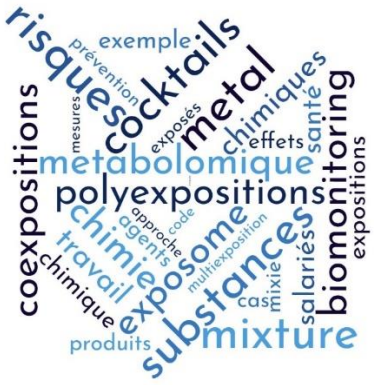


# Bulletin de veille
# Polyexpositions chimie-chimie
# N°6 - novembre 2024

Objectif : la polyexposition homogène chimie/chimie est un sujet de plus en plus préconisé pour étudier l'évaluation du risque professionnel et sa prévention. L'objectif est de connaitre les travaux récents qui sont publiés sur le sujet et identifier des moyens d'analyse, et d'interprétation de cette co-exposition à plusieurs composés chimiques.

Ce bulletin a été réalisé à partir d'une surveillance de littérature récente sur les bases Web of Sciences et la base documentaire INRS-Biblio.

*La validation des informations fournies (exactitude, fiabilité, pertinence par rapport aux principes de prévention, etc.) est du ressort des auteurs des articles signalés dans la veille. Les informations ne sont pas le reflet de la position de l'INRS. Les éléments issus de cette veille sont fournis sans garantie d'exhaustivité.*

*Les liens mentionnés dans le bulletin donnent accès aux documents sous réserve d'un abonnement à la ressource.*

## Actualités web sélectionnées

- 2 octobre 2024, EPA Finalizes Rule to Protect Farmworkers, Families and Communities from Pesticide Exposures. « L'Agence de protection de l'environnement des États-Unis annonce une règle finale visant à rétablir les exigences relatives à la zone d'exclusion d'application de pesticides (ZAE) en vertu de la Norme de protection des travailleurs agricoles (WPS) de 2015. La ZEE est une zone entourant l'équipement d'application de pesticides à l'extérieur où il est interdit d'appliquer des pesticides ». https://www.epa.gov/newsreleases/epa-finalizes-rule-protect-farmworkers-families-and-communities-pesticide-exposures
- 18 octobre 2024. Dans une étude portant sur des échantillons de sang de femmes enceintes prélevés entre 2006 et 2008, les chercheurs rapportent avoir quantifié de nombreux mélanges complexes de produits chimiques pouvant présenter des risques neurotoxiques, même lorsque les produits chimiques individuels étaient présents à des niveaux apparemment inoffensifs. Une nouvelle méthode de biosurveillance révèle des mélanges chimiques neurotoxiques dans le sang humain (ma-clinique.fr)

- 21 octobre 2024. Rapport de Santé publique France. L'exposition des populations aux abords des bassins industriels Santé publique France a proposé la mise en œuvre d'une étude visant à mieux connaitre les impacts des bassins industriels sur la santé. Les riverains de bassins industriels sont exposés à diverses nuisances environnementales : substances chimiques, nuisances sonores, olfactives ou visuelles. Etudier et surveiller l'impact sanitaire de ces nuisances revêt un enjeu majeur de santé publique, afin de mettre en place et adapter le cas échéant les mesures de gestion et de prévention pour protéger la santé des riverains de telles zones. Pour lire le rapport : Rapport de description des bassins industriels
- 24 octobre 2024. Anses. Cancers professionnels : quels sont les procédés de travail à risque ? | Anses - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail
  Certains procédés de travail, incluant des activités ou conditions de travail, peuvent provoquer l'apparition de cancers. Comment mettre en évidence le caractère cancérogène de ces procédés de travail afin de pouvoir mieux protéger les travailleurs exposés ? L'Anses a proposé une méthode pour identifier les procédés cancérogènes et a évalué la cancérogénicité de trois d'entre eux. Elle a également établi une liste des procédés à expertiser prioritairement dans les années à venir.
- 25 novembre 2024. Le yearbook santé et environnement 2024 est publié Environnement Risques & Santé - YearBook Santé et Environnement : dans ce rapport, un article fait la lumière sur l'exposome et l'évaluation des risques sanitaires : Fondements scientifiques - méthodologie - exposome

# Sommaire

## 1. Biomonitoring, metabolomique, modèles et multi-expositions chimiques

Ochoa-Leite, C., Rodrigues, S., Ramos, A. S., Ribeiro, F., Barbosa, J., Jeronimo, C.*, et al.*
**Metabolomics and proteomics in occupational medicine: a comprehensive systematic review.**
Journal of occupational medicine and toxicology (London, England) 2024; Vol. 19 (1), p 38-38.
BACKGROUND: Occupational biomonitoring is essential for assessing health risks linked to workplace exposures. The use of 'omics' technologies, such as metabolomics and proteomics, has become crucial in detecting subtle biological alterations induced by occupational hazards, thereby opening novel avenues for biomarker discovery. AIMS: This systematic review aims to evaluate the application of metabolomics and proteomics in occupational health.
METHODS: Following the PRISMA guidelines, we conducted a comprehensive search on PubMed, Scopus, and Web of Science for original human studies that use metabolomics or proteomics to assess occupational exposure biomarkers. The risk of bias was assessed by adapting the Cochrane Collaboration tool and the Newcastle-Ottawa Quality Assessment Scale.
RESULTS: Of 2311 initially identified articles, 85 met the eligibility criteria. These studies were mainly conducted in China, Europe, and the United States of America, covering a wide range of occupational exposures. The findings revealed that metabolomics and proteomics approaches effectively identified biomarkers related to chemical, physical, biomechanical, and psychosocial hazards. Analytical methods varied, with mass spectrometry-based techniques emerging as the most prevalent. The risk of bias was generally low to moderate, with specific concerns about exposure measurement and confounding factors.
CONCLUSIONS: Integrating metabolomics and proteomics in occupational health biomonitoring significantly advances our understanding of exposure effects and facilitates the development of personalized preventive interventions. However, challenges remain regarding the complexity of data analysis, biomarker specificity, and the translation of findings into preventive measures. Future research should focus on longitudinal studies and biomarker validation across diverse populations to improve the reliability and applicability of occupational health interventions.
https://doi.org/10.1186/s12995-024-00436-3

