



Bulletin de veille Perturbateurs Endocriniens N°18 - Janvier 2023

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

Adverse Health Effects and Mercury Exposure in a Colombian Artisanal and Small-Scale Gold Mining Community.

Vergara-Murillo F, González-Ospino S, Cepeda-Ortega N, Pomares-Herrera F, Johnson-Restrepo B. *Toxics*. 2022 Nov 25;10(12).

The aim of this study was, first of all, to associate the mercury (Hg) concentrations and respiratory functions of the gold miners in the artisanal small-scale gold mining (ASGM) environment in San Martín de Loba, Colombia. We carried out a cross-sectional study using a survey whereby we collected basic demographic information, occupational medical history, and applied two validated questionnaires (Q16 and SF36). We measured Hg levels in all volunteers using direct thermal decomposition-atomic absorption spectrometry. Univariate and bivariate statistical analyses were carried out for all variables, performing logistic regression to assess the effect of ASGM on health outcomes. Volunteers enrolled (n = 124) were between the ages of 20 and 84 years (84% miners and 79% males). No changes were

found in the systolic blood pressure, diastolic blood pressure, and heart rate from the ASGM miners, in crude and adjusted statistical analyses. ASGM miners increased 8.91 (95% confidence interval, 1.55-95.70) times the risk of having these than of having neurotoxic effects. Concentrations of total whole blood mercury (T-Hg) in all participants ranged from 0.6 to 82.5 with a median of 6.0 µg/L. Miners had higher T-Hg concentrations than non-miners (p-value = 0.011). Normal and abnormal respiratory spirometry patterns showed significant differences with the physical role and physical function of quality-of-life scales (the (p-value was 0.012 and 0.004, respectively). The spirometry test was carried out in 87 male miners, with 25% of these miners reporting abnormalities. Out of these, 73% presented a restrictive spirometry pattern, and 27%, an obstructive spirometry pattern. The ASGM population had higher Hg concentrations and worse neurotoxic symptomatology than non-miners of the same community.

[Lien vers l'article](#)

Metabolome-wide association study of the relationship between chlorpyrifos exposure and first trimester serum metabolite levels in pregnant Thai farmworkers.

Liang D, Batross J, Fiedler N, Prapamontol T, Suttiwan P, Panuwet P, et al. *Environ Res.* 2022 Dec;215(Pt 2):114319.

INTRODUCTION: Organophosphate (OP) insecticides, including chlorpyrifos, have been linked with numerous harmful health effects on maternal and child health. Limited data are available on the biological mechanisms and endogenous pathways underlying the toxicity of chlorpyrifos exposures on pregnancy and birth outcomes. In this study, we measured a urinary chlorpyrifos metabolite and used high-resolution metabolomics (HRM) to identify biological perturbations associated with chlorpyrifos exposure among pregnant women in Thailand, who are disparately exposed to high levels of OP insecticides. **METHODS:** This study included 50 participants from the Study of Asian Women and their Offspring's Development and Environmental Exposures (SAWASDEE). We used liquid chromatography-high resolution mass spectrometry to conduct metabolic profiling on first trimester serum samples collected from participants to evaluate metabolic perturbations in relation to chlorpyrifos exposures. We measured 3,5,6-trichloro-2-pyridinol (TCPy), a specific metabolite of chlorpyrifos and chlorpyrifos-methyl, in first trimester urine samples to assess the levels of exposures. Following an untargeted metabolome-wide association study workflow, we used generalized linear models, pathway enrichment analyses, and chemical annotation to identify significant metabolites and pathways associated with urinary TCPy levels. **RESULTS:** In the 50 SAWASDEE participants, the median urinary TCPy level was 4.36 µg TCPy/g creatinine. In total, 691 unique metabolic features were found significantly associated with TCPy levels ($p < 0.05$) after controlling for confounding factors. Pathway analysis of metabolic features associated with TCPy indicated perturbations in 24 metabolic pathways, most closely linked to the production of reactive oxygen species and cellular damage. These pathways include tryptophan metabolism, fatty acid oxidation and peroxisome metabolism, cytochromes P450 metabolism, glutathione metabolism, and vitamin B3 metabolism. We confirmed the chemical identities of 25 metabolites associated with TCPy levels, including glutathione, cystine, arachidic acid, itaconate, and nicotinamide adenine dinucleotide. **DISCUSSION:** The metabolic perturbations associated with TCPy levels were related to oxidative stress, cellular damage and repair, and systemic inflammation, which could ultimately contribute to health outcomes, including neurodevelopmental deficits in the child. These findings support the future development of sensitive biomarkers to investigate the metabolic underpinnings related to pesticide exposure during pregnancy and to understand its link to adverse outcomes in children.

[Lien vers l'article](#)

Impact of Pesticides on Cancer and Congenital Malformation: A Systematic Review.

Melanda VS, Galiciolli MEA, Lima LS, Figueiredo BC, Oliveira CS. *Toxics*. 2022 Nov 9;10(11).

Pesticide exposure has deleterious effects on human health and development; however, no review has been conducted on human exposure to pesticides and the risk of congenital malformations and cancer in the same cohort. We systematically reviewed the evidence for this relationship following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. Four databases, namely, PubMed, Scopus, Cochrane Library, and BVS, were searched for studies deposited till July 2020 that examined the influence of pesticide exposure on congenital malformations and cancer outcomes in the same cohort. Seven studies were systematically included in this review. Among these, four were case-control studies, two were cross-sectional studies, and one was a longitudinal cohort study. The sources of contamination were food, water, or exposure during agricultural work. A link between the occurrence of cancer, congenital malformations, and exposure to pesticides was observed in most studies.

[Lien vers l'article](#)

Assessing the relationship between hypospadias risk and parental occupational exposure to potential endocrine-disrupting chemicals.

Das D, Dutta HK, Borbora D, Brahma RC, Das JM. *Occup Environ Med*. 2022 Dec 26.

OBJECTIVE: The association between periconceptional parental exposure to endocrine-disrupting chemicals (EDCs) and hypospadias remains inconclusive and controversial. Therefore, we conducted a hospital-based retrospective study to assess the relationship between hypospadias risk and parental occupational exposure to potential EDCs. **METHODS:** Incident cases (n=73) were boys between 0 and 14 years diagnosed with hypospadias with no micropenis or cryptorchidism. Controls (n=146) were an age-matched group of boys without any congenital malformations, inguinal hernia, nephrological, urological and genital disorders. Their selection was independent of exposures to EDCs. Data on parental occupation and sociodemographic variables were collected using a structured questionnaire. We evaluated parental occupational exposures using a previously validated job-exposure matrix (JEM) for EDCs. **RESULTS:** In our case-control study, 30.1% of all pregnancies had likely exposure to potential EDCs. The most prevalent occupations conferring possible exposure were related to activities on farms. Maternal and paternal occupational exposure to potential EDCs significantly increased the risk of mild hypospadias than moderate-to-severe hypospadias (OR=6.55 vs OR=4.63). Among various categories, parental occupational exposure to pesticides was associated with at least a twofold increased risk of hypospadias. Maternal EDC exposure during the first trimester significantly increased the risk of bearing a hypospadiac child (OR=4.72 (95% CI 2.10 to 10.60)). **CONCLUSION:** This study suggests that EDCs are a risk factor for hypospadias through occupational exposure during fetal life.

[Lien vers l'article](#)

Breast cancer incidence in a national cohort of female workers exposed to special health hazards in Taiwan: a retrospective case-cohort study of ~ 300,000 occupational records spanning 20 years.

Chuang YS, Lee CY, Lin PC, Pan CH, Hsieh HM, Wu CF, et al. *Int Arch Occup Environ Health*. 2022 Dec;95(10):1979-93.

OBJECTIVE: Breast cancer is the most common cancer among women worldwide. In Taiwan, workers exposed to any of 31 hazardous chemicals or carcinogens in the work environment are designated as especially exposed workers (EEWs) by Taiwan's Ministry of Labor. We assessed the risk of breast cancer in this nationwide female EEW cohort. **METHODS:** We conducted a nationwide retrospective study of 4,774,295 workers combining data collected from Taiwan's Ministry of Labor's EEW database between 1997 and 2018 and Taiwan's Cancer Registry between 1997 and 2016. Standardized incidence ratios (SIRs) for women exposed to different hazards and breast cancer incidence rate ratios (IRRs) were calculated by Poisson regression, adjusting for age and duration of exposure. **RESULTS:** 3248 female workers with breast cancer and 331,967 without breast cancer were included. The SIRs and adjusted IRRs were 1.27 (95% CI 1.18-1.35) and 1.31 (95% CI 1.21-1.42) for lead, 1.74 (95% CI 1.23-2.24) and 1.52 (95% CI 1.13-2.04) for 1,1,2,2-tetrachloroethane, 1.47 (95% CI 1.12-1.82) and 1.42 (95% CI 1.12-1.81) for trichloroethylene/tetrachloroethylene, 1.40 (95% CI 1.23-1.57) and 1.38 (95% CI 1.22-1.57) for benzene, and 2.07 (95% CI 1.06-3.09) and 1.80 (95% CI 1.10-2.94) for asbestos. The results remained similar when factoring in a 2- or 5-year latency period. **CONCLUSION:** This study found possible correlations between occupational exposure to lead, chlorinated solvents (such as 1,1,2,2-tetrachloroethane, trichloroethylene, and tetrachloroethylene), benzene, and asbestos with breast cancer risk among female EEW, suggesting a need for regular screening for breast cancer for employees exposed to these special workplace hazards.

[Lien vers l'article](#)

Night shift work and risk of aggressive prostate cancer in the Norwegian Offshore Petroleum Workers (NOPW) cohort.

Berge LAM, Liu FC, Grimsrud TK, Babigumira R, Støer NC, Kjærheim K, et al. *Int J Epidemiol*. 2022 Dec 22.

BACKGROUND: Night shift work may acutely disrupt the circadian rhythm, with possible carcinogenic effects. Prostate cancer has few established risk factors though night shift work, a probable human carcinogen, may increase the risk. We aimed to study the association between night shift work and chlorinated degreasing agents (CDAs) as possible endocrine disruptors in relation to aggressive prostate cancer as verified malignancies. **METHODS:** We conducted a case-cohort study on 299 aggressive prostate cancer cases and 2056 randomly drawn non-cases in the Norwegian Offshore Petroleum Workers cohort (1965-98) with linkage to the Cancer Registry of Norway (1953-2019). Work history was recorded as years with day, night, and rollover (rotating) shift work, and CDA exposure was assessed with expert-made job-exposure matrices. Weighted Cox regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for aggressive prostate cancer, adjusted for education and year of first employment, stratified by 10-year birth cohorts, and with 10, 15, and 20 years of exposure lag periods. **RESULTS:** Compared with day work only, an increased hazard of aggressive prostate cancer (HR = 1.86, 95% CI 1.18-2.91; P-trend = 0.046) was found in workers exposed to ≥19.5 years of rollover shift work. This persisted with longer lag periods (HR = 1.90, 95% CI 0.92-3.95; P-trend = 0.007). The exposure-hazard curve for a non-linear model increased linearly (HRs ≥1.00) for 18-26 years

of rollover shift work. No association was found with CDA exposure. **CONCLUSIONS:** Long-term exposure to rollover shift work may increase the hazard of aggressive prostate cancer in offshore petroleum workers.

[Lien vers l'article](#)

Exposure Levels of Pyrethroids, Chlorpyrifos and Glyphosate in EU-An Overview of Human Biomonitoring Studies Published since 2000.

Andersen HR, Rambaud L, Riou M, Buekers J, Remy S, Berman T, et al. *Toxics*. 2022 Dec 15;10(12).

Currently used pesticides are rapidly metabolised and excreted, primarily in urine, and urinary concentrations of pesticides/metabolites are therefore useful biomarkers for the integrated exposure from all sources. Pyrethroid insecticides, the organophosphate insecticide chlorpyrifos, and the herbicide glyphosate, were among the prioritised substances in the HBM4EU project and comparable human biomonitoring (HBM)-data were obtained from the HBM4EU Aligned Studies. The aim of this review was to supplement these data by presenting additional HBM studies of the priority pesticides across the HBM4EU partner countries published since 2000. We identified relevant studies (44 for pyrethroids, 23 for chlorpyrifos, 24 for glyphosate) by literature search using PubMed and Web of Science. Most studies were from the Western and Southern part of the EU and data were lacking from more than half of the HBM4EU-partner countries. Many studies were regional with relatively small sample size and few studies address residential and occupational exposure. Variation in urine sampling, analytical methods, and reporting of the HBM-data hampered the comparability of the results across studies. Despite these shortcomings, a widespread exposure to these substances in the general EU population with marked geographical differences was indicated. The findings emphasise the need for harmonisation of methods and reporting in future studies as initiated during HBM4EU.

[Lien vers l'article](#)

Low-Dose Occupational Exposure to Nickel and Thyroid Hormones.

