Bulletin de veille
Perturbateurs Endocriniens
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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

Occupational exposure to pesticides deregulates systemic cortisol levels in women with breast cancer and correlates with poor prognosis features.
Jumes JJ, Jaques HS, Dalla Vecchia MF, Ferreira MO, Orrutéa JFG, Machado MG, et al. *Braz J Med Biol Res*. 2024;57:e13060.

Pesticides have been pointed out as hormone disruptors and may significantly affect the prognosis of hormone-dependent diseases such as breast cancer (BC). Here, we investigated the impact of occupational pesticide exposure on systemic cortisol levels in female rural workers diagnosed with BC.

Occupational exposure was assessed by interviews with a standardized questionnaire. Plasma samples (112 from pesticide-exposed women and 77 from unexposed women) were collected in the afternoon, outside the physiological cortisol peak, and analyzed by a chemiluminescent paramagnetic immunoassay for the quantitative determination of cortisol levels in serum and plasma. The results from both groups were categorized according to patients' clinicopathological and exposure data. BC pesticide-exposed women presented higher levels of cortisol than the unexposed. Higher cortisol levels were also detected in the exposed group with more aggressive disease (triple-negative BC), with tumors over 2 cm, with lymph node metastases, and with high risk of disease recurrence and death. These findings demonstrated that there is an association between pesticide exposure and BC that affected cortisol levels and correlated to poor disease prognosis. Lien vers l'article

The Relationship Between Polychlorinated and Polybrominated Biphenyls and Glycated Hemoglobin among Electronics Workers.
Aly HM, Ibraheem RB, Mahmoud RM, Ismail A, Hussein SM. *Indian J Occup Environ Med*. 2024 Apr-Jun;28(2):143-7.

BACKGROUND: Polychlorinated biphenyls (PCBs) are persistent organic pollutants classified as endocrine disruptors related to prediabetes and diabetes. Polybrominated biphenyls are similar in structure to PCBs and are used as flame retardants. Due to the increased worldwide prevalence of diabetes, there is increased interest in understanding the role of environmental and occupational pollutants in its development. The study aims to assess the relation between PCBs and PBBs in the serum of electronic workers and glycated hemoglobin level as an early indicator of prediabetes and type 2 diabetes mellitus among occupationally exposed workers. METHODS: Blood samples were collected from 152 workers to assess PCBs (by GCMS), random blood sugar (RBS), and glycated hemoglobin (HbA1c). Participants were classified into two groups according to the presence or absence of PCBs in their serum and were compared for RBS and HbA1c levels. RESULTS: Only two participants had detectable PCB derivate in their serum by GCMS, PCB 1 with methyl and benzole side chains. Regarding PBBs, 18 participants (12%) had detectable PBBs in their serum by GCMS. All participants had RBS and HbA1c levels within the normal range. No statistically significant difference was found between mean levels of RBS and HbA1c between participants with detected biphenyls and those without. CONCLUSION: The banning of PCB use in industry and modern automated techniques have prevented exposure to PCBs among electronics workers. However, exposure to PBBs continues in electronic industries, but it has no association with diabetes or prediabetes. Lien vers l'article

Identification of pesticide mixtures to which French agricultural workers and farm-owners are exposed: Results from the Agriculture and Cancer (AGRICAN) cohort study.
Hippert J, Talibov M, Morlais F, Brugioni M, Perrier S, Baldi I, et al. *Sci Total Environ*. 2024 Dec 10;955:176607.

Farmers, particularly in Europe, are exposed to multiple pesticides during their working life. Such exposures can cause adverse health outcomes. We aimed to identify the main pesticide mixtures to which French agricultural workers are exposed and to classify farmers into clusters based on their mixture exposure profile. The AGRICAN cohort includes farm-owners and farm workers enrolled from 2005 to 2007, with information on exact years of beginning and end of pesticide use on 11 crops and five livestock. We estimated duration of exposure to 390 pesticides identified with the PESTIMAT crop-exposure matrix for 16,905 male pesticide users from 1950 to 2009. We used a Sparse Non-negative Matrix Under-approximation to identify the main pesticide mixtures based on exposure duration, and then applied hierarchical agglomerative clustering to classify farmers sharing similar profiles of co-exposure to the mixtures. SNMU suggested 6 optimal numbers of mixtures (4, 7, 11, 15, 27, 38) explaining from 29 to 91 % of total variance. We selected 27 mixtures. Mixtures contained between

four to 22 pesticides and mostly concerned the use of pesticides on wheat/barley, vineyards, corn, fruit and vegetables or on multiple crops together. We selected 11 clusters composed of 395 to 4521 farmers. Some had a higher proportion of individuals working on specific crops (as vineyard or corn), while others were characterized by the diversity of crops (cluster 8:"Permanent crops, potatoes and tobacco"). This is the first study to identify pesticide mixtures in farmers and to classify them into clusters based on their mixture exposure profiles. The next step will be to study the associations between pesticide mixtures and health outcomes such as prostate cancer in AGRICAN. Lien vers l'article

Serum concentrations of persistent endocrine-disrupting chemicals in US military personnel: A comparison by race/ethnicity and sex,
Alcover, K. C., Mcadam, J., Denic-Roberts, H., Byrne, C., Sjodin, A., Davis, M., Jones, R., Zhang, Y. W. and Rusiecki, J. A., *International Journal of Hygiene and Environmental Health*, Apr 2025, Vol. 265.

Objectives/background: We evaluated patterns of serum concentrations of endocrine disrupting chemicals (EDCs), namely polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), and polybrominated diphenyl ethers (PBDEs), in a U.S. military sample by race/ethnicity (R/E) and sex. Methods: Twenty-three EDCs were measured in stored serum samples obtained between 1995 and 2010 for 708 service members from the Department of Defense Serum Repository. For each EDC, geometric means (GM) were estimated using log-transformed concentrations in a linear regression model, for eight combined R/E/sex groups: non-Hispanic White (NHW), non-Hispanic Black (NHB), non-Hispanic Asian (NHA), and Hispanic men and women, adjusted for age and service branch and stratified by age tertile ("younger age": 17-23, "middle age": 24-30, and "older age": 31-52 years). Comparisons were made between our military sample and the National Health and Nutrition Examination Survey (NHANES) 2003-2004 data for NHW and NHB groups. Results: Within our military sample, the highest PCB concentrations were among older age NHB men and women and highest OCP concentrations among older age NHB women and NHA men. PBDE concentrations were generally highest in middle age Hispanic women and NHA men, though based on small sample size. Generally, NHB men and women had higher concentrations of EDCs in both the military and NHANES. Conclusions: We found patterns of elevated EDC concentrations among NHB, NHA, and Hispanic groups in the military sample and for NHB men and women in NHANES. There were no consistent patterns of higher or lower EDCs comparing the military to NHANES. Future studies of EDCs and health outcomes should stratify by R/E/sex to account for potential disparities in EDC concentrations. https://doi.org/10.1016/j.ijheh.2025.114540

Development of a novel HPLC-HRMS method for quantitative analysis of resorcinol in urine: Application to hairdressers' occupational exposure,
Cambrai-Erb, A., Denis, F., Pons, R., Radauceanu, A., Ndaw, S. and Grova, N., *Journal of Chromatography B-Analytical Technologies in the Biomedical and Life Sciences*, Mar 2025, Vol. 1253.

Resorcinol is a widespread substance used in a large variety of manufacturing industries, including cosmetics, with endocrine-disrupting activity on the thyroid function. The aim of the present study was to develop and validate a sensitive, selective and robust method to quantify resorcinol in urine and thereby assess hairdressers' occupational exposure. As resorcinol is mainly excreted in urine as glucuronide or sulfate forms, the first step consisted in hydrolyzing urine samples with a beta-glucuronidase-arylsulfatase enzyme for 16 h. Then, after cleaning with a supported-liquid extraction cartridge, the samples were derivatized with dansyl chloride to improve signal and signal-to-noise ratio. Analysis was carried out using an accurate high-resolution liquid chromatography-mass

spectrometry instrument on a Kinetex Biphenyl analytical column. Particular attention was paid to the chromatographic separation of resorcinol from its two isomers, catechol and hydroquinone, also present in urine. Acquisition was performed in positive ESI mode, at m / z 577.14615 for dansylated resorcinol and m / z 581.17126 for dansylated resorcinol-d4, with respective retention times of 8.63 and 8.60 min. The method passed all the performance tests included in the validation process. The lowest limit of quantification (LLOQ) was 0.3 mu g/L resorcinol, which was sufficient to quantify resorcinol in all samples tested. The calibration curves were linear from LLOQ to 2000 mu g/L, with coefficients of determination R2 ranging from 99.82 % to 100 %. The method was accurate, reaching 95.6 to 101.7 % of target intraday and 99.8 to 105.0 % interday, and precise with RSDs between 0.88 and 1.99 % intraday and with RSDs between 1.75 and 8.65 % in interday assessments. It also proved robust, with a matrix effect of 8.25 %. Resorcinol stability was determined by studying long-term stability at-20 degrees C for sample storage up to 6 months, short-term stability (at + 20 degrees C and + 4 degrees C for possible short-term storage), freeze-thaw cycles, and post derivatization stability. This method was successfully applied on samples from 17 women working as hairdressers. Urinary resorcinol concentrations ranged from 2 mu g/ L to 1824 mu g/L (6 to 4475 mu g/g creatinine) and were in line with those reported in the literature.
https://doi.org/10.1016/j.jchromb.2025.124472

Urinary metabolic alterations associated with occupational exposure to metals and polycyclic aromatic hydrocarbons based on non-target metabolomics,
Lu, P., He, R. J., Wu, Y. J., Wu, B. Z., Li, H. L., He, C., Lin, M. Q., Wang, M. M., Cai, W. W., Shen, X. T., Li, G. Y., Cao, Z. G. and An, T. C., *Journal of Hazardous Materials*, Apr 2025, Vol. 487.

Long-term occupational exposure to metals and organics have been reported to be under great health risks. However, limited data are available on the molecular mechanism between combined exposure to metals and polycyclic aromatic hydrocarbons (PAHs) and harmful health effects. In present work, non-target metabolomics study was conducted based on urine samples from nonferrous metal smelting workers (n = 207), surrounding residents (n = 180), and the control residents (n = 187) by using ultra-high-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (UHPLC-QTOF-MS). Differential and correlation analyses among metabolic features indicate that total 22 differential metabolites in smelting workers were associated (p <0.05) with metal and PAH exposure. Particularly, amino acid metabolism was strongly disturbed, and other metabolic pathways, including steroid hormone biosynthesis, citrate cycle, and pantothenate and coenzyme A (CoA) biosynthesis were also perturbed. Among them, steroid hormone biosynthesis was more affected by PAH exposure than metals, especially for hydroxyphenanthrene. These altered pathways were closely associated with oxidative stress, inflammation, and energy metabolism disorder. Additionally, our results indicate that endogenous metabolism in surrounding residents were also affected by nonferrous metal smelting activities to some extent. Our work provides valuable insights into molecular mechanisms of adverse health effects probably induced by combined exposure to metals and PAHs.
https://doi.org/10.1016/j.jhazmat.2025.137158

Occupational exposure to flame retardants following production replacement and their effect on thyroid function indicators,
Meng, L., Guo, T. T., Liu, Y. Z., Wu, H., An, K., Xu, X. Z. and Li, Y. C., *Emerging Contaminants*, Jun 2025, Vol. 11, no. 2.

With the ban of commercial Penta-BDEs, Octa-BDEs, and Deca-BDEs, many manufacturers have been transition to the production of novel brominated flame retardants (NBFRs), organophosphate ester flame retardants (OPFRs), and other alternatives. In this study, we recruited 165 employees

with typical occupational exposure from a flame retardants (FRs) production plant in Laizhou Bay, which is the main FRs production area in China, to analyze the internal exposure characteristics of FRs and their potential impacts on thyroid function during the historical production and replacement process. The results showed that the detection frequencies of only triphenyl phosphate (TPHP), BDE-138 and BDE-197 (82.4 %, 61.2 % and 60.6 %, respectively) exceeded 60 % among the 34 compounds of interest, while the median concentrations of BDE-138 and BDE-197 were much higher than TPHP (medians of 103.6, 60.6 and 20.5 ng/g lw, respectively). In addition, the concentrations of these compounds in exposed group are higher than those in the control group (P < 0.05). The correlations among FRs indicated they mainly originated from the production and the debromination process. Overall, these results reflect the changes in the product structure. Free triiodothyronine (fT3) was moderately positively correlated with BDE-138, BDE-197, and TPHP (P < 0.05), and regression analysis further identified BDE-138 as a significant factor influencing fT3 levels. Despite TPHP having a rapid metabolism and short half-life, it was still widely detected in this study, indicating that future research should not only focus on the health risks of BDEs or their degradation products but also consider the health risks associated with TPHP and their mixed exposure, especially given the increasing production of OPFRs as substitutes.
https://doi.org/10.1016/j.emcon.2025.100476

The impact of triadimenol on male fertility: An in vitro study and molecular docking examination,
Merve, A., Aysenur, B., Dogukan, D. E. and Gül, Ö., *Reproductive Toxicology*, Mar 2025, Vol. 132.

Triadimenol, a triazole fungicide, induces various adverse effects including neurotoxicity, hepatotoxicity, and developmental/reproductive toxicity in non-target organisms. Occupational exposure generally occurs in male agricultural workers. Investigating the effects of triadimenol on three different testicular cell lines would be valuable in elucidating the mechanisms underlying male reproductive issues or infertility. This preliminary study examines the potential toxic effects of triadimenol exposure in Leydig (TM3), Sertoli (TM4), and mouse-derived Spermatogonia (GC-1) cell lines, which are representative of the male reproductive system in vitro. The median inhibitory concentration (IC50) values of triadimenol were found to be 121.35 mu M, 332.1 mu M, and 349.49 mu M in TM3, TM4, and GC-1 cells, respectively. The exposure doses were determined to range from 0 to 100 mu M in TM3 cell line and 0-300 mu M in TM4 and GC-1 cell lines. Reactive oxygen species (ROS) production, reduced glutathione (GSH) content, malondialdehyde (MDA) and protein carbonyl levels, and genotoxicity were examined. TM3 cell line was more resistant to oxidative damage than the other cell lines, while TM4 cell line was found to be more sensitive in terms of protein carbonyl formation. Triadimenol damaged DNA in TM3 cell line (>= 16.93), TM4 cell line (>= 9.18), and GC-1 cell line (>= 3.28). Additionally, the docking score of triadimenol on the active site of steroid 5-alpha-reductase 2 (5 alpha R2), which converts testosterone to 5 alpha-dihydrotestosterone, was not close. The results emphasised that the toxicity of triadimenol was cell-specific. Overall, triadimenol disrupted male fertility by affecting spermatogenesis, testosterone production, germ cell support, and sperm quality. https://doi.org/10.1016/j.reprotox.2025.108861

The effects of occupational aluminum exposure on blood pressure and blood glucose in workers - A longitudinal study in northern China,
Xue, L. S., Guo, S. H., Huan, J. P., Li, C. Y., Song, J., Wang, L. P., Zhang, H. F., Pan, B. L., Niu, Q., Lu, X. T. and Yin, J. Z., *Toxicology Letters*, Feb 2025, Vol. 404, p. 47-57.

Background: Trace element and metal exposure is closely related to the occurrence of chronic diseases, particularly affecting blood pressure and blood glucose. Current studies suggest that heavy metal exposure is a risk factor for hypertension and diabetes. Aluminum can enter the human body

through daily life and occupational exposure from food, environment, drugs, and other sources, affecting the cardiovascular, endocrine, and other systems. Therefore, it is significant to observe the effect of aluminum on blood pressure and blood glucose in workers with high concentration. Objective: In this study, electrolytic workers naturally exposed to high concentrations of aluminum were selected. The aim of the 5-year cohort study was to investigate the effects of continuous occupational aluminum exposure on blood pressure and blood glucose in workers and to assess the risk of potential cardiovascular and metabolic diseases due to heavy metal exposure. Methods: In 2014, 183 participants from an electrolysis workshop at an aluminum plant in Shanxi were enrolled. Inductively coupled plasma mass spectrometry (ICP-MS) was performed to determine the plasma aluminum (PAl) concentration of the workers and measured their blood pressure and glucose levels. At the 2019 follow-up, all parameters were measured again in the same workers. The relationship of the P-Al concentration with blood pressure and glucose levels was assessed using generalized linear regression, and risks of developing hypertension and hyperglycemia (diabetes or pre-diabetes) due to Al exposure were assessed using binary logistic regression. Dose-response relationships between average annual rates of change in P-Al and average annual rates of change in blood pressure and blood glucose were analyzed using RCS. The relative risk (RR) and attributable risk (AR) were also calculated. Results: Generalized linear regression showed that the average annual rate of change in P-Al concentration was positively correlated with the annual rates of change in SBP, DBP, and blood glucose levels, with each e-fold increase in P-Al concentration increasing the annual rates of change in SBP and DBP by 3.55 % ($P < 0.01$) and 3.43 % ($P = 0.03$), respectively. Binary logistic regression showed that as the average annual rate of change in PAl concentration (categorical variable) increased, the risk of developing hypertension increased (P-trend < 0.05). The RCS results showed that the relationship between the average annual rate of change in P-Al and the average annual rate of change in SBP was a showed a dose-response relationship (P for overall association<0.05). RR and AR increased with increasing P-Al concentration in both hypertensive and diabetic patients. Conclusion: Persistent occupational aluminum exposure is associated with elevated blood pressure levels in workers and increases the risk of developing hypertensive disorders.
https://doi.org/10.1016/j.toxlet.2025.01.005

Epidémiologie

Phthalate exposure profiles during baby delivery and their association with reproductive hormone changes and newborn outcomes,
Abderrezak, K., Chakib, F., Iyad, F., Kahina, A., Lyece, Y., Mohamed, M., Mohamed, C., Youcef, T., Lounas, B., Amel, D.-D., Fadila, M. and Mohamed, A., *Chemosphere*, 2025/04/01/ 2025, Vol. 374, p. 144208.

Background Phthalates are organic compounds and emerging pollutants of health concern. Exposure to phthalates may have an impact on hormone physiology, especially during pregnancy, as it represents a period of heightened vulnerability to disruptions for the newborn. Objective The aim of this study was to identify perinatal exposure profiles to phthalates in pregnant women living in Algiers and to explore associations between umbilical cord blood levels of phthalates and reproductive hormone concentrations. The aim also extends to explore the link that could exist between potential sources and the exposure profiles to phthalates. Methods This descriptive study was carried out on 154 couples of women-newborns. After gathering necessary information, umbilical cord blood samples were collected. Reproductive hormones were measured by electrochemiluminescence, while phthalate metabolites were detected using LC-MS/MS. Results The results showed that MEHP, MEP, and MnBP were detected in 97.4%, 74.7%, and 53.9% of samples. Mean concentrations were 18.680, 11.805, and 7.151 ng/mL for MEHP, MEP, and MnBP,

respectively. High concentrations of MEP and MEHP were associated with low umbilical cord levels of testosterone, progesterone, and estradiol. A positive and meaningful association between MnBP and LH levels was found as well. The results indicated that MEHP was associated with changes in the anogenital distance (AGD) in both male and female newborns, as positive significant correlation has been found between MEHP levels and female AGD as well as an inverse correlation between the same metabolite and male AGD. The evaluation of exposure sources revealed a significant association between the consumption of bottled water and levels of MnBP. Conclusions In this study, phthalates were associated with altered levels of reproductive hormones in umbilical cord plasma. These changes may have adverse effects on children development. Results also suggest that the consumption of bottled water may impact the newborns' endocrine integrity.
https://doi.org/https://doi.org/10.1016/j.chemosphere.2025.144208

Concurrent Lead and Cadmium Exposure Among Diabetics: A Case-Control Study of Socio-Demographic and Consumption Behaviors,
Adokwe, J. B., Pouyfung, P., Kuraeiad, S., Wongrith, P., Inchai, P., Yimthiang, S., Satarug, S. and Khamphaya, T., *Nutrients*, Feb 2025, Vol. 17, no. 4.

Introduction/Objectives: Type 2 diabetes (T2D) continues to pose a substantial global public health challenge. Current evidence has linked an increase in the risk of T2D to chronic exposure to the heavy metals cadmium (Cd) and lead (Pb). The present study aimed to examine whether the reported links existed in an area of southern Thailand with known Pb contamination. Materials and Methods: A case-control study design was used to recruit 88 diagnosed T2D cases and 90 age-, gender- and locality-matched non-diabetic controls. Blood levels of Cd and Pb were used as exposure indicators. Exposure-related risk factors and socio-demographic data were collected through questionnaires. Results: A significant association was found between blood Pb and T2D diagnosis, but the association between blood Cd and T2D was not statistically significant. Factors related to high Pb exposure were education, occupation, income, smoking habits, alcohol consumption, and dietary patterns, particularly the consumption of sweet and fatty foods. Participants with higher blood Pb levels had poorer glycemic control, thereby suggesting potential interference of Pb with oral hypoglycemic agents. Conclusions: This study confirms the connection between Pb exposure and increased risk of having T2D. Additionally, it identified socio-demographic factors, and consumption habits that contributed to such an enhanced T2D risk. The role of Cd exposure requires further studies, using urinary Cd excretion, which reflects long-term exposure conditions. These findings suggest the need to incorporate environmental and occupational exposure in diabetes care strategies. From the clinical and public health perspectives, targeted interventions should focus on reducing heavy metal exposure, improving risk awareness, and strengthening occupational safety measures to prevent disease progression.
https://doi.org/10.3390/nu17040710

The correlation of bisphenol A exposure on inflammatory cytokines in preschool children,
Cai, W. Y., Yan, Q. S., Deng, Y. H. and Guo, Y., *Cytokine*, Feb 2025, Vol. 186.