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Eguchi, A., Sakurai, K., Yamamoto, M., Mori, C.
**Elucidation of endogenous and exogenous chemicals in maternal serum using high-resolution mass spectrometry.**
Ecotoxicology and environmental safety 2024; Vol. 286 p 117256.
The increasing exposure to environmental chemicals calls for comprehensive non-targeted analysis to detect unrecognized substances in human samples. We examined human serum samples to classify compounds as endogenous or exogenous using public databases and to explore the relationships between exposure markers and metabolic patterns. Serum samples from 84 pregnant women at 32 weeks gestation were analyzed using LC-QToFMS. Using the PubChemLite for Exposomics database, we annotated and classified 106 compounds (51 endogenous, 55 exogenous). The compound patterns were analyzed using three dimensional reduction methods: Principal Component Analysis (PCA), regularized Generalized Canonical Correlation Analysis (rGCCA), and Uniform Manifold Approximation and Projection (UMAP). OPTICS clustering applied to these methods revealed two distinct clusters, with 89 % of significant compounds overlapping between clusters. The detected exogenous compounds included dietary substances, phthalates, nitrogenous compounds, and parabens. Pathway enrichment analysis showed that chemical exposure was linked to changes in amino acid metabolism, protein and mineral transport, and energy metabolism. While we found associations between exposure and metabolite changes, we could not establish causality. Our approach of analyzing both exogenous and endogenous chemicals from the same dataset using PubChemLite database presents a new method for exposome research, despite limitations in sample size and peak annotation accuracy. These findings contribute to understanding multiple chemical exposures and their metabolic effects in human biomonitoring.
https://doi.org/10.1016/j.ecoenv.2024.117256

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Hopf, N. B., De Luca, H. P., Borgatta, M., Koch, H. M., Paelmke, C., Benedetti, M.*, et al.*
**Human skin absorption of three phthalates.**
Toxicology Letters 2024; Vol. 398,p 38-48.
Population studies reveal widespread exposure to phthalates. Understanding their absorption, distribution, metabolism, and excretion is vital to reduce exposure. However, data on skin absorption remain limited. We thus aim to characterize the skin permeation of three phthalates in a mixture, neat or in emulsion; di(2-ethylhexyl) phthalate (d4-DEHP), dibutyl phthalate (d4-DBP), and diethyl phthalate (d4-DEP), by comparing in vitro human skin (800 mu m) permeation (24 hours) results using flow-through diffusion cells with urine results obtained from volunteers exposed to the same mixture applied to a forearm (40 cm(2)). Metabolites were analyzed in receptor fluids and urine. Phthalates crossed the skin barrier and metabolized into monoesters before elimination. Increased permeation was observed for phthalates in emulsion compared to neat substances, with polyethylene glycol (PEG) in the receptor fluid enhancing emulsion permeation, but not affecting neat substances. In vitro results mirrored in vivo findings: DEP showed rapid permeation (J: similar to 2 ug/cm(2)/h) and urinary excretion peaking at six hours post-application, whereas DBP exhibited slower kinetics (J: similar to 0.1 ug/cm(2)/h), with a urinary peak at 15-17 hours post-application. DEHP had minimal permeation (J: similar to 0.0002 ug/cm(2)/h) with no observable urinary peak. These findings underscore the importance of comprehending phthalate skin absorption for effective exposure mitigation strategies.
https://doi.org/10.1016/j.toxlet.2024.05.016

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Kersch, C., Alsaleh, R., Schmitz-Spanke, S.
**Effect of simultaneous exposure to mixtures of skin sensitizers and irritants on a 3D skin model: A metabolomics approach.**
Naunyn-Schmiedebergs Archives of Pharmacology 2024; Vol. 397 p S2-S2.

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Nikpay, M.
**Multiomics Screening Identified CpG Sites and Genes That Mediate the Impact of Exposure to Environmental Chemicals on Cardiometabolic Traits.**
Epigenomes 2024; Vol. 8 (3), 29.
An understanding of the molecular mechanism whereby an environmental chemical causes a disease is important for the purposes of future applications. In this study, a multiomics workflow was designed to combine several publicly available datasets in order to identify CpG sites and genes that mediate the impact of exposure to environmental chemicals on cardiometabolic traits. Organophosphate and prenatal lead exposure were previously reported to change methylation level at the cg23627948 site. The outcome of the analyses conducted in this study revealed that, as the cg23627948 site becomes methylated, the expression of the GNA12 gene decreases, which leads to a higher body fat percentage. Prenatal perfluorooctane sulfonate exposure was reported to increase the methylation level at the cg21153102 site. Findings of this study revealed that higher methylation at this site contributes to higher diastolic blood pressure by changing the expression of CHP1 and GCHFR genes. Moreover, HKR1 mediates the impact of B12 supplementation -> cg05280698 hypermethylation on higher kidney function, while CTDNEP1 mediates the impact of air pollution -> cg03186999 hypomethylation on higher systolic blood pressure. This study investigates CpG sites and genes that mediate the impact of environmental chemicals on cardiometabolic traits. Furthermore, the multiomics approach described in this study provides a convenient workflow with which to investigate the impact of an environmental factor on the body's biomarkers, and, consequently, on health conditions, using publicly available data.
https://doi.org/10.3390/epigenomes8030029