Monti C, Giammichele G, Antuono V, Loreti B, Tomei F, De Marco F, et al. *J Occup Environ Med*. 2022 Nov 1;64(11):e667-e71.

INTRODUCTION: The aim of this study was to evaluate the effects of a low-dose exposure to nickel, as it is present in urban air, on thyroid hormones and on thyrotropin in outdoor workers exposed to urban pollutants. **MATERIALS AND METHODS:** A total of 164 outdoor workers were studied and divided by sex and smoking habit. Each worker underwent measurement of urinary nickel and of blood triiodothyronine, L-thyroxine, and thyrotropin levels. The statistical analysis was performed. **RESULTS:** Statistical analysis shows a significant and positive correlation between urinary nickel and L-thyroxine, both in total sample and in males. **DISCUSSION AND CONCLUSION:** The study suggests that occupational exposure to a low dose of nickel may affect thyroid function in municipal police workers. These data may provide information on other categories of outdoor workers with similar exposure.

[Lien vers l'article](#)

Epidémiologie

Application of growth modeling to assess the impact of hospital-based phthalate exposure on preterm infant growth parameters during the neonatal intensive care unit hospitalization,

BUSGANG S. A., E. A. SPEAR, S. S. ANDRA, S. NARASIMHAN, J. B. BRAGG, S. RENZETTI, P. CURTIN, M. BATES, M. ARORA, C. GENNINGS and A. STROUSTRUP,
Science of the Total Environment 850 (Dec 2022),

In this study, we use advanced growth modeling techniques and the rich biospecimen and data repositories of the NICU Hospital Exposures and Long-Term Health (NICU-HEALTH) study to assess the impact of NICU-based phthalate exposure on extrauterine growth trajectories between birth and NICU discharge. Repeated holdout weighed quantile sum(WQS) regression was used to assess the effect of phthalate mixtures on the latency to first growth spurt and on the rate of first growth spurt. Further, we assessed sex as an effect modifier of the relationship between a phthalate mixture and both outcomes. Nine phthalate metabolites, mono-ethyl phthalate (MEP), mono-benzyl phthalate (MBzP), mono- n-butyl phthalate (MBP), mono-isobutyl phthalate (MiBP), mono-(3-carboxypropyl) phthalate (MCP), mono-2-ethylhexyl phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) were measured in weekly urine specimens from 101 NICU-HEALTH participants between birth and the first growth spurt. Phthalate levels varied by species but not by infant sex, and decreased over the course of the NICU hospitalization as presented in detail in Stroustrup et al., 2018. There was evidence of nonlinearity when assessing the effect of phthalates on latency to first growth spurt. Above a threshold level, a higher phthalate mixture with dominant contributors MCP, MBzP, and MEP predicted a shorter latency to the first inflection point, or an earlier growth spurt. A higher phthalate mixture with dominant contributors MECPP, MEHHP, and MEOHP was associated with an increased rate of growth. Results of both models were clearly different for boys and girls, consistent with other studies showing the sexually dimorphic impact of early life phthalate exposure. These results suggest that growth curve modeling facilitates evaluation of discrete periods of rapid growth during the NICU hospitalization and exposure to specific phthalates during the NICU hospitalization may both alter the timing of the first growth spurt and result in more rapid growth in a sexually dimorphic manner.

<https://doi.org/10.1016/j.scitotenv.2022.157830>

Association between endocrine-disrupting chemical mixture and metabolic indices among children, adolescents, and adults: A population-based study in Korea,

KIM B., B. PARK, C. H. KIM, S. KIM and B. PARK,
Environmental Pollution 315 (Dec 2022),

Exposure to endocrine-disrupting chemicals (EDCs) play a role in the etiology of obesity and dyslipidemia. However, few studies have analyzed the combined effects of EDC mixtures. This study explored the association between concurrent exposure to EDCs and obesity or dyslipidemia in children, adolescents, and adults. A total of 1454 children, 891 adolescents, and 3758 (for BMI) and 3424 (for TG/HDL) adults from the Korean National Environmental Health Survey 2015 to 2017 were included in this cross-sectional study. Urinary concentrations of eight phthalate metabolites, three phenols, three parabens, and one pyrethroid pesticides metabolite were quantified. Body mass index (BMI) was measured for all participants, and triglyceride (TG) and high-density lipoprotein cholesterol (HDL-c) levels were measured for adolescents and adults. Associations between combined EDC mixtures with the BMI and TG to HDL-c ratio were evaluated using Bayesian Kernel Machine Regression (BKMR). In all age groups, most of the chemical exposures, with the exception of BPF and BPS, were detected in more than 90% of participants. There were significant moderate to high correlations within phthalate metabolites and a high correlation within parabens. The BKMR showed that EDC mixtures were associated with higher BMI in both adolescents and adults, with greater significance in adults compared with adolescents, and a higher TG/HDL in male adolescents. In adolescents, MEP and MCP drove the main effects on BMI and TG/HDL, respectively. In adults, 3PBA and BPA drove the main effects on BMI. The findings of this study suggest that exposure to EDC mixtures is associated with higher BMI and TG/HDL, and adolescence may be a critical period for EDC mixture in terms of both outcomes. Further studies are needed, but strategies to reduce EDC exposure from early life stages may be necessary to lower the risk of metabolic disease.

<https://doi.org/10.1016/j.envpol.2022.120399>

Association between polychlorinated biphenyl exposure and thyroid hormones: a systematic review and meta-analysis,

LITTLE C. C., J. BARLOW, M. ALSEN and M. VAN GERWEN,

Journal of Environmental Science and Health Part C-Toxicology and Carcinogenesis (Purpose: To conduct a comprehensive meta-analysis investigating the association between polychlorinated biphenyl (PCB) exposure and serum thyroid hormone levels among adults. Methods: Eleven studies met inclusion criteria for analysis following systematic search of PubMed, Embase, and Scopus databases. Of these, 7 studies measured exposure by the total sum of PCB congeners (n-ary summation PCB), 1 study measured individual PCB congener levels, and 3 studies measured both n-ary summation PCB levels and PCB congener levels. Correlation coefficients (r) were extracted from each study. Summary estimates were calculated for n-ary summation PCB levels and PCB congeners reported by 2 or more studies: PCB 28, 52, 101, 105, 118, 138, 153, and 180, using random effects model. Results: Significant negative correlation was found between n-ary summation PCBs and T3 (r: -0.09; 95% CI: -0.17, -0.02) and FT3 (r: -0.24; 95% CI: -0.36, -0.12). Congener-specific analysis found T3 to be negatively correlated with PCB-153 (r: -0.19; 95% CI: -0.34, -0.03) and PCB-180 (r: -0.14; 95% CI: -0.26, -0.01), whereas TSH was positively correlated with PCB-105 (r: 0.15; 95% CI: 0.02, 0.28). Conclusions: The present study is the first meta-analysis to investigate the association between PCB exposure and thyroid hormone dysfunction among adults. Results suggest a significant association between PCB exposure and thyroid hormone dysregulation. <https://doi.org/10.1080/26896583.2022.2149213>

Associations between Phthalate Exposure and Gestational Age at Delivery in a Diverse Pregnancy Cohort,

SIENAS L., C. ALBRIGHT, Y. NI, A. SZPIRO, N. R. BUSH, C. LOFTUS, K. KANNAN, F. TYLAVSKY, C. J. KARR, K. Z. LEWINN and S. SATHYANARAYANA,

Toxics 10, no. 12 (Dec 2022),

The association between prenatal phthalate exposure and late preterm birth (LPTB) is unclear. We examined singleton pregnancies (2006-2011) from a racially and socioeconomically diverse sample of women in the CANDLE cohort of the ECHO-PATHWAYS Consortium. Urine collected in the second and third trimester was analyzed for 14 phthalate metabolites. Multivariate logistic and linear regressions were performed for LPTB, defined as delivery 34-37 weeks, and gestational week, respectively. Models were controlled for socio-demographics, behavioral factors, clinical measurements, medical history, and phthalates in the other trimester. Effect modification by race and pregnancy stress, indicated by intimate partner violence (IPV), was investigated. We conducted a secondary analysis in women with spontaneous preterm labor. The rate of LPTB among 1408 women (61% Black, 32% White) was 6.7%. There was no evidence of decreased gestational age (GA) in association with any phthalate metabolite. Each two-fold increase in third trimester mono-benzyl phthalate (MBzP) was associated with 0.08 weeks longer gestational age (95% CI: 0.03, 0.12). When restricting to women with spontaneous labor, second trimester mono-n-butyl phthalate (MBP) was associated with 54% higher odds (95% CI: 2%, 132%) of LPTB. Associations were not modified by maternal race or IPV exposure. In conclusion, we observed mixed evidence concerning our hypothesis that prenatal phthalate exposure increases risk of LPTB, though secondary analyses suggest increased risk of spontaneous LPTB associated with MBP, which is consistent with a recent pooled analysis of 16 cohorts. <https://doi.org/10.3390/toxics10120754>

Associations of Prenatal First Trimester Essential and Nonessential Metal Mixtures with Body Size and Adiposity in Childhood,

SMITH A. R., P. I. D. LIN, S. L. RIFAS-SHIMAN, R. O. WRIGHT, B. COULL, M. F. HIVERT, A. HUBBARD, E. OKEN and A. CARDENAS,

Epidemiology 34, no. 1 (Jan 2023): 80-89,

Background: Prenatal nonessential metals may contribute to postnatal adiposity, whereas essential metals may have metabolic benefits. We evaluated joint and individual associations between prenatal metals and childhood adiposity. Methods: We measured concentrations of six nonessential (arsenic, barium, cadmium, cesium, lead, and mercury) and four essential (magnesium, manganese, selenium, and zinc) metals in first trimester maternal blood from a prebirth cohort. We collected anthropometric measures in early childhood, mid-childhood, and early adolescence including subscapular+tricep skinfold thickness (mm) (N = 715-859), waist circumference (cm) (N = 717-882), and body mass index (BMI) (z-score) (N = 716-875). We measured adiposity in mid-childhood and early adolescence using bone densitometry total- and trunk- fat mass index (kg/m²) (N = 511-599). We estimated associations using adjusted quantile g-computation and linear regression. Results: The nonessential metal mixture was associated with higher total (beta = 0.07, 95% CI = 0.01, 0.12) and trunk fat mass index (beta

= 0.12, CI = 0.02, 0.22), waist circumference (beta = 0.01, CI = 0.00, 0.01), and BMI (beta = 0.24, CI = 0.07, 0.41) in mid-childhood, and total fat mass index (beta = 0.07, CI = 0.01, 0.14), and BMI (beta = 0.19, CI = 0.02, 0.37) in early adolescence. The essential metal mixture was associated with lower early adolescence total- (beta = -0.11, CI = -0.17, -0.04) and trunk- fat mass index (beta = -0.13, CI = -0.21, -0.05), subscapular+tricep skinfold thickness (beta = -0.02, CI = -0.03, -0.00), waist circumference (beta = -0.003, CI = -0.01, -0.00), and BMI (beta = -0.16, CI = -0.28, -0.04). Cadmium and cesium were individually associated with childhood adiposity at different timepoints. Conclusions: Prenatal first-trimester essential metals were associated with lower childhood adiposity, whereas nonessential metals were associated with higher adiposity into adolescence.