Objective: Based on current evidence suggesting that bisphenol A (BPA) may contribute to obesity through the modulation of inflammatory markers, this study aims to investigate the correlation between BPA exposure and cellular inflammatory factors in preschool children. Methods: A total of 155 preschool children aged 4-6 years were included. Urine and blood samples were collected. BPA exposure was detected by liquid chromatography-tandem mass spectrometry through urine samples. The levels of six inflammatory cytokines (IL-2, IL-4, IL-6, IL-10, TNF-alpha, and IFN-gamma) were determined by flow fluorescence technique. The correlation between urinary BPA exposure and cellular inflammatory factors was analyzed using Spearman's correlation and respectively

stratified by gender and BMI. Results: The detection rate of BPA in urine samples was 100 %. The median urinary BPA concentration was 0.48 mu g/L(IQR:0.25-1.02 mu g/L), and the creatinine-adjusted BPA concentration was 0.94 mu g/g(IQR:0.57-1.66 mu g/g). BPA level was negatively correlated with IL-10 (r = -0.172, P < 0.05). After stratification by gender, the negative association between BPA exposure and IL-10 was found in females (r = -0.257, P < 0.05), while no association was found in males. According to BMI stratification, BPA exposure in overweight/obese children was positively correlated with IL-6 (r = 0.354, P < 0.05). Conclusions: Our study demonstrated that BPA exposure in preschool children was correlated with a decrease in levels of IL-10, and this effect was significantly expressed in girls. In addition, BPA exposure in overweight/obese children was correlated with increased levels of IL-6. However, the mechanism between BPA and inflammatory factors remains to be further explored. https://doi.org/10.1016/j.cyto.2024.156835

Associations of combined exposure to selected metal mixtures with thyroid hormones in children: a cross-sectional study in China,
Cao, Y. H., Xiang, S. T., Du, Y. W., Chen, M. L., Xue, R. M., Li, Q., Qiu, J. and Duan, Y. Y., *Frontiers in Public Health*, Jan 2025, Vol. 13.

Background: Exposure to several metal elements has been found to be associated with thyroid hormone homeostasis. However, evidence for combined exposure is inconclusive, especially for children. Objective: To examine the individual and joint effects of blood metal elements on thyroid hormones in children. Methods: A total of 12,470 children aged 0-14 were collected from January 2018 to December 2021 in Hunan Children's Hospital. The concentrations of lead (Pb), iron (Fe), calcium (Ca), copper (Cu), zinc (Zn) and magnesium (Mg) in blood were detected via atomic absorption spectrometry (AAS). The levels of thyroid stimulating hormone (TSH), triiodothyronine (TT3, FT3) and total and free thyroxine (TT4, FT4) were measured by electrochemiluminescence immunoassay (ECLIA). Generalized linear regression (GLR) model and Quantile-based g-computation (QGC) were employed to estimate the association between metal exposure and thyroid hormone homeostasis. Results: GLR model showed that a unit increase in ln-transformed Fe was associated with increases in TT3 (beta = 0.163; P-FDR < 0.001), TT4 (beta = 12.255; P-FDR < 0.001) and FT3 (beta = 0.615; P-FDR < 0.001), as well as decreases in TSH (beta = -0.471; P-FDR = 0.005) and FT4 (beta = -1.938; P-FDR < 0.001). The result of QGC analysis indicated a positive relationship of the ln-transformed concentration of metal mixture with the levels of TT3 (beta = 0.018; P = 0.012), TT4 (beta = 2.251; P < 0.001) and FT3 (beta = 0.074; P < 0.001) in children. Fe was the predominant contributor among the metal mixture with positive contributions to TT3 (weight = 0.439), TT4 (weight = 0.502) and FT3 (weight = 0.450). Conclusions: The combined metal exposure was associated with increased levels of TT3, TT4, and FT3 in children and Fe appeared to be the major contributor. Further studies are warranted to confirm our findings and elucidate the underlying mechanisms. https://doi.org/10.3389/fpubh.2025.1387702

Typical endocrine disrupting chemicals in newborns with congenital hypothyroidism: Concentrations, exposure assessment, and potential risks,
Chen, Y. T., Xu, L. Y., Zhu, Q. Q., Hu, L. G. and Liao, C. Y., *Journal of Hazardous Materials*, Mar 2025, Vol. 486.

Congenital hypothyroidism (CH) has been reported as a prevalent endocrine disorder in newborns. Endocrine disrupting chemicals (EDCs) have been widely detected in humans and can influence endocrine function, especially thyroid function, and neonates as a susceptible population may be more prone to suffer from CH through exposure to various EDCs. In this study, the concentrations and composition profiles of several typical EDCs were determined in 266 serum samples collected from newborns with (n = 136) and without CH (n = 130) in Beijing, China from 2018 to 2020. All

detection rates of target chemicals were higher in newborns with CH than without CH, except for triclosan. Relatively higher levels of phthalate metabolites, parabens, and tetrabromobisphenol A and its alternatives were found in the sera of newborns with CH. Based on the measured concentrations, exposure to and risk of such EDCs were assessed. The median estimated daily intakes of target EDCs ranged from 0.343 (benzophenones) to 161 mu g/kg-bw/day (parabens) in the CH group. To explore the possible mechanism of thyroid function damage caused, binary logistic analysis was performed and results revealed that exposure to monocyclohexyl phthalate (mCHP), ethyl-paraben (EtP), bisphenol-Z (BPZ), tetrabromobisphenol A (TBBPA), and 4-hydroxybenzophenone (4-OH-BP) may increase the risk of suffering from CH (adjusted odds ratio (OR): 1.35-1.71). Taken together, this study findings preliminarily uncover the association between exposure to several typical EDCs and the common endocrine disorder CH. Such associations and possible causes should be determined in vitro and in vivo in the follow-up studies. https://doi.org/10.1016/j.jhazmat.2024.136991

Associations Between Brominated Flame Retardant Exposure and Depression in Adults: A Cross-Sectional Study,
Cheng, Y. L., Fei, Y., Xu, Z. M., Huang, R. Y., Jiang, Y. L., Sun, L. H., Wang, X. H., Yu, S. L., Luo, Y. H., Mao, X. B. and Zhao, X. Y., *Toxics*, Dec 2024, Vol. 12, no. 12.

Background: Brominated flame retardants (BFRs) are a type of widespread pollutant that can be transmitted through particulate matter, such as dust in the air, and have been associated with various adverse health effects, such as diabetes, metabolic syndrome, and cardiovascular disease. However, there is limited research on the link between exposure to mixtures of BFRs and depression in the general population. Methods: To analyze the association between exposure to BFRs and depression in the population, nationally representative data from the National Health and Nutrition Examination Survey (NHANES; 2005-2016) were used. In the final analysis, a total of 8138 adults aged 20 years and older were included. To investigate the potential relationship between BFRs and outcomes, we used binary logistic regression, restricted cubic spline (RCS), quantile-based g computation (QGC), and weighted quantile sum (WQS) regression. Results: The findings showed that serum BFR concentrations were associated with depressive symptoms over a broad spectrum. Binary logistic regression and RCS analysis showed that certain BFRs, particularly PBB153, were significantly and positively associated with the incidence of depression, even after adjustment for various confounders ($p < 0.05$). Mixed exposure to BFRs was also found to be associated with depression in the population, with a stronger association in men. The two most influential BFRs, PBB153 and PBDE85, were identified in both mixed exposure models and are potential risk factors of concern. Conclusion: Our study identified new insights into the relationship between BFRs and depression, but sizable population-based cohort studies and toxicology mechanism studies will be needed to establish causality. https://doi.org/10.3390/toxics12120918

Influence of prenatal hexachlorobenzene, PCB and selenium levels on growth trajectories in the first year of life: Findings from the NEHO birth cohort,
Cosentini, I., Ruggieri, S., Colombo, P., Bianchi, F., Cori, L., Casella, M., Tavormina, E. E., Cibella, F. and Drago, G., *Environment International*, Jan 2025, Vol. 195.

Prenatal exposure to endocrine-disrupting chemicals (EDCs) may impact postnatal growth trajectories, increasing the risk of various diseases later in life. This issue is of particular concern in industrially contaminated areas, where environmental matrices contain mixtures of pollutants. This study aimed to evaluate the associations between cord serum concentrations of organochlorine pollutants (hexachlorobenzene-HCB and polychlorinated biphenyls-PCBs) and essential elements (EEs), and weight growth trajectories during the first year of life. We analyzed data from 237 infants

enrolled in the Neonatal Environment and Health Outcomes (NEHO) cohort. Using the Group-Based Multivariate Trajectory modeling approach, we identified three distinct growth trajectories from birth to 12 months, classified as "Higher," "Normal," and "Lower." Multinomial regression models were then applied to the whole sample and stratified by sex to assess the associations between individual exposures and the identified child growth trajectories. HCB exposure was associated with an increased risk of reduced growth during the first year of life in both the overall sample and among males [higher vs normal: ORMale = 0.33 (95 % CIMale:0.12;0.87); lower vs normal: ORMale = 2.17 (95 % CIMale:0.94;5.00)]. Conversely, PCB-180 exposure was linked to higher growth only in females [higher vs normal: ORFemale = 24.10 (95 % CIFemale:1.33;438.24)]. Elevated levels of selenium in cord serum were negatively associated with excessive growth [higher vs normal: OROverall = 0.50 (95 % CIOverall: 0.26;0.97)]. These findings suggest sex-specific effects on the growth profile during the first year of life, with different chemical exposures contributing to different outcomes. https://doi.org/10.1016/j.envint.2024.109225

The Relationship Between Maternal Exposure to Endocrine-Disrupting Chemicals and the Incidence of Congenital Heart Diseases: A Systematic Review and Meta-Analysis,
Elhassan, Y. H., Alahmadi, F., Albadawi, E. A., Albarakati, A., Aljohany, A. H., Alzaman, N. S. and Albadrani, M., *Metabolites*, Dec 2024, Vol. 14, no. 12.

Background: Congenital heart diseases are among the most common birth defects, significantly impacting infant health. Recent evidence suggests that exposure to endocrine-disrupting chemicals may contribute to the incidence of congenital heart diseases. This study systematically reviews and analyzes the association between maternal endocrine-disrupting chemicals exposure and congenital heart diseases. Methodology: This systematic review and meta-analysis followed the Cochrane Handbook and PRISMA guidelines. We included studies assessing the link between maternal exposure to various endocrine-disrupting chemicals and the incidence of congenital heart diseases without restricting the study design or exposure assessment methods. Data were extracted from four databases, including PubMed, Scopus, Web of Science, and Cochrane Library, up to June 2024. Quality assessment of observational studies was conducted using the Newcastle-Ottawa Scale. Statistical analysis was performed using RevMan software version 5.3, presenting results as odds ratios with 95% confidence intervals. Results: Fifty-nine studies were included in the meta-analysis. The pooled analysis revealed a significant association between maternal endocrine-disrupting chemical exposure and the incidence of congenital heart diseases when measured using human samples (odds ratio = 1.63, 95% confidence interval [1.35-1.97], p < 0.00001). Notably, exposure to heavy metals, polycyclic aromatic hydrocarbons, and perfluoroalkyl compounds was strongly associated with congenital heart diseases. However, non-sample-based methods showed no significant overall correlation (odds ratio = 1.08, 95% confidence interval [0.93-1.26], p = 0.30), except for housing renovation compounds, which were linked to a higher incidence of congenital heart diseases. Conclusions: Maternal exposure to specific endocrine-disrupting chemicals, particularly heavy metals and polycyclic aromatic hydrocarbons, significantly increases the risk of congenital heart diseases. These findings underscore the need for preventive measures to reduce endocrine-disrupting chemicals exposure during pregnancy and further research to elucidate the underlying mechanisms. https://doi.org/10.3390/metabo14120709

Relationship between mixed exposure to phenyl hydroxides, polycyclic aromatic hydrocarbons, and phthalates and the risk of arthritis,
Fu, Q. S. and Yuan, X. H., *Bmc Public Health*, Sep 2024, Vol. 24, no. 1.

Background To determine the relationship between mixed exposure to three types of endocrine-disrupting chemicals (EDCs), namely phenyl hydroxides, polycyclic aromatic hydrocarbons (PAHs),

and phthalates (PAEs), and risk of arthritis. Methods Participants were selected from National Health and Nutrition Examination Survey (NHANES). The relationships between the urinary concentrations of phenyl hydroxides, PAHs, and PAEs and the risk of arthritis were analyzed by generalized linear regression model. The mixed exposure to these EDCs and the risk of arthritis was analyzed by weighted quantile sums (WQSs) and Bayesian kernel machine regression (BKMR) model. Results Our analysis showed that participants with urinary benzophenone-3 and methylparaben concentrations in the highest quartile (Q4) had an increased risk of arthritis compared with those in Q1. For each one-unit increase in the natural logarithm-converted urinary concentrations of 1-hydroxynapthalene and 2-hydroxynapthalene, the risk of arthritis increased by 5% and 8%, respectively. Chemical mixing index coefficients were significantly associated with risk of arthritis in both WQS positive- and negative-constraint models. In the BKMR model, there was a significant positive correlation between mixed exposure and the risk of arthritis. Conclusion Mixed exposure to phenyl hydroxides, PAHs, and PAEs increased the risk of arthritis, with exposure to PAHs being the key factor. https://doi.org/10.1186/s12889-024-19971-z

Sex- and trimester-specific impact of gestational co-exposure to organophosphate esters and phthalates on insulin action among preschoolers: Findings from the Ma'anshan birth cohort, Gan, H., Lu, M. J., Tong, J., Li, H. J., Zhou, Q., Han, F. F., Wang, X. R., Yan, S. Q., Huang, K., Wang, Q. N., Wu, X. Y., Zhu, B. B., Gao, H. and Tao, F. B., *Environment International*, Feb 2025, Vol. 196.

Introduction: Prenatal exposure to organophosphate esters (OPEs) and phthalic acid esters (PAEs) is ubiquitous among pregnant individuals. However, research exploring the relationship between prenatal co-exposure to OPEs and PAEs and childhood insulin function remains limited. Methods: In this study, utilizing data from 2,246 maternal-fetal dyads in the Ma'anshan Birth Cohort, associations between co-exposure to OPEs and PAEs and insulin action were analyzed. Repeated measures of tris (2-chloroethyl) phosphate, six OPE metabolites, and seven PAE metabolites were collected from maternal urine. Homeostasis model assessment of insulin resistance (HOMA-IR) and the insulin action index (IAI) served as outcome measures. After adjusting for potential confounders, the effects of repeated exposure on insulin action were evaluated using generalized estimating equations, while mixture effects were assessed through BayesianKernel Machine Regression and Quantile-Based G-Computation. Results: The average age of the children at the time of the study was 5.33 years. Repeated measures analysis revealed that prenatal exposure to MEP was positively associated with increased HOMA-IR (beta, 0.027; 95 % CI: 0.002, 0.053), while IAI was inversely correlated with rising MEP levels (beta, 0.025; 95 % CI: -0.046, -0.004) and MEHHP exposure (beta, -0.128; 95 % CI: -0.218, -0.037). Mixed exposure modeling further indicated that coexposure to OPEs and PAEs was positively linked to HOMA-IR (beta, 0.058; 95 % CI: 0.001, 0.114) and negatively correlated with IAI (beta, -0.054; 95 % CI: -0.097, -0.010), with stronger effects observed during the second trimester. Notably, the association was more pronounced in female children compared to males. Conclusions: This study provides the first epidemiological evidence highlighting the pregnancy- and sex-specific links between prenatal co-exposure to OPEs and PAEs and childhood insulin action. https://doi.org/10.1016/j.envint.2025.109287

Systematic Review of the Epidemiology of Hair Relaxer Use and Hormone-Sensitive Reproductive Outcomes Among Black Adult Women in the United States, Hernandez, A. M., Smith, S. J., Vahora, M. S., Campbell, D., Krevanko, C. F., Lewis, R. C. and Pierce, J. S., *Journal of Applied Toxicology*, 2025 Jan 2025.

Hair relaxers are predominantly used by Black women in the United States. It has been recently suggested that exposure to potential endocrine-disrupting compounds from the use of these products may be associated with the development of gynecological and breast cancers and

anatomically relevant nonmalignancies. We conducted a systematic literature review using PubMed to identify original studies reporting measures of association between hair relaxer use and relevant adverse outcomes, focusing specifically on Black women in the United States. A total of 1382 studies were initially identified, and after consideration of the exclusion and inclusion criteria, the final set of studies consisted of seven cohort studies and one case-control study. The overall findings suggest that Black women in the United States do not experience an increased risk of breast cancer, ovarian cancer, or uterine cancer due to hair relaxers. One study found a statistically significant association between hair relaxer use and uterine leiomyomata, but there were no other studies identified to support these findings. None of the studies characterized the chemical constituents of hair relaxers. From an epidemiologic perspective, the weight of the evidence does not support the hypothesis that the use of hair relaxers is a risk factor for gynecological and breast cancers in US Black women.
https://doi.org/10.1002/jat.4744

Associations between urinary parabens and thyroid hormone homeostasis across trimesters in Taiwanese pregnant women,
Huang, P. C., Chen, H., Kuo, P. L., Chen, H. C., Chang, W. T. and Chang, J. W., *Ecotoxicology and Environmental Safety*, Feb 2025, Vol. 291.

Few studies have explored the link between paraben exposure and thyroid hormone homeostasis in pregnant women across trimesters. The present study involved 97 pregnant women from southern Taiwan (2013-2014), and involved measuring urinary methyl, ethyl, propyl, and butyl parabens, as well as serum thyroid hormones and related indices, such as Structure Parameter Inference Approach-Glandular Disturbance [SPINA-GD], and SPINA Global Turnover [SPINA-GT]). Generalized estimating equations (GEE) were applied to examine the effect of longitudinal paraben exposure on thyroid hormone homeostasis. We found that propylparaben and butylparaben levels were associated with increased FT4 levels at the second visit ((3 = 0.07, p = 0.019; (3 = 0.08, p = 0.002), respectively. The GEE analysis further supported these associations, indicating the positive association between propylparaben levels and both T3 and FT4 levels over time ((3 = 0.05, p = 0.019 and (3 = 0.05, p = 0.026, respectively). Moreover, butylparaben levels were positively associated with FT4 ((3 = 0.05, p = 0.004) and inversely associated with the T4/FT4 ratio and SPINA-GD values ((3 = -0.04, p = 0.039 and (3 = -1.63, p = 0.004, respectively). In the GEE and BKMR analyses, a positive association was observed between PrP or paraben mixtures and T3 and FT4 levels, respectively. The findings of this study indicate that paraben and paraben mixtures have the potential to disrupt thyroid homeostasis by exerting a diverse hormonal effect. Further research is required to substantiate these conclusions in larger sample size populations.
https://doi.org/10.1016/j.ecoenv.2025.117818

Urinary phthalate metabolites associated with increased prevalence of gallstone disease in US adults: data from the NHANES study,
Jia, F., Chang, Y., Li, Y. G., Li, F. Q., Chen, X. Q., Liu, X. L., Li, W. and Cui, J. W., *Bmc Public Health*, Jan 2025, Vol. 25, no. 1.

Phthalate exposure has been hypothesized to influence cholesterol metabolism and gallstone pathogenesis, but previous studies are limited. We aimed to examine the associations between urinary phthalate metabolites and prevalence of gallstone disease in a nationally representative sample. We analyzed data on 1,696 adults aged >= 30 years from the National Health and Nutrition Examination Survey (NHANES) 2017-2018. Gallstone disease was defined based on self-reported physician-diagnosis. Exposure was measured by urinary concentrations of 10 phthalate metabolites. Multivariable logistic regression model was to assess individual exposure-effect associations. Weighted quantile sum (WQS) regression, Quantile g-computation (Qgcomp) analysis and Bayesian

kernel machine regression (BKMR) assessed metabolite mixtures in relation to gallstones. In the multivariable logistic regression model, compared to the lowest quartile (Q1) of urinary mono (2-ethyl-5-carboxypentyl) phthalate (MECPP), the highest quartile (Q4) was associated with an 82% increased risk of gallstone formation (OR: 1.82, 95% CI: 1.17, 2.85). Similarly, for mono(3-carboxypropyl) phthalate (MCPP), the risk increased by 78% in the Q4 group compared to Q1 (OR: 1.78, 95% CI: 1.02, 3.14). The WQS index exhibited a significant positive association with gallstone prevalence (OR: 1.37, 95%CI: 1.02, 1.84). In the Qgcomp model, four urinary phthalate metabolites, including MECPP, MCPP, mono benzyl phthalate (MBzP) and mono-carboxynonyl phthalate (MCNP), were positively associated with an increased risk of gallstones. BKMR identified exposure-response trends for MECPP, MCPP, and MBzP.ConclusionHigher urinary phthalate metabolite concentrations were associated with increased gallstone risk. These novel findings suggest phthalate exposure may contribute to lithogenic pathogenesis. Future prospective and mechanistic research is warranted. https://doi.org/10.1186/s12889-025-21417-z

Distribution of Environmental Phenols into Follicular Fluid and Urine of Women Attending Infertility Clinic,
Klimowska, A., Jurewicz, J., Radwan, M., Radwan, P., Pol, P. and Wielgomas, B., *Journal of Xenobiotics*, Feb 2025, Vol. 15, no. 1.