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Shao, K., Zou, R., Zhang, Z., Mandemaker, L. D. B., Timbie, S., Smith, R. D.*, et al.*
**Advancements in Assays for Micro- and Nanoplastic Detection: Paving the Way for Biomonitoring and Exposomics Studies.**
Annual review of pharmacology and toxicology 2024; Vol 65
Although plastic pollution and exposure to plastic-related compounds have received worldwide attention, health risks associated with micro- and nanoplastics (MNPs) are largely unknown. Emerging evidence suggests MNPs are present in human biofluids and tissue, including blood, breast milk, stool, lung tissue, and placenta; however, exposure assessment is limited and the extent of human exposure to MNPs is not well known. While there is a critical need to establish robust and scalable biomonitoring strategies to assess human exposure to MNPs and plastic-related chemicals, over 10,000 chemicals have been linked to plastic manufacturing with no existing standardized approaches to account for even a fraction of these exposures. This review provides an overview of the status of methods for measuring MNPs and associated plastic-related chemicals in humans, with a focus on approaches that could be adapted for population-wide biomonitoring and integration with biological response measures to develop hypotheses on potential health effects of plastic exposures. We also examine the exposure risks associated with the widespread use of chemical additives in plastics. Despite advancements in analytical techniques, there remains a pressing need for standardized measurement protocols and untargeted, high-throughput analysis methods to enable comprehensive MNP biomonitoring to identify key MNP exposures in human populations. This review aims to merge insights into the toxicological effects of MNPs and plastic additives with an evaluation of analytical challenges, advocating for enhanced research methods to fully assess, understand, and mitigate the public health implications of MNPs.
https://doi.org/10.1146/annurev-pharmtox-030424-112828

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Tariq, F., Ahrens, L., Alygizakis, N. A., Audouze, K., Benfenati, E., Carvalho, P. N.*, et al.*
**Computational Tools to Facilitate Early Warning of New Emerging Risk Chemicals.**
Toxics 2024; Vol. 12 (10) p 736.
Innovative tools suitable for chemical risk assessment are being developed in numerous domains, such as non-target chemical analysis, omics, and computational approaches. These methods will also be critical components in an efficient early warning system (EWS) for the identification of potentially hazardous chemicals. Much knowledge is missing for current use chemicals and thus computational methodologies complemented with fast screening techniques will be critical.
This paper reviews current computational tools, emphasizing those that are accessible and suitable for the screening of new and emerging risk chemicals (NERCs). The initial step in a computational EWS is an automatic and systematic search for NERCs in literature and database sources including grey literature, patents, experimental data, and various inventories. This step aims at reaching curated molecular structure data along with existing exposure and hazard data. Next, a parallel assessment of exposure and effects will be performed, which will input information into the weighting of an overall hazard score and, finally, the identification of a potential NERC. Several challenges are identified and discussed, such as the integration and scoring of several types of hazard data, ranging from chemical fate and distribution to subtle impacts in specific species and tissues.
To conclude, there are many computational systems, and these can be used as a basis for an integrated computational EWS workflow that identifies NERCs automatically.
https://doi.org/10.3390/toxics12100736

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Willey, J. B., Liang, C. L., Pollock, T., Khoury, C., Thomson, E. M., Walker, M., St-Amand, A.
**Cumulative Health Risk from Exposure Load (CHREL): Looking at multi-chemical exposures through the lens of biomonitoring guidance values.**
Toxicology letters 2024; Vol. 401, p 139-149.
Exposure load (EL) is an indicator of multiple chemical exposures based on human biomonitoring data. We used EL methodology and human biomonitoring health-based guidance values (HB2GVs) as exposure thresholds to create a new metric called Cumulative Health Risk from Exposure Load (CHREL). HB2GVs are derived by calculating the concentration of a biomarker consistent with a health protective exposure

guidance value. CHREL analysis was conducted using Canadian Health Measures Survey (CHMS) cycle 3 and 4 biomonitoring data. Based on 18 chemicals, more than half of the Canadian population had an estimated CHRELTOTAL of 1 or more, indicative of chemical exposures potentially above selected exposure guidance values. Females had a significantly lower CHRELTOTAL compared to males, 12-19 year olds had a lower CHRELTOTAL compared to older age groups (significant compared to 40-59 year olds), and nonsmokers had a significantly lower CHRELTOTAL than smokers. Small segments of the population had a CHRELLIVER or a CHRELNERV of 1 or more, indicating exposures potentially above guideline levels for chemicals affecting the liver or nervous system. CHRELCANC was calculated based on 6 chemicals with HB2GVs derived for cancer endpoints. At the 10-5 risk level, most people had an estimated CHRELCANC of 3, indicative of multiple chemicals that may exceed negligible cancer risk. The most important contributors to exposures above HB2GVs were inorganic arsenic, mercury, acrylamide, xylenes, benzene and triclosan. Keeping certain assumptions, uncertainties and limitations in mind, the CHREL indicator can be used to obtain a picture of potential cumulative health risks from combined chemical exposures in a population, and as a comparative measure between subpopulations, including vulnerable subgroups.
https://doi.org/10.1016/j.toxlet.2024.09.006

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Paolozzi, M. C. M., T.; D'arco, A. ; Mosesso, L.;Macis, S.;Lupi, S.