<https://doi.org/10.1097/ede.0000000000001560>

Bisphenol-A and Female Fertility: An Update of Existing Epidemiological Studies,

STAVRIDIS K., O. TRIANTAFYLIDOU, M. PISIMISI and N. VLAHOS,

Journal of Clinical Medicine 11, no. 23 (Dec 2022),

Humans interfere with a variety of endocrine disruptors on a daily basis, which may result in adverse health effects. Among them, Bisphenol-A (BPA) is the most debated endocrine disruptor, despite being widely studied, regarding its effects on fertility. The aim of this review was to investigate the interrelation of BPA and female fertility. PubMed (Medline) was searched from 2013 until 2022 to identify epidemiological studies that report the association of BPA with fertility parameters, in vitro fertilization (IVF) outcomes, polycystic ovarian syndrome (PCOS) and endometriosis. Regarding general fertility, most studies report an inverse association between BPA and ovarian reserve markers, namely antral follicle count (AFC) and anti-Müllerian hormone (AMH). The BPA and estradiol (E2) levels did not correlate significantly in the majority of studies. No definite conclusions can be reached regarding BPA and IVF endpoints or endometriosis. Lastly, most studies report higher prevalence of PCOS in women with higher BPA concentrations, although no casualty has been proven. Although most studies fail to reach definite conclusion regarding the impact of BPA on fertility, there is accumulating evidence suggesting a negative role of BPA in female reproductive health. <https://doi.org/10.3390/jcm11237227>

Do phthalates and their metabolites cause poor semen quality? A systematic review and meta-analysis of epidemiological studies on risk of decline in sperm quality,

WANG H. P., H. HE, Y. WEI, X. GAO, T. F. ZHANG and J. X. ZHAI,

Environmental Science and Pollution Research (A systematic review and meta-analysis were conducted to understand the association of phthalates and their metabolites with sperm quality in humans. By June 30, 2022, relevant literature on the effects of phthalates and their metabolites on sperm quality were searched and collected using three English-language databases including PubMed, Embase, and Web of Science. Two researchers independently screened literature, extracted data, and assessed risk of bias. Stata 11 and RevMan 5.3 were used to conduct meta-analysis, test publication bias, and sensitivity analysis. A total of 12 literature were included for meta-analysis, excluding literature with different effect sizes. The results of meta-analysis indicated that monobutyl phthalate (MBP) and monobenzyl phthalate (MBzP) in urine were negatively correlated with semen concentration, and the results were statistically significant (MBP, pooled odds ratio (OR), 95% confidence interval (CI): 2.186 (1.471, 3.248), $P < 0.05$) and (MBzP, pooled OR (95%CI): 1.882 (1.471, 3.248), $P < 0.05$). Furthermore, the level of Di-(2-ethylhexyl) phthalate (DEHP) in semen was negatively correlated with semen concentration and the combined effect size was (pooled correlation coefficients (r) (95%CI): -0.225 (-0.319, -0.192), $P < 0.05$). However, the associations between MBP and MBzP with sperm motility and sperm morphology were not statistically significant ($P > 0.05$). And there was also no significant correlation between monoethyl phthalate (MEP), monomethyl phthalate (MMP), and mono-2-ethylhexyl phthalate (MEHP) and semen parameters, including semen concentration, sperm motility, and sperm morphology ($P > 0.05$). In summary, this current study provides moderate-certainty evidence for the data demonstrated that is a negative correlation between urine MBP levels, urine MBzP levels, and semen DEHP levels with semen concentration. In the future, more longitudinal cohort studies are needed to help elucidate the overall association.

<https://doi.org/10.1007/s11356-022-24215-x>

Exposure to Bisphenol A Substitutes, Bisphenol S and Bisphenol F, and Its Association with Developing Obesity and Diabetes Mellitus: A Narrative Review,

ALHARBI H. F., R. ALGONAIMAN, R. ALDUWAYGHIRI, T. ALJUTAILY, R. M. ALGHESHAIRY, A. S. ALMUTAIRI, R. M. ALHARBI, L. A. ALFURAYH, A. A. ALSHAHWAN, A. F. ALSADUN and H. BARAKAT,

International Journal of Environmental Research and Public Health 19, no. 23 (Dec 2022),

Bisphenol A, a well-known endocrine-disrupting chemical, has been replaced with its analogs bisphenol S (BPS) and bisphenol F (BPF) over the last decade due to health concerns. BPS and BPF are present in relatively high concentrations in different products, such as food products, personal care products, and sales receipts. Both BPS and BPF have similar structural and chemical properties to BPA; therefore, considerable scientific efforts have investigated the safety of their exposure. In this review, we summarize the findings of relevant epidemiological studies investigating the association between urinary concentrations of BPS and/or BPF with the incidence of obesity or diabetes. The results showed that BPS and BPF were detected in many urinary samples at median concentrations ranging from 0.03 to 0.4 $\mu\text{g center dot L}^{-1}$. At this exposure level, BPS median urinary concentrations (0.4 $\mu\text{g center dot L}^{-1}$) were associated with the development of obesity. At a lower exposure level (0.1-0.03 $\mu\text{g center dot L}^{-1}$), two studies showed an association with developing diabetes. For BPF exposure, only one study showed an association with obesity. However, most of the reported studies only assessed BPS exposure levels. Furthermore, we also summarize the findings of experimental studies in vivo and in vitro regarding our aim; results support the possible obesogenic effects/metabolic disorders mediated by BPS and/or BPF exposure. Unexpectedly, BPS may promote worse obesogenic effects than BPA. In addition, the possible mode of action underlying the obesogenic effects of BPS might be attributed to various pathophysiological mechanisms, including estrogenic or androgenic activities, alterations in the gene expression of critical adipogenesis-related markers, and induction of oxidative stress and an inflammatory state. Furthermore, susceptibility to the adverse effects of BPS may be altered by sex differences according to the results of both epidemiological and experimental studies. However, the possible mode of action underlying these sex differences is still unclear. In conclusion, exposure to BPS or BPF may promote the development of obesity and diabetes. Future approaches are highly needed to assess the safety of BPS and BPF regarding their potential effects in promoting metabolic disturbances. Other studies in different populations and settings are highly suggested. <https://doi.org/10.3390/ijerph192315918>

Exposure to endocrine-disrupting chemicals and risk of gestational hypertension and preeclampsia: A systematic review and meta-analysis*,

HIRKE A., B. VARGHESE, S. VARADE and R. ADELA,

Environmental Pollution 317 (Jan 2023),

Prenatal exposure to endocrine-disrupting chemicals has been linked to gestational hypertension (GH) and preeclampsia (PE). However, the results were conflicting and inconclusive. We conducted a systematic review and meta-analysis for an overview of these relationships. We searched PubMed, and Google Scholar for studies investigating bisphenol A, phthalates, and per or poly-fluoroalkyl substances and GH or PE. Pooled odds ratio (OR) with a 95% confidence interval (CI) were calculated for risk estimate using the generic inverse variance method. A total of 14 studies were included in the present analysis. The pooled results demonstrated that perfluorooctanoic acid (PFOA, OR:1.20, 95% CI: 1.04, 1.39), perfluoro octane sulfonic acid (PFOS, (OR:1.23, 95% CI: 1.10, 1.38), and perfluorononanoic acid (PFNA, OR:1.20, 95% CI: 1.03, 1.40) were significantly associated with an increased risk of PE. There was no significant association observed with perfluoro hexane sulfonic acid (PFHxS), perfluoro decanoic acid (PFDA), perfluoro heptanoic acid (PFHpA), and perfluoro undecanoic acid (PFUnDA) and PE. For GH, a statistically significant positive association was found with PFOA (OR:1.18, 95% CI: 1.01, 1.39) and PFHxS (OR:1.15, 95% CI: 1.02, 1.29). Among various phthalates analysed only mono-ethyl phthalate (MEP, OR:1.37, 95% CI: 1.11, 1.70) showed an association with GH. From our analysis, bisphenol A exposure during pregnancy did not show a significant association with the risk of PE. Our findings indicated that exposure to PFASs such as PFOA, PFOS, and PFNA during pregnancy is associated with an increased risk of PE and PFOA and PFHxS with GH. We also found that MEP was associated with GH. Most of the results were unstable in sensitivity analysis. Since most of these associations have limited evidence, more research is needed to confirm these findings. <https://doi.org/10.1016/j.envpol.2022.120828>

Influence of BPA exposure, measured in saliva, on childhood weight,

HERAS-GONZALEZ L., D. ESPINO, M. J. JIMENEZ-CASQUET, A. LOPEZ-MORO, F. OLEA-SERRANO and M. MARISCAL-ARCAS,

Frontiers in Endocrinology 13 (Dec 2022),

IntroductionEndocrine disruptors such as bisphenol A (BPA), BPA glycidyl methacrylate, and other BPA acrylate-based derivatives have been related to type 2 diabetes, the metabolic syndrome, and obesity, among other metabolic disorders. The objective of this study is to examine the influence of BPA exposure by saliva analysis and daily physical activity on the risk of overweight/obesity in schoolchildren from southern Spain. MethodsThe study included 300 children (53.5% girls) aged 7-10 years. Participants completed a questionnaire with four sections: participant data, including demographic information and life and family habits; semi-quantitative food frequency questionnaire; anthropometric variables; and physical activity variables. All participants underwent dental examination, when the presence of sealants/composites in each tooth and other dental alterations was recorded, and samples of whole saliva were collected for UHPLC-MS/MS analyses. ResultsRisk of overweight/obesity was significantly influenced by body fat composition (OR = 10.77), not walking to and from school (OR = 1.38), lesser energy expenditure in sedentary activities (OR = 12.71), greater energy expenditure in sports (OR = 1.62), and exposure to BPA from dental sealants/composites (OR = 1.38; $p = 0.058$).

DiscussionFurther research is warranted on this issue in children, who may be especially vulnerable to the negative health effects of endocrine disruption. <https://doi.org/10.3389/fendo.2022.1040583>

Per- and polyfluoroalkyl substances (PFAS) exposure in melanoma patients: a retrospective study on prognosis and histological features,

DEL FIORE P., F. CAVALLIN, M. MAZZA, C. BENNA, A. DAL MONICO, G. TADIOTTO, I. RUSSO, B. FERRAZZI, S. TROPEA, A. BUJA, C. COZZOLINO, R. CAPPELLESO, L. NICOLE, L. PICCIN, J. PIGOZZO, V. CHIARION-SILENI, A. VECCHIATO, C. MENIN, F. BASSETTO, A. P. DEI TOS, M. ALAIBAC and S. MOCELLIN,

Environmental Health 21, no. 1 (Dec 2022),

Per- and polyfluoroalkyl substances (PFAS) are endocrine disrupting chemicals which could be associated with cancer development, such as kidney and testicular cancers, pancreatic and hepatocellular carcinoma and thyroid tumor. Available scientific literature offers no information on the role of PFAS in melanoma development/progression. Since 1965, a massive environmental contamination by PFAS has occurred in northeastern Italy. This study compared histopathology and prognosis between melanoma patients exposed ($n = 194$) and unexposed ($n = 488$) to PFAS. All patients were diagnosed and/or treated for melanoma at the Veneto Oncological Institute and the University Hospital of Padua (Italy) in 1998-2014. Patients were categorized in exposed or unexposed groups according to their home address and the geographical classification of municipalities affected by PFAS contamination as provided by Veneto Government in 2018. Presence of mitoses was found in 70.5% of exposed patients and 58.7% of unexposed patients ($p = 0.005$). Median follow-up was 90 months (IQR 59-136). 5-year overall survival was 83.7% in exposed patients and 88.0% in unexposed patients ($p = 0.20$); 5-year disease-specific survival was 88.0% in exposed patients and 90.9% in unexposed patients ($p = 0.50$); 5-year disease-free survival was 83.8% in exposed patients and 87.3% in unexposed patients ($p = 0.20$). Adjusting for imbalanced characteristics at baseline (presence of mitoses), survival was not statistically different between exposed and unexposed patients (overall survival: HR 1.10, 95% CI 0.77 to 1.58, $p = 0.57$; disease-specific survival: HR 0.99, 95% CI 0.62 to 1.59, $p = 0.99$; disease-free survival: HR 1.10, 95% CI 0.74 to 1.64, $p = 0.62$). Although the magnitude of PFAS exposure was not quantifiable, our findings suggested that exposure to PFAS was associated with higher level of mitosis in melanoma patients, but this did not translate into a survival difference. Further studies are required to investigate this relationship and all effects of PFAS on prognosis.