Infertility and environmental pollution are two globally prevalent and related issues. To explore women's reproductive health, the composition of follicular fluid (FF) has been studied and it was found that changes to its composition, including the presence of exogenous chemicals, can adversely affect the fertilization process. Two groups of women (idiopathic infertility and controls) who were patients at a fertility clinic were recruited for this study. Samples of urine and FF were gathered from each participant to determine the concentration of 14 common phenols (four parabens, six bisphenols, two benzophenones, and two naphthols). Associations between phenol concentrations (free and total) in both matrices were described using Spearman's correlation coefficient and were compared between two groups by the Mann-Whitney U test. Eight phenols were quantified in more than 50% of the urine samples, while only three parabens were quantified in hydrolyzed FF samples, and only methylparaben was quantified in non-hydrolyzed FF samples. Conjugates were the predominant form in FF samples. However, a significant correlation of 0.533 ($p < 0.0001$) was observed between free and total methylparaben concentrations in FF. Differences in concentrations between cases and controls in both matrices were not statistically significant, except for benzophenone-3 in urine, with a higher median observed in the control group ($p = 0.04$). The total paraben concentrations in urine and FF samples were rather weakly correlated ($r = 0.232$-0.473), implying that urine concentrations may not be appropriate for predicting their concentration in FF. https://doi.org/10.3390/jox15010017

Associations of PFAS and pesticides with lung function changes from adolescence to young adulthood in the ESPINA study,
Kornher, K., Gould, C. F., Manzano, J. M., Baines, K., Kayser, G., Tu, X., Suarez-Torres, J., Martinez, D., Peterson, L. A., Huset, C. A., Barr, D. B. and Suarez-Lopez, J. R., *International Journal of Hygiene and Environmental Health*, Apr 2025, Vol. 265.

Per- and polyfluoroalkyl substances (PFAS) and pesticides are widespread environmental contaminants linked to adverse health outcomes; yet, their impact on lung function-individually and as mixtures-remains poorly understood. This study analyzed data from 381 adolescents in a longitudinal cohort in Ecuador, measuring serum levels of three PFAS (perfluorooctanoic acid [PFOA], perfluorooctanesulfonic acid [PFOS], and perfluorononanoic acid [PFNA]) and urinary levels of three pesticides (glyphosate, 2,4-dichlorophenoxyacetic acid [2,4-D], and ethylene thiourea

[ETU]). Spirometric lung function was assessed in 2016 and 2022. We evaluated associations between individual chemical levels and lung measures in log-log models estimated via ordinary least squares regression. We used quantile g-computation to assess the association of the mixture of PFAS and pesticides with lung function outcomes. After accounting for multiple hypothesis testing, and in a range of socioeconomic, geographic variables, and tobacco exposure, no statistically significant associations were observed for individual or combined exposures with lung function outcomes, after correcting for multiple hypothesis testing. Slight, non-significant increases in FEV1/FVC were noted for PFOA, glyphosate, and ETU levels between 2016 and 2022. Our findings suggest that PFAS and pesticides, either individually or in combination, may not have substantial effects on adolescent lung function in this mid-to-high-altitude agricultural population. Further research is needed to assess these relationships in larger cohorts and over longer exposure periods.
https://doi.org/10.1016/j.ijheh.2025.114526

Exposome-wide association study of thyroid function using US National Health and Nutrition Examination Survey data,
Lee, J., Jang, H., Pearce, E. N. and Shin, H. M., *Environmental Research*, Mar 2025, Vol. 269.

Previous epidemiologic studies examining thyroid function and chemical exposures have typically focused on a single or a limited number of chemical classes, often neglecting the effects of chemical mixtures. This study addressed this gap by exploring the associations between exposure to hundreds of chemicals and thyroid function using an exposome-wide association study (ExWAS) approach and National Health and Nutrition Examination Survey (NHANES) data. We analyzed data from three NHANES cycles (2007-2008, 2009-2010, and 2011-2012), which include measures of thyroid function (free and total triiodothyronine [T3], free and total thyroxine [T4], thyroid-stimulating hormone [TSH]) and chemical biomarker concentrations from 9,082 participants. For adolescents (aged 12-19 years) and adults (aged >= 20 years), we employed multiple regression by accounting for survey weights to identify biomarkers associated with thyroid function test levels and used Bayesian group weighted quantile sum (BGWQS) regression to assess the effects of chemical mixtures on these measurements. After adjusting for multiple comparisons, we found in single exposure scenarios that 44 and 67 biomarkers were associated with at least one thyroid function measure in adolescents and adults, respectively (adjusted p-value <0.05). In scenarios involving mixed chemical exposures, groups such as pesticides, sodium/iodide symporter (NIS) inhibitors, and metals were associated with alterations in thyroid hormones or TSH across both age groups. Volatile organic compounds were specifically linked to lower T4 levels in adolescents, whereas phenols and parabens were associated with lower TSH levels exclusively in adults. Although limited by the cross-sectional data, this study identified chemical biomarkers linked to thyroid function.
https://doi.org/10.1016/j.envres.2025.120884

Repeated measurements of urinary bisphenol A and its analogues in relation to sperm DNA damage,
Li, Y. J., Liu, A. X., Zeng, J. Y., Miao, Y., Zhang, M., Liu, X. Y., Yang, W., Li, R. C., Zhu, J. Q., Liu, C. J. and Zeng, Q., *Journal of Hazardous Materials*, Apr 2025, Vol. 487.

Bisphenol A (BPA), a common endocrine disrupting chemical (EDC), has shown detrimental effects on sperm quality and function in experimental models. However, epidemiological evidence is inconsistent and also there exists a notable lack of data on its analogues, such as bisphenol F (BPF) and bisphenol S (BPS). To investigate the relationships between BPA, BPF and BPS exposures and sperm DNA damage, we conducted a cross-sectional study recruiting 474 Chinese men from an infertility clinic in Wuhan, China. We repeated measurements of urinary BPA, BPF and BPS concentrations to enhance the exposure assessments and evaluated sperm DNA damage using

three comet assay indicators: tail length (TL), tail distributed moment (TDM) and percentages of tail DNA (Tail%). We observed positive associations of BPA exposure with TL and TDM (both P for trends < 0.05) and an association of elevated BPF exposure with increased Tail% (P for trend = 0.066). Furthermore, BPA exposure in relation to increased TL and TDM were more pronounced in men with body mass index (BMI) below 24 kg/m(2) and non-smokers (all P for interactions < 0.05). Our findings strengthened human evidence that BPA and its analogue BPF exposures were in relation to increased sperm DNA damage. https://doi.org/10.1016/j.jhazmat.2025.137157

Insights into Triclosan-Induced Endocrine Disruption: Evidence from the National Health and Nutrition Examination Survey and Zebrafish Models,
Li, Z. M., Xian, H. Y., Ren, X. H., Ye, R. Y., Zhong, Y. Z., Huang, Y. J., Liang, B. X., Deng, Y. H., Dai, M. Z., Guo, J., Tang, S. Q., Pan, J. L., Feng, Y., Bai, R. B., Chen, X. P., Ichihara, S., Ichihara, G., Chen, D., Yang, X. F. and Huang, Z. L., *Environment & Health*, May 2024, Vol. 2, no. 7, p. 424-440.

Triclosan (TCS) has garnered significant attention due to its widespread use and associated endocrine-disrupting effects. However, its impact on the neuroendocrine system and underlying mechanisms remain poorly understood. Here, we established correlations between TCS exposure and serum sex hormone levels in participants of the National Health and Nutrition Examination Survey (NHANES). Additionally, we investigated TCS's influence on the neuroendocrine system using adult zebrafish exposed to environmentally relevant concentrations of TCS (0.361-48.2 mu g/L) for 21 days. Assessment of reproductive and neurotoxicity included histopathological examination and behavioral tests. Transcriptomics, proteomics analyses, and biochemical detection were employed to elucidate mechanisms underlying TCS-induced neuroendocrine disruption. Significant correlations were found between TCS exposure and estradiol, testosterone, and sex hormone-binding globulin levels in NHANES participants. In addition, TCS exposure inhibited ovary development and spermatogenesis in zebrafish. Transcriptomics and proteomics analysis revealed gender-specific key signaling and metabolism-related pathways implicated in TCS-induced reproductive toxicity. Moreover, TCS exposure induced nervous system impairment, as evidenced by histological changes and altered motor behavior, possibly associated with oxidative damage. Correlation analysis further highlighted the potential connection between endocrine system disruption and nervous system impairment following TCS exposure. Overall, this study provided evidence supporting TCS-induced endocrine disruption and offered insights into its underlying mechanisms.
https://doi.org/10.1021/envhealth.4c00045

Association between bisphenol A exposure and adiposity measures in children,
Liu, C., Liu, Y., Ning, J., Wu, C. Y., Lu, X. X., Guo, Y., He, P. S., Qiu, C. H. and Wu, J. L., *Medicine*, Dec 2024, Vol. 103, no. 52.

Bisphenol A (BPA) is a chemical that has adverse effects on human health and may cause childhood obesity. Nevertheless, the association between BPA exposure and adiposity measures in children remains controversial, especially in young children. A cross-sectional study was conducted on 208 randomly selected children 4 to 6 years old attending preschools in Guangzhou, China. BPA exposure was assessed through ultra-high performance liquid chromatography-tandem mass spectrometry of urinary samples. Childhood adiposity measures were determined, including body mass index, waist circumference, skinfold thickness, and upper arm circumference. BPA was detected in all urinary samples, and the median urinary BPA concentration was 0.54 (interquartile range, 0.05-5.81) mu g/L. In the adjusted models, children with higher urinary BPA concentrations had a higher body mass index z-score (beta = 0.471; 95% confidence interval [CI]: 0.303, 0.640), and they were at a greater risk of overweight or obesity (odds ratio [OR] = 3.308; 95% CI: 2.151, 5.089). Higher urinary BPA concentrations were associated with an elevated waist-to-height ratio (beta = 0.007; 95% CI:

0.002, 0.012), and they were at a higher risk of abdominal obesity (OR = 1.711; 95% CI: 1.102, 2.655). Higher urinary BPA concentrations were also associated with increased upper arm circumference and skinfold thickness in the adjusted models (beta = 0.546; 95% CI: 0.278, 0.813; beta = 0.702; 95% CI: 0.139, 1.266, respectively). Higher urinary BPA concentrations in children 4 to 6 years old were associated with a greater risk of overweight/obesity and abdominal obesity. BPA exposure might increase the risk of obesity in children. Further investigations are needed to confirm this association and explore the underlying mechanisms.
https://doi.org/10.1097/md.0000000000041065

Association between dietary intake estimated levels of PCDD/Fs and human sperm quality, Martínez, M. A., Salas-Huetos, A., De La Puente, M. F., Valle-Hita, C., Khoury, N., Sánchez-Resino, E., Ramos-Rodríguez, C., Davila-Cordova, E., Salas-Salvadó, J. and Babio, N., *Reproductive Toxicology*, Mar 2025, Vol. 132.

This study aimed to investigate the association between estimated dietary intake of polychlorinated dibenzo-pdioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) and human sperm quality. This study crosssectionally assessed the associations between estimated dietary intake of PCDD/Fs and sperm quality parameters in 200 participants aged 18-40 years from the Led-Fertyl study. Linear regression models, accounting for potential confounding variables, were employed to evaluate the relationships. To estimate the PCDD/Fs exposure, food frequency questionnaires and the latest data on PCDD/Fs concentrations in food, primarily from Spanish sources, were used. Our findings indicate that, in comparison to participants in the lowest tertile, those in the highest tertile (T3) of PCDD/Fs dietary intake exhibited significantly elevated body mass index, increased consumption of meat, fish and eggs, and decreased consumption of nuts. Furthermore, individuals in T3 demonstrated a higher percentage of sperm head abnormalities (4.65 % [0.10; 9.24]; p-trend= 0.037) and a corresponding increase per 1-SD increment in energy-adjusted total PCDD/Fs dietary intake (1.84 % [0.38; 3.68]). No significant associations for other sperm parameters were found. Minimal research exists on PCDD/F dietary exposure and human sperm quality. This study shows significant direct association between higher PCDD/Fs intake and the percentage of sperm head abnormalities which potentially may compromise human reproductive health.
https://doi.org/10.1016/j.reprotox.2025.108831

The negative impacts of bisphenols on thyroid function in adults with bisphenol A exposure level exceeding the tolerable daily intake,
Pei, Z. W., Zhang, L., Bao, Y., Li, J. G. and Zhuo, Q., *Ecotoxicology and Environmental Safety*, Jan 2025, Vol. 290.

In 2023, European Food Safety Authority (EFSA) published a re-evaluation of the safety of bisphenol A (BPA), establishing the new tolerable daily intake (TDI) as 0.2 ng/kg center dot bw/day with a 20,000-fold reduction compared to 2015, which regained public concern about the impact of bisphenols (BPs) on human health. In order to explore the health risk to thyroid function of BPs, in this study, we assessed the internal exposure levels of BPs and the relationships between urinary BPs and thyroid function in general adults. We carried out a cross-sectional study in Chengdu, China, recruiting 1486 adults without special indentities and diseases (aged 18-68), and measured 6 BPs in urine. We found BPA was the predominant compound in urinary samples of this population, and the estimated daily intake (EDI) of BPA was 0.027 mu g/kg center dot bw/day (geometric mean), exceeding the TDI value by two orders of magnitude. Using multivariable regression model, we observed a negative association between BPA and T3 and T3/T4 in males. Trend tests indicated that higher BPA levels were correlated with higher rates of subclinical hypothyroidism (SCH) in males (OR=1.383, 95 % CI [1.024, 1.867]). We also observed that bisphenol F (BPF) contributed to the

occurrence of thyroid globulin antibody positivity (TGAb.P) in both males and females. Although the use of BPs has been restricted, the adverse health effects still deserve public attention. https://doi.org/10.1016/j.ecoenv.2025.117790

Impact of Endocrine Disrupting Pesticide Use on Obesity: A Systematic Review, Pérez-Bermejo, M., Barrezueta-Aguilar, C., Pérez-Murillo, J., Ventura, I., Legidos-García, M. E., Tomás-Aguirre, F., Tejeda-Adell, M., Martínez-Peris, M., Marí-Beltrán, B. and Murillo-Llorente, M. T., *Biomedicines*, Dec 2024, Vol. 12, no. 12.

Background/Objectives: Endocrine disruptors are substances capable of altering the functions of the endocrine system. There is evidence that some pesticides can be endocrine disruptors and, among some of their effects, we find alterations in pubertal development and in the function of the thyroid gland, which could be related to a greater tendency of obesity. The aim was to evaluate the evidence from clinical and preclinical studies on the association between pesticides used in agriculture and found in plant-based foods with overweight/obesity. Methods: This is a systematic review of articles on the impact of the use of endocrine disrupting pesticides on obesity, conducted according to the PRISMA-2020 guidelines. Results: There was evidence that some pesticides, such as chlorpyrifos, pyrethroids, and neonicotinoids, may promote obesity and other anthropometric changes by altering lipid and glucose metabolism, modifying genes, or altering hormone levels such as leptin. Other studies suggest that perinatal exposure to chlorpyrifos or pesticides such as vinclozolin may alter lipid metabolism and promote weight gain in adulthood, whereas other pesticides such as boscalib, captan, thiacloprid, and ziram were not associated with changes in weight. Exposure to pesticides such as vinclozolin may be associated with a higher prevalence of overweight/obesity in later generations. Conclusions: The few studies that do not show these associations have methodological limitations in data collection with confounding variables. Further studies are needed to provide more and higher quality evidence to determine the true effect of these substances on obesity. https://doi.org/10.3390/biomedicines12122677

Gestational exposure to environmental chemical mixtures and cognitive abilities in children: A pooled analysis of two North American birth cohorts, Puvvula, J., Hwang, W. T., Mccandless, L., Xie, C. C., Braun, J. M., Vuong, A. M., Oulhote, Y., Schisterman, E. F., Shinohara, R. T., Booij, L., Bouchard, M. F., Linn, K., Borghese, M. M., Seguin, J. R., Zidek, A., Till, C., Fraser, W., Yolton, K., Cecil, K. M., Ashley-Martin, J., Arbuckle, T. E., Lanphear, B. and Chen, A. M., *Environment International*, Feb 2025, Vol. 196.

Background: Gestational exposures to single toxic chemicals have been associated with cognitive deficits in children, but few studies have explored chemical mixtures. Objectives: To evaluate the associations between gestational chemical biomarker mixtures and cognitive abilities in children from two prospective cohorts. Methods: This study includes 617 birthing parent-child pairs from the Health Outcomes and Measures of the Environment (HOME) and Maternal-Infant Research on Environmental Chemicals (MIREC) Studies. We measured 29 chemical biomarkers (metals, persistent organic pollutants, perfluoroalkyl substances, organo- phosphate esters, phenols, phthalates, organophosphate pesticides, and parabens) in pregnant individuals during early pregnancy and their children's cognitive abilities at ages 3 to 5 years using Wechsler Intelligence Scales. We assessed linear associations using quantile g-computation and non-linear associations using Bayesian Kernel Machine Regression (BKMR) methods, adjusted for covariates. Results: Using quantile g-computation, we observed overall null associations between the chemical biomarker mixture and cognitive outcomes among preschool-age children. Although statistical significance was not attained for child sex as an effect modifier, our stratified analysis unveiled a moderate divergence in association trends. We noted a marginal inverse trend between the chemical

biomarker mixture and cognitive scores [Full-Scale Intelligence Quotient (FSIQ) & Performance Intelligence Quotient (PIQ)] among males. Using quantile g- computation and BKMR methods, we observed that PBDE47, PFHxS, and di-ethyl organophosphates commonly contributed towards a decline in FSIQ scores in males. Among males, a quartile increase in the chemical biomarker mixture was associated with a 0.64-point decrease (95% CI:-2.59, 1.31) in the FSIQ score and a 1.59- point decrease (95% CI:-3.72, 0.54) in the PIQ score. Conclusion: In this study, we observed a weak negative trend between the gestational chemical biomarker mixture and cognitive scores (FSIQ/PIQ) among males. Further studies are needed to confirm the findings be- tween the longitudinal chemical biomarkers and child cognitive scores at school ages.
https://doi.org/10.1016/j.envint.2025.109298

Associations between per- and polyfluoroalkyl substances (PFAS) and female sexual function in a preconception cohort,
Schildroth, S., Bond, J. C., Wesselink, A. K., Abrams, J., Calafat, A. M., Botelho, J. C., White, K. O., Wegienka, G., Hatch, E. E. and Wise, L. A., *Environmental Research*, Feb 2025, Vol. 266.

Background: Female sexual function is important for sexual well-being, general health, fertility, and relationship satisfaction. Distressing impairments in sexual function, clinically recognized as female sexual dysfunction (FSD), can manifest as issues with interest/desire, arousal, orgasm, and pain during vaginal penetration. Some evidence suggests that exposure to endocrine-disrupting chemicals may adversely affect female sexual function, but associations for per- and polyfluoroalkyl substances (PFAS) have not been previously evaluated. Objective: We investigated associations between serum PFAS concentrations and female sexual function among U. S. pregnancy planners. Methods: We used cross-sectional data from participants from Pregnancy Study Online (PRESTO), a prospective preconception cohort study. Participants reported sexual function and distress at baseline on two validated measures: a modified version of the Female Sexual Function Index-6 (FSFI-6) and the Female Sexual Distress Scale (FSDS). We quantified PFAS serum concentrations in samples collected in the preconception period (i.e., at baseline) using solid phase extraction-high performance liquid chromatography-isotope-dilution-mass spectrometry. Participants reported sociodemographic information on structured baseline questionnaires. We included 78 participants with complete PFAS and sexual function data and fit multivariable linear regression models to estimate mean differences in FSFI-6 scores (beta) or percent differences (%) in FSDS scores per interquartile range (IQR) increase in PFAS concentrations, adjusting for age, annual household income, years of education, parity, and body mass index. We further investigated effect measure modification by parity (parous vs. nulliparous) in stratified models. Results: An IQR increase in perfluorohexanesulfonic acid was associated with a 1.0-point decrease (95% CI = -1.8, -0.1) in reported FSFI-6 scores, reflecting poorer sexual function. PFAS were consistently associated with lower FSFI-6 scores among parous participants. PFAS were also associated, though imprecisely, with greater sexual distress. Conclusion: Some PFAS were associated with poorer sexual function among U.S. pregnancy planners, but future studies are needed to clarify the extent to which PFAS influences female sexual health. https://doi.org/10.1016/j.envres.2024.120556

Prenatal polycyclic aromatic hydrocarbons exposure and child growth and adiposity: A longitudinal study,
Shahin, S., Ghassabian, A., Blaauwendraad, S. M., Duh-Leong, C., Kannan, K., Long, S. E., Herrera, T., Seok, E., Pierce, K. A., Liu, M. L. and Trasande, L., *Environmental Research*, Mar 2025, Vol. 268.