**FT-IR spectroscopy coupled with machine learning for a high sensitive detection and discrimination of gaseous volatile organic compounds.**

Intervento presentato al convegno 110° Congresso Nazionale della Società Italiana di Fisica tenutosi a Bologna 2024; Vol.

Volatile Organic Compounds (VOCs), such as styrene and its co-products, are organic chemical compounds able to evaporate at room temperature. They are classified as a possible human carcinogen in the short and long term and in co-exposure to other physical-chemical agent. During the last years, we systematically used Fourier Transform Infrared (FTIR) spectroscopy for quantifying VOCs in air, increasing the sensitivity of IR systems down to the parts per million (ppm) level.

Here, we investigate five selected aromatic compounds, of extreme importance in occupational safety with the aim of filling the gap in IR gas-phase database. Benzene, Toluene and Xylene (BTXs) are studied and their calibration curves are carried out. A Machine Learning (ML) algorithm is developed, providing the automatization of the single VOC detection and discrimination starting from the spectra of random mixtures. The dataset processing is optimized and different algorithms are evaluated over each single VOC recognition between styrene, ethanol, isopropanol, acetone and BTXs. This work is a very promising starting point for building a portable setup for the detection at very high sensitivity.

https://iris.uniroma1.it/handle/11573/1722018#tab_default

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Zhao, F., Gao, W., Lu, J., Jiang, H.

**Machine learning-based precise monitoring of aluminium-magnesium alloy dust.**

Journal of Loss Prevention in the Process Industries 2024; Vol. 92,p 105471.

Al-Mg alloys are widely used in industrial production, which can lead to occupational health issues and explosion hazards. The study focuses on applying a machine learning-enhanced Kalman filtering algorithm to detect the concentration of Al-Mg alloy dust, significantly reducing dust hazards and constructing an efficient and safe dust reduction and removal system. A machine learning-based Kalman filter algorithm is proposed for fast and accurate detection of high Al-Mg dust concentrations (200–1200 g/m$^3$). The results show that the KFGRU approach outperforms the traditional line filter method, achieving answer times between 2.6 s and 6 s—an improvement of 62.5% over the traditional method. As far as the forecast accuracy is concerned, the KFGRU method yields a minimal curve deviation value, reaching as low as 0.097, which represents a significant improvement compared to the 0.151 of the Kalman filter algorithm, the 0.217 of the sliding average method, and the 0.177 of the median filter methods.

https://doi.org/https://doi.org/10.1016/j.jlp.2024.105471

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Gohel, V. R., Gaev, A., Simonenko, N. P., Simonenko, T. L., Simonenko, E. P., Lantsberg, A., et al.

**Gas sensing beyond classification: Analysis of gas mixtures using multisensor array based on Al-doped zinc oxide.**

Microchemical Journal 2024; Vol. 206

Understanding the composition of gas mixtures is still a primary prerogative of complex analytical units or biological olfaction systems. Attempts to mimic the olfactory processes by using a multisensor array combined with machine learning algorithms led mainly to solving a problem of a selective classification of odors or regression over the range of concentrations of the same odor. The identification of individual analytes in a mixture remains a difficult task. In this study, we test the identification of individual chemicals in the composition of the gas mixture with a feature extraction algorithm using a multisensor array based on aluminum-doped zinc oxide. Our approach is based on matching the selected parameters of the response curves which share considerable similarity if a volatile compound is common in any two mixture combinations. We demonstrate the efficiency of the method by analyzing five analytes such as acetone, benzene, methanol, ethanol, and isopropanol, and their mixtures.

As a result, we were able to efficiently classify all 31 odors with an accuracy of about 99%. We have achieved the mean values of F1 scores of 0.52, 0.63, and 0.59 reaching up to 0.80-0.86 for the prediction of every individual analyte in 2-, 3- and 4-component gas mixtures, respectively. While using just raw signals at steady state, we found that the results become rather biased as the number of analytes increases in a mixture. Thus, our approach enables an improved, more accurate, and thorough examination of the gas mixtures, expanding the scope of application of multisensor systems beyond the common "classification" tasks.

https://doi.org/10.1016/j.microc.2024.111547

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## 2. Co-expositions aux métaux lourds

Bai, L., Wen, Z., Zhu, Y., Jama, H. A., Sawmadal, J. D., Chen, J.

**Association of blood cadmium, lead, and mercury with anxiety: a cross-sectional study from NHANES 2007-2012.**

Frontiers in Public Health 2024; Vol. 12

Objectives: The purpose of this paper is to explore the relationship between blood levels of cadmium, lead, and mercury and anxiety in American adults. Methods: Blood metals and self-reported anxiety days were extracted from laboratory data and questionnaire data, respectively, using NHANES data from 2007-2012. Weighted logistic regression was used to assess the relationship between cadmium, lead and mercury with anxiety. Restricted cubic spline was used to visualize the non-linear relationship between metal concentrations and anxiety. Weighted quantile sum (WQS) regression was used to investigate the effect of combined exposure to the three metals on anxiety.