<https://doi.org/10.1186/s12940-022-00944-x>

Prenatal polycyclic aromatic hydrocarbon (PAH) exposure in relation to placental corticotropin releasing hormone (pCRH) in the CANDLE pregnancy cohort,

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Frontiers in Endocrinology 13 (Nov 2022),

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous endocrine-disrupting combustion by-products that have been linked to preterm birth. One possible mechanism is through disruption of placental corticotropin releasing hormone (pCRH), a key hormone implicated in parturition. As an extension of recent research identifying pCRH as a potential target of endocrine disruption, we examined maternal PAH exposure in relation

to pCRH in a large, diverse sample. Participants, drawn from the CANDLE cohort, part of the ECHO-PATHWAYS Consortium, completed study visits at 16-29 weeks (V1) and 22-39 weeks (V2) gestation (n=812). Seven urinary mono-hydroxylated PAH metabolites (OH-PAHs) were measured at V1 and serum pCRH at V1 and V2. Associations between individual log-transformed OH-PAHs (as well as two summed PAH measures) and log(pCRH) concentrations across visits were estimated using mixed effects models. Minimally-adjusted models included gestational age and urinary specific gravity, while fully-adjusted models also included sociodemographic characteristics. We additionally evaluated effect modification by pregnancy complications, fetal sex, and maternal childhood trauma history. We observed associations between 2-OH-Phenanthrene (2-OH-PHEN) and rate of pCRH change that persisted in fully adjusted models ($\beta=0.0009, 0.00006, 0.0017$), however, positive associations with other metabolites (most notably 3-OH-Phenanthrene and 1-Hydroxypyrene) were attenuated after adjustment for sociodemographic characteristics. Associations tended to be stronger at V1 compared to V2 and we observed no evidence of effect modification by pregnancy complications, fetal sex, or maternal childhood trauma history. In conclusion, we observed modest evidence of association between OH-PAHs, most notably 2-OH-PHEN, and pCRH in this sample. Additional research using serial measures of PAH exposure is warranted, as is investigation of alternative mechanisms that may link PAHs and timing of birth, such as inflammatory, epigenetic, or oxidative stress pathways. <https://doi.org/10.3389/fendo.2022.1011689>

Reduced Birth Weight and Exposure to Per- and Polyfluoroalkyl Substances: A Review of Possible Underlying Mechanisms Using the AOP-HelpFinder,

GUNDACKER C., K. AUDOUZE, R. WIDHALM, S. GRANITZER, M. FORSTHUBER, F. JORNOD, M. WIELSOE, M. LONG, T. I. HALLDORSSON, M. UHL and E. C. BONEFELD-JORGENSEN, *Toxics* 10, no. 11 (Nov 2022),

Prenatal exposure to per- and polyfluorinated substances (PFAS) may impair fetal growth. Our knowledge of the underlying mechanisms is incomplete. We used the Adverse Outcome Pathway (AOP)-helpFinder tool to search PubMed for studies published until March 2021 that examined PFAS exposure in relation to birth weight, oxidative stress, hormones/hormone receptors, or growth signaling pathways. Of these 1880 articles, 106 experimental studies remained after abstract screening. One clear finding is that PFAS are associated with oxidative stress in in vivo animal studies and in vitro studies. It appears that PFAS-induced reactive-oxygen species (ROS) generation triggers increased peroxisome proliferator-activated receptor (PPAR)gamma expression and activation of growth signaling pathways, leading to hyperdifferentiation of pre-adipocytes. Fewer proliferating pre-adipocytes result in lower adipose tissue weight and in this way may reduce birth weight. PFAS may also impair fetal growth through endocrine effects. Estrogenic effects have been noted in in vivo and in vitro studies. Overall, data suggest thyroid-damaging effects of PFAS affecting thyroid hormones, thyroid hormone gene expression, and histology that are associated in animal studies with decreased body and organ weight. The effects of PFAS on the complex relationships between oxidative stress, endocrine system function, adipogenesis, and fetal growth should be further explored. <https://doi.org/10.3390/toxics10110684>

Serum multiple organochlorine pesticides in relation to testosterone concentrations among Chinese men from an infertility clinic,

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Background: Organochlorine pesticides (OCPs) are endocrine-disrupting chemicals and may alter male reproductive hormone concentrations. Objective: To explore the associations between multiple OCP exposures and serum testosterone concentrations among Chinese men. Methods: We investigated 421 men who provided serum samples from an infertility clinic in Wuhan, China. Each man completed a questionnaire concerning demographic characteristics and lifestyle habits. Serum concentrations of 18 OCPs and total testosterone were measured. Linear regression models were used to explore whether serum OCP levels were associated with altered testosterone concentrations, and potential effect modifications by age and body mass index (BMI) were also examined. Results: After adjusting for potential confounders, elevated dieldrin and p,p'-DDD levels had monotonically negative and positive exposure-response associations with testosterone concentrations, respectively (-30.98 ng/dL, 95% CI: -72.34, 10.37; P for trend = 0.12 and 41.31 ng/dL, 95% CI: -0.32, 82.93; P for trend = 0.06 for the highest vs. non-detectable exposure category, respectively). After stratification by age and BMI, dieldrin in relation to decreased testosterone concentrations was more pronounced among men aged <30 years old, and p, p'-DDD in relation to increased testosterone concentrations was stronger among men aged ≥ 30 years old and among men with a BMI <24 kg/m², though the differences were not statistically significant.

Conclusion: The study found evidence that serum dieldrin and p,p'-DDD concentrations might be associated with altered serum testosterone concentrations. <https://doi.org/10.1016/j.chemosphere.2022.134469>

Susceptibility of male reproductive system to bisphenol A, an endocrine disruptor: Updates from epidemiological and experimental evidence,

YADAV S. K., V. BIJALWAN, S. YADAV, K. SARKAR, S. DAS and D. P. SINGH,

Journal of Biochemical and Molecular Toxicology (Bisphenol A (BPA) is an omnipresent environmental pollutant. Despite being restrictions in-force for its utilization, it is widely being used in the production of polycarbonate plastics and epoxy resins. Direct, low-dose, and long-term exposure to BPA is expected when they are used in the packaging of food products and are used as containers for food consumption. Occupationally, workers are typically exposed to BPA at higher levels and for longer periods during the manufacturing process. BPA is a known endocrine disruptor chemical (EDC), that causes male infertility, which has a negative impact on human life from emotional, physical, and societal standpoints. To minimize the use of BPA in numerous consumer products, efforts and regulations are being made. Despite legislative limits in numerous nations, BPA is still found in consumer products. This paper examines BPA's overall male reproductive toxicity, including its impact on the hypothalamic-pituitary-testicular (HPT) axis, hormonal homeostasis, testicular steroidogenesis, sperm parameters, reproductive organs, and antioxidant defense system. Furthermore, this paper highlighted the role of non-monotonic dose-response (NMDR) in BPA exposure, which will help to improve the overall understanding of the harmful effects of BPA on the male reproductive system. <https://doi.org/10.1002/jbt.23292>

Temporal trends in sperm count: a systematic review and meta-regression analysis of samples collected globally in the 20th and 21st centuries,

LEVINE H., N. JØRGENSEN, A. MARTINO-ANDRADE, J. MENDIOLA, D. WEKSLER-DERRI, M. JOLLES, R. PINOTTI and S. H. SWAN,

Human Reproduction Update (2022),

Numerous studies have reported declines in semen quality and other markers of male reproductive health. Our previous meta-analysis reported a significant decrease in sperm concentration (SC) and total sperm count (TSC) among men from North America–Europe–Australia (NEA) based on studies published during 1981–2013. At that time, there were too few studies with data from South/Central America–Asia–Africa (SAA) to reliably estimate trends among men from these continents. The aim of this study was to examine trends in sperm count among men from all continents. The broader implications of a global decline in sperm count, the knowledge gaps left unfilled by our prior analysis and the controversies surrounding this issue warranted an up-to-date meta-analysis. We searched PubMed/MEDLINE and EMBASE to identify studies of human SC and TSC published during 2014–2019. After review of 2936 abstracts and 868 full articles, 44 estimates of SC and TSC from 38 studies met the protocol criteria. Data were extracted on semen parameters (SC, TSC, semen volume), collection year and covariates. Combining these new data with data from our previous meta-analysis, the current meta-analysis includes results from 223 studies, yielding 288 estimates based on semen samples collected 1973–2018. Slopes of SC and TSC were estimated as functions of sample collection year using simple linear regression as well as weighted meta-regression. The latter models were adjusted for predetermined covariates and examined for modification by fertility status (unselected by fertility versus fertile), and by two groups of continents: NEA and SAA. These analyses were repeated for data collected post-2000. Multiple sensitivity analyses were conducted to examine assumptions, including linearity. Overall, SC declined appreciably between 1973 and 2018 (slope in the simple linear model: -0.87 million/ml/year, 95% CI: -0.89 to -0.86 ; $P < 0.001$). In an adjusted meta-regression model, which included two interaction terms [time $\times$ fertility group ($P = 0.012$) and time $\times$ continents ($P = 0.058$)], declines were seen among unselected men from NEA (-1.27 ; -1.78 to -0.77 ; $P < 0.001$) and unselected men from SAA (-0.65 ; -1.29 to -0.01 ; $P = 0.045$) and fertile men from NEA (-0.50 ; -1.00 to -0.01 ; $P = 0.046$). Among unselected men from all continents, the mean SC declined by 51.6% between 1973 and 2018 (-1.17 ; -1.66 to -0.68 ; $P < 0.001$). The slope for SC among unselected men was steeper in a model restricted to post-2000 data (-1.73 ; -3.23 to -0.24 ; $P = 0.024$) and the percent decline per year doubled, increasing from 1.16% post-1972 to 2.64% post-2000. Results were similar for TSC, with a 62.3% overall decline among unselected men (-4.70 million/year; -6.56 to -2.83 ; $P < 0.001$) in the adjusted meta-regression model. All results changed only minimally in multiple sensitivity analyses. This analysis is the first to report a decline in sperm count among unselected men from South/Central America–Asia–Africa, in contrast to our previous meta-analysis that was underpowered to examine those continents. Furthermore, data suggest that this world-wide decline is continuing in the 21st century at an accelerated pace. Research on the causes of this continuing

decline and actions to prevent further disruption of male reproductive health are urgently needed.

<https://doi.org/10.1093/humupd/dmac035>

Urinary Concentrations of Endocrine-Disrupting Metals and Prevalent Breast Cancer in US Women,

BELL B. C., J. M. ZHU and Y. D. WEI,

Biological Trace Element Research (The toxic metals cadmium, lead, and mercury are endocrine-disrupting agents that could produce estrogenic effects involving breast carcinogenesis. In this study, we further explored the relationship between exposure to these metals and prevalent breast cancer among female participants, aged 20 years or older, in the 2007-2016 National Health and Nutrition Examination Survey (NHANES). Exposure was determined by measuring urinary concentrations of metals using inductively coupled plasma mass spectrometry. Urine creatinine-corrected concentrations of metals were calculated for each study participant. Multivariate logistic regression models were constructed to examine the association between urinary metals and prevalent breast cancer, adjusting for potential confounders. Of the 3352 study participants, 106 had been diagnosed with breast cancer (weighted prevalence, 3.13%). The results show that women with breast cancer had significantly higher urinary concentrations of lead and cadmium (both $p < 0.0001$) than those without breast cancer. After adjusting for all the covariates included in the study, however, only urinary lead was shown to be significantly associated with increased prevalence of breast cancer, with an odds ratio of 2.95 (95% CI: 1.13, 7.70) in the highest quartile of urinary lead concentrations (≥ 0.71 $\mu\text{g/g}$ creatinine) as compared with the lowest quartile. No statistically significant associations were observed between urine cadmium or mercury levels and breast cancer. This study demonstrates a potential association between lead exposure and prevalent breast cancer among US women. Prospective and mechanistic studies are warranted to further investigate this interaction and explore the role of lead in breast carcinogenesis. <https://doi.org/10.1007/s12011-022-03512-z>

What Happens In Utero Does Not Stay In Utero: a Review of Evidence for Prenatal Epigenetic Programming by Per- and Polyfluoroalkyl Substances (PFAS) in Infants, Children, and Adolescents,

PERNG W., D. NAKIWALA and J. M. GOODRICH,

Current Environmental Health Reports (Purpose of Review Review human literature on the relationship between prenatal exposure to per- and polyfluoroalkyl substances (PFAS) and epigenetic modifications in infants, children, and adolescents < 18 years of age. Recent Findings Eleven studies were identified, with study populations located in the U.S., Taiwan, Japan, and the Kingdom of Denmark. Many studies ($n = 5$) were cross-sectional, with PFAS exposure and epigenetic outcomes measured in the same tissue collected at delivery via cord blood or dried newborn blood spots. The other six studies were prospective, with prenatal PFAS measured on maternal blood during pregnancy and DNA methylation (DNAm) assessed in cord blood and childhood peripheral leukocytes ($n = 1$ study). Epigenetic marks of interest included global DNAm measures (LINE-1, Alu, and an ELISA-based method), candidate genes (IFG2, H19, and MEST), and epigenome-wide DNA methylation via array-based methods (Infinium 450 K and EPIC). Two studies using array-based methods employed discovery and validation paradigms, in which a small subset of loci ($n = 6$ and $n = 4$) were replicated in the discovery population. One site (TNXB) was a hit in two independent studies. Collectively, loci associated with PFAS were in regions involved in growth and development, lipid metabolism, and nutrient metabolism. There is moderate human evidence supporting associations of prenatal PFAS exposure on DNAm at birth, with one study suggesting sustained effects into childhood. Future studies are warranted to link PFAS-associated DNAm to health outcomes, as well as to investigate the role of other epigenetic marks such as hydroxymethylation, miRNA expression, and histone modifications. <https://doi.org/10.1007/s40572-022-00387-z>

Toxicité sur l'homme

Bitter Taste Receptors and Endocrine Disruptors: Cellular and Molecular Insights from an In Vitro Model of Human Granulosa Cells,