Background: Exposure to polycyclic aromatic hydrocarbons (PAHs) during childhood has been associated with altered growth and adiposity in children. The effects of prenatal exposure to PAHs on developmental programming of growth and adiposity are still unknown. Objective: To study the

association of prenatal exposure to PAHs with early childhood growth and adiposity measures. Methods: In NYU Children's Health and Environment Study (2016-2019), we studied 880 mother-child pairs for maternal urinary PAH metabolites in early, mid, and late pregnancy and measured child weight, length/height, triceps, and subscapular skinfold thicknesses at 1, 2, 3, and 4 years. We used linear mixed models to investigate associations between average pregnancy exposure to PAHs and the z-scores of child repeated measures. The models were adjusted for sociodemographic and health-related factors. Results: Children prenatally exposed to higher levels of PAHs had greater weight and length/height z scores. We found an interaction with time-point of child assessment, showing stronger associations at later ages. For instance, PAH exposure was associated with higher weight z-scores at 3 years: coefficient per Ln-unit increase in 2-NAP = 0.25 (95%CI: 0.13, 0.37), 2-PHEN = 0.25 (95%CI: 0.11, 0.39), 1-PYR = 0.13 (95%CI: 0.02, 0.24), and 4-PHEN = 0.09 (95%CI: 0.02, 0.15). Higher concentrations of 2-NAP (coefficient = 0.21, 95%CI: 0.11, 0.31), 2PHEN (coefficient = 0.24, 95%CI: 0.12, 0.35), 3-PHEN (coefficient = 0.13, 95%CI: 0.02, 0.24]), 4-PHEN (coefficient = 0.09, 95%CI: 0.04, 0.15), and 1-PYR (coefficient = 0.11, 95%CI: 0.02, 0.21) were associated with higher weight z-score at 4 years. Conclusion: Prenatal PAH exposure may contribute to the developmental programming of growth in childhood. https://doi.org/10.1016/j.envres.2025.120756

Effect of occupational exposure to vat-textile dyes on follicular and luteal hormones in female dye workers in Abeokuta, Nigeria,
Soyinka, O. O., Akinsanya, A. F., Odeyemi, F. A., Amballi, A. A., Oritogun, K. S. and Ogundahunsi, O. A., *African Health Sciences*, Mar 2024, Vol. 24, no. 1, p. 135-144.

Background: Some synthetic dyes used mainly in textile industries have been associated with endocrine disruption, resulting in infertility, among other disorders. It is unknown if occupational exposure to Vat textile dyes among premenopausal dyers alters hormonal levels. Objectives: We aimed at determining the probable effects of occupational exposure to Vat dyes on reproductive hormones of female textile dyers in the follicular and luteal phases while relating this to age categories and duration of exposure. Methods: Thirty-three premenopausal Vat textile dyers at "Itoku", Abeokuta, Nigeria, among a population of about 80 female dyers were age and sex-matched with 55 non-exposed (control) female participants. Using semi-structured questionnaires, socio-demographic, occupational details and the LMP of participants were obtained. Serum samples were collected in follicular and luteal phases and assayed for female sex hormones using Enzyme Immunoassay. Mann-Whitney U and Z- statistic were used for comparison of the two groups. P-value < 0.05 was considered to be significant. Results: In the follicular phase, the result showed a lower mean FSH ranking (in age category <= 20 years) and higher (p<0.05) Estradiol ranking (in age category 31-40 years) in the exposed than the unexposed. Mean ranks of Progesterone and Estradiol in the luteal phase (age category 31-40 years) were higher (p<0.05) in the exposed, while Estradiol (age category >= 41years) ranked lower (p<0.05). Prolactin demonstrated a significant inverse relationship with the duration of exposure. Conclusion: Occupational exposure to Vat dye among female dyers in Abeokuta is associated with some sex hormone disruption which appears to be age and duration of exposure-related. https://doi.org/10.4314/ahs.v24i1.17

An Umbrella Review of Meta-Analyses Evaluating Associations between Human Health and Exposure to Major Classes of Plastic-Associated Chemicals,
Symeonides, C., Aromataris, E., Mulders, Y., Dizon, J., Stern, C., Barker, T. H., White, A., Pollock, D., Marin, T. and Dunlop, S., *Annals of Global Health*, 2024, Vol. 90, no. 1.

Background: Epidemiological research investigating the impact of exposure to plastics, and plastic-associated chemicals, on human health is critical, especially given exponentially increasing plastic production. In parallel with increasing production, academic research has also increased

exponentially both in terms of the primary literature and ensuing systematic reviews with meta-analysis. However, there are few overviews that capture a broad range of chemical classes to present a state of play regarding impacts on human health. Methods: We undertook an umbrella review to review the systematic reviews with meta-analyses. Given the complex composition of plastic and the large number of identified plastic-associated chemicals, it was not possible to capture all chemicals that may be present in, and migrate from, plastic materials. We therefore focussed on a defined set of key exposures related to plastics. These were microplastics, due to their ubiquity and potential for human exposure, and the polymers that form the matrix of consumer plastics. We also included plasticisers and flame retardants as the two classes of functional additive with the highest concentration ranges in plastic. In addition, we included bisphenols and per- and polyfluoroalkyl substances (PFAS) as two other major plastic-associated chemicals with significant known exposure through food contact materials. Epistemonikos and PubMed were searched for systematic reviews with meta-analyses, meta-analyses, and pooled analyses evaluating the association of plastic polymers, particles (microplastics) or any of the selected groups of high-volume plastic-associated chemicals above, measured directly in human biospecimens, with human health outcomes. Results: Fifty-two systematic reviews were included, with data contributing 759 meta- analyses. Most meta-analyses (78%) were from reviews of moderate methodological quality. Across all the publications retrieved, only a limited number of plastic-associated chemicals within each of the groups searched had been evaluated in relevant meta-analyses, and there were no meta-analyses evaluating polymers, nor microplastics. Synthesised estimates of the effects of plastic-associated chemical exposure were identified for the following health outcome categories in humans: birth, child and adult reproductive, endocrine, child neurodevelopment, nutritional, circulatory, respiratory, skin-related and cancers. Bisphenol A (BPA) is associated with decreased anoclitoral distance in infants, type 2 diabetes (T2D) in adults, insulin resistance in children and adults, polycystic ovary syndrome, obesity and hypertension in children and adults and cardiovascular disease (CVD); other bisphenols have not been evaluated. Phthalates, the only plasticisers identified, are associated with spontaneous pregnancy loss, decreased anogenital distance in boys, insulin resistance in children and adults, with additional associations between certain phthalates and decreased birth weight, T2D in adults, precocious puberty in girls, reduced sperm quality, endometriosis, adverse cognitive development and intelligence quotient (IQ) loss, adverse fine motor and psychomotor development and elevated blood pressure in children and asthma in children and adults. Polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) but not other flame retardants, and some PFAS were identified and are all associated with decreased birth weight. In general populations, PCBs are associated with T2D in adults and endometriosis, bronchitis in infants, CVD, non-Hodgkin's lymphoma (NHL) and breast cancer. In PCB-poisoned populations, exposure is associated with overall mortality, mortality from hepatic disease (men), CVD (men and women) and several cancers. PBDEs are adversely associated with children's cognitive development and IQ loss. PBDEs and certain PFAS are associated with changes in thyroid function. PFAS exposure is associated with increased body mass index (BMI) and overweight in children, attention deficit hyperactive disorder (ADHD) in girls and allergic rhinitis. Potential protective associations were found, namely abnormal pubertal timing in boys being less common with higher phthalate exposure, increased high-density lipoprotein (HDL) with exposure to mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) and reduced incidence of chronic lymphocytic lymphoma (a subtype of NHL) with PCB exposure. Conclusions: Exposure to plastic-associated chemicals is associated with adverse outcomes across a wide range of human health domains, and every plastic-associated chemical group is associated with at least one adverse health outcome. Large gaps remain for many plastic-associated chemicals. Recommendations: For research, we recommend that efforts are harmonised globally to pool resources and extend beyond the chemicals included in this umbrella review. Priorities for primary research, with ensuing systematic reviews, could include micro- and nanoplastics as well as emerging plastic-associated chemicals of concern such as

bisphenol analogues and replacement plasticisers and flame retardants. With respect to chemical regulation, we propose that safety for plastic-associated chemicals in humans cannot be assumed at market entry. We therefore recommend that improved independent, systematic hazard testing for all plastic-associated chemicals is undertaken before market release of products. In addition because of the limitations of laboratory-based testing for predicting harm from plastic in humans, independent and systematic post-market bio-monitoring and epidemiological studies are essential to detect potential unforeseen harms. https://doi.org/10.5334/aogh.4459

Individual and joint effects of exposure to multiple organophosphate esters and the risk of depression in adults: Differences in sex, age, and physical activity,
Wei, Q. M., Wei, J. Y. and Liang, J., *Ecotoxicology and Environmental Safety*, Jan 2025, Vol. 290.

Depression, a severe mental disorder, is a prominent cause of global disability and worldwide. Organophosphate esters (OPEs) are neuron-disrupting chemicals that potentially cause depression. However, the effects of OPEs on depression remain unclear. We aimed to assess the associations among five OPE levels in urine and depression by using NHANES 2011-2018. Generalized linear model, quantile g-computation (Qgcomp), and Bayesian kernel machine regression (BKMR) were utilized to assess the effects of OPEs on depression. In the generalized linear model, a one-unit increase in the natural logarithm (ln) of the urinary level of diphenyl phosphate (DPHP) was related to a respective ln-increase of 0.038(95 % CI: 0.002, 0.074) in the square root-transformed depression score, and each unit increase in the ln values of DBUP levels was related to a 1.163-fold (95 % CI: 1.013, 1.334) increase in the odds of depression in the crude models. Additionally, the effects of OPE exposure on depression and depression scores were pronounced in females, younger individuals, and physically inactive individuals. RCS revealed a U-shaped relationship between bis (1,3-dichloro-2-propyl) phosphate (BDCPP) level and the risk of depression (P-nonlinear=0.023). BKMR suggested that BDCPP and DPHP levels had a U-shaped relationship with the risk of depression. In the Qgcomp model, each one quartile increment in a mixture of OPEs was related to a 0.186 increase (95 % CI: 0.034, 0.338) in the depression score. In the BKMR, a positive association was noted between OPE mixtures and depression scores, and a U-shaped nonlinear association was noted between OPE mixtures and the risk of depression. The results indicated that exposure to single and multiple OPEs can increase the risk of depression in adults, indicating nonmonotonic dose-response relationships. Potential sex specific, age dependent, and exercise-related effects were found.
https://doi.org/10.1016/j.ecoenv.2024.117611

Exposure to Multiple Endocrine-Disrupting Chemicals and Associations with Female Infertility: A Case-Control Study,
Wei, X. P., Zhang, N., Zhu, Q. Q., Hu, Y., Wang, X., Weng, X. Y., Liao, C. Y. and Jiang, G. B., *Environment & Health*, Sep 2024, Vol. 2, no. 12, p. 902-911.

Parabens (PBs) and their metabolites (MBs), triclocarban (TCC), triclosan (TCS), bisphenols (BPs), benzophenones (BzPs), and phthalate metabolites (mPAEs) are typical endocrine-disrupting chemicals (EDCs) used in industrial production and daily life. Studies have suggested that these EDCs affect the reproductive system and may cause infertility; however, epidemiological evidence linking EDC exposure to infertility is still lacking. Herein, a total of 302 serum samples from women of reproductive age were collected, and six categories of typical EDCs were analyzed. The results revealed that EDCs are ubiquitous in female serum. The geometric mean (GM) concentrations of ∑PBs, ∑MBs, ∑(TCS+TCC), ∑BPs, ∑BzPs, and ∑mPAEs were 3.36, 297, 3.87, 4.39, 0.257, and 4.56 ng/mL, respectively. The serum concentrations of ∑PBs, ∑MBs, ∑(TCS+TCC), and ∑mPAEs from infertile women (GM: 4.16, 397, 4.01, and 7.33, respectively) were higher than those from fertile women (2.45, 192, 3.65, and 2.27, respectively) ($p < 0.05$). The results of binary logistic regression

and random forest suggest that mPAEs, such as mBP/miBP and mEHP, may contribute to infertility. This study provides insight into the relationship between the EDC exposure and reproductive outcomes. https://pubmed.ncbi.nlm.nih.gov/39722846/

Associations between exposure to volatile organic compounds with obesity in adults,
Wu, R. M., Jia, L., Zhu, X., Guan, G. C., Wang, J. K., Hui, R. T., Ma, M. J., Zhao, Z., Pang, H. and Zhu, L., *Human Nutrition & Metabolism*, Mar 2025, Vol. 39.

Objective: This study was to investigate the correlation between urine volatile organic compound (VOC) metabolites and obesity-related outcomes, including BMI, waist circumference, obesity, and abdominal obesity. Methods: Data from the National Health and Nutrition Examination Survey (NHANES) conducted between 2011 and 2016 were utilized for this analysis. Linear regression and logistic regression models were employed to estimate beta-coefficients or odds ratios (ORs) along with their corresponding 95 % confidence intervals (CIs). Quantile g-computation (Qgcomp) regression, a method designed to evaluate the combined effects of multiple correlated chemical exposures, was used to assess the mixed influence of VOC metabolites on obesity-related outcomes. Results: A total of 4950 adults were included in this analysis. The median age of the participants was 47 (33, 60) years, with 49.3 % being male. The median BMI was 27.7 (24.2, 32.4) kg/m2, and the median waist circumference was 98.0 (87.3, 109.0) cm. The prevalence of obesity and abdominal obesity was 36.8 % and 56.5 %, respectively. After adjusting for all covariates, urine VOC metabolites (including AAMA, AMCC, BMA, CYMA, DHBMA, 3HPMA, 2HPMA, MA, 2MHA, 3MHA+4MHA, MHBMA3, PGA, and HPMMA) exhibited a negative association with obesity. With the exception of BMA and DHBMA, similar results were observed regarding the association between urine VOC metabolites and the prevalence of abdominal obesity. Additionally, Qgcomp regression analysis revealed a significant negative correlation between the mixture of urine VOC metabolites and all obesity-related outcomes, with 2HPMA demonstrating the strongest influence on this negative association. Conclusion: Our findings suggest a negative relationship between exposure to VOCs, as measured by urine VOC metabolite levels, and obesity in adults.
https://doi.org/10.1016/j.hnm.2024.200296

Associations between phenol and paraben exposure and the risk of developing breast cancer in adult women: a cross-sectional study,
Xiong, Y., Li, Z. Y., Xiong, X., Luo, Z. X., Zhong, K. X., Hu, J. W., Sun, S. R. and Chen, C., *Scientific Reports*, Feb 2025, Vol. 15, no. 1.

Increasing evidence suggests that endocrine-disrupting chemicals (EDCs) have adverse effects on breast cancer (BC). The aim of this study was to assess the association between exposure to prevalent EDCs-phenols and parabens-and the risk of developing BC. Data on urinary bisphenol A (BPA), triclosan (TRS), benzophenone-3 (BP3), methyl paraben (MPB), ethyl paraben (EPB), propyl paraben (PPB), and butyl paraben (BUP) were obtained from the 2005-2014 National Health and Nutrition Examination Survey. A total of 4455 subjects were included in this cross-sectional study. The results from the weighted multivariable regression models indicated that exposure to elevated concentrations of TRS increased the risk of developing BC by 2.33 (Q2: 95% CI = 1.45-3.75, p < 0.001) and 1.94 times (Q3: 95% CI = 1.21-3.09, p = 0.006), respectively. The nonlinear association between TRS concentrations and the risk of developing BC was statistically significant (P nonlinear = 0.007), with the restricted cubic splines (RCS) curve exhibiting an inverted U shape. The association between TRS concentrations and the risk of developing BC was more pronounced among overweight individuals (BMI >= 25 kg/m2), those aged < 60 years, and white individuals. Weighted quantile sum (WQS) and Bayesian Kernel Machine Regression (BKMR) analysis revealed no significant overall association between mixtures of urinary phenol and paraben metabolites and BC risk. However, TRS

exposure was the most influential, with higher TRS concentrations (both continuous and categorical) significantly associated with an increased BC risk, particularly in overweight individuals (BMI >= 25 kg/m2), those aged < 60 years, and white individuals. https://doi.org/10.1038/s41598-025-88765-z

Toxicité sur l'homme

Establishing the Mechanisms Involved in the Environmental Exposure to Polychlorinated Biphenyls (PCBs) in the Risk of Male Infertility,
Anvari, E., Noorimotlagh, Z., Mirzaee, S. A., Nourmoradi, H., Bahmani, M., Rashan, N., Martinez, S. S., Kamran, S. and Ahmadi, I., *Reproductive Sciences*, 2025 Feb 2025.

Exposure to toxic chemicals, such as plasticizers, alkylphenol compounds, and polychlorinated biphenyls (PCBs), has increased due to environmental contamination. PCBs, categorized as persistent organic pollutants (POPs), are lipophilic chemicals commonly used in lubricants, cutting oils, and electrical insulators. PCBs may have detrimental effects on hormone-producing glands, potentially contributing to male infertility. Thus, the objective of this study was to provide a comprehensive overview of the adverse effects of PCBs on the male reproductive system. Searches of three electronic databases were performed using MESH terms and 32 studies were included. Although the exact mechanism of action for PCBs remains unclear, several PCBs are regarded as potential endocrine disruptors due to their ability to interact with hormone signaling pathways. PCBs have been found to disrupt physiological functions by mimicking endogenous hormones as agonists or antagonists, altering patterns of hormone synthesis, hormone receptor affinities or numbers, and modulating enzymes involved in hormone secretion. These reports highlight the pleiotropic nature of PCB function and the susceptibility of the reproductive system. Endocrine-disrupting PCBs can mimic, alter, or block hormonal responses, inhibiting natural signaling to the testes and epididymis via various mechanisms such as binding to sex hormone-binding globulin and androgen-binding protein or blocking cell surface receptors. Furthermore, PCBs can alter the hormonal environment in the prostate or seminal vesicles by changing the affinity of androgens for their receptors. The testicles and genital organs may be susceptible to various estrogenic effects, leading to changes in the quality or quantity of their secretions and the volume of semen.
https://doi.org/10.1007/s43032-025-01794-x

Hydranencephaly in a newborn due to occupational toluene exposure during pregnancy: a case report,
Aydin, B., Botan, E., Gülensoy, B. and Akyol, S., *Acute and Critical Care*, Nov 2024, Vol. 39, no. 4, p. 647-651.

The etiopathogenesis of hydranencephaly remains unclear; however, exposure to toxic substances during pregnancy likely increases hydranencephaly risk. Head computed tomography (CT) was performed in a neonate 9 hours post-delivery because the anterior fontanelle was large and there were clinical signs of encephalopathy. Head CT revealed a lack of both cerebral hemispheres and significant cystic enlargement, while the cerebellar hemispheres and pons were found to have developed normally. History-taking revealed that the mother worked in the automotive industry, specifically in the car paint cleaning business and was exposed to toluene during the pregnancy. The patient was diagnosed with hydranencephaly, central diabetes insipidus and central hypothyroidism. Due to the increased head circumference and tense anterior fontanelle, a ventriculoperitoneal shunt was placed. Toluene exposure during pregnancy should be considered among the causes of hydranencephaly. Furthermore, central diabetes insipidus and central hypothyroidism may develop in such cases. https://doi.org/10.4266/acc.2021.01081

Bisphenol A and its potential mechanism of action for reproductive toxicity,
Cull, M. E. and Winn, L. M., *Toxicology*, Feb 2025, Vol. 511.

Bisphenol A (BPA) is an organic synthetic chemical used worldwide. Billions of pounds of BPA are produced annually through industrial processes to be used in commercial products, making human exposure to BPA ubiquitous. Concerns have been raised due to the potential adverse health effects of BPA, specifically in vulnerable populations, such as pregnant persons and children. BPA is an endocrine-disrupting chemical, and through this function has been linked to reproductive toxicity. We review BPA's historical and current use, health and safety concerns and regulations, sources of exposure, and evidence for male and female reproductive toxicity. Evidence from epidemiological and animal studies idenfity that low- and high-exposure levels of BPA (prenatal, postnatal and adulthood exposure) can adversely affect male and female fertility and reproductive organs. While the cause of BPA-induced reproductive toxicity is not fully understood, we discuss BPA's estrogenic and androgenic activity, and its ability to disrupt the hypothalamic-pituitary-gonadal axis as a potential associated mechanism. There are significant differences in tolerable daily intakes of BPA set by global agencies, making interpretation of previous and emerging research findings challenging and inconsistent. Although BPA is deemed toxic by some government agencies, most do not currently consider it a health risk due to low populational exposure levels. However, we highlight evidence that even at acute, low exposure, BPA can adversely affect reproductive function. We recommend continuing research into the adverse effects of BPA on human health and revisiting the regulatory measures of BPA to limit exposure and promote public awareness of its potential to cause reproductive toxicity. https://doi.org/10.1016/j.tox.2024.154040

Utilization of Artificial Intelligence Coupled with a High-Throughput, High-Content Platform in the Exploration of Neurodevelopmental Toxicity of Individual and Combined PFAS,
Currie, S. D., Benson, D. B., Xie, Z. R., Wang, J. S. and Tang, L. L., *Journal of Xenobiotics*, Feb 2025, Vol. 15, no. 1.