Results: The prevalence of anxiety in adults was 26.0%. After adjusting for potential confounding variables, cadmium levels in the highest quartile (Q4) were associated with a higher risk of anxiety compared to the lowest quartile (Q1) (OR = 1.279, 95% CI: 1.113-1.471, $p < 0.01$). Restricted cubic spline analysis indicated a positive association between blood cadmium levels and anxiety. Furthermore, co-exposure to multiple heavy metals was positively associated with anxiety risk (WQS positive: OR = 1.068, 95% CI: 1.016-1.160, $p < 0.05$), with cadmium contributing the most to the overall mixture effect. Compared to the Light RPA, the Vigorous/Moderate RPA group had a relatively low risk of anxiety after cadmium exposure.

Conclusion: High levels of blood cadmium are positively associated with the development of anxiety disorders, which needs to be further verified in future studies.

https://doi.org/10.3389/fpubh.2024.1402715

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Fan, G., Liu, Q., Wu, M., Bi, J., Qin, X., Fang, Q.*, et al.*
**Association between multiple metal exposure and bone mineral density among Chinese adults.**
Environmental Geochemistry and Health 2024; Vol. 46 (11), p
Previous studies about metal exposures and bone mineral density (BMD) have mainly focused on individual metals. The objective of this study was to explore the association of single and multiple metal exposures with BMD among Chinese adults. We recruited 2 922 participants from Tongji Hospital in Wuhan, China. The urinary concentrations of 21 metals were measured by the inductively coupled plasma mass spectrometer. BMD was measured using dual-energy X-ray absorptiometry. We applied linear regression and Bayesian kernel machine regression (BKMR) to examine the association of single and multiple metal exposure with BMD, respectively. The linear regression model showed that cadmium (Cd) and strontium (Sr) were associated with lower BMD (all P-trend < 0.05). Compared with the lowest quantiles, the beta (95% CI) of BMD in the highest quartile of Cd and Sr was - 0.032 (- 0.049, - 0.016) and - 0.033 (- 0.049, - 0.018), respectively. The BKMR results showed that co-exposure to 21 metals was negatively associated with BMD among the total participants and males. Our study suggested that exposure to multiple metals was negatively associated with BMD, particularly among males. More prospective studies are needed to identify these associations and reveal the underlying mechanisms.
https://doi.org/10.1007/s10653-024-02261-3

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Hong, S., Wu, S., Wan, Z., Wang, C., Guan, X., Fu, M.*, et al.*
**Associations between multiple metals exposure and cognitive function in the middle-aged and older adults from China: A cross-sectional study.**
Environmental Research 2024; Vol. 263, p 120038.
The rapidly rising risk of cognitive decline is a serious challenge for the elderly. As the wide-distributed environmental chemicals, the effects of metals exposure on cognitive function have attracted much attention, but the results remain inclusive. This study aimed to investigate the roles of multiple metals co-exposure on cognition. We included a total of 6112 middle-aged and older participants, detected their plasma levels of 23 metals by using inductively coupled plasma mass spectrometry, and assessed their cognitive function by using the Mini-Mental State Examination (MMSE). The results showed that increased plasma levels of iron (Fe) and zinc (Zn) were positively associated with MMSE score, but the increased levels of nickel (Ni) and lead (Pb) were associated with decreased MMSE score (all FDR < 0.05). Subjects exposed to both high levels of Ni and Pb showed the lowest MMSE score [β (95% CI) = −0.310 (−0.519, −0.100)], suggesting that Ni and Pb had a synergistic toxic effect on cognitive function. In addition, the hazardous roles of Ni and Pb were mainly found among subjects with low plasma level of Zn, but were not significant among those with high-Zn level [Ni: β (95% CI) = −0.281 (−0.546, −0.015) vs. −0.146 (−0.351, 0.058); Pb: β (95% CI) = −0.410 (−0.651, −0.169) vs. −0.060 (−0.275, 0.155)], which suggested that Zn could attenuate the adverse effects of Pb and Ni on cognitive function. The cognitive function was gradually decreased among subjects with increased number of adverse exposures to the above four metals (Ptrend < 0.001). In conclusion, our findings revealed the individual, interactive, and combined effects of Fe, Ni, Pb, and Zn on cognitive function, which may provide new perspectives on cognitive protection, but further prospective cohort studies and biological researches are needed to validate these findings.
https://doi.org/https://doi.org/10.1016/j.envres.2024.120038

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Kim, I.-G., Hong, S., Yim, S., Jeong, J.-H., Choi, K., Lee, J.-H.*, et al.*
**Sex-Specific Effects of Combined Heavy Metal Exposure on Blood Pressure: A Bayesian Kernel Machine Regression Analysis.**
Atmosphere 2024; Vol. 15 (10),p 1157.
https://www.mdpi.com/2073-4433/15/10/1157

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Kim, J., Kim, B.-G., Hong, Y.-S., Lee, E.-Y.
**Effects of mixed metal exposure on MRI metrics in basal ganglia.**
Toxicological Sciences 2024; Vol.
Welding fumes contain various metals. Past studies, however, mainly focused on Manganese (Mn)-related neurotoxicity. This study investigated welding-related mixed metal exposure effects on MRI metrics in the basal ganglia (BG) and their dose–response relationship. Subjects with (N = 23) and without (N = 24) a welding exposure history were examined. Metal exposure was estimated with an exposure history questionnaire and whole blood metal levels. T1 (weighted-intensity and relaxation time; estimates of brain Mn accumulation), diffusion tensor imaging (axial [AD], mean [MD], radial diffusivity, and fractional anisotropy [FA]; estimates of microstructural differences) metrics in BG (caudate nucleus, putamen, and globus pallidus [GP]), and voxel-based morphometry (for volume) were examined and related with metal exposure measures. Compared with controls, welders showed higher GP R1 (1/T1; P = 0.034) but no differences in blood metal and T1-weighted (T1W) values in any ROIs (P's > 0.120). They also had higher AD and MD values in the GP (P's < 0.033) but lower FA values in the putamen (P = 0.039) with no morphologic differences. In welders, higher blood Mn and Vanadium (V) levels predicted higher BG R1 and T1W values (P's < 0.015). There also were significant overall metal mixture effects on GP T1W and R1 values. Moreover, GP AD and MD values showed nonlinear associations with BG T1W values: They increased with increasing T1W values only above certain threshold of T1 values. The current findings suggest that Mn and V individually but also metal mixtures jointly predict GP T1 signals that may in turn contribute to altered DTI metrics in the BG after certain exposure threshold levels.
https://doi.org/10.1093/toxsci/kfae117