LUONGO F. P., S. PASSAPONTI, A. HAXHIU, M. RAEISPOUR, G. BELMONTE, L. GOVERNINI, L. CASARINI, P. PIOMBONI and A. LUDDI,

International Journal of Molecular Sciences 23, no. 24 (Dec 2022),

Endocrine disrupting chemicals (EDCs) are compounds that interfere with the synthesis, transport and binding action of hormones responsible for reproduction and homeostasis. Some EDCs compounds are activators of Taste bitter Receptors, a subclass of taste receptors expressed in many extraoral locations, including sperm and follicular somatic cells. This makes TAS2Rs attractive molecules to study and investigate to shed light on the effect of EDCs on female reproduction and fertility. This study aims to assess the effect of selected EDCs [namely Biochanin A (BCA), caffeine, Daidzein, Genistein and Isoflavone] on hGL5, an immortalized cell line exhibiting characteristics coherent with primary follicular granulosa cells. After demonstrating that this model expresses all the TAS2Rs (TAS2R3, TAS2R4, TAS2R14, TAS2R19, TAS2R43) specifically expressed by the primary human granulosa cells, we demonstrated that BCA and caffeine significantly affect mitochondrial footprint and intracellular lipid content, indicating their contribution in steroidogenesis. Our results showed that bitter taste receptors may be involved in steroidogenesis, thus suggesting an appealing mechanism by which these compounds affect the female reproductive system. <https://doi.org/10.3390/ijms232415540>

Consequences of the exposome to gestational diabetes mellitus,

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Biochimica Et Biophysica Acta-General Subjects 1867, no. 2 (Feb 2023),

The exposome is the cumulative measure of environmental influences and associated biological responses throughout the lifespan, including those from the environment, diet, behaviour, and endogenous processes. The exposome concept and the 2030 Agenda for the Sustainable Development Goals (SDGs) from the United Nations are the basis for understanding the aetiology and consequences of non-communicable diseases, including gestational diabetes mellitus (GDM). Pregnancy may be developed in an environment with adverse factors part of the immediate internal medium for fetus development and the external medium to which the pregnant woman is exposed. The placenta is the interface between maternal and fetal compartments and acts as a protective barrier or easing agent to transfer exposome from mother to fetus. Under and over-nutrition in utero, exposure to adverse environmental pollutants such as heavy metals, endocrine-disrupting chemicals, pesticides, drugs, pharmaceuticals, lifestyle, air pollutants, and tobacco smoke plays a determinant role in the development of GDM. This phenomenon is worsened by metabolic stress postnatally, such as obesity which increases the risk of GDM and other diseases. Clinical risk factors for GDM development include its aetiology. It is proposed that knowledge-based interventions to change the potential interdependent ecto-exposome and endo-exposome could avoid the occurrence and consequences of GDM.

<https://doi.org/10.1016/j.bbagen.2022.130282>

Effects of endocrine disrupting chemicals on the expression of RACK1 and LPS-induced THP-1 cell activation,

MASI M., A. MADDALON, M. IULINI, P. LINCiano, V. GALBIATI, M. MARINOVICH, M. RACCHI, E. CORSINI and E. BUOSO,

Toxicology 480 (Oct 2022),

The existence of a complex hormonal balance among glucocorticoids, androgens and estrogens involved in the regulation of Receptor for Activated C Kinase 1 (RACK1) expression and its related immune cells activation, highlights the possibility to employ this protein as screening tool for the evaluation of the immunotoxic profile of endocrine disrupting chemicals (EDCs), hormone-active substances capable of interfering with the physiologic hormonal signaling. Hence, the aim of this work was to investigate the effect of the exposure of EDCS 17 alpha-ethynylestradiol (EE), diethyl phthalate (DEP) and perfluorooctanesulfonic acid (PFOS) on RACK1 expression and on lipopolysaccharide (LPS)-induced activation of the human monocytic cell line THP-1, a validated model for

this investigation. In line with our previous results with estrogen-active compounds, EE treatment significantly induced RACK1 promoter transcriptional activity, mRNA expression, and protein levels, which paralleled an increase in LPS-induced IL-8, TNF-alpha production and CD86 expression, previously demonstrated to be dependent on RACK1/PKC beta activation. EE mediates its effect on RACK1 expression through G-protein-coupled estrogen receptor (GPER) and androgen receptor (AR) ligand-independent cascade, as also suggested by in silico molecular docking simulation. Conversely, DEP and PFOS induced a dose-dependent downregulation of RACK1 promoter transcriptional activity, mRNA expression, and protein levels, which was mirrored by a reduction of IL-8, TNF-alpha production and CD86 expression. Mifepristone pre-treatments abolish DEP and PFOS effects, confirming their GR agonist profile, also corroborated by molecular docking. Altogether, our data confirm that RACK1 represents an interesting target of steroid active compounds, which expression offers the opportunity to screen the immunotoxic potential of different hormone-active substances of concerns due to their human exposure and environmental persistence. <https://doi.org/10.1016/j.tox.2022.153321>

The effects of endocrine-disrupting chemicals on ovarian- and ovulation-related fertility outcomes,

LAND K. L., F. G. MILLER, A. C. FUGATE and P. R. HANNON,

Molecular Reproduction and Development (Exposure to endocrine-disrupting chemicals (EDCs) is unavoidable, which represents a public health concern given the ability of EDCs to target the ovary. However, there is a large gap in the knowledge about the impact of EDCs on ovarian function, including the process of ovulation. Defects in ovulation are the leading cause of infertility in women, and EDC exposures are contributing to the prevalence of infertility. Thus, investigating the effects of EDCs on the ovary and ovulation is an emerging area for research and is the focus of this review. The effects of EDCs on gametogenesis, uterine function, embryonic development, and other aspects of fertility are not addressed to focus on ovarian- and ovulation-related fertility issues. Herein, findings from epidemiological and basic science studies are summarized for several EDCs, including phthalates, bisphenols, per- and poly-fluoroalkyl substances, flame retardants, parabens, and triclosan. Epidemiological literature suggests that exposure is associated with impaired fecundity and in vitro fertilization outcomes (decreased egg yield, pregnancies, and births), while basic science literature reports altered ovarian follicle and corpora lutea numbers, altered hormone levels, and impaired ovulatory processes. Future directions include identification of the mechanisms by which EDCs disrupt ovulation leading to infertility, especially in women. <https://doi.org/10.1002/mrd.23652>

Endocrine-disrupting chemicals (EDCs) and cancer: new perspectives on an old relationship,

MODICA R., E. BENEVENTO and A. COLAO,

Journal of Endocrinological Investigation (Purpose Environmental endocrine-disrupting chemicals (EDCs) are a mixture of chemical compounds capable to interfere with endocrine axis at different levels and to which population is daily exposed. This paper aims to review the relationship between EDCs and breast, prostate, testicle, ovary, and thyroid cancer, discussing carcinogenic activity of known EDCs, while evaluating the impact on public health. Methods A literature review regarding EDCs and cancer was carried out with particular interest on meta-analysis and human studies. Results The definition of EDCs has been changed through years, and currently there are no common criteria to test new chemicals to clarify their possible carcinogenic activity. Moreover, it is difficult to assess the full impact of human exposure to EDCs because adverse effects develop latently and manifest at different ages, even if preclinical and clinical evidence suggest that developing fetus and neonates are most vulnerable to endocrine disruption. Conclusion EDCs represent a major environmental and health issue that has a role in cancer development. There are currently some EDCs that can be considered as carcinogenic, like dioxin and cadmium for breast and thyroid cancer; arsenic, asbestos, and dioxin for prostate cancer; and organochlorines/organohalogens for testicular cancer. New evidence supports the role of other EDCs as possible carcinogenic and pregnant women should avoid risk area and exposure. The relationship between EDCs and cancer supports the need for effective prevention policies increasing public awareness. <https://doi.org/10.1007/s40618-022-01983-4>

Evolutionary Implications of Environmental Toxicant Exposure,

BOLOGNESI G., M. G. BACALINI, C. PIRAZZINI, P. GARAGNANI and C. GIULIANI,

Biomedicines 10, no. 12 (Dec 2022),

Homo sapiens have been exposed to various toxins and harmful compounds that change according to various phases of human evolution. Population genetics studies showed that such exposures lead to adaptive genetic

changes; while observing present exposures to different toxicants, the first molecular mechanism that confers plasticity is epigenetic remodeling and, in particular, DNA methylation variation, a molecular mechanism proposed for medium-term adaptation. A large amount of scientific literature from clinical and medical studies revealed the high impact of such exposure on human biology; thus, in this review, we examine and infer the impact that different environmental toxicants may have in shaping human evolution. We first describe how environmental toxicants shape natural human variation in terms of genetic and epigenetic diversity, and then we describe how DNA methylation may influence mutation rate and, thus, genetic variability. We describe the impact of these substances on biological fitness in terms of reproduction and survival, and in conclusion, we focus on their effect on brain evolution and physiology. <https://doi.org/10.3390/biomedicines10123090>

Exposure to Pollutants with Endocrine Disrupting Properties Is Associated with Early Cartilage Defects and Chondrocyte Inflammatory and Oxidative Activation,

BERKANI S., I. KOUKI, S. BABAJKO, A. PIGENET, P. NATARAJAN, P. ORDOUKHANIAN, X. HOUARD, M. LOTZ, B. DEMENEIX, J. B. FINI, F. BERENBAUM, J. SELLAM and A. COURTIES,
Arthritis & Rheumatology 74 (Sep 2022): 33-35,

Identification of biomarkers and outcomes of endocrine disruption in human ovarian cortex using In Vitro Models,

LI T., P. VAZAKIDOU, P. E. G. LEONARDS, A. DAMDIMOPOULOS, E. M. PANAGIOTOU, C. ARNELO, K. JANSSON, K. PETTERSSON, K. PAPAICONOMOU, M. VAN DUURSEN and P. DAMDIMOPOULOU,
Toxicology 485 (2023/02/01/ 2023): 153425,

Endocrine disrupting chemicals (EDCs) are raising concerns about adverse effects on fertility in women. However, there is a lack of information regarding mechanisms and effects in humans. Our study aims to identify mechanisms of endocrine disruption using two EDCs, diethylstilbestrol (DES) and ketoconazole (KTZ). Human ovarian cortical tissue obtained from Caesarean section patients was exposed to 10⁻⁹ M - 10⁻⁵ M KTZ and 10⁻¹⁰ M - 10⁻⁶ M DES in vitro for 6 days. Follicle survival and growth were studied via histology analysis and liquid-chromatography-mass spectrometry-based steroid quantification. RNA-sequencing was performed on COV434, KGN, and primary ovarian cells that were exposed for 24 h. Significantly lower unilaminar follicle densities were observed in DES 10⁻¹⁰ M group, whereas low KTZ exposure reduced secondary follicle density. KTZ 10⁻⁵ M reduced levels of pregnenolone and progesterone. RNA-sequencing revealed that 445 and 233 differentially expressed genes (false discovery rate < 0.1) altogether in DES and KTZ exposed groups. Gene set variation analysis showed that both chemicals modulated pathways that are important for folliculogenesis and steroidogenesis. We selected stearoyl-CoA desaturase (SCD) and 7-dehydrocholesterol reductase (DHCR7) for further validation. Up-regulation of both genes in response to KTZ was confirmed by qPCR and in situ RNA hybridization. Further validation with immunofluorescence focused on the expression of SCD in growing follicles in exposed ovarian tissue. In conclusion, SCD may serve as a potential novel human-relevant biomarker of EDC exposure and effects on ovaries.

<https://doi.org/https://doi.org/10.1016/j.tox.2023.153425>

An insight into bisphenol A, food exposure and its adverse effects on health: A review,

MANZOOR M. F., T. TARIQ, B. FATIMA, A. SAHAR, F. TARIQ, S. MUNIR, S. KHAN, M. RANJHA, A. SAMEEN, X. A. ZENG and S. A. IBRAHIM,
Frontiers in Nutrition 9 (Nov 2022),

Bisphenol A (BPA) is a synthetic chemical widely employed to synthesize epoxy resins, polymer materials, and polycarbonate plastics. BPA is abundant in the environment, i.e., in food containers, water bottles, thermal papers, toys, medical devices, etc., and is incorporated into soil/water through leaching. Being a potent endocrine disrupter, and has the potential to alter several body mechanisms. Studies confirmed its anti-androgen action and estrogen-like effects, which impart many negative health impacts, especially on the immune system, neuroendocrine process, and reproductive mechanism. Moreover, it can also induce mutagenesis and carcinogenesis, as per recent scientific research. This review focuses on BPA's presence and concentrations in different environments, food sources and the basic mechanisms of BPA-induced toxicity and health disruptions. It is a unique review of its type because it focuses on the association of cancer, hormonal disruption, immunosuppression, and infertility with BPA. These issues are widespread today, and BPA significantly contributes to their incidence because of its wide usage in daily life utensils and other accessories.

The review also discusses researched-based measures to cope with the toxic chemical.