Per- and polyfluoroalkyl substances (PFAS) are synthetic chemicals used in various products, such as firefighting foams and non-stick cookware, due to their resistance to heat and degradation. However, these same properties make them persistent in the environment and human body, raising public health concerns. This study selected eleven PFAS commonly found in drinking water and exposed Caenorhabditis elegans to concentrations ranging from 0.1 to 200 mu M to assess neurodevelopmental toxicity using a high-throughput, high-content screening (HTS) platform coupled with artificial intelligence for image analysis. Our findings showed that PFAS such as 6:2 FTS, HFPO-DA, PFBA, PFBS, PFHxA, and PFOS inhibited dopaminergic neuron activity, with fluorescence intensity reductions observed across concentrations from 0.1 to 100 mu M. PFOS and PFBS also disrupted synaptic transmission, causing reduced motility and increased paralysis in aldicarb-induced assays, with the most pronounced effects at higher concentrations. These impairments in both neuron activity and synaptic function led to behavioral deficits. Notably, PFOS was one of the most toxic PFAS, affecting multiple neurodevelopmental endpoints. These results emphasize the developmental risks of PFAS exposure, highlighting the impact of both individual compounds and mixtures on neurodevelopment. This knowledge is essential for assessing PFAS-related health risks and informing mitigation strategies. https://doi.org/10.3390/jox15010024

Effects of tributyltin on placental and reproductive abnormalities in offspring,
Da Costa, C. S., Alahmadi, H., Nunes, M. T., Dias, G. R. M., Miranda-Alves, L. and Graceli, J. B., *Archives of Endocrinology Metabolism*, 2024, Vol. 68.

Tributyltin (TBT) is an organotin compound and a common persistent environmental pollutant with endocrine-disrupting chemical (EDC) actions. It can accumulate in the environment at various concentrations throughout the food chain in the ecosystem, posing a risk to human health, especially during critical periods such as gestation and fetal and offspring development. In this review, we report the results of studies describing the consequences of TBT exposure on placental and reproductive parameters in offspring of both sexes. Results from in vivo and in vitro studies clearly indicate that TBT causes adverse effects on placental development and reproductive parameters in offspring. However, substantial knowledge gaps remain in the literature, requiring further research to better understand the mechanisms behind TBT effects on placental and reproductive disruption in offspring. https://doi.org/10.20945/2359-4292-2024-0186

Role of the endocannabinoid system in gonadal development: Implications for endocrine disruption and reproductive toxicity,
De Araújo-Ramos, A. T. and Martino-Andrade, A. J., *Reproductive Toxicology*, Mar 2025, Vol. 132.

The endocannabinoid system (ECS) plays a pivotal role in reproductive physiology, including gonadal development, though its influence on testis and ovary development has only recently gained attention. The ECS comprises lipid-derived ligands such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), along with cannabinoid receptors CB1 and CB2, which are expressed in various gonadal cells. Emerging research indicates that ECS signaling is critical for testosterone synthesis and gonadal cell proliferation and differentiation. This review explores the expression and function of ECS components in developing gonads, highlighting the differential roles of CB1 and CB2 receptors in species-specific contexts. Furthermore, the ECS has been suggested to be involved in the adverse effects of endocrine-disrupting chemicals (EDCs) on reproductive development. EDCs, such as phthalates, may interfere with ECS signaling, potentially leading to reproductive abnormalities that resemble the human Testicular Dysgenesis Syndrome (TDS). Understanding the molecular interactions between EDCs and the ECS could reveal novel mechanisms underlying reproductive toxicities. Future research should focus on the detailed localization and temporal expression of ECS components in fetal gonads, the mechanisms of cannabinoid-mediated testosterone inhibition, and the potential direct interaction of EDCs with the ECS. This knowledge could be crucial for developing strategies to mitigate reproductive health risks associated with EDC exposure.
https://doi.org/10.1016/j.reprotox.2024.108822

Impact of 17-alpha ethinyl estradiol (EE2) and diethyl phthalate (DEP) exposure on microRNAs expression and their target genes in differentiated SH-SY5Y cells,
Graziosi, A., Corrieri, C., Sita, G., Ghelli, L., Angelini, S., Bianca, R. D. D., Mitidieri, E., Sorrentino, R., Hrelia, P. and Morroni, F., *Scientific Reports*, Jan 2025, Vol. 15, no. 1.

Environmental endocrine disruptor chemicals (EDCs) have raised significant concerns due to their potential adverse effects on human health, particularly on the central nervous system (CNS). This study provides a comparative analysis of the effects of 17-alpha ethinyl estradiol (EE2) and diethyl phthalate (DEP) on neuronal cell proliferation and neurotoxicity. Using differentiated SH-SY5Y human neuronal cells, we evaluated cell viability, microRNA (miRNA) regulation, and RNA expression following exposure to subtoxic concentrations of EE2 and DEP. Our results show that both EDCs downregulated specific miRNAs-miR-18b-5p, miR-200a-3p, and miR-653-5p-affecting key processes such as cell proliferation, survival, and apoptosis. Gene expression analysis revealed the upregulation of EGFR, IGF1R, BTG2, and SH3BP4, implicating these miRNAs in the regulation of the Ras and PI3K/Akt/mTOR pathways. Our findings highlight distinct cellular responses: DEP disrupts PTEN activity, while EE2 enhances phosphorylation within the PI3K/Akt/mTOR pathway, promoting pro-survival and anti-apoptotic signals. This study emphasizes the urgent need for regulatory

measures to mitigate the neurotoxic effects of EDCs and offers valuable insights into their molecular impacts on brain health. https://doi.org/10.1038/s41598-025-86911-1

Environmental Exposure to Bisphenol A Enhances Invasiveness in Papillary Thyroid Cancer, Huang, C. Y., Xie, R. H., Li, P. H., Chen, C. Y., You, B. H., Sun, Y. C., Chou, C. K., Chang, Y. H., Lin, W. C. and Chen, G. Y., *International Journal of Molecular Sciences*, Jan 2025, Vol. 26, no. 2.

Bisphenol A (BPA) is a prevalent environmental contaminant found in plastics and known for its endocrine-disrupting properties, posing risks to both human health and the environment. Despite its widespread presence, the impact of BPA on papillary thyroid cancer (PTC) progression, especially under realistic environmental conditions, is not well understood. This study examined the effects of BPA on PTC using a 3D thyroid papillary tumor spheroid model, which better mimicked the complex interactions within human tissues compared to traditional 2D models. Our findings demonstrated that BPA, at environmentally relevant concentrations, could induce significant changes in PTC cells, including a decrease in E-cadherin expression, an increase in vimentin expression, and reduced thyroglobulin (TG) secretion. These changes suggest that BPA exposure may promote epithelial-mesenchymal transition (EMT), enhance invasiveness, and reduce cell differentiation, potentially complicating treatment, including by increasing resistance to radioiodine therapy. This research highlights BPA's hazardous nature as an environmental contaminant and emphasizes the need for advanced in vitro models, like 3D tumor spheroids, to better assess the risks posed by such chemicals. It provides valuable insights into the environmental implications of BPA and its role in thyroid cancer progression, enhancing our understanding of endocrine-disrupting chemicals. https://doi.org/10.3390/ijms26020814

Effects of long-term treatment with low concentration butylparaben on prostate organoids, Hwang, Y., Kim, Y., Choi, D. and Lee, J. H., *Environmental Pollution*, Feb 2025, Vol. 366.

Endocrine-disrupting compounds (EDCs), such as butylparaben (BP), which are used as preservatives in food and cosmetics, have been shown to negatively affect male reproductive health. Organs under the control of hormones such as androgens and estrogens, such as the prostate, are vulnerable to EDC stimulation. It is well known that BP can cause hormonal imbalances in the prostate and lead to various prostate diseases. However, studies on the long-term exposure of low-dose BP, which is common in daily life, are lacking, and existing studies rely heavily on in vitro tests to assess the risk of EDCs. Therefore, in this study, we investigated the long-term exposure effects of low-dose BP using a prostate organoid model that more closely resembles the target organ. When prostate organoids were treated with BP for a long period, hormonal imbalance was confirmed through differences in the expression of hormone receptors. In addition, reactive oxygen species (ROS) production was confirmed by DCFDA staining, and the protective effect of prostate organoids against stimulation was confirmed by increased protein levels of antioxidant factors. Through transcriptome analysis, we confirmed the occurrence of reproductive toxicity caused by BP. The long-term treatment of prostate organoids with BP causes hormonal imbalance and increased ROS exhibits reproductive toxicity and exerts a protective mechanism against BP through the expression of antioxidant factors. Our results highlight the potential of prostrate organoids as an alternative to animal experimental model and the need for further research on the effects of low EDC concentrations on male reproductive function. https://doi.org/10.1016/j.envpol.2024.125502

Distribution of Environmental Phenols into Follicular Fluid and Urine of Women Attending Infertility Clinic, Klimowska, A., Jurewicz, J., Radwan, M., Radwan, P., Pol, P. and Wielgomas, B., *Journal of Xenobiotics*, Feb 2025, Vol. 15, no. 1.

Infertility and environmental pollution are two globally prevalent and related issues. To explore women's reproductive health, the composition of follicular fluid (FF) has been studied and it was found that changes to its composition, including the presence of exogenous chemicals, can adversely affect the fertilization process. Two groups of women (idiopathic infertility and controls) who were patients at a fertility clinic were recruited for this study. Samples of urine and FF were gathered from each participant to determine the concentration of 14 common phenols (four parabens, six bisphenols, two benzophenones, and two naphthols). Associations between phenol concentrations (free and total) in both matrices were described using Spearman's correlation coefficient and were compared between two groups by the Mann-Whitney U test. Eight phenols were quantified in more than 50% of the urine samples, while only three parabens were quantified in hydrolyzed FF samples, and only methylparaben was quantified in non-hydrolyzed FF samples. Conjugates were the predominant form in FF samples. However, a significant correlation of 0.533 ($p < 0.0001$) was observed between free and total methylparaben concentrations in FF. Differences in concentrations between cases and controls in both matrices were not statistically significant, except for benzophenone-3 in urine, with a higher median observed in the control group ($p = 0.04$). The total paraben concentrations in urine and FF samples were rather weakly correlated ($r = 0.232$-0.473), implying that urine concentrations may not be appropriate for predicting their concentration in FF. https://doi.org/10.3390/jox15010017

The impact of mercury exposure on male reproduction: Mechanistic insights,
Kushawaha, B., Yadav, R., Garg, S. K. and Pelosi, E., *Journal of Trace Elements in Medicine and Biology*, Feb 2025, Vol. 87.

Mercury is a pervasive environmental toxin with significant negative effects on human health. In occupational settings, incidents such as the Minamata and Niigata disease in Japan and the large-scale methylmercury poisoning in Iraq have highlighted the severe health impacts of mercury exposure. It is widely accepted that all forms of mercury including methylmercury and mercuric chloride have the potential to induce toxic effects in mammals, and there is increasing concern about the impact of environmentally relevant levels of mercury on reproductive functions. This review summarizes current knowledge on the mechanisms of mercury toxicity, focusing specifically on its impact on male reproductive health across species. We searched the literature and found that mercury exposure is associated with testicular degeneration, altered spermatogenesis, and Leydig cell deformation. In addition, mercury can disrupt sperm motility, steroidogenesis and interfere with the hypothalamic-pituitary-gonadal axis by generation of reactive oxygen species, inducing mitochondrial dysfunction, epigenetic changes, and DNA damage. At the molecular level, mercury has been found to dysregulate the expression of key steroidogenic and spermatogenic genes, significantly reducing overall fertility potential. However, specific mechanisms of action remain to be fully elucidated. Similarly, comprehensive data on the potential transgenerational effects of paternal mercury exposure are lacking. In this review, we discuss both animal and human studies, and highlight the need for further research due to lack of standardization and control for variables such as lifestyle, immune system function, and exposure concentrations.
https://doi.org/10.1016/j.jtemb.2025.127598

Evaluation of the endocrine disrupting potential of Di-isodecyl phthalate,
Lea, I. A., Feifarek, D., Mihalchik, A., Heintz, M., Haws, L., Nyambego, H., Goyak, K., Palermo, C. and Borghoff, S. J., *Current Research in Toxicology*, 2025, Vol. 8.

Low molecular weight ortho-phthalates have been implicated in perturbing androgen pathways when administered during the masculinization programming window. Di-isodecyl phthalate (DIDP)

is a high molecular weight phthalate and as a high production volume chemical, its ability to disrupt endocrine pathways is important to understand its potential hazard. Both DIDP (and its metabolites) were evaluated to determine the potential to perturb endocrine pathways through a weight of evidence (WoE) assessment in accordance with the European Chemicals Agency (ECHA)/European Food Safety Authority (EFSA) Endocrine Disruptor Guidance (2018). A literature review was performed of toxicological data for DIDP related to estrogen, androgen, thyroid, or steroidogenesis pathways. Literature searches returned 41 relevant articles from which data were extracted and assessed in conjunction with data from 105 high-throughput assays. Because some of the in vitro assays lack metabolic capabilities, an in silico assessment of estrogen (E), androgen (A), thyroid (T) or steroidogenesis (S) activity was conducted. Based on the available evidence for the T pathway, DIDP did not elicit adverse thyroid outcomes in vivo. When considering the T mechanistic data, there was evidence that DIDP induced the liver pregnane X receptor (PXR) and some indication that DIDP increased iodide uptake in the thyroid. As there were no studies evaluating thyroid hormone levels in vivo, a data gap was identified because per the ECHA/EFSA guidance, the lack of this information prevents drawing a conclusion on the T pathway. However, the E, A and S pathways were sufficiently assessed to conclude a limited or lack of E, A or S related apical outcomes in in vivo studies; there was also a lack of endocrine activity in in vitro or in vivo mechanistic studies. These results suggest that DIDP does not meet the ECHA/EFSA criteria for an endocrine disruptor, therefore DIDP is unlikely to disrupt the androgen pathway during development. https://doi.org/10.1016/j.crtox.2025.100221

The potential endocrine-disrupting of fluorinated pesticides and molecular mechanism of EDPs in cell models,
Liu, Y. L., Wang, F. Z., Li, L., Fan, B., Kong, Z. Q., Tan, J. X. and Li, M. M., *Ecotoxicology and Environmental Safety*, Jan 2025, Vol. 289.

Environmental endocrine disruptors constitute a category of exogenous compounds that interfere with the endocrine system's functions in organisms or cells. As a class of particularly representative endocrine-disrupting chemicals, the accumulation of per- and polyfluoroalkyl substances potentially leads to adverse health effects, including hormonal disruptions, developmental issues, and cancer. However, the classification of these disruptors is intricate, and the data on their potential health risks is scattered. The research into fluorinated pesticides is somewhat superficial, with the majority of review articles in this field focusing on the structural characteristics, biodegradation processes, and environmental risks associated with these pesticides. In this study, we compared and investigated the research development processes of seven types of fluorine-containing pesticides and five types of fluorinated endocrine disruptors. The varying toxic effects of these endocrine disruptors are highly dependent on exposure conditions. Their actions are complex, affecting behavioral substances throughout the organism, and monitoring some complex biological phenotypes, sex- or age-specific effects, and behavioral learning poses significant challenges. The findings will serve as a reference for future studies on the toxicity of pesticides to humans and other organisms. https://doi.org/10.1016/j.ecoenv.2024.117615

Contamination Characterization, Toxicological Properties, and Health Risk Assessment of Bisphenols in Multiple Media: Current Research Status and Future Perspectives,
Long, F. Y., Ren, Y. Q., Bi, F., Wu, Z. H., Zhang, H. J., Li, J. L., Gao, R., Liu, Z. Y. and Li, H., *Toxics*, Feb 2025, Vol. 13, no. 2.

Bisphenols (BPs) are ubiquitous environmental endocrine disruptors that cause various human health hazards and pollute water, soil, and the atmosphere to varying degrees. Although various studies have investigated the pollution characteristics and health hazards of BPs in different media,

a systematic review of BPs in the broader environmental context is still lacking. This study highlights the pollution characteristics, detection methods, and risk assessment status of BPs by combining relevant studies from both domestic and international sources, and their environmental distribution characteristics are summarized. The results show that BP pollution is a widespread and complex global phenomenon. Bisphenol A (BPA) remains the predominant component of BPs, which can damage the nervous and reproductive systems. At present, high-performance liquid chromatography-tandem mass spectrometry, high-performance liquid chromatography, and liquid chromatography-tandem mass spectrometry are the main detection methods used for BPs. BPs can also damage the reproductive system, leading to germ cell apoptosis and ovarian damage. Future research should focus on expanding the BP testing repertoire, advancing rapid detection techniques, elucidating toxic mechanisms, conducting comprehensive safety assessments, and developing systematic health risk assessment methods. These efforts will provide a scientific foundation for preventing and controlling emerging pollutants. https://doi.org/10.3390/toxics13020109

Screening of estrogen receptor activity of per- and polyfluoroalkyl substances based on deep learning and in vivo assessment,
Pang, X., Lu, M., Yang, Y., Cao, H., Sun, Y., Zhou, Z., Wang, L. and Liang, Y., *Environ Pollut*, Mar 15 2025, Vol. 369, p. 125843.

Over the past decades, exposure to per- and polyfluoroalkyl substances (PFAS), a group of synthetic chemicals notorious for their environmental persistence, has been shown to pose increased health risks. Despite that some PFAS were reported to have endocrine-disrupting toxicity in previous studies, accurate prediction models based on deep learning and the underlying structural characteristics related to the effect of molecular fluorination remain limited. To address these issues, we proposed a stacking deep learning architecture, GXDNet, that integrates molecular descriptors and molecular graphs to predict the estrogen receptor α (ERα) activities of compounds, enhancing the generalization ability compared to previous models. Subsequently, we screened the ERα activity of 10,067 PFAS molecules using the GXDNet model and identified potential ERα binders. The representative PFAS molecules with the top docking scores showed that the introduction of fluorinated alkane chains significantly increased the binding affinities of parent molecules with ERα, suggesting that the combination of phenol structural fragments and fluorinated alkane chains has a synergistic effect in improving the binding capacity of the ligands to ERα. The binding modes, SHapley Additive Explanations analysis, and attention map emphasized the importance of π-π stacking and hydrogen bonding interactions with the phenol group, while the fluorinated alkane chain enhanced the interaction with the hydrophobic amino acids of the active pocket. Experimental validation using zebrafish models further confirmed the ERα activity of the representative PFAS molecules. Overall, the current computational workflow is beneficial for the toxicological screening of emerging PFAS and accelerating the development of eco-friendly PFAS molecules, thereby mitigating the environmental and health risks associated with PFAS exposure.
https://doi.org/10.1016/j.envpol.2025.125843

Environmental Exposures and Polycystic Ovary Syndrome: A Review,
Peebles, E. and Mahalingaiah, S., *Seminars in Reproductive Medicine*, 2025 Feb 2025.

Polycystic ovary syndrome (PCOS) is the most common heterogeneous endocrine disorder in women of reproductive age, affecting around 5 to 10% of women and up to 21% depending on the applied diagnostic criteria and study population. People with PCOS may experience oligomenorrhea, androgen excess, and polycystic ovary morphology. The etiology of the disease is not completely understood, with genetics, epigenetics, endocrine, metabolic, lifestyle, and environmental factors contributing to its development and severity. Environmental exposures are an important,

burgeoning field in menstrual research, as they potentially link to menstrual cycle disruption and the risk of reproductive disorders such as PCOS. This review examines the recent research investigating environmental exposures-air pollution, micro- and nanoplastics, heavy metals, and endocrine-disrupting chemicals-and PCOS in human and animal models, concluding with potential mechanisms, limitations, and considerations for future work. Overall, research on environmental exposures and PCOS is limited and yields heterogeneous results across studies. Specifically, exposures such as air pollutants, micro- and nanoplastics, persistent organic pollutants, and parabens have noticeably limited research. Future research can help fill the gap in understanding how environmental exposures, particularly across gestational, childhood, and reproductive adult life stages, may impact PCOS. https://doi.org/10.1055/s-0044-1801405

Early-life exposure to PCBs and PFAS exerts negative effects on the developing central nervous system,
Peixoto-Rodrigues, M. C., Monteiro-Neto, J. R., Teglas, T., Toborek, M., Quinete, N. S., Hauser-Davis, R. A. and Adesse, D., *Journal of Hazardous Materials*, Mar 2025, Vol. 485.