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Levilly, R., Sauvain, J.-J., Andre, F., Demange, V., Bourgkard, E., Wild, P., Hopf, N. B.
**Characterization of occupational inhalation exposures to particulate and gaseous straight and water-based metalworking fluids.**
Scientific Reports 2024; Vol. 14 (1),p
Exposure assessments to metalworking fluids (MWF) is difficult considering the complex nature of MWF. This study describes a comprehensive exposure assessment to straight and water-based MWFs among workers from 20 workshops. Metal and organic carbon (OC) content in new and used MWF were determined. Full-shift air samples of inhalable particulate and gaseous fraction were collected and analysed gravimetrically and for metals, OC, and aldehydes. Exposure determinants were ascertained through observations and interviews with workers. Determinants associated with personal inhalable particulate and gaseous fractions were systematically identified using mixed models. Similar inhalable particle exposure was observed for straight and water-based MWFs (64-386 mu g/m3). The gaseous fraction was the most important contributor to the total mass fraction for both straight (322-2362 mu g/m3) and water-based MWFs (101-699 mu g/m3). The aerosolized particles exhibited low metal content irrespective of the MWF type; however, notable concentrations were observed in the sumps potentially reaching hazardous concentrations. Job activity clusters were important determinants for both exposure to particulate and gaseous fractions from straight MWF. Current machine enclosures remain an efficient determinant to reduce particulate MWF but were inefficient for the gaseous fraction. Properly managed water-based MWF meaning no recycling and no contamination from hydraulic fluids minimizes gaseous exposure. Workshop temperature also influenced the mass fractions. These findings suggest that exposures may be improved with control measures that reduce the gaseous fraction and proper management of MWF.
https://doi.org/10.1038/s41598-024-69677-w

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Li, Y., Jiao, Y., Hu, R., Hu, G., Shi, G., Wang, K., *et al.*
**Association between urinary mixture metal levels and olfactory function in coal miners.**
Frontiers in Public Health 2024; Vol. 12,p
Background Exposure to occupational metallic mixtures has a potential impact on olfactory function. However, research evidence is limited on the potential impact of exposure to metallic mixtures and olfactory dysfunction. Furthermore, the coal dust generated contains multiple various metals during coal mining, and no study yet has focus on the olfactory dysfunction of coal miners.

Objectives In this study, we evaluate the association between urinary metallic mixtures and olfactory function in coal miners, while also exploring the potential applicability of plasma olfactory marker protein (OMP) as a biomarker for assessing olfaction.
Methods From July to October 2023, coal workers from seven different coal mining enterprises were recruited for the survey when they come for the employee health checkup. Ultimately, 376 participants were met the inclusion criteria and, respectively, determined with the concentrations of urine (16 metals) and plasma (OMP). Meanwhile, applying UPSIT to access their olfactory function. Binary logistic regression and restricted cubic spline (RCS) model were used to estimate the association of individual metals with olfactory function. Bayesian kernel machine regression (BKMR) and Quantile g-computation (QG-C) regression were employed to assess the overall association between metal mixtures and olfactory function and identify the major contributing elements.
Results In a single-metal model, two metals in urine were found to be significantly associated with olfactory function. RCS analysis further revealed that the association between Iron (Fe) and olfactory function was linear, while Lead (Pb) exhibited a non-linear. The BKMR model demonstrated a significant positive association between metal mixture concentration and olfactory function. Combined QG-C regression analysis suggested that metals Cr, Fe, Se, Sb, and Pb could impact the performance of the olfactory test (UPSIT), with Pb being identified as the most influential contributor. The correlation between plasma OMP protein levels and urinary metal concentrations was weak.
Conclusion Multiple metals are associated with olfactory function in the coal miners. A significant positive association was observed between metal mixture concentrations and olfactory function, with Pb being the most important contributor. In this study, plasma OMP has not been demonstrated to serve as a biomarker for olfactory function.
https://doi.org/10.3389/fpubh.2024.1447290

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Liang, D. Y., Peng, J. C., Xie, B. Y., Qin, W. X., Aschner, M., Ou, S. Y., Jiang, Y. M.
**Effects of combined exposure of manganese and iron on serum inflammatory factor levels among workers.**
Human & Experimental Toxicology 2024; Vol. 43,p
ObjectiveThe aim of the study is to examine the association between long-term occupational exposure to Mn and Fe and their health effects in workers.
Methods108 Mn workers were selected for the Mn exposure groups; 92 non-Mn workers were in the control group. Inductively coupled plasma-mass spectrometry was used to determine the Mn and Fe concentration in the working environment. Graphite furnace-atomic absorption spectroscopy was used to determine the blood Mn concentration of workers. Serum inflammatory factors were measured by enzyme-linked immunosorbent assay.
Results : The blood Mn concentration, positive rate of clinical symptoms and serum inflammatory response in the Mn exposure group was higher than in the control group.
Conclusions Low levels of Mn exposure may increase blood Mn concentrations, the rate of complaints of neurological symptoms and promote increased serum inflammatory response in workers.
https://doi.org/10.1177/09603271241293112