<https://doi.org/10.3389/fnut.2022.1047827>

Mechanisms of Male Reproductive Toxicity of Polybrominated Diphenyl Ethers,

AROWOLO O., J. R. PILSNER, O. SERGEYEV and A. SUVOROV,

International Journal of Molecular Sciences 23, no. 22 (Nov 2022),

Polybrominated diphenyl ethers (PBDE) are a group of flame retardants used in a variety of artificial materials. Despite being phased out in most industrial countries, they remain in the environment and human tissues due to their persistence, lipophilicity, and bioaccumulation. Populational and experimental studies demonstrate the male reproductive toxicity of PBDEs including increased incidence of genital malformations (hypospadias and cryptorchidism), altered weight of testes and other reproductive tissues, altered testes histology and transcriptome, decreased sperm production and sperm quality, altered epigenetic regulation of developmental genes in spermatozoa, and altered secretion of reproductive hormones. A broad range of mechanistic hypotheses of PBDE reproductive toxicity has been suggested. Among these hypotheses, oxidative stress, the disruption of estrogenic signaling, and mitochondria disruption are affected by PBDE concentrations much higher than concentrations found in human tissues, making them unlikely links between exposures and adverse reproductive outcomes in the general population. Robust evidence suggests that at environmentally relevant doses, PBDEs and their metabolites may affect male reproductive health via mechanisms including AR antagonism and the disruption of a complex network of metabolic signaling.

<https://doi.org/10.3390/ijms232214229>

The p-Phthalates Terephthalic Acid and Dimethyl Terephthalate Used in the Manufacture of PET Induce In Vitro Adipocytes Dysfunction by Altering Adipogenesis and Thermogenesis Mechanisms,

MOLONIA M. S., C. MUSCARA, A. SPECIALE, F. L. SALAMONE, G. TOSCANO, A. SAIJA and F. CIMINO,

Molecules 27, no. 21 (Nov 2022),

Public health concerns associated with the potential leaching of substances from Polyethylene terephthalate (PET) packaging have been raised due to the role of phthalates as endocrine-disrupting chemicals or obesogens. In particular, changes in the environment such as pH, temperature, and irradiation can improve contaminant migration from PET food packaging. In this study, the in vitro effects of p-phthalates terephthalic acid (TPA) and dimethyl terephthalate (DMT) on murine adipocytes (3T3-L1) were evaluated using concentrations that might be obtained in adult humans exposed to contaminated sources. TPA and, in particular, DMT exposure during 3T3-L1 differentiation increased the cellular lipid content and induced adipogenic markers PPAR-gamma, C/EBP α , FABP4, and FASN, starting from low nanomolar concentrations. Interestingly, the adipogenic action of TPA- and DMT-induced PPAR-gamma was reverted by ICI 182,780, a specific antagonist of the estrogen receptor. Furthermore, TPA and DMT affected adipocytes' thermogenic program, reducing pAMPK and PGC-1 α levels, and induced the NF-kappa B proinflammatory pathway. Given the observed effects of biologically relevant chronic concentrations of these p-phthalates and taking into account humans' close and constant contact with plastics, it seems appropriate that ascertaining safe levels of TPA and DMT exposure is considered a high priority. <https://doi.org/10.3390/molecules27217645>

Rapid and reagent-free bioassay using autoluminescent yeasts to detect agonistic and antagonistic activities of bisphenols against rat androgen receptor and progesterone receptor,

HUANG Y., W. ZHANG, C. D. ZHANG, N. CUI, Z. M. XIAO, R. G. WANG and X. O. SU,

Journal of Steroid Biochemistry and Molecular Biology 222 (Sep 2022),

Bisphenol A (BPA) and its analogues have been classified as endocrine disruptors via binding to nuclear receptors. Two novel bioassays, BLYrARS and BLYrPRS, were developed for rapid detection of agonistic and antagonistic activities of BPA and five of its analogues binding rat androgen receptor (rAR) and rat progesterone receptor (rPR). The reporter bioassay was based on two autonomously bioluminescent strains of the yeast *Saccharomyces cerevisiae*, recombined with a bacterial luciferase reporter gene cassette (lux) that can produce autofluorescence, regulated by the corresponding hormone response element acting as the responsive promoter. The bioluminescent signal is autonomous and continuous without cell lysis or addition of exogenous reagents. The AR agonist R1881 could be detected at 4 h with a half-maximal effective concentration (EC₅₀) of -9.4 nM. The PR agonist progesterone could be determined at 4 h with an EC₅₀ of -2.74 nM. None of the sixteen bisphenols presented agonistic activities against rAR and rPR. However, thirteen BPs were rAR antagonists and

eleven BPs acted as rPR antagonists with different potency. The BLYrARS and BLYrPRS bioassay characterized by automated signal acquisition without additional manipulations or cost can be applied for simple and rapid detection of agonistic and antagonistic activities of BPs and other compounds acting as agonists or antagonists of rAR and rPR. Based on data derived by use of this bioassay endocrine-disrupting activities of some BPA analogues are more potent than BPA. <https://doi.org/10.1016/j.jsbmb.2022.106151>

Redox Status, Estrogen and Progesterone Production by Swine Granulosa Cells Are Impaired by Triclosan,
BASINI G., F. GRASELLI, F. QUINTAVALLA, S. BUSSOLATI, V. ANDREOLI, A. M. C. HEREDERO and S. BERTINI,
Animals 12, no. 24 (Dec 2022),

Simple Summary Triclosan is widely used in cosmetics and hygiene products, including anti-bacterial hand sanitizers and disinfectants whose utilization has been greatly increased during the COVID-19 pandemic. Since critical health effects have been demonstrated for this substance we tested its potential harmful action on ovarian cells collected from pigs, a valuable animal model. We demonstrated that Triclosan impairs cell function, thus suggesting an impairment of reproductive function. Triclosan is a chlorinated biphenolic with a broad spectrum of antiseptic activities used in cosmetics and hygiene products. Continuous exposure can lead to absorption and bioaccumulation of this substance with harmful health effects. In fact, previous studies have shown that Triclosan acts as an endocrine-disrupting chemical on reproductive organs, with consequent negative effects on reproductive physiology. Therefore, to assess potential adverse impacts on fertility, we tested Triclosan on swine granulosa cells, a model of endocrine reproductive cells. We examined its effects on the main features of granulosa cell functions such as cell growth (BrdU incorporation and ATP production) and steroidogenesis (17-beta estradiol and progesterone secretion). Moreover, since oxidant-antioxidant balance plays a pivotal role in follicular function, redox status markers (superoxide, hydrogen peroxide and nitric oxide production, enzymatic and non-enzymatic scavenging activity) were studied. Our results show that Triclosan significantly inhibits cell growth ($p < 0.001$), steroidogenesis ($p < 0.001$), superoxide and nitric oxide production ($p < 0.001$), while it increases ($p < 0.05$) enzymatic defense systems. Collectively, these data suggest a disruption of the main granulosa cell functions, i.e., proliferation and hormone production, as well as an imbalance in redox status. On these bases, we can speculate that Triclosan would impair granulosa cell functions, thus exerting negative effects on reproductive function. Further studies are needed to explore lower Triclosan concentrations and to unravel its mechanisms of action at gene level. <https://doi.org/10.3390/ani12243559>

A scientometric analysis of research trends on emerging contaminants in the field of cancer in 2012-2021,
ZHENG D. T., L. Z. CHEN, H. T. TIAN, Q. P. YANG, J. Y. WU, Z. Q. JI, J. H. CAI, Y. X. CHEN and Z. Y. LI,
Frontiers in Public Health 10 (Nov 2022),

Introduction Recently, emerging contaminants have been discovered in the aquatic environment that can cause a range of human diseases, including cancer. In this study, our scientometric analysis provides a comprehensive overview of emerging contaminants and cancer research from 2012 to 2021. Methods The Web of Science Core Collection Database was used to retrieve all related publications. The bibliometrix R-package, CiteSpace, and VOSviewer were applied to collect information on annual citations and publications, famous journals and authors, the most productive countries and organizations, popular topics, and keywords. Results A total of 2378 publications were retrieved. The publication's output showed a gradual upward trend from 2012 to 2021. The most-cited paper was a review article by Vandenberg et al. that was published in 2012. According to the analysis results, the United States published the most articles. The closest collaboration was between the United States and China. Environmental Research and Science of The Total Environment published the most paper. It was Choi KC who was the most productive and had the highest h-index, g-index, and m-index among the authors. The most frequently used keywords were "exposure," "endocrine-disrupting chemicals," "endocrine disruptors," "cancer," "bisphenol-a," and so on. Discussion Emerging contaminants play a significant role in cancer development. However, most studies are conducted in vivo with human cells or animal models, and relatively few are on human models. The scientometric analysis offers researchers a clear picture of the current state of research and hotspots in this field. From our study, researchers may find some hotspots that merit in-depth investigation. <https://doi.org/10.3389/fpubh.2022.1034585>

Thyroid Carcinoma: A Review for 25 Years of Environmental Risk Factors Studies,

KRUGER E., E. A. TORAIH, M. H. HUSSEIN, S. A. SHEHATA, A. WAHEED, M. S. FAWZY and E. KANDIL,
Cancers 14, no. 24 (Dec 2022),

Simple Summary Increasing awareness of thyroid cancer-related environmental risk factors is considered an essential tool for cancer prevention through risk prevention/management. Various studies have identified correlations between environmental pollutants and thyroid cancer incidence rates, and others have proposed mechanisms for thyroid cancer development. This review seeks to consolidate the known environmental risk factors contributing to thyroid carcinoma to ensure that future research endeavors may identify key focus areas. These factors have been established as contributors to the development of thyroid carcinoma and thus require further investigation to establish mechanisms by which they act and influence thyroid pathology. Identifying pathophysiology involving these environmental risk factors can allow more rapid development of hazard reduction plans, exposure remedies, and medical treatments to prevent and perhaps even reverse disease course. Environmental factors are established contributors to thyroid carcinomas. Due to their known ability to cause cancer, exposure to several organic and inorganic chemical toxicants and radiation from nuclear weapons, fallout, or medical radiation poses a threat to global public health. Halogenated substances like organochlorines and pesticides can interfere with thyroid function. Like phthalates and bisphenolates, polychlorinated biphenyls and their metabolites, along with polybrominated diethyl ethers, impact thyroid hormones biosynthesis, transport, binding to target organs, and impair thyroid function. A deeper understanding of environmental exposure is crucial for managing and preventing thyroid cancer. This review aims to investigate the relationship between environmental factors and the development of thyroid cancer.

<https://doi.org/10.3390/cancers14246172>

Triclosan Reprograms Immunometabolism and Activates the Inflammasome in Human Macrophages,

YUAN P., F. G. SHEN, J. Q. ZHANG, S. H. OUYANG, Y. M. CHEN, W. ZOU and Q. X. ZHOU,

Environmental Science & Technology (To gather enough energy to respond to harmful stimuli, most immune cells quickly shift their metabolic profile. This process of immunometabolism plays a critical role in the regulation of immune cell function. Triclosan, a synthetic antibacterial component present in a wide range of consumer items, has been shown to cause immunotoxicity in a number of organisms. However, it is unclear whether and how triclosan impacts immunometabolism. Here, human macrophages were used as model cells to explore the modulatory effect of triclosan on immunometabolism. Untargeted metabolomics using integrated liquid chromatography-mass spectrometry (LC-MS) and gas chromatography-mass spectrometry (GC-MS) revealed that triclosan changed the global metabolic profile of macrophages. Furthermore, Seahorse energy analysis and ¹³C isotope-based metabolic flux analysis revealed that triclosan decreased mitochondrial respiratory activity and promoted a metabolic transition from oxidative phosphorylation to glycolysis. Triclosan also polarizes macrophages to the proinflammatory M1 phenotype and activates the nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing receptor 3 (NLRP3) inflammasome, which is consistent with triclosan-induced metabolic phenotypic modifications. Collectively, these findings showed that triclosan exposure at micromolar concentrations caused metabolic reprogramming in macrophages, which triggered an inflammatory response. These findings are important for understanding the immunotoxicity caused by triclosan, which is necessary for determining the risk posed by triclosan in the environment.

<https://doi.org/10.1021/acs.est.2c0525>

Xeno-Estrogenic Pesticides and the Risk of Related Human Cancers,

KUMAR V., C. S. YADAV and B. D. BANERJEE,

Journal of Xenobiotics 12, no. 4 (Dec 2022): 344-355,

In recent decades, "environmental xenobiotic-mediated endocrine disruption", especially by xeno-estrogens, has gained a lot of interest from toxicologists and environmental researchers. These estrogen-mimicking chemicals are known to cause various human disorders. Pesticides are the most heavily used harmful xenobiotic chemicals around the world. The estrogen-mimicking potential of the most widely used organochlorine pesticides is well established. However, their effect is not as clearly understood among the plethora of effects these persistent xenobiotics are known to pose on our physiological system. Estrogens are one of the principal risk modifiers of various disorders, including cancer, not only in women but in men as well. Despite the ban on these xenobiotics in some parts of the world, humans are still at apparent risk of exposure to these harmful chemicals as they are still widely persistent and likely to stay in our environment for a long time owing to their high chemical stability.