Persistent organic pollutants (POPs) are ubiquitous in the environment and display the capacity to bioaccumulate in living organisms, constituting a hazard to both wildlife and humans. Although restrictions have been applied to prohibit the production of several POPs since the 1960s, high levels of these compounds can still be detected in many environmental and biological matrices, due to their chemical properties and significantly long half-lives. Some POPs can be passed from mother to the fetus and can gain entry to the central nervous system (CNS), by crossing the blood-brain barrier (BBB), resulting in significant deleterious effects, including neurocognitive and psychiatric abnormalities, which may lead to long-term socio-economic burdens. A growing body of evidence obtained from clinical and experimental studies has increasingly indicated that these POPs may influence neurodevelopment through several cellular and molecular mechanisms. However, studies assessing their mechanisms of action are still incipient, requiring further research. Polychlorinated biphenyls (PCBs) and per- and polyfluoroalkyl substances (PFAS) are two of the main classes of POPs associated with disturbances in different human systems, mainly the nervous and endocrine systems. This narrative review discusses the main PCB and PFAS effects on the CNS, focusing on neuroinflammation and oxidative stress and their consequences for neural development and BBB integrity. Moreover, we propose which mechanisms could be involved in POP-induced neurodevelopmental defects. In this sense, we highlight potential cellular and molecular pathways by which these POPs can affect neurodevelopment and could be further explored to propose preventive therapies and formulate public health policies.
https://doi.org/10.1016/j.jhazmat.2024.136832

Exposure of the human placental primary cells to nanoplastics induces cytotoxic effects, an inflammatory response and endocrine disruption,
Poinsignon, L., Lefrère, B., Ben Azzouz, A., Chissey, A., Colombel, J., Djelidi, R., Ferecatu, I., Fournier, T., Beaudeux, J. L., Lespes, G. and Zerrad-Saadi, A., *J Hazard Mater*, Feb 26 2025, Vol. 490, p. 137713.

Humans are inevitably exposed to micro- and nanoplastics (MP/NP). These particles are able to cross the biological barriers and enter the bloodstream with levels close to 1.6 µg mL(-1); MP/NP have been detected in placentas and meconium of newborns. However, the consequences of this exposure on the integrity, development and functions of the human placenta are not documented. In this study, trophoblasts purified from human placentas at term were exposed for 48 h, to two different sizes of polystyrene nanoparticles (PS-NP) of 20 nm (PS-NP(20)) and 100 nm (PS-NP(100)), at environmental and supra-environmental concentrations (0.01-100 µg mL(-1)). Cell viability,

oxidative stress, mitochondrial dynamics, lysosomal degradation processes, autophagy, inflammation/oxidative responses and consequences for placental endocrine and angiogenic functions were assessed. PS-NP size determines their internalization rate and their behavior in trophoblasts. Indeed, PS-NP(20) are more rapidly translocated, and accumulated in lysosomes as shown by confocal and TEM imaging. They induce higher cytotoxicity than PS-NP(100), as early as 1 µg mL(-1) ($p < 0.05$). In addition, they induce a pro-inflammatory cytokines response: IL-1ß is induced from 0.01 µg mL(-1) for the both nanoparticle sizes; IL-6, and TNF-α are overexpressed at 100 µg mL(-1) only for PS-NP(20) ($p < 0.05$). For the first time, we report that PS-NP disrupt endocrine function, as observed by a decreased hCG release at concentrations found in human blood. This work, provides an in-depth in vitro assessment of the effects of PS-NP on the human placenta. https://doi.org/10.1016/j.jhazmat.2025.137713

The Potential Metalloestrogenic Effect of Aluminum on Breast Cancer Risk for Antiperspirant Users,
Sawicka, E. and Wiatrowska, N., *International Journal of Molecular Sciences*, Jan 2025, Vol. 26, no. 1.

The etiopathogenesis of breast cancer depends on genetic conditions, but recently more attention has been paid to the dependence of BC on certain environmental factors, for example, metalloestrogens, which include aluminum (Al) contained in antiperspirants used daily. The use of Al derivatives in antiperspirants in concentrations specified by the FDA, as well as European regulations (SCCS, 2020), do not classify Al as a hazardous and carcinogenic substance for humans. However, Al used to treat excessive sweating raises concerns, as many in vitro studies indicate that it can cause gene instability, change gene expression or increase oxidative stress, and also affect the body's hormonal balance as a metalloestrogen. The environmental reality is that the breast is constantly exposed to many different chemicals, such as Al. This article reviews the literature to determine whether Al-based products can harm the body, as there are many facts and myths on the subject. The aim of the study is to present the current state of knowledge on the use of aluminum antiperspirants and the risk of breast cancer (BC). The article is based on data from the scientific literature, published in the PubMed and Google Scholar databases, as well as Science Direct, Scopus, Ovid MEDLINE, Ovid EMbase. It includes articles published in the years 2003-2023 mainly in English. Literature databases regarding human and animal studies were searched. To sum up, evaluating the effect of Al as a risk factor for breast cancer requires many studies using different research models focused on long-term exposure to Al-containing antiperspirants. Consumers are advised to limit their exposure to Al by making a conscious choice to minimize exposure to this compound. https://doi.org/10.3390/ijms26010099

Does Bisphenol A (BPA) Exposure Cause Human Diseases?
Stein, T. P., *Biomedicines*, Dec 2024, Vol. 12, no. 12.

Background: Autism spectrum disorders (ASDs), attention-deficit disorder (ADHD), Parkinson's disease (PD), polycystic ovary disease (PCOS), and Alzheimer's disease (AD) have all been linked to exposure to bisphenol A (BPA). Methods: This paper is a review and discussion of the published literature. Results: Animal studies have shown BPA to be a broad-spectrum endocrine disruptor. BPA is metabolized via the glucuronidation pathway, which involves the addition of glucose to the target molecule, and is catalyzed by uridine 5 '-diphospho-glucuronosyltransferases (UGTs). Evidence of compromised glucuronidation has been found for ASD, DHD, PD, and PCOS. Genetic polymorphisms that alter the catalytic activity of the UGTs and efflux transporters involved are common. There are two ways to interpret the findings of associations between BPA glucuronidation efficiency and disease, a 'direct' pathway and an 'indirect' pathway. With the 'direct' pathway, free BPA is the

actual causative agent. Compromised BPA detoxification leads to higher concentrations of free BPA in vulnerable tissues. Decreased BPA detoxification leads to increased exposure of vulnerable tissues to free BPA, where it can function as an endocrine disruptor. With the 'indirect' pathway, BPA is not the causative agent. BPA serves as a marker for the decreased glucuronidation efficiency of another unknown compound of endogenous origin detoxified by a similar combination of UGTs and efflux transporters as BPA. It is this compound(s), acting as an endocrine disruptor, that leads to a metabolic environment that favors disease development over an extended time period. Conclusion: A review of the existing literature supports the indirect 'marker' hypothesis over the 'direct' hypothesis. https://doi.org/10.3390/biomedicines12122678

Estrogenic and anti-estrogenic assessment of the flame retardant, 2-ethyl-hexyl diphenyl phosphate (EHDPP), and its metabolites: Evidence from in vitro, in silico, and transcriptome studies,
Tachachartvanich, P., Sangsuwan, R., Duangta, S., Navasumrit, P., Ruchirawat, S. and Ruchirawat, M., *Journal of Hazardous Materials*, May 2025, Vol. 488.

2-Ethylhexyl diphenyl phosphate (EHDPP) is a replacement flame-retardant commonly found in several environmental matrices and human biospecimens. Although some adverse effects of EHDPP have been identified, the endocrine-disrupting effects of EHDPP and its key metabolites on the human estrogen receptor (ER) are largely unknown. Herein, we report for the first time that EHDPP, at concentrations found in the environment and humans, significantly promoted estrogenic activity and synergized with 17 beta-estradiol-induced ER trans- activation. However, two major EHDPP metabolites 2-ethyl-3-hydroxyhexyl diphenyl phosphate (3-OH-EHDPP) and 2-ethyl-5-hydroxyhexyl diphenyl phosphate (5-OH-EHDPP), inhibited the ER through a non-competitive binding mechanism. Molecular docking showed that Pi-Pi stacking, hydrogen, and hydrophobic bonds primarily stabilize intermolecular interactions between EHDPP and the binding pockets of human ER alpha and ER beta. Moreover, transcriptome analysis confirmed the estrogenic effects of EHDPP, revealing notable enrichments in ER-mediated signaling and breast cancer pathways, consistent with the validated estrogenic gene expression profile. Intriguingly, EHDPP markedly promoted the clonogenic growth of two ER+ breast cancer cell lines, corroborating the expression levels of ER alpha protein. Our findings indicate that the common flame-retardant EHDPP activates the ER and downstream signaling, providing far-reaching implications for environmental and health risks associated with estrogen-related adversities such as the development of ER+ breast cancer.
https://doi.org/10.1016/j.jhazmat.2025.137303

Exploring PANoptosis in head and neck cancer: A novel approach to cancer therapy,
Wang, L., Lin, B. S., Wang, F. X., Dai, Z. L., Xie, G. F. and Zhang, J., *Ecotoxicology and Environmental Safety*, Jan 2025, Vol. 289.

PANoptosis is a newly discovered complex programmed cell death (PCD) form. In the field of cancer research, PANoptosis is involved in multiple cell death pathways that affect tumor cell survival, proliferation, and response to treatment, serving as an innovative strategy for cancer therapy. Endocrine-disrupting chemicals (EDCs) impact the endocrine system, including cancer. However, research on their influence on head and neck carcinoma (HNSC) through PANoptosis genes remains limited. This study utilises transcriptomic and clinical data related to HNSC from the Cancer Genome Atlas (TCGA) and the Gene Expression Omnibus (GEO) databases. We developed a risk model based on PANoptosis-related genes through LASSO Cox regression analysis. Finally, we utilized a Sankey diagram to depict the relationships between EDCs and key genes, identifying DSCAM, IL-6, and SYCP2 as critical predictors of HNSC PANoptosis. These essential genes identified 214 EDCs potentially influencing HNSC, including 3 (Aroclor 1242, Pentachlorobenzene, and Propanil)

previously unreported to HNSC. These findings elucidate novel relationships between PANoptosis-related genes mediated by EDCs and the pathogenesis of HNSC. https://doi.org/10.1016/j.ecoenv.2025.117678

Environmental Obesogens and Their Perturbations in Lipid Metabolism,
Wang, X. Y., Sun, Z. D., Liu, Q. S., Zhou, Q. F. and Jiang, G. B., *Environment & Health*, Feb 2024, Vol. 2, no. 5, p. 253-268.

Epidemiological data show that obesity is now a pandemic. Lipid homeostasis requires the coordination of multiple tissues and organs, including the liver, kidney, cardiovascular system, and adipose tissues, to maintain bodily homeostasis. As increasing amounts of chemicals are being synthesized, applied, and released into the environment, their obesogenic effects have triggered serious concern. Currently, more than 50 types of chemicals with high human exposure levels have been identified as environmental obesogens that can interfere with lipid metabolism and induce obesity. Experimental studies have shown that the lipid metabolism interference effects of obesogens have multiple targets, including nuclear receptors, transcription factors, cytokines, and hormones. The interfering factors of environmental obesogen-induced obesity include transgenerational effects, susceptibility windows, gender differences, structure-effect relationships, and diet habits. Various research approaches have been established to conduct obesogenic effect research. This comprehensive review summarizes the mechanisms underlying obesogen actions and the research progress on obesogen-disrupted lipid metabolism, along with the influencing factors and research approaches, aiming to provide a framework for understanding the effects of environmental obesogens on lipid metabolism. https://doi.org/10.1021/envhealth.3c00202

Endocrine-Disrupting Chemicals and Female Reproductive Aging,
Wu, J. X., Harlow, S. D., Randolph, J. F., Gold, E. B. and Park, S. K., *Seminars in Reproductive Medicine*, 2025 Jan 2025.

Female reproductive aging often affects women's emotional, physical, and physiological well-being. Ovarian aging is characterized by fluctuations in reproductive hormones and determines the age at which menopause occurs. Understanding potentially modifiable factors that influence this process is essential for addressing health disparities, improving quality of life, and informing relevant public health strategies. This review synthesizes in vivo, in vitro, and epidemiological findings about the effects of endocrine-disrupting chemicals (EDCs), specifically heavy metals and perfluoroalkyl and polyfluoroalkyl substances (PFAS) on female reproductive aging. Most in vivo and in vitro studies have demonstrated that heavy metals alter ovarian morphology, folliculogenesis, and steroidogenesis. Evidence regarding the effects of PFAS is limited and inconsistent. Epidemiological studies have consistently shown that heavy metals are associated with a higher risk of diminished ovarian reserve (indicated by decreased anti-Mullerian hormone) and earlier menopause, with limited findings regarding reproductive hormone changes. PFAS exposure has been associated with decreased estradiol and earlier menopause but not significantly with ovarian reserve. Gaps in the literature require more comprehensive epidemiological research on the effects of EDCs on female reproductive aging, including ovarian reserve, age at menopause, and vasomotor symptoms, to inform future interventions to reduce hazardous exposures and improve women's health. https://doi.org/10.1055/s-0044-1801388

Obesogens and Energy Homeostasis: Definition, Mechanisms of Action, Exposure, and Adverse Effects on Human Health,
Yilmaz, B., Erdogan, C. S., Sandal, S., Kelestimur, F. and Carpenter, D. O., *Neuroendocrinology*, 2024 Dec 2024.

Background: Obesity is a major risk factor for non- communicable diseases and is associated with a reduced life expectancy of up to 20 years, as well as with other consequences such as unemployment and increased economic burden for society. It is a multifactorial disease, and physiopathology of obesity involves dysregulated calorie utilization and energy balance, disrupted homeostasis of appetite and satiety, lifestyle factors including sedentary lifestyle, lower socioeconomic status, genetic predisposition, epigenetics, and environmental factors. Some endocrine- disrupting chemicals (EDCs) have been proposed as " obesogens " that stimulate adipogenesis leading to obesity. In this review, definition of obesogens, their adverse effects, underlying mechanisms, and metabolic implications will be updated and discussed. Summary: Disruption of lipid homeostasis by EDCs involves multiple mechanisms including increase in the number and size of adipocytes, disruption of endocrine-regulated adiposity and metabolism, alteration of hypothalamic regulation of appetite, satiety, food preference and energy balance, and modification of insulin sensitivity in the liver, skeletal muscle, pancreas, gastrointestinal system, and the brain. At a cellular level, obesogens can exert their endocrine disruptive effects by interfering with peroxisome proliferator-activated receptors and steroid receptors. Human exposure to chemical obesogens mainly occurs by ingestion and, to some extent, by inhalation and dermal uptake, usually in an unconscious manner. Persistent pollutants are lipophilic features; thus, they bioaccumulate in adipose tissue. Key Messages: Although there are an increasing number of reports studying the effects of obesogens, their mechanisms of action remain to be elucidated. In addition, epidemiological studies are needed in order to evaluate human exposure to obesogens.
https://doi.org/10.1159/000542901

Méthodes

Reproductive and Metabolic Health Following Exposure to Environmental Chemicals: Mechanistic Insights from Mammalian Models,
Bellingham, M., Evans, N. P., Lea, R. G., Padmanabhan, V. and Sinclair, K. D., *Annual Review of Animal Biosciences*, 2025, Vol. 13, p. 411-440.

The decline in human reproductive and metabolic health over the past 50 years is associated with exposure to complex mixtures of anthropogenic time and differs across geographical locations. Health-related issues include declining sperm quality, advanced puberty onset, premature ovarian insufficiency, cancer, obesity, and metabolic syndrome. Prospective animal studies with individual and limited EC mixtures support these observations and provide a means to investigate underlying physiological and molecular mechanisms. The greatest impacts of EC exposure are through programming of the developing embryo and/or fetus, with additional placental effects reported in eutherian mammals. Single-chemical effects and mechanistic studies, including transgenerational epigenetic inheritance, have been undertaken in rodents. Important translational models of human exposure are provided by companion animals, due to a shared environment, and sheep
https://doi.org/10.1146/annurev-animal-111523-102259

Rapid non-separative determination of prevailing organophosphate flame retardants metabolites in urine by means of a restricted access material coupled to tandem mass spectrometry,
Chango, G., Ballester-Caudet, A., García-Gómez, D., Pinto, C. G., Rodríguez-Gonzalo, E. and Pavón, J. L. P., *Microchemical Journal*, Jan 2025, Vol. 208.

Organophosphate flame retardants (OPFRs) are used to reduce the flammability of various materials. Among these compounds, triphenyl phosphate (TPhP) and tris(1,3-dichloro-2-propyl) phosphate (TDCIPP) are prominent OPFRs associated with reproductive and endocrine-disrupting effects. Monitoring their urinary metabolites, diphenyl phosphate (DPhP) and bis(1,3-dichloro-2-propyl) phosphate (BDCPP), are crucial for assessing bioaccumulation, toxicity, and exposure. This study presents a novel, non-separative analytical method combining restricted access material (RAM) with tandem mass spectrometry (MS/MS), eliminating the need for chromatographic separation. This innovation significantly reduces total analysis time down to less than five minutes per sample (12 samples per hour), compared to up to 37 min (only one sample per hour) required by state-of-the-art separative methods. The method achieves sub-ppb limits of quantification (LOQ <= 0.1 ng mL- 1) that are equal or better than those achieved by separative methodologies. Matrix effects were minimized (similar or equal to 20 %) with a conventional clean-up pretreatment based on SPE. The whole methodology was validated by analyzing certified urine samples provided by Centre de toxicologie du Que<acute accent>bec and applied to the analysis of real urine samples from non-exposed individuals. The accuracy (86-108 %), precision (RSD < 20 %) and high recovery (98-109 %) confirm the robustness and suitability of this method in routine laboratory applications. This is the first report, to the best of our knowledge, to fully integrate RAM with direct MS/MS analysis for most prominent urinary OPFR metabolites without chromatographic separation. This methodological advance offers substantial advantages in speed, simplicity, and adaptability to high-throughput biomonitoring studies, setting a new benchmark for the determination of DPhP and BDCPP in human urine. https://doi.org/10.1016/j.microc.2024.112525

Endocrine disruptor identification and multitoxicity level assessment of organic chemicals: An example of multiple machine learning models,
Hao, N., Zhao, Y. Y., Sun, P. X., Deng, Z. Y., Cui, X. R., Liu, J. P. and Zhao, W. J., *Journal of Hazardous Materials*, Mar 2025, Vol. 485.

Endocrine-disrupting chemicals (EDCs) pollution is a major global environmental issue. Assessing the multiple toxic effects of EDCs is key to managing their risks. This study successfully developed an EDCs classification and recognition model based on recursive feature elimination and random forest coupling, which passed external validation. Furthermore, the study classified the hormonal effects of EDCs and elucidated their hormonal roles. Molecular dynamics simulations were employed to investigate the toxicity of EDCs, and a regression model for such toxicity was developed using neural networks. A multi-toxicity regression model for EDCs was also developed using the XGBoost algorithm. This model can evaluate carcinogenicity, teratogenicity, and potential developmental toxicity of EDCs. The Spearman and Kendall correlation coefficient methods were used to assess the relations between toxicities. This study combines data filtering with model optimisation to ensure the use of efficient and concise methods. This allows for a comprehensive assessment of EDCs toxicity. It also helps analyse the link between EDCs molecular structure and their toxic effects, providing ideas for designing new chemicals. However, the model exhibits high complexity, and some processes are difficult to fully explain. https://doi.org/10.1016/j.jhazmat.2024.136896

An Enhanced Protocol to Expand Human Exposome and Machine Learning-Based Prediction for Methodology Application,
He, A., Yao, Y. M., Chen, S. J., Li, Y. C., Xiao, N., Chen, H., Zhao, H. Z., Wang, Y., Cheng, Z. P., Zhu, H. K., Xu, J. P., Luo, H. N. and Sun, H. W., *Environmental Science & Technology*, Feb 2025, Vol. 59, no. 7, p. 3376-3387.

The human exposome remains limited due to the challenging analytical strategies used to reveal low-level endocrine-disrupting chemicals (EDCs) and their metabolites in serum and urine. This limits

the integrity of the EDC exposure assessment and hinders understanding of their cumulative health effects. In this study, we propose an enhanced protocol based on multi-solid-phase extraction (multi-SPE) to expand human exposome with polar EDCs and metabolites and train a machine learning (ML) model for methodology prediction based on molecular descriptors. The protocol enhanced the measurement of 70 (25%) and 34 (12%) out of 295 well-acknowledged EDCs in serum and urine compared to the hydrophilic-lipophilic balance sorbent alone. In a nontarget analysis of serum and urine from 20 women of childbearing age in a cohort of 498, controlling occupational factors and daily behaviors for high chemical exposure potential, the multi-SPE protocol increased the measurement of 10 (40%) and 16 (53%) target EDCs and identification of 17 (77%) and 70 (36%) nontarget chemicals (confidence >= level 3) in serum and urine, respectively. Interestingly, the ML model predicted that the multi-SPE protocol could identify an additional 38% of the most bioactive chemicals. In conclusion, the multi-SPE protocol advances human exposome by expanding the measurement and identification of exposure profiles. https://doi.org/10.1021/acs.est.4c09522

Efficient enrichment and sensitive determination of endocrine disruptors in PPCPs by novel magnetic covalent organic framework extraction coupled with HPLC-MS/MS,
Hu, Z., Yang, Y. H., Li, Z., Tao, Q. Y., Huang, Y. H. and Wang, X., *Talanta*, May 2025, Vol. 287.