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Luo, K.-H., Tu, H.-P., Chung, Y.-C., Huang, M.-H., Yang, C.-C., Chen, T.-H.*, et al.*
**Unveiling the Interaction and Combined Effects of Multiple Metals/Metalloids Exposure to TNF-α and Kidney Function in Adults using Bayesian Kernel Machine Regression and Quantile-based G-computation.**
Journal of Trace Elements in Medicine and Biology 2024; Vol. p 127552.
Background Exposure to multiple metals may cause adverse effects, particularly in the kidneys. However, studies on the combined and interaction effects of metal mixtures on human health remain limited. Objective The study aims to evaluate the interaction between metals and assess the combined effects of exposure to metal mixtures on tumor necrosis factor-alpha (TNF-α) levels and kidney function.
Methods Particular emphasis has been placed on the impact of various metals, including arsenic (As), cadmium (Cd), lead (Pb), as well as essential trace elements, such as cobalt (Co), copper (Cu), selenium (Se), and zinc (Zn), on human health and their potential collective influence on both TNF-α and kidney function. This cross-sectional study analyzed the data of 421 adults who underwent a health examination.

Generalized linear model (GLM), Bayesian kernel machine regression (BKMR), and quantile-based G-computation (qgcomp) were used to evaluate the association and joint effects between the metals and TNF-α, as well as kidney function.
Results Increased concentrations of As (β = 0.11, 95% CI = 0.05, 0.17) and Pb (β = 0.30, 95% CI = 0.23, 0.37) in the blood were associated with elevated levels of TNF-α, while elevated Cu (β = -0.42, 95% CI = -0.77, -0.07) levels were linked to a significant reduction in TNF-α. The overall effect of metals mixture showed a significant association with a decline in eGFR and an increase TNF-α in the BKMR model. Qgcomp analysis of the metals mixture (β = -0.06, 95% CI = -0.07, -0.05) indicated that As, Pb, and Zn were the primary contributors to the reduction in eGFR, while As and Pb were the major contributors in metals mixture (β = 0.12, 95% CI = 0.08, 0.15) to the elevation of TNF-α levels.
Conclusion Exposure to multiple metals could have joint association with the TNF-α levels and kidney function. Furthermore, TNF-α could act as a mediator between metal mixtures and eGFR.
https://doi.org/https://doi.org/10.1016/j.jtemb.2024.127552

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Pálešová, N., Řiháčková, K., Kuta, J., Pindur, A., Šebejová, L., Čupr, P.
**Internal Flames: Metal(loid) Exposure Linked to Alteration of the Lipid Profile in Czech Male Firefighters (CELSPAC-FIREexpo Study).**
Environmental Science & Technology Letters 2024; Vol. 11 (7) ,p 679-686.
https://doi.org/10.1021/acs.estlett.4c00272

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Scarselli, A., Corfiati, M., Di Marzio, D., Marinaccio, A.
**Occupational carcinogens in Italy: an overview on exposure to cadmium and its compounds.**
Industrial Health 2024; Vol. 62 (3), p 170-181.
Given the recognized carcinogenicity of cadmium, several regulatory interventions have been carried out over the years to protect exposed workers. The aim of the study is to investigate the prevalence and extent of exposure to cadmium among Italian workers. Data was collected from a nation-wide occupational exposure registry (SIREP, 1996-2022). Gender-specific statistical analysis was carried out for some exposure-related variables (cadmium compound, activity sector, occupational group, firm size). Potentially exposed workers were estimated for some industrial sectors. Concurrent exposures were investigated using cluster analysis. Overall 4,264 measurements were analyzed. Four industrial sectors were found to be most involved by cadmium exposure: base metal manufacturing, fabricated metal products, machinery and equipment, and other transport equipment (55% of measurements). Jewellery/precious-metal workers, and glass/ceramic plant operators were found to be most at exposure risk. A total of 26,470 workers potentially exposed was estimated (69% men). Concurrent exposures to other occupational carcinogens were detected quite frequently (52% of workers). Several situations of exposure and co-exposure to cadmium deserve attention and awareness in order to minimize the risks associated with workers' health. Recognition of potentially hazardous exposure conditions is an important step in prevention strategies to better protect workers against cancer-causing agents.
https://doi.org/10.2486/indhealth.2023-0128

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Silva-Caicedo, R. F., Contreras-Llanes, M., Capelo, R., Zumel-Marne, A., Garcia-Sevillano, M. A., Santos-Sanchez, V., Alguacil, J.
**Impact of Fish, Mollusk and Seafood Consumption before Sample Donation on Urinary and Toenail Metal Levels in Workers Exposed to Heavy Metals.**
Applied Sciences-Basel 2024; Vol. 14 (18)
Introduction: We assessed the impact on metal levels of seafood, mollusk and fish consumption (SMFc) before urine and toenail sample donation among workers exposed to metals.
Methods: This is a cross-sectional epidemiological study with 101 workers from the chemical and metal industry and 40 unexposed workers from the services sector. We measured urinary (As, Ba, Be, Cd, Co, Cu, Hg, Li, Mo, Pb, Se, Sr, Tl, V, W and Zn) and toenail (same plus Al, Cr, Fe, Mn, Ni and U) metal levels.

