenatal Exposure to Benzophenone-3 Demonstrate Sex- and Region-Dependent Neurotoxic and Pro-Apoptotic Effects in Mouse Brain,
Przepiórska-Drońska, K., Łach, A., Pietrzak-Wawrzyńska, B. A., Rzemieniec, J., Kajta, M., Wawrzczak-Bargieła, A., Bilecki, W., Noworyta, K. and Wnuk, A., *Toxics*, Dec 13 2024, Vol. 12, no. 12.

Benzophenone-3 (BP-3), commonly used as a UV filter in personal care products and as a stabilizer, is an alleged endocrine disruptor with potential neurodevelopmental impacts. Despite its abundance in the environment, the studies on its effect on brain development are scarce, especially in terms of multigenerational impact. In this work, for the first time, we examined neurotoxic and pro-apoptotic effects of BP-3 on mouse brain regions (cerebral cortex and hippocampus) in both the first (F(1)) and second (F(2)) generations after maternal exposure to environmentally relevant BP-3 levels. We found disregulated markers of cell damage (LDH, H(2)O(2), caspase-3 and -8) and observed

increased expression of pro-apoptotic Fas/FAS or Fasl/FASL. BP-3 exposure disrupted the BAX/BCL2 pathway, showing stronger effects in the F(1) than in the F(2) generation, with a dominance of extrinsic pathway (FAS, FASL, caspase-8) over intrinsic one (BAX, BCL2), suggesting that BP-3-induced apoptosis primarily operates via the extrinsic pathway and could impair brain homeostasis across generations. This study underscores the potential of BP-3 to increase multigenerational risks associated with disrupted neurodevelopment and highlights the importance of understanding its long-term neurotoxic effects. https://doi.org/10.3390/toxics12120906

Transcriptomic Analysis of Effects of Developmental PCB Exposure in the Hypothalamus of Female Rats,
Streifer, M., Hilz, E. N., Raval, R., Wylie, D. C. and Gore, A. C., *Mol Cell Endocrinol*, Jan 9 2025, p. 112460.

This study investigated the consequences of perinatal exposure to Aroclor 1221 (A1221), a weakly estrogenic polychlorinated biphenyl (PCB) mixture and known endocrine-disrupting chemical (EDC), in female rats. Previous work has shown behavioral and physiological effects of A1221, and the current study extended this work to comprehensive transcriptomic profiling of two hypothalamic regions involved in the control of reproduction: the arcuate nucleus (ARC) and anteroventral periventricular nucleus (AVPV). Female Sprague-Dawley rats were fed a cookie treated with a small volume of A1221 (1 mg/kg) or vehicle (3% DMSO in sesame oil) during pregnancy from gestational days 8-18 and after birth from postnatal (P) days 1-21, exposing the offspring via placental and lactational transfer. In female offspring, developmental, physiological, and hormonal effects of A1221 were relatively modest. However, because prior work has implicated this exposure in neurobehavioral disruptions, we sought to determine whether developmental programming of the brain transcriptome could underlie these phenotypes. We used 3' targeted RNA sequencing in the hypothalamus (arcuate nucleus, anteroventral periventricular nucleus) of experimental females at P8, 30, and 60 and identified significant alterations in gene expression and gene ontology (GO) terms in an age- and tissue-specific manner. Most notably, terms related to synaptic signaling, neurotransmitter regulation, immune response, and cellular structure were identified. Changes in pathways associated with synaptic functions and cellular metabolism were further identified, indicating that A1221 exposure can impact neurodevelopmental and neuroendocrine processes at a molecular level, even in the absence of overt developmental changes. These findings of molecular reprogramming may explain the behavioral effects of A1221 and highlight novel molecular targets and pathways that warrant further investigation to understand the effects of EDCs on the developing brain. https://doi.org/10.1016/j.mce.2025.112460

Adolescent exposure to organophosphate insecticide malathion induces spermatogenesis dysfunction in mice by activating the HIF-1/MAPK/ PI3K pathway,
Xiao, S. C., Cui, J. N., Cao, Y., Zhang, Y. R., Yang, J. X., Zheng, L., Zhao, F. R., Liu, X. K., Zhou, Z. Q., Liu, D. H. and Wang, P., *Environmental Pollution*, Dec 2024, Vol. 363.

Chemical-caused reproductive dysfunction has emerged as a global public health concern. This study investigated the adverse effects of the organophosphorus pesticide malathion on reproductive function in adolescent male mice at environmentally relevant concentrations. The results indicated that eight-week malathion exposure reduced testis weight, caused sex and thyroid hormone disorders, and induced testicular spermatogenic epithelium damage and oxidative stress. Testicular RNA sequencing indicated that malathion significantly affected testicular energy metabolism, hypoxia-inducible factor 1 (HIF-1) signaling, and steroid hormone biosynthesis pathways. Malathion significantly increased the gene and protein expression of HIF-1 alpha by upregulating key genes in the mitogen-activated protein kinase (MAPK) pathway (Map2k2, Mapk3, and Eif4e2) and the

phosphatidylinositol 3-kinase (PI3K) pathway (Pik3r2 and Akt1). Furthermore, malathion downregulated HIF-1 alpha degradation-regulating genes while upregulating anaerobic metabolism and inflammation-related genes, thereby inhibiting normoxia and promoting hypoxia processes. Testicular hypoxia subsequently induced steroid hormone biosynthesis disorders and spermatogenesis dysfunction. Molecular docking verified that malathion interfered with HIF-1 alpha and steroid hormone synthases (CYP11A1, CYP17A1 and CYP19A1) by forming hydrogen bonds and hydrophobic interactions with these proteins. This study presents the first evidence that malathion triggers spermatogenesis dysfunction in mice through activating the HIF-1/MAPK/PI3K pathway, providing a comprehensive understanding of the reproductive toxicity risks associated with organophosphorus pesticides. https://doi.org/10.1016/j.envpol.2024.125209

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