Endocrine-disrupting chemicals (EDCs) are a growing class of pollutants commonly found in environmental matrices due to their extensive use in pharmaceuticals and personal care products (PPCPs). In this study, a novel magnetic covalent organic framework (COF), Fe3O4-COOH@TFP-BHBD, was successfully synthesized and utilized as an adsorbent for magnetic solid-phase extraction (MSPE) of EDCs from PPCPs. The core-shell structured adsorbent demonstrated a high specific surface area, strong magnetic responsiveness and excellent stability. A COF-MSPE-high-performance liquid chromatography-tandem mass spectrometry (COF-MSPE-HPLC-MS/MS) method was developed for the quantitative analysis of EDCs in PPCPs. Under the optimized condition, the detection and quantification limits of this method reached as low as 0.001-0.007 ng/mL and 0.004-0.025 ng/ mL, respectively. This method was validated and proven capable to analyze real PPCP samples, while the spiked recovery rates in ranged from 85.62 to 107.83 % with RSD of 2.28-8.58 %. Moreover, the adsorption mechanism was investigated using density functional theory (DFT) calculations. The DFT results revealed that the efficient enrichment capacity of Fe3O4-COOH@TFP-BHBD for EDCs can be attributed to it-it interactions and hydrogen bondings. This proposed method provides excellent adsorption ability and sensitivity for the extraction and precise detection of EDCs in PPCPs. https://doi.org/10.1016/j.talanta.2025.127667

High-throughput screening to identify endocrine disruptors: Contribution of low-resolution tandem MS and high-resolution MS,
Léger, T., Le Guével, R., Solhi, H., Evrard, B., Darde, T., Desdoits-Lethimonier, C., Glorennec, P., Bonvallot, N., Chalmel, F. and David, A., *Analytica Chimica Acta*, Feb 2025, Vol. 1338.

Background: Considering the large diversity of chemicals present in the environment and the need to study their effects (alone or as mixtures), the development of high-throughput in vitro assays in line with the Replacement, Reduction, Refinement (3R) strategy is essential for chemical risk assessments. Results: We developed a robust analytical workflow based on both low resolution tandem mass spectrometry (MS/MS) and high-resolution mass spectrometry (HRMS) to quantify 13 steroids in NCI-H295R cell culture medium, human plasma and serum. The workflow was validated by screening media from the NCI-H295R cell line exposed in dose-response experiments to 5 endocrine disruptors (EDs) such as bisphenol A, prochloraz, ketoconazole, atrazine and forskolin. Absolute quantifications of the 13 steroids performed on a triple quadrupole (QqQ) MS/MS demonstrated that the performances obtained were in line with OECD recommendations. HRMS

(MS1-HRMS) provided measurements nearly as sensitive and as reproducible as those obtained using multiple reaction monitoring (MRM) and ELISA. A bioinformatics workflow, using HRMS, was implemented to detect and annotate disrupted metabolites. HRMS allowed to detect disruptions in pathways associated to fatty acids, purines and amino acids metabolisms after exposure to the EDs tested, in addition to that linked to steroidogenesis. Significance: We developed a robust MS1-HRMS workflow, from sample preparation to compound quantification or annotation, compatible with absolute steroid quantification, to screen NCI-H295R cell media exposed to potential EDs. Using only 200 mu L of medium, the method integrates MS/MS and HRMS analyses, 96-well plate solid-phase extraction for high throughput, and automated pre-annotation for cost efficiency. This optimized workflow identifies EDs in cell assays by detecting disruptions in steroidogenesis and other biological pathways. https://doi.org/10.1016/j.aca.2024.343594

A three-dimensional mouse liver organoid platform for assessing EDCs metabolites simulating liver metabolism,
Moon, J. H., Roh, H. S., Park, Y. J., Song, H. H., Choi, J., Jung, D. W., Park, S. J., Park, H. J., Park, S. H., Kim, D., Kim, G., Auh, J. H., Ha Bhang, D., Lee, H. J. and Lee, D. Y., *Environment International*, Jan 2025, Vol. 195.

Hepatic metabolism is an important process for evaluate the potential activity and toxicity of endocrine disrupting chemicals (EDCs) metabolites. Organization for Economic Co-operation and Development (OECD) has advocated the development of in vitro assays that mimic in vivo hepatic metabolism to eventually replace classical animal tests. In response to this need, we established a 3D mouse liver organoid (mLO) platform that mimics the animal model and is distinct from existing models. We evaluated the effects the activity of EDC metabolites generated through mLOs based on human cell-based reporter gene assays in addition to existing models. This study emphasizes the importance of hepatic ex-vivo and suggests the need a new metabolic model through a 3D mLOs platform. These results indicate that mLOs provides a novel biological method to screen for potential endocrine-disrupting activities of EDC metabolites.
https://doi.org/10.1016/j.envint.2024.109184

Toxic Alerts of Endocrine Disruption Revealed by Explainable Artificial Intelligence,
Rosa, L. C. S., Sarhan, M. and Pimentel, A. S., *Environment & Health*, 2025 Jan 2025.

The local interpretable model-agnostic explanation method was used to unveil substructures (toxic alerts) that cause endocrine disruption in chemical compounds using machine learning models. The random forest classifier was applied to build explainable models with the TOX21 data sets after data curation. Using these models applied to the EDC and EDKB-FDA data sets, the substructures that cause endocrine disruption in chemical compounds were unveiled, providing stable, more specific, and consistent explanations, which are essential for trust and acceptance of the findings, mainly due to the difficulty of finding relevant experimental evidence for different receptors (androgen, estrogen, aryl hydrocarbon, aromatase, and peroxisome proliferator-activated receptors). This approach is significant because of its contribution to the interpretability of explainable machine learning algorithms, particularly in the context of unveiling substructures associated with endocrine disruption in five targets (androgen receptor, estrogen receptor, aryl hydrocarbon receptors, aromatase receptors, and peroxisome proliferator-activated receptors), thereby advancing the relevant field of environmental toxicology, where a careful evaluation of the potential risks of exposure to new compounds is needed. The specific substructures thiophosphate, sulfamate, anilide, carbamate, sulfamide, and thiocyanate are presented as toxic alerts that cause endocrine disruption to better understand their potential risks and adverse effects on human health and the environment. https://doi.org/10.1021/envhealth.4c00218

Exploring the application of machine learning to identify the correlations between phthalate esters and disease: enhancing nursing assessments,
Wu, H. T., Liao, C. C., Peng, C. F., Lee, T. Y. and Liao, P. H., *Health Information Science and Systems*, Dec 2024, Vol. 13, no. 1.

Health risks associated with phthalate esters depend on exposure level, individual sensitivities, and other contributing factors. This study employed artificial intelligence algorithms while applying data mining techniques to identify correlations between phthalate esters [di(2-ethylhexyl) phthalate, DEHP], lifestyle factors, and disease outcomes.MethodsWe conducted exploratory analysis using demographic and laboratory data collected from the Taiwan Biobank. The study developed a prediction model to examine the relationship between phthalate esters and the risk of developing certain diseases based on various artificial intelligence algorithms, including logistic regression, artificial neural networks, and Bayesian networks. The results indicate that phthalate esters exhibited a greater impact on bone and joint issues than heart problems. We observed that DEHP metabolites, such as mono(2-carboxymethylhexyl) phthalate, mono-n-butyl phthalate, and monoethylphthalate, leave higher residue in females than in males, with statistically significant differences. Monoethylphthalate levels were lower in individuals who exercised regularly than those who did not, indicating statistically significant differences. This study's findings can serve as a valuable reference for clinical nursing assessments regarding diseases related to osteoporosis, arthritis, and musculoskeletal pain. Medical professionals can enhance care quality by considering factors beyond patients' essential physical assessment items.. https://doi.org/10.1007/s13755-024-00324-4

Agenda, actualité, politique et évaluation de l'exposition

HEEDS publishes timeline on the history of the EDC field,
HEEDS (2025),
Healthy Environment and Endocrine Disruptor Strategies (HEEDS) now provides a comprehensive history of the endocrine disruptor scientific field via an online timeline. Complete with citations, it covers industrial and scientific developments from the 1800s until today. Let us know what you think! https://heeds.org/heeds-timeline/

L'Anses propose de classer le résorcinol comme perturbateur endocrinien dans le règlement européen CLP,
(février 2025),
Après avoir démontré que le résorcinol impacte la fonction thyroïdienne, avec des effets délétères, l'agence porte une proposition pour classer cette substance comme perturbateur endocrinien pour la santé humaine. Cette proposition est rendue possible par la création récente dans le règlement CLP (classification, étiquetage et emballage) de cette classe de danger. Le dossier scientifique est en consultation publique depuis le 20 janvier sur le site de l'Agence européenne des produits chimiques (ECHA) pour commentaires ou apport d'informations complémentaires sur cette substance.
https://www.anses.fr/fr/content/l-Anses-propose-de-classer-le-resorcinol-comme-perturbateur-endocrinien-dans-le-reglement-europeen-CLP

Replay webinar : Ultrashort-Chain PFAS: The global threat of trifluoroacetic acid,
The Collaborative for Health and Environment (CHE) (février 2025),
Trifluoroacetic acid (TFA) is one of the ultrashort-chain perfluoroalkyl acids, a subset of the larger family of per- and polyfluoroalkyl substances (PFAS). TFA is a degradation product of many refrigerants and is also directly released from industrial products and processes; it is now

widespread as a contaminant in the environment. This raises serious concerns about global health and environmental impacts.
In this EDC Strategies Partnership webinar, Dr. Hans Peter Arp discussed a new study, The Global Threat from the Irreversible Accumulation of Trifluoroacetic Acid (TFA). A review of 43 studies reporting on TFA concentrations was conducted for the new study. Monitoring data was analyzed based on research spanning from the late 1990s to the 2020s. Collectively, these data indicate that TFA exposure is widespread and is increasing.
The study authors note that shorter-chain PFAS have been assumed to be less hazardous than longer-chain PFAS, but that widespread exposures have not been taken into account in making this assessment. They note "TFA's ubiquitous accumulation in the environment, in particular its observed accumulation in water resources and bioaccumulation in various plants, including crops." They argue that TFA poses a planetary boundary threat, based on increasing exposure world-wide, irreversible environmental contamination, and "long-lasting disruptive effects on human health and vital earth system processes." The authors call for binding actions to reduce emissions of TFA and its precursors. https://www.healthandenvironment.org/che-webinars/96949

Melamine regulatory assessment for endocrine disruption,
Charron, I., Le Magueresse-Battistoni, B., Habert, R., Canivenc-Lavier, M. C., Mhaouty-Kodja, S. and Michel-Caillet, C., *Environment International*, Dec 2024, Vol. 194.

Melamine has several domestic and industrial uses as a flame retardant or in the manufacture of melamine-formaldehyde resins. Based on available scientific literature data, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) included this substance in the list of "chemicals that may present endocrine disruptor (ED) properties", and the substance was prioritized to assess whether it should be classified as an ED in European Union (EU) regulations for hazard identification. This review reports the assessment of melamine based on relevant studies from the registration dossier under REACH, and peer-reviewed literature. Among the various adverse effects, reproductive, neurodevelopmental, and thyroid effects were analyzed in particular, because they could be the consequence of an endocrine disruption. The different modes of action (endocrine or non-endocrine) potentially leading to these effects were scrutinized to understand whether the WHO definition for ED and the criteria for hazard identification were met. It was concluded that the reproductive effect on spermatogenesis was not a consequence of endocrine activity. A biologically plausible link between this effect and endocrine activity was not established, and other modes of action (oxidative stress or altered energy metabolism) could be involved. Similarly, thyroid and neurodevelopmental effects appeared at higher doses than those leading to renal toxicity. Our assessment confirms that melamine is a reprotoxic substance but does not support ED classification. This assessment illustrates the scientific and regulatory challenges in differentiating specific endocrine disruption from an indirect endocrine effect resulting from non-ED mediated systemic toxicity. https://doi.org/10.1016/j.envint.2024.109188

The benefits of removing toxic chemicals from plastics,
Cropper, M., Dunlop, S., Hinshaw, H., Landrigan, P., Park, Y. and Symeonides, C., *Proceedings of the National Academy of Sciences of the United States of America*, Dec 2024, Vol. 121, no. 52.

More than 16,000 chemicals are incorporated into plastics to impart properties such as color, flexibility, and durability.These chemicals may leach from plastics, resulting in widespread human exposure during everyday use. Two plastic- associated chemicals- bisphenol A (BPA) and di(2-ethylhexyl) phthalate (DEHP)-and a class of chemicals-brominated flame retardants [polybrominated diphenyl ethers (PBDEs)]-are credibly linked to adverse health and cognitive impacts. BPA exposures are associated with ischemic heart disease (IHD) and stroke, DEHP exposure

with increased all- cause mortality among persons 55 to 64 y old, and prenatal PBDE exposures in mothers with IQ losses in their children. We estimate BPA, DEHP, and PBDE exposures in 38 countries containing one- third of the world's population. We find that in 2015, 5.4 million cases of IHD and 346,000 cases of stroke were associated with BPA exposure; that DEHP exposures were linked to approximately 164,000 deaths among 55- to- 64 y olds; and that 11.7 million IQ points were lost due to maternal PBDE exposure. We estimate the costs of these health impacts to be $1.5 trillion 2015 purchasing power parity dollars. If exposures to BPA and DEHP in the United States had been at 2015 levels since 2003, 515,000 fewer deaths would have been attributed to BPA and DEHP between 2003 and 2015. If PBDE levels in mothers had been at 2015 levels since 2005, over 42 million IQpoints would have been saved between 2005 and 2015.
https://doi.org/10.1073/pnas.2412714121

The characteristics of phthalate acid esters and bisphenol A in PM2.5 of a petrochemical city: Concentrations, compositions, and health risk assessment in Dongying,
Long, F. Y., Ren, Y. Q., Ji, Y. Y., Bai, X. R., Li, H., Wang, G. H., Yan, X. Y., Chen, Y. B., Li, J. L., Zhang, H. J., Gao, R., Bi, F. and Wu, Z. H., *Environmental Pollution*, Feb 2025, Vol. 367.

Phthalate acid esters (PAEs) and bisphenol A (BPA) are recognized as common endocrine disruptors associated with various adverse effects on human health. However, limitations in existing systematic studies, particularly in air detection, have raised concerns about potential health risks from inhalation exposure. In this study, PM2.5 samples were collected in Dongying, a petrochemical city, from October 27 to December 6, 2021. The concentrations and compositions of PAEs and BPA in PM2.5 were analyzed, and health risks associated with inhalation exposure were assessed. The hazard index (HI) and cancer risk (CR) were calculated according to EPA standard methods for both adults and children. The mean concentrations of PAEs and BPA were determined to be 1152 and 3.7 ng/m3, respectively. BPA concentrations were found to increase during heating, whereas PAE concentrations were observed to decrease slightly. Diisobutyl phthalate (DiBP), a major PAE, was reduced by approximately 20% during heating. However, 1,4-dimethylphthalazine (DMP) and bis(2-ethylhexyl) phthalate (DEHP) were observed to increase from 4.2 to 14% and from 5.9 to 11%, respectively. It is hypothesized that variations in the concentrations and compositions of airborne PAEs and BPA were influenced by district heating. An increase in the percentage of DEHP in PM2.5 was noted on polluted days, likely influenced by saturated vapor pressure. The estimated daily intake (EDI) for children was calculated to be higher than that for adults, indicating that children were exposed to significantly greater potential risks, although overall risks were observed to be low. The results of this study provide essential baseline data, such as concentration, for the management and control of emerging pollutants like endocrine disruptors in the urban atmosphere.
https://doi.org/10.1016/j.envpol.2024.125568

Migration of phthalate compounds from polyethylene terephthalate bottles under different temperature conditions- probabilistic human health risk assessment,
Massahi, T., Omer, A. K., Kiani, A., Mansouri, B., Fattahi, N., Soleimani, H., Moradi, M. and Sharafi, K., *Journal of Food Science and Technology-Mysore*, 2025 Feb 2025.

This study analyzed the migration of benzyl butyl phthalate (BBP), di(2-ethylhexyl) phthalate (DEHP), and dibutyl phthalate (DBP) from polyethylene terephthalate (PET) bottles used for beverages and edible liquids at different temperatures (4, 15, 25, and 40 degrees C). Solid phase extraction coupled with gas chromatography-mass spectrometry (GC/MS) was used for analysis. The results showed that higher temperatures increased the migration of phthalates from PET bottles into beverages/edible liquids. The lowest phthalate release occurred at 4 degrees C, while higher temperatures (15, 25, and 40 degrees C) increased leaching. The health risk assessment

concluded that the levels of these phthalate compounds in the PET bottles do not pose a significant health risk in terms of non-carcinogenic and carcinogenic effects, even when stored at higher temperatures. It can be concluded that controlling storage conditions and storing PET bottles at lower temperatures can help reduce the migration of phthalates and contribute to a safer use of PET containers for food and beverage storage. https://doi.org/10.1007/s13197-025-06232-z

Atmospheric Estrogenic Semi-Volatile Compounds and PAH in PM_{2.5} in Mexico City, Ronderos-Lara, J. G., Millán-Vázquez, F., Murillo-Tovar, M. A., Saldarriaga-Noreña, H. A., Valle-Hernández, B. L., López-Velázquez, K. and Mugica-Alvarez, V., *Atmosphere*, Feb 2025, Vol. 16, no. 2.

The quantification of semi-volatile organic compounds with potential endocrine-disrupting activity contained in fine atmospheric particles (PM2.5) is essential to understand their temporal behavior, identify their sources, and evaluate the health risks resulting from population exposure to said compounds. Since information and research outcomes regarding their presence in the atmosphere in developing countries are scarce, the main objective of this work was the development of a methodology devoted to extracting, characterizing, and quantifying, for the first time in Mexico, the concentration levels of three important groups of endocrine-disrupting compounds (EDCs) bonded to PM2.5 and collected during a year, namely: alkylphenols (4-n-nonylphenol (4NP) and 4-tert-octylphenol (4tOP)); bisphenols (bisphenol A (BPA) and bisphenol F (BPF)); natural and synthetic hormones (17 beta-estradiol (E-2), estriol (E-3) and 17 alpha-ethinyl estradiol (EE2)). Further, priority polycyclic aromatic hydrocarbons (PAH) that also disrupt endocrine activity were analyzed. All compounds were determined by gas chromatography coupled to tandem mass spectrometry, and the concentration levels were analyzed for different climatic seasons. Cold-dry (CD) season displayed higher levels of 4NP, bisphenols, and hormones (between 0.71 (4NP) and 1860 pg m(-3) (BPA)), as well as PAH concentrations (9.12 ng m(-3)). Regarding health effects, concentrations of alkylphenols, bisphenols, and hormones quantified had a value of estradiol equivalent concentration (EEQ(E2)) between 0.07 and 0.17 ng m(-3). PAH concentrations did not have carcinogenic and mutagenic risk with BaP(PEQ) < 1 ng m(-3). These results can be used by policymakers in the design of strategies for air pollution control. https://doi.org/10.3390/atmos16020178

Temporal and spatial variations of urinary phthalate metabolites for adults in China (2005-2020): A synthesis of biomonitoring data,
Zhang, Y. X., Wang, X. K., Sabel, C. E., He, H., Thomsen, M., Zhong, M., Chen, Z. K., Wang, W. X. and Huang, B., *Environmental Research*, Mar 2025, Vol. 268.

Chinese people are experiencing phthalate exposure risks. However, temporal and regional phthalate internal exposure variations amongst Chinese have not been established. To address this gap, we integrated our 69 adult participants' bio-monitored urinary phthalate metabolite (UPM) concentration data by high-performance liquid chromatography with mass spectrometry in Xi'an and Nanjing and the data from 35 literature (total sample size: 18768). Then, we analyzed China's temporal and spatial variations of adult UPM levels from 2005 to 2020 based on multi statistical methods. The results showed that the sum of eight UPM concentrations (i.e., monomethyl phthalate (MMP), mono-ethyl phthalate (MEP), mono-n-butyl phthalate (MNBP), mono-2-isobutyl phthalate, mono-benzyl phthalate, and three metabolites from di-2-ethylhexyl phthalate (DEHPM3)) had slightly increased in 2013-2020 (median: 230 (5th-95th: 73.7-653) ng/mL) compared with the period 2005-2012, which were about two times higher than the levels in most EU countries. The MNBP concentration between 2013 and 2020 (120 ng/mL, shared 52% of the eight UPM concentrations) has significantly increased to over two times the level between 2005 and 2012, followed by the DEHPM3 with a similar trend. Conversely, MEP and MMP concentrations in the later period decreased from the former period. In China, adults had the highest UPM concentrations in the East

and the lowest in the Middle. The adults in the East, the North, the South, and the Northeast had higher adverse phthalate exposure risks than the adults in the West and the Middle, and the Hazard index (HI) values were the highest in the East (1.61 (5th-95th: 1.01-3.07)). The adult exposure risks in the West had large heterogeneities (HIs: 0.46 (0.11-2.37). Regional variations in climate, the economy, industrial technology, and living styles could cause phthalate exposure differences. China needs to enhance tight regulation and enforcement of di-n-butyl phthalate (DNBP) (the parent of MNBP) and DEHP to protect public health. https://doi.org/10.1016/j.envres.2024.120748

Toxicité sur les animaux

Perinatal exposure to bisphenol A or S alters differently sexual behavior and kisspeptin system in mice,
Bonaldo, B., Casile, A., Bettarelli, M., Marraudino, M. and Gotti, S., *Environmental Research*, Mar 2025, Vol. 269.