The present work intends to understand how these harmful chemicals may affect the risk of the development of estrogen-mediated human cancer. <https://doi.org/10.3390/jox12040024>

Evaluation de l'exposition

Exposure to Endocrine Disruptors (Di(2-Ethylhexyl)phthalate (DEHP) and Bisphenol A (BPA)) in Women from Different Residing Areas in Italy: Data from the LIFE PERSUADED Project,

CARLI F., S. TAIT, L. BUSANI, D. CIOCIARO, V. DELLA LATTA, A. P. PALA, A. DEODATI, A. RAFFAELLI, F. PRATESI, R. CONTE, F. MARANGHI, R. TASSINARI, E. FABBRI, G. TOFFOL, S. CIANFARANI, C. LA ROCCA, A. GASTALDELLI and L. P. P. GRP,

International Journal of Molecular Sciences 23, no. 24 (Dec 2022),

Phthalates and bisphenol A (BPA) are plasticizers used in many industrial products that can act as endocrine disruptors and lead to metabolic diseases. During the LIFE PERSUADED project, we measured the urinary concentrations of BPA and Di(2-ethylhexyl)phthalate (DEHP) metabolites in 900 Italian women representative of the Italian female adult population (living in the north, centre, and south of Italy in both rural and urban areas). The whole cohort was exposed to DEHP and BPA with measurable levels above limit of detection in more than 99% and 95% of the samples, respectively. The exposure patterns differed for the two chemicals in the three macro-areas with the highest urinary levels for DEHP in south compared to central and northern Italy and for BPA in northern compared to central and southern Italy. BPA levels were higher in women living in urban areas, whereas no difference between areas was observed for DEHP. The estimated daily intake of BPA was 0.11 $\mu\text{g/kg}$ per day, about 36-fold below the current temporary tolerable daily intake of 4 $\mu\text{g/kg}$ per day established by the EFSA in 2015. The analysis of cumulative exposure showed a positive correlation between DEHP and BPA. Further, the reduction of exposure to DEHP and BPA, through specific legislative measures, is necessary to limit the harmfulness of these substances. <https://doi.org/10.3390/ijms232416012>

Plasma bisphenol a and phthalate levels in children with cerebral palsy: a case-control study,

TEZOL O., S. S. YALCIN, A. YIRUN, A. B. OZYURT, C. OKUYAZ and P. ERKEKOGLU,

International Journal of Environmental Health Research (The case-control study aimed to evaluate potential sources of exposure and the plasma concentrations of bisphenol A (BPA) and phthalates in prepubertal children having cerebral palsy (CP) and healthy control. Blood samples of 68 CP and 70 controls were analyzed for BPA, di-(2-ethylhexyl)-phthalate (DEHP), mono-(2-ethylhexyl)-phthalate (MEHP), and dibutyl phthalate (DBP). BPA and DBP levels were similar in groups. The median DEHP and MEHP levels of the children with CP were significantly lower than those of the controls ($p = 0.035$, $p < 0.001$, respectively). Exposure to plastic food containers/bags, personal care hygiene products, household cleaners, wood/coal stove heating, and city water supplies were associated with increased odds of higher BPA and phthalate levels in children with CP. In conclusion, potential exposure sources for BPA and phthalates differ in children with CP and healthy controls, and children with CP are not exposed to higher levels of BPA and phthalates. <https://doi.org/10.1080/09603123.2022.2153811>

Méthodes

Capsule phase microextraction of six bisphenols from human breast milk using a monolithic polyethylene glycol sorbent-based platform prior to high performance liquid chromatography-photo-diode array detection determination,

ALAMPANOS V., A. KABIR, K. G. FURTON, I. PANDERI and V. SAMANIDOU,

Journal of Chromatography A 1685 (Dec 2022),

The determination of bisphenols in human breast milk is a matter of ongoing interest since it reveals the exposure levels in both lactating mothers, fetuses, and infants. Herein, capsule phase microextraction (CPME) is applied for the first time for the extraction of a mixture of bisphenols from human breast milk followed by their subsequent determination by high-performance liquid chromatography-photodiode array detection (HPLC-DAD). CPME is a recently introduced as an advanced micro preparative technique that meets the principles of Green Analytical Chemistry. Moreover, it integrates filtration, extraction and stir-ring mechanism into one single

device, a composite attribute that allows selective extraction of analytes without any sample cleanup and facilitates faster extraction kinetics, resulting in enhancing the performance of the equilibrium-based extraction techniques that ensure better reproducibility and operational simplicity. Among four tested CPME devices, the sol-gel poly(ethylene glycol) capsules showed the best extraction efficiency. Critical factors of the extraction performance were investigated and optimized. The developed CPME-HPLC-PDA method was validated. Limits of detection and quantification were 7.58 ng/mL and 25 ng/mL, respectively. Relative recoveries were estimated between 89.7 and 110.5%, while the RSD values were < 11% in all cases. CPME is poised to be a useful tool both for routine bioanalysis and research purposes. <https://doi.org/10.1016/j.chroma.2022.463615>

Comprehensive monitoring of a special mixture of prominent endocrine disrupting chemicals in human urine using a carefully adjusted hydrolysis of conjugates,

DENGHEL H. and T. GOEN,

Analytical and Bioanalytical Chemistry (Many xenobiotics were identified as possible endocrine disruptors during the last decades. Structural analogy of these substances to natural hormones may lead to agonists or antagonists of hormone receptors. For a comprehensive human biomonitoring of such substances, we developed a simple, reliable, and highly sensitive method for the simultaneous monitoring of the parameters bisphenol A, triclosan, methylparaben, ethylparaben, propylparaben, butylparaben, benzophenone-1, benzophenone-3, 3,5,6-trichloropyridin-2-ol, p-nitrophenol, genistein, and daidzein in urine. Thereby, optimization of the enzymatic hydrolysis and the use of beta-glucuronidase from *E. coli* K12 as well as sulfatase from *Aerobacter aerogenes* ensures the acquisition of intact analytes without cleavage of ester bonds among parabens. Validation of the method revealed limits of detection between 0.02 and 0.25 $\mu\text{g/L}$ as well as limits of quantification between 0.08 and 0.83 $\mu\text{g/L}$. Thereby, the use of analyte-free surrogate matrix for calibration and control material influenced the sensitivity of the procedure positively. Furthermore, excellent precision in and between series was observed. Good absolute and relative recoveries additionally proved the robustness of the multimethod. Thus, the procedure can be applied for exploring the exposome to these prominent endocrine disruptors in the general population. <https://doi.org/10.1007/s00216-022-04438-0>

Human-Based New Approach Methodologies in Developmental Toxicity Testing: A Step Ahead from the State of the Art with a Feto-Placental Organ-on-Chip Platform,

LUCONI M., M. A. SOGORB, U. R. MARKERT, E. BENFENATI, T. MAY, S. WOLBANK, A. RONCAGLIONI, A. SCHMIDT, M. STRACCIA and S. TAIT,

International Journal of Environmental Research and Public Health 19, no. 23 (Dec 2022),
Developmental toxicity testing urgently requires the implementation of human-relevant new approach methodologies (NAMs) that better recapitulate the peculiar nature of human physiology during pregnancy, especially the placenta and the maternal/fetal interface, which represent a key stage for human lifelong health. Fit-for-purpose NAMs for the placental-fetal interface are desirable to improve the biological knowledge of environmental exposure at the molecular level and to reduce the high cost, time and ethical impact of animal studies. This article reviews the state of the art on the available in vitro (placental, fetal and amniotic cell-based systems) and in silico NAMs of human relevance for developmental toxicity testing purposes; in addition, we considered available Adverse Outcome Pathways related to developmental toxicity. The OECD TG 414 for the identification and assessment of deleterious effects of prenatal exposure to chemicals on developing organisms will be discussed to delineate the regulatory context and to better debate what is missing and needed in the context of the Developmental Origins of Health and Disease hypothesis to significantly improve this sector. Starting from this analysis, the development of a novel human feto-placental organ-on-chip platform will be introduced as an innovative future alternative tool for developmental toxicity testing, considering possible implementation and validation strategies to overcome the limitation of the current animal studies and NAMs available in regulatory toxicology and in the biomedical field. <https://doi.org/10.3390/ijerph192315828>

The Italian Wall Lizard *Podarcis siculus* as a Biological Model for Research in Male Reproductive Toxicology,

ROSATI L., T. CHIANESE, P. SIMONIELLO, C. M. MOTTA and R. SCUDIERO,

International Journal of Molecular Sciences 23, no. 23 (Dec 2022),

Spermatogenesis is a genetically driven differentiation process that occurs in the testis and leads to the formation of spermatozoa. This process is extensively studied in several experimental models, particularly in

vertebrates that share the morphological structure and functionality of the mammalian testis. Although reptiles are not generally considered biological models, the lizard *Podarcis siculus* has represented a suitable organism for the study of spermatogenesis over the years. In this lizard, the process of spermatogenesis is regulated by the interaction between systemic factors such as gonadotropins and local factors, i.e., molecules produced by the somatic and germinal cells of the testis. Many exogenous substances are able to alter the production of these regulative factors, thus altering the course of spermatogenesis, and *P. siculus* has proven to be an excellent model for studying the effects of various endogenous or exogenous substances on mechanisms underlying spermatogenesis. This review summarizes the available data on the effects of different substances on the control of spermatogenesis, highlighting the induced morphological and molecular alterations. Overall, the data show that sex hormone levels as well as the final stages of spermatogenesis are most affected by an imbalance of endogenous compounds or contamination by environmental pollutants. This is helpful for the male individual, since the damage, not affecting the spermatogonial stem cells, can be considered transient and not irreversible. <https://doi.org/10.3390/ijms232315220>

Agenda, actualité et politique

Avis de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif à la publication de la proposition d'acte délégué de la Commission sur l'intégration de nouvelles classes de dangers dans le règlement relatif à la classification, à l'étiquetage et à l'emballage des substances et des mélanges (CLP),

ANSES (octobre 2022),

L'Anses a été saisie le 11 octobre 2022 par les Ministères du Travail, du Plein emploi et de l'Insertion, celui de la Transition écologique et solidaire, et des Solidarités et celui de la Santé et de la Prévention, pour l'analyse du projet d'acte délégué de la Commission visant à intégrer de nouvelles classes de dangers dans le règlement relatif à la classification, à l'étiquetage et à l'emballage des substances et des mélanges (CLP), dans le cadre de la consultation publique mise en œuvre jusqu'au 18 octobre 2022 <https://www.anses.fr/fr/system/files/REACH2022SA0169.pdf>

Commission sets up rules to identify endocrine disruptors and long-lasting chemicals and to improve labelling,

European commission (19 décembre 2022),

La Commission européenne a publié le 19 décembre dernier l'acte délégué CLP créant les classes de danger suivantes :

- perturbateur endocrinien pour la santé humaine,
- perturbateur endocrinien pour l'environnement,
- persistant, bioaccumulable et toxique ou très persistant et très bioaccumulable,
- persistant, mobile et toxique ou très persistant et très mobile.

https://ec.europa.eu/commission/presscorner/detail/en/ip_22_7775

ECHA has added nine chemicals to the Candidate List because of their hazardous properties. ,

ECHA (17 janvier 2023),

Parmi les 9 substances, 2 substances sont ajoutées en raison de leurs propriétés PE :

4,4'-sulphonyldiphenol / 201-250-5 / 80-09-1 / Toxic for reproduction (Article 57 c); Endocrine disrupting properties (Article 57 f – environment); Endocrine disrupting properties (Article 57 f – human health) / In the manufacture of: pulp, paper and paper products, textile, leather or fur and chemicals.
Isobutyl 4-hydroxybenzoate/ 224-208-8/ 4247-02-3 / Endocrine disrupting properties (Article 57 f – human health) / endocrine in the manufacture of substances and in the following products: coating products, fillers, putties, plasters, modelling clay and inks and toners. <https://echa.europa.eu/fr/-/echa-adds-nine-hazardous-chemicals-to-candidate-list?cldee=y2RCxjRq3vGqv1QxzZSg5e7d5InYitUYbsBsTNE-OP7iw27XIe65TILw8-Vn6X&recipientid=lead-44d9ccac935ceb118128005056b9310e-b0be87d072164c1b9afb201daa9a76b5&esid=19c1a89a-1097-ed11-8144-005056b9310e>

Economic interests cloud hazard reductions in the European regulation of substances of very high concern,

CORIA J., E. KRISTIANSSON and M. GUSTAVSSON,

Nature Communications 13, no. 1 (Nov 2022),

The most important variable explaining the regulation of chemical substances of very high concern in the European REACH regulation is not how dangerous a chemical is but the fact that it is not produced nor imported into the European Economic Area. Here we investigate how the conflicts between hazard reduction and economic interests have shaped the regulation of substances of very high concern (SVHCs) under the Authorization program of the European chemical regulation Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH). Since regulation starts with listing SVHCs on the Candidate List, we analyze the relative importance of toxicological properties, economic motivations, and available scientific knowledge on the probability of inclusion on the Candidate List. We find that the most important factor in whether a substance is listed is whether it is being produced in, or imported into, the European Economic Area (EEA), with the regulators less likely to place a substance on the list if it is currently being produced or imported in the EEA. This evidence suggests that regulators have listed chemicals of secondary importance leading to lesser than anticipated hazard reductions, either because production and imports had already ceased before the listing, or because the compound has never been produced or imported in the EEA at all. <https://doi.org/10.1038/s41467-022-34492-2>

EDLists - List Updates,

Endocrine Disruptor List (décembre 2022),

List II

Tert-butyl-4-methoxyphenol (BHA) has been renamed as 2-tert-butyl-4-methoxyphenol.