The effects of bisphenol A (BPA), a highly diffused endocrine-disrupting chemical found mainly in plastics, on neural circuits and behaviors are well-known. However, the effects of its substitutes have not been fully investigated. Thus, in the present study, we compare the effects of perinatal exposure to bisphenol A or S (BPS) on reproductive behaviors and related hypothalamic kisspeptin system in mice. C57BL/6J dams were orally treated with 4 mu g/kg body weight/day of BPA, BPS, or vehicle from mating until the weaning of the offspring. In the adult offspring, we performed the two-bedding T-Maze test, and we observed the spontaneous sexual behavior. Exposure to BPA caused a delay in puberty onset in females, while BPS caused anticipation in males, and both altered the estrous cycle in females. The sexual and sexual-related behaviors were partially altered in males, especially in the BPA-exposed ones. Regarding the kisspeptin immunoreactivity in the analyzed hypothalamic nuclei, in BPA- or BPS-treated females, we observed an increase within the rostral periventricular area, while BPA led to an increase in the paraventricular nucleus, and BPS induced a reduction compared to control females. Among males, we observed a significant increase in the arcuate nucleus of BPA-treated males and a significant decrease in the paraventricular nucleus of BPS-treated ones. These results support the idea that perinatal exposure to low doses of either BPA or BPS is altering, in a sexually differentiated way, some reproductive-relevant parameters, sexual behaviors, and kisspeptin hypothalamic nuclei. https://doi.org/10.1016/j.envres.2025.120888

Prenatal exposure to nitrate alters uterine morphology and gene expression in adult female F1 generation rats,
Cassiani, A. G., Aloia, P. A., Sousa-Vidal, E. K., Podgaec, S., Piccinato, C. D. and Serrano-Nascimento, C., *Archives of Endocrinology Metabolism*, 2024, Vol. 68.

Objective: Nitrate is ubiquitously found in the environment and is one of the main components of nitrogen fertilizers. Previous studies have shown that nitrate disrupts the reproductive system in aquatic animals, but no study has evaluated the impact of nitrate exposure on the uterus in mammals. This study aimed to evaluate the impact of maternal exposure to nitrate during the prenatal period on uterine morphology and gene expression in adult female F1 rats. Materials and methods: Pregnant Wistar rats were either treated with sodium nitrate 20 mg/L or 50 mg/L dissolved in drinking water from the first day of pregnancy until the birth of the offspring or were left untreated. On postnatal day 90, the uteri of female offspring rats were collected for histological and gene expression analyses. Morphometric analyses of the uterine photomicrographs were performed to determine the thickness of the layers of the uterine wall (endometrium, myometrium,

and perimetrium) and the number of endometrial glands. Results: The highest nitrate dose increased the myometrial thickness of the exposed female rats. Treatment with both nitrate doses reduced the number of endometrial glands compared with no treatment. Additionally, nitrate treatment significantly increased the expression of estrogen receptors and reduced the expression of progesterone receptors in the uterus. Conclusion: Our results strongly suggest that prenatal exposure to nitrate programs gene expression and alters the uterine morphology in female F1 rats, potentially increasing their susceptibility to developing uterine diseases during adulthood. https://doi.org/10.20945/2359-4292-2024-0085

Heritable dysregulation of DNA methylation may underlie the diabetogenic effects of paternal preconception exposure to inorganic arsenic in C57BL/ 6J mice,
Hartwell, H. J., Shang, B. Z., Douillet, C., Bousquet, A. G., Liu, T. Y., Zou, F., Ideraabdullah, F., Styblo, M. and Fry, R. C., *Toxicology and Applied Pharmacology*, Mar 2025, Vol. 496.

Chronic exposure to inorganic arsenic (iAs) has been linked with the development of diabetes mellitus (DM). We recently showed that parental exposure to iAs (200 ppb) prior to mating was associated with diabetic phenotypes in offspring and altered gene expression in parents and offspring. The goal of the present study was to determine if DNA methylation underlies the differential gene expression in the livers of offspring. DNA methylation was assessed in paternal (G0) sperm and livers of their offspring (G1) using a genome wide DNA methylation array. We found that iAs exposure significantly altered CpG methylation ($p < 0.05$) in 54.3 %, 49.4 %, and 63.7 % of the differentially expressed genes in G0 sperm, G1 female livers, and G1 male livers, respectively. Importantly, a subset of differentially methylated CpG sites were shared across generations. Sensitivity analyses (FDR < 0.1) of imprinted and DM-associated genes revealed differential methylation of 74 imprinted genes and 100 DM-associated genes in the livers of G1 males. These male-specific results are intriguing given the prior findings of diabetic phenotypes found exclusively in male offspring from parents exposed to iAs. In summary, these data demonstrate that heritable changes in DNA methylation through the paternal germline may underlie the diabetogenic effects of preconception iAs exposure. https://doi.org/10.1016/j.taap.2025.117242

Two Hits of EDCs Three Generations Apart: Evaluating Multigenerational Anxiety-Like Behavioral Phenotypes in Female Rats Exposed to Aroclor 1221 and Vinclozolin,
Hilz, E. N., Gillette, R., Thompson, L. M., Ton, L., Pham, T., Kunkel, M. N., Crews, D. and Gore, A. C., *Environmental Health Perspectives*, Dec 2024, Vol. 132, no. 12.

BACKGROUND: Endocrine-disrupting chemicals (EDCs) are exogenous chemical compounds that interfere with the normal function of the endocrine system and are linked to direct and inherited adverse effects in both humans and wildlife. Legacy EDCs such as polychlorinated biphenyls (PCBs) are no longer used yet remain detectable in biological specimens around the world; concurrently, we are exposed to newer EDCs like the fungicide vinclozolin (VIN). This combination of individuals' direct environmental chemical exposures and any heritable changes caused by their ancestors' chemical exposures leads to a layered pattern of both direct and ancestrally inherited exposures that might have cumulative effects over generations. OBJECTIVES: We assessed consequences of both direct and ancestral exposure to EDCs over six generations, examining anxiety-like behaviors in maternal and paternal lines of female rats. We used the "two hits, three generations apart" multigenerational exposure model to explore how two distinct EDCs-the weakly estrogenic PCB mixture Aroclor 1221 (A1221) and the antiandrogenic VIN-interact on behavior across generations. We also explored serum hormones as a potential mechanism. METHODS: Rats were prenatally exposed to A1221, VIN, or vehicle (DMSO) in the F1 generation, and a second exposure (same or

different) was administered to the F4 generation. Anxiety-like behavior was measured in the Open Field test, Light:Dark box, and Elevated Plus Maze in the F1, F3, F4, and F6 generations. Serum concentrations of estradiol and corticosterone were analyzed. RESULTS: Behavioral effects were not detectable in the F1 generation but emerged and became more robust across generations. Rats with ancestral VIN exposure demonstrated less anxiety-like behavior in the F3 paternal line in comparison with controls. Rats exposed to ancestral then prenatal A1221/VIN and VIN/A1221 had more anxiety-like behavior in the F4 maternal line, and those with two ancestral hits of VIN/VIN had more anxiety in the F6 paternal line, in comparison with controls. DISCUSSION: Our findings suggest that anxiety-like behavioral phenotypes can manifest in rats following germline exposure to EDCs and that subsequent exposures across generations can intensify these effects in a lineage-dependent manner. https://doi.org/10.1289/EHP15621 https://doi.org/10.1289/ehp15621

Developmental immunotoxicity study of tris(chloropropyl) phosphate in Hsd:Sprague Dawley SD rats exposed through dosed feed,
Johnson, V. J., Ryan, K., Luster, M., Pandiri, A., Hobbie, K., Cora, M., Shockley, K. R., Burleson, G. R., Xie, G. H. and Germolec, D. R., *Toxicological Sciences*, 2025 Feb 2025.

Tris(chloropropyl) phosphate (TCPP) is a member of organophosphate flame retardants used commonly as a replacement for polybrominated diphenyl ethers in consumer and commercial products. Flame retardants have been shown to modulate immune function in vivo and in vitro and there is evidence that at least some related compounds such as organophosphate pesticides can cause developmental immunotoxicity. Developmental immunotoxicology studies were conducted by administering 0, 2500, 5000, or 10,000 ppm TCPP in feed to pregnant Hsd:Sprague Dawley SD rats from gestation day 6 through weaning on postnatal day 28. Feed exposure to TCPP was continued in the F1 offspring until terminal euthanasia at similar to 16 to 21 weeks of age when assessments for developmental immunotoxicity were conducted. Innate, humoral, and cell-mediated immune function were assessed in the F1 adults. The antibody-forming cells (AFCs) response to sheep red blood cells was reduced in male and female F1 rats in the 10,000 ppm treatment group but coincided with reduced bodyweights. The AFC response was also significantly reduced in male rats exposed to 5000 ppm where only moderate effects on bodyweights occurred. TCPP exposure affected baseline T-cell proliferation without stimulation; however, the relevance of this change for immunotoxicity risk is unknown. TCPP exposure did not affect cytotoxic T-lymphocyte activity. Only minor and inconsistent treatment-related effects on hematology, innate NK cell function, and immune cell population distributions in the spleen were observed. Taken together, these data indicate that TCPP has the potential to impact humoral immune responses following developmental exposure. https://doi.org/10.1093/toxsci/kfaf006

Prenatal bisphenol A and/or diethylhexyl phthalate exposure followed by adult estradiol treatment affects behavior and brain monoamines in female rat offspring,
Kaimal, A., Hooversmith, J. M., Al Mansi, M. H., Cherry, A. D., Garrity, J. T., Holmes, P. V., Mohankumar, P. S. and Mohankumar, S. M. J., *Frontiers in Endocrinology*, Jan 2025, Vol. 15.

Women are at increased risk for mood disorders, which may be partly attributed to exposure to endocrine-disrupting chemicals (EDCs) during sensitive periods such as pregnancy. Exposure during these times can impact brain development in the offspring, potentially leading to mood disorders in later life. Additionally, fluctuating levels of endogenous estrogens, as seen during pregnancy, or the use of oral contraceptives, can further elevate this risk. This study examines the cumulative effects of prenatal EDC exposure combined with chronic low-dose 17 beta-estradiol (E2) treatment in adulthood on neurobehavioral outcomes. Pregnant Sprague-Dawley rats were orally dosed with vehicle, bisphenol A (BPA) (5 mu g/kg body weight (BW)/day), low-dose (LD) diethylhexyl phthalate

(DEHP) (5 mu g/kg BW/day), high-dose (HD) DEHP (7.5 mg/kg BW/day), or a combination of the two (BPA+DEHP) from gestational days 6-21. At 3 months of age, female offspring were implanted with slow-release E2 pellets or were sham-implanted. Following a 90-day treatment period, behavioral testing was conducted, and serum hormones and brain monoamine levels were analyzed. Chronic E2 treatment in controls increased anxiety and reduced active coping behaviors. In DEHP- and BPA+DEHP-exposed offspring, E2 treatment reversed some of these effects. Dose-dependent alterations in circulating hormone levels and brain monoamines were observed. Dysregulation of the stress axis was particularly notable with the higher dose of DEHP. Overall, prenatal EDC exposure altered behavior, hormones, and brain monoamines, with adult E2 treatment further exacerbating some of these effects in female offspring.
https://doi.org/10.3389/fendo.2024.1479838

Prepubertal phthalate exposure can cause histopathological alterations, DNA methylation and histone acetylation changes in rat brain,
Koc, S., Erdogmus, E., Bozdemir, O., Ozkan-Vardar, D., Yaman, U., Erkekoglu, P., Zeybek, N. D. and Kocer-Gumusel, B., *Toxicology and Industrial Health*, Mar 2025, Vol. 41, no. 3, p. 163-175.

Di-2-(ethylhexyl)phthalate (DEHP) is a phthalate derivative used extensively in a wide range of materials, such as medical devices, toys, cosmetics, and personal care products. Many mechanisms, including epigenetics, may be involved in the effects of phthalates on brain development. In this study, Sprague-Dawley male rats were obtained 21-23 days after their birth (post-weaning) and were exposed to DEHP during the prepubertal period with low-dose DEHP (DEHP-L, 30 mg/kg/day) and high-dose DEHP (DEHP-H, 60 mg/kg/day, 37 days) until the end of adolescence (PND 60). The rats in the study groups were sacrificed during adulthood, and histopathological changes, epigenetic changes, and oxidative stress parameters were evaluated in brain tissues. Histopathological findings indicating the presence of deterioration in brain tissue morphology were obtained, more prominently in the DEHP-H group. Examining the hippocampus under the light microscope, pyramidal neuron loss was detected only in CA1 of the DEHP-L group, while in DEHP-H rats, pyramidal neuron losses were detected in the CA1, CA2, and CA3 regions. No significant change was observed in brain lipid peroxidation levels with DEHP compared to control. Significant increases in total glutathione (GSH) in both dose groups were considered to be an adaptive response to DEHP-induced oxidative stress. The decrease in DNA methylation in the brain, although not statistically significant, and the increase in histone modification showed that exposure to DEHP may cause epigenetic changes in the brain and these epigenetic changes may also take place as one of the mechanisms underlying the damage observed in the brain. The results suggest that DEHP exposure during early development may have a significant effect on brain development.
https://doi.org/10.1177/07482337251315212

Altered Expression of Thyroid- and Calcium Ion Channels-Related Genes in Rat Testes by Short-Term Exposure to Commercial Herbicides Paraquat or 2,4-D,
Luis, E., Conde-Maldonado, V., García-Nieto, E., Juárez-Santacruz, L., Alvarado, M. and Anaya-Hernández, A., *Journal of Xenobiotics*, Dec 2024, Vol. 14, no. 4, p. 1450-1464.

Exposure to pesticides such as paraquat and 2,4-dichlorophenoxyacetic acid (2,4-D) has been linked to harmful health effects, including alterations in male reproduction. Both herbicides are widely used in developing countries and have been associated with reproductive alterations, such as disruption of spermatogenesis and steroidogenesis. The thyroid axis and Ca2+-permeable ion channels play a key role in these processes, and their disruption can lead to reproductive issues and even infertility. This study evaluated the short-term effects of exposure to commercial herbicides based on paraquat and 2,4-D on gene expression in rat testes. At the molecular level, exposure to

paraquat increased the expression of the thyroid hormone transporters monocarboxylate transporter 8 (Mct8) and organic anion-transporting polypeptide 1C1 (Oatp1c1) and the thyroid receptor alpha (TR alpha), suggesting a possible endocrine disruption. However, it did not alter the expression of the sperm-associated cation channels (CatSper1-2) or vanilloid receptor-related osmotically activated channel (Trpv4) related to sperm motility. In contrast, exposure to 2,4-D reduced the expression of the Mct10 transporter, Dio2 deiodinase, and CatSper1, which could affect both the availability of T3 in testicular cells and sperm quality, consistent with previous studies. However, 2,4-D did not affect the expression of CatSper2 or Trpv4. Deregulation of gene expression could explain the alterations in male reproductive processes reported by exposure to paraquat and 2,4-D. These thyroid hormone-related genes can serve as molecular biomarkers to assess endocrine disruption due to exposure to these herbicides, aiding in evaluating the health risks of pesticides. https://doi.org/10.3390/jox14040081

Prenatal exposure to diethylstilbestrol has multigenerational effects on folliculogenesis, Rogers, R. E., Fowler, K. A., Pask, A. J. and Mattiske, D. M., *Scientific Reports*, Dec 2024, Vol. 14, no. 1.

Diethylstilbestrol (DES) is an estrogenic endocrine disrupting chemical (EDC) that was prescribed to millions of pregnant women worldwide, leading to increased rates of infertility in the exposed offspring. We have previously demonstrated that this reduced fertility persists for multiple generations in the mouse. However, how altered ovarian function contributes to this infertility is unknown. Therefore, this study sought to determine if DES exposure promotes two common ovarian disorders, primary ovarian insufficiency (POI) and polycystic ovary syndrome, contributing to the reduced fertility in DES offspring. Moreover, we investigated if these impacts are transgenerational. Gestating mice were exposed to 100 mu g/kg DES, and ovarian morphology was observed in F1-F3 female descendants. F1 females trended towards fewer primordial and more secondary follicles and similarly, F2 females had fewer primordial and significantly more secondary follicles compared to controls. No differences in follicle proportions were observed in the F3. Moreover, DES exposure did not increase follicular cysts. These results show that DES accelerates folliculogenesis, indicative of a POI phenotype and that this is likely contributing to the reduced fertility observed in DES descendants. Moreover, this study highlights the ability of estrogenic EDCs to disrupt folliculogenesis, which may exacerbate the onset of POI in women already at risk. https://doi.org/10.1038/s41598-024-81093-8

Developmental programming: Sex-specific effects of prenatal exposure to a real-life mixture of environmental chemicals on liver function and transcriptome in sheep, Thangaraj, S. V., Bellingham, M., Lea, R., Evans, N., Sinclair, K. and Padmanabhan, V., *Environmental Pollution*, Feb 2025, Vol. 367.

Humans are chronically exposed to a mixture of environmental chemicals (ECs), many with metabolic and endocrine disrupting potential, contributing to non-communicable disease burden. Understanding the effects of chronic exposure to low-level mixtures of ECs requires an animal model that reflects real-world conditions, lags behind studies on single ECs. Biosolids, from wastewater treatment, offers a real-life model to investigate the developmental health risks from EC mixtures. Prenatal biosolids exposure studies have documented metabolic perturbations including heavier thyroid glands in male fetuses and reduced bodyweight in prepubertal male lambs followed by catchup growth. We hypothesized that maternal preconceptional and gestational exposure of sheep to biosolids programs sex-specific transcriptional and functional changes in the offspring liver. Ewes (F0) were grazed on either inorganic fertilizer (C) or biosolids-treated pastures (BTP) preconception till parturition. All lambs (n = 15/group with male n = 7/group and females n = 8/group) were raised

on Control pastures until euthanasia at 9.5 weeks. Next generation sequencing of liver RNA and DESeq2 was used to identify exposurespecific differentially expressed genes (DEG) and sex-differentially expressed genes (SDG). Liver function was assessed with markers of oxidative stress, triglyceride and fibrosis markers. Control lambs exhibited 647 SDGs confirming the inherent sexual dimorphism in hepatic gene expression. A sex-stratified analysis identified 10 DEG, mostly affecting metabolism, in male and none in female lambs. Biosolids exposure diminished the sexual dimorphism in hepatic gene expression barring 41 genes, potentially due to the increase in androgenic steroids found in F0 maternal circulation. Additionally, BTP male lambs showed elevated plasma triglyceride and a trend towards increased liver triglyceride concentrations. The identified effects of prenatal exposure to low-dose mixture of ECs via biosolids, in a precocial species paralleling human developmental patterns holds translational importance for understanding the sexually dimorphic origin of non-communicable diseases.
https://doi.org/10.1016/j.envpol.2025.125630

Prenatal exposure to bisphenol A causes reproductive damage in F1 male rabbits due to inflammation and oxidative stress,
Zhao, Q. H., Pan, J. L., Bao, Y. Z., Wang, X. and Shi, W. Y., *Ecotoxicology and Environmental Safety*, Jan 2025, Vol. 290.

Bisphenol A (BPA) is used extensively in producing industrial chemicals such as plastic products, resin, and paper coatings. Concerns have been expressed regarding its possible detrimental consequences, especially on the reproductive system of mammals. Despite extensive study in this domain, there has been no targeted examination of the impact of BPA on F1 generation rabbits. BPA exposure model was developed in pregnant female rabbits to examine the effects of BPA on reproductive hormones, cellular apoptosis, oxidative stress, inflammatory response, and tissue integrity in weaning rabbits. The results indicated that BPA exposure triggered an inflammatory response and oxidative stress, consequently impacting the reproductive system of weaned rabbits and altering reproductive hormone levels. By modulation of the Nrf2 and NF-kappa B axes, BPA could influence the expression of antioxidant enzymes and inflammatory mediators in the rabbit reproductive system, leading to cell apoptosis and tissue damage. These results underscore the importance of monitoring BPA exposure during pregnancy and emphasize the necessity of implementing measures to mitigate its potential effects on the reproductive health of offspring.
https://doi.org/10.1016/j.ecoenv.2025.117735

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