Tetraphenyl m-phenylene bis(phosphate) has been renamed as reaction mass of 3-[(diphenoxyphosphoryl)oxy]phenyl triphenyl 1,3-phenylene bis(phosphate) and tetraphenyl 1,3-phenylene bis(phosphate).

(±)-1,7,7-trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-(4-MBC) has been removed from list II since the SCCS evaluations has been completed. It still appears on list I.

2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine) has been removed: Substance evaluation concluded.

Acetic acid, oxo-, sodium salt, reaction products with ethylenediamine and phenol, iron sodium salts has been removed: Substance evaluation concluded.

Carbon disulphide has been removed: Substance evaluation concluded.

Iron(III) chloride, complex with reaction products of 2,2'-(ethane-1,2-diylidimino)diacetic acid, formaldehyde, phenol and potassium hydroxide has been removed: Substance evaluation concluded.

Triclosan and Triclocarban: SCCS evaluations have been completed. Both are still on CoRAP, and therefore still appears on list II.

3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl acrylate: Studies on ED-ENV requested.

3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl methacrylate : Studies on ED-ENV requested.

Bis(2-propylheptyl) phthalate: Studies on ED-ENV requested.

<https://edlists.org/about-this-site/list-updates>

Funding & tender opportunities. European Commission. Health impacts of endocrine-disrupting chemicals: bridging science-policy gaps by addressing persistent scientific uncertainties,

European Commission (2023),

Open for submission. Programme : Horizon Europe Framework Programme (HORIZON). Opening date : 12 January 2023. Deadline date : 13 April 2023. This topic aims at supporting activities that are enabling or contributing to one or several expected impacts of destination 2 'Living and working in a health-promoting environment'. <https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/horizon-hlth-2023-envhlth-02-03>

Note d'appui scientifique et technique de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relative à l'application au cholestérol (vitamine D3) des dispositions relatives aux substances présentant des propriétés de perturbation endocrinienne au titre de la loi n° 2020-105 du 10 février 2020 dite « loi AGECE »,

ANSES (octobre 2022),

L'Anses a été saisie le 30 mai 2022 par la Direction générale de la santé (DGS) et la Direction générale de la prévention des risques (DGPR) pour la réalisation de l'appui scientifique et technique suivant : Saisine relative à la substance cholestérol (vitamine D3) dans le cadre

de la mise en œuvre des dispositions de l'article 13-II de la loi n° 2020-105 du 10 février 2020 relative à la lutte contre le gaspillage et à l'économie circulaire, dite « loi AGECE », concernant la mise à disposition du public des informations permettant d'identifier les perturbateurs

endocriniens (PE) dans un produit. <https://www.anses.fr/fr/system/files/NUT2022AST0099.pdf>

Thèse d'exercice de médecine. Connaissances de la population française sur les perturbateurs endocriniens,

BONNERANDI É.,

Aix-Marseille Université - École de médecine (mai 2022),

Introduction : les perturbateurs endocriniens (PE) jouent un rôle dans l'augmentation de l'incidence de nombreuses pathologies chroniques et sont à ce titre un problème de santé publique majeur. Le nombre colossal de ces substances, de leurs usages et de leurs effets les rend complexes à appréhender. À l'aube du commencement du Plan National Santé et Environnement numéro 4, nous avons voulu réaliser un état des lieux des connaissances de la population française de plus de 16 ans sur les perturbateurs endocriniens. Matériels et Méthodes : le recueil des données s'est fait à travers un questionnaire en accès libre diffusé sur des réseaux sociaux entre le 30/10/2021 et le 28/01/2022. L'analyse des données a été réalisée sur un échantillon de 521 personnes. Résultats : notre étude a été réalisée sur un échantillon non représentatif de la population française âgée de plus de 16 ans. Notre étude suggère que les connaissances de la population sur les PE ont considérablement augmenté au cours des 10 dernières années. Cependant, le niveau de connaissances est insuffisant pour pouvoir réellement impacter les niveaux d'imprégnation de la population et les conséquences sanitaires qui en découlent. En effet, même si les impacts possibles sur la santé humaine étaient relativement bien connus de notre échantillon, les modes d'exposition, les populations vulnérables et les moyens de se protéger des PE semblent moins bien acquis. Ce travail de thèse a permis de mettre en évidence que les hommes ont de moins bonnes connaissances que les femmes sur les PE. Notre étude montre également que les professionnels de santé ont un rôle à jouer dans les campagnes de prévention et d'information des populations sur les perturbateurs endocriniens. Conclusion : la protection de la population contre les perturbateurs endocriniens s'inscrit dans un défi plus global de lutte contre la pollution environnementale que devront relever les instances gouvernementales mondiales pour préserver notre planète et la santé de ses occupants.

<https://dumas.ccsd.cnrs.fr/dumas-03667644v1>

Unlocking India's Potential in Managing Endocrine-Disrupting Chemicals (EDCs): Importance, Challenges, and Opportunities,

SHARMA B. M., M. SCHERINGER, P. CHAKRABORTY, G. K. BHARAT, E. H. STEINDAL, L. TRASANDE and L. NIZZETTO,

Exposure and Health (Endocrine-disrupting chemicals (EDCs) are a prime concern for the environment and health globally. Research shows that in developing countries such as India both the environment and human populations are severely exposed to EDCs and consequently experience rising incidents of adverse health effects such as diabetes and cancers. In this paper, we discuss the current EDC management approach in India, critically assess its limitations, and describe opportunities for potential improvements. Foremost, current EDC management actions and interventions in India are fragmented and outdated, and far behind the modern and comprehensive approaches adopted in the European Union and other developed countries. Strong and well-planned actions are required on various fronts of science, policy, commerce, and public engagement. These actions include the adoption of a dedicated and modern regulatory framework for managing EDCs, enhancing capacity and infrastructure for EDC monitoring in the environment and human population, employing public-private partnership programs for not only managing EDCs but also in the sectors that indirectly contribute toward the mismanagement of EDCs in the country, and raising awareness on EDCs and promoting health-preserving consumption habits among the public. As India hosts a large proportion of the global human

population and biodiversity, the success or failure of its actions will substantially affect the direction of global efforts to manage EDCs and set an example for other developing countries. <https://doi.org/10.1007/s12403-022-00519-8>

Toxicité sur les animaux

4,4'-(9-Fluorenylidene)dianiline (BAFL) is antiestrogenic and has adverse effects on female development in CD-1 mice,

JIA X. J., Y. ZHOU, X. T. MAO, N. HUAI, X. GUO and Z. B. ZHANG,
Ecotoxicology and Environmental Safety 246 (Nov 2022),

Many phenolic compounds have been found to have endocrine disrupting activities, but their arylamine analogs, the phenolic hydroxyl groups substituted by aniline amino groups, have rarely been reported. 4,4'-(9-Fluorenylidene)dianiline (BAFL) is an arylamine analog of fluorene-9-bisphenol (BHPF) and BHPF has been reported to be a strong antiestrogen which could cause endometrial atrophy, ovarian damage and adverse pregnancy outcomes in animals. BAFL has been widely used as material to synthesize polymers, such as polyimides, polyamide, and polyamine, for various uses since the 1970s. Here, we assessed the antiestrogenicity of BAFL using a variety of methods and looked into its impacts on the development of females in CD-1 mice. With the aid of a yeast estrogen screen assay, we found BAFL possessed obviously antiestrogenic activity ($IC_{50} = 8.15 \times 10^{-6} M$), which close to that of tamoxifen and BHPF. Using a 10-d mouse uterotrophic assay, we found that BAFL obviously decreased uterine weight in a dose-dependent way. Histological analyses of mouse uteri revealed that BAFL induced marked endometrial atrophy and inhibited the uterine development. Immunohistochemical analyses showed that Sprr2d, an estrogen-responsive gene encoding protein, was mainly expressed in endometrial epithelial cells and BAFL decreased the areas and levels of Sprr2d staining in mouse uteri. It was clear from uterine transcriptome investigations that BAFL significantly downregulated the expressions of multiple genes responding to estrogen. Molecular docking showed that BAFL could effectively occupy the antagonist-binding pocket of hER alpha, and one of the amino groups of BAFL formed hydrogen bonds with the side chains of Arg394 and Glu353 in the receptor. These results indicated that BAFL exhibited clearly antiestrogenic characteristics and could interfere with normal female development in mice, which should be avoided using in commodities that come into direct contact with humans. Moreover, this study indicated that the arylamine analogs of phenolic endocrine disrupting chemicals might also have endocrine disrupting activities. <https://doi.org/10.1016/j.ecoenv.2022.114202>

Bisphenol S induces oxidative stress-mediated impairment of testosterone synthesis by inhibiting the Nrf2/HO-1 signaling pathway,

WANG Y. X., W. DAI, Y. Z. LI, Z. Y. WU, Y. Q. KAN, H. C. ZENG and Q. Z. HE,

Journal of Biochemical and Molecular Toxicology (Bisphenol S (BPS) is an environmental endocrine disruptor widely used in industrial production. BPS induces oxidative stress and exhibits male reproductive toxicity in mice, but the mechanisms by which BPS impairs steroid hormone synthesis are not fully understood. Nuclear factor erythroid 2-related factor 2(Nrf2)/HO-1 signaling is a key pathway in improving cellular antioxidant defense capacities. Therefore, this study explored the effects of exposure to BPS on testosterone synthesis in adult male mice and its mechanisms with regard to the Nrf2/HO-1 signaling pathway. Adult male C57BL/6 mice were orally exposed to BPS (2, 20, and 200 mg/kg BW) with sesame oil as a vehicle (0.1 ml/10 g BW) per day for 28 consecutive days. The results showed that compared with the control group, serum testosterone levels were substantially reduced in the 20 and 200 mg/kg BPS treatment groups, and testicular testosterone levels were reduced in all BPS treatment groups. These changes were accompanied by a prominent decrease in the expression levels of testosterone synthesis-related enzymes (STAR, CYP11A1, CYP17A1, HSD3B1, and HSD17B3) in the mouse testis. In addition, BPS induced oxidative stress in the testis by upregulating the messenger RNA and protein levels of Keap1 and downregulating the levels of Nrf2, HO-1, and downstream antioxidant enzymes (CAT, SOD1, and Gpx4). In summary, our results indicate that exposure of adult male mice to BPS can inhibit Nrf2/HO-1 signaling and antioxidant enzyme activity, which induces oxidative stress and thereby may impair testosterone synthesis in testicular tissues, leading to reproductive damage. <https://doi.org/10.1002/jbt.23273>

Exposure to the pesticides linuron, dimethomorph and imazalil alters steroid hormone profiles and gene expression in developing rat ovaries,

BOBERG J., H. K. L. JOHANSSON, D. FRANSSEN, M. K. DRASKAU, S. CHRISTIANSEN, J. CRAMER, M. PEDERSEN, A.-S. PARENT and T. SVINGEN,

Toxicology Letters 373 (2023/01/15/ 2023): 114-122,

Inhibition of androgen signaling during critical stages of ovary development can disrupt folliculogenesis with potential consequences for reproductive function later in life. Many environmental chemicals can inhibit the androgen signaling pathway, which raises the question if developmental exposure to anti-androgenic chemicals can negatively impact female fertility. Here, we report on altered reproductive hormone profiles in prepubertal female rats following developmental exposure to three pesticides with anti-androgenic potential: linuron (25 and 50 mg/kg bw/d), dimethomorph (60 and 180 mg/kg bw/d) and imazalil (8 and 24 mg/kg bw/d). Dams were orally exposed from gestational day 7 (dimethomorph and imazalil) or 13 (linuron) until birth, then until end of dosing at early postnatal life. Linuron and dimethomorph induced dose-related reductions to plasma corticosterone levels, whereas imazalil mainly suppressed gonadotropin levels. In the ovaries, expression levels of target genes were affected by linuron and dimethomorph, suggesting impaired follicle growth. Based on our results, we propose that anti-androgenic chemicals can negatively impact female reproductive development. This highlights a need to integrate data from all levels of the hypothalamic-pituitary-gonadal axis, as well as the hypothalamic-pituitary-adrenal axis, when investigating the potential impact of endocrine disruptors on female reproductive development and function. <https://doi.org/https://doi.org/10.1016/j.toxlet.2022.11.010>