Results: Urinary arsenic levels were higher among workers eating seafood or mollusks (102 ppm vs. 55.4 ppm; p = 0.042) or fish (109 ppm vs. 48 ppm; p = 0.007) 8 h before sample donation. Urinary mercury was associated with consumption of blue fish (11.865 ppm) and canned sardines (19.125 ppm) (p = 0.028). With respect to toenails, fish consumption was associated with aluminum (17 ppm vs. 8.6 ppm; p = 0.012) and beryllium (5 ppb vs. 1 ppb; p = 0.017). Arsenic urinary levels were associated with numbers of hours prior to sample collection since latest SMFc (p = 0.001).
Conclusion: Among workers exposed to metals, seafood, mollusk and fish consumption is an important determinant of urinary arsenic levels, as sea fish for urinary mercury, but not for other metals.
https://doi.org/10.3390/app14188174

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Singh, D., Bist, P., Choudhary, S.
**Co-exposure to multiple heavy metals and metalloid induces dose dependent modulation in antioxidative, inflammatory, DNA damage and apoptic pathways progressing to renal dysfunction in mice.**
Environmental Toxicology and Pharmacology 2024; Vol. 111
Humans are exposed to a cocktail of heavy metal toxicants at the same time in the environment rather than single metal. The kidney is often a site of early damage due to high renal contact to these pollutants. This study was done to examine the cumulative toxic effect of multiple elements prevalent in the environment. To explore the effect of subchronic exposure to heavy metal mixture male and female Swiss albino mice were randomly divided into 14 groups and given varying doses [MPL (maximum permissible limit), 1X, 5X, 10X, 50X, or 100X] of the multiple metals and metalloid mixtures via drinking water for 8 weeks. It was determined that metal treatment caused increased metal load in renal tissue. The kidney function deteriorated in response to 10X, 50X, 100X concentration of the dosing mixture was found associated to oxidative stress, glomerular damage, necrosis, cell death and further exacerbation of the inflammation.
https://doi.org/10.1016/j.etap.2024.104537

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Singh, D., Bist, P., Choudhary, S.
**Effect of co-exposure to multiple metals (Pb, Cd, Cr, Hg, Fe, Mn and Ni) and metalloid (As) on liver function in Swiss albino mice.**
BioMetals 2024;
The study examined the cumulative toxic effect of multiple elements, As, Pb, Cd, Cr, Hg, Fe, Mn and Ni on the liver function and their association with inflammation and apoptosis. To explore the health consequence of simultaneous exposure to multiple metals and metalloid, male and female Swiss Albino mice were randomly divided into 14 groups and subjected to different doses [MPL (maximum permissible limit), 1×, 5×, 10×, 50× or 100×] of metal(loid)s mixture via drinking water for 8 weeks. Data showed that combined effect of multiple elements impaired the liver function. This was associated with significant decrease in the antioxidant enzymes and the elevation in lipid peroxidation for high exposure dose of 50× and 100× ($p < 0.05$). The metal(loid)s mixture exposure led to significant increase ($p < 0.05$) in cytokines, TNF-α, IL-6 and effector caspases (3 and 6) in exposure groups above 10× dose. Histopathological observation also revealed significant damage in the hepatic tissue on exposure to high dose. Dose dependent accumulation of respective elements (As, Cd, Cr, and Pb) in the liver was observed in each of the exposure groups. However, similar dose related increment was not observed for essential metals such as Ni, Fe and Mn. Differential accumulation of metals in the liver may be attributed to the effect of co-contaminant exposure, which could affect the divalent cation absorption due to antagonism and competitive transport process. Overall findings in this study manifest the complexity of possible joint effect of co-exposure to multiple metals and metalloid on the liver function.
https://doi.org/10.1007/s10534-024-00643-9

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Singh, D., Bist, P., Choudhary, S.
**Co-exposure to multiple heavy metals and metalloid induces dose dependent modulation in antioxidative, inflammatory, DNA damage and apoptic pathways progressing to renal dysfunction in mice.**

Environmental Toxicology and Pharmacology 2024; Vol. 111
Humans are exposed to a cocktail of heavy metal toxicants at the same time in the environment rather than single metal. The kidney is often a site of early damage due to high renal contact to these pollutants. This study was done to examine the cumulative toxic effect of multiple elements prevalent in the environment. To explore the effect of subchronic exposure to heavy metal mixture male and female Swiss albino mice were randomly divided into 14 groups and given varying doses [MPL (maximum permissible limit), 1X, 5X, 10X, 50X, or 100X] of the multiple metals and metalloid mixtures via drinking water for 8 weeks. It was determined that metal treatment caused increased metal load in renal tissue. The kidney function deteriorated in response to 10X, 50X, 100X concentration of the dosing mixture was found associated to oxidative stress, glomerular damage, necrosis, cell death and further exacerbation of the inflammation.
https://doi.org/10.1016/j.etap.2024.104537

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Vilela, L., Schenk, L., Julander, A., Midander, K.
**Retention of nickel, cobalt and chromium in skin at conditions mimicking intense hand hygiene practices using water, soap, and hand-disinfectant in vitro.**
Journal of Occupational Medicine and Toxicology 2024; Vol. 19 (1)
Background During the COVID-19 pandemic, increased hand hygiene practices using water, soap and hand disinfectants, became prevalent, particularly among frontline workers. This study investigates the impact of these practices on the skin's ability to retain the allergenic metals nickel, cobalt, and chromium. The study constitutes three parts: (I) creating an impaired skin barrier, (II) exposing treated and untreated skin to nickel alone, and (III) in co-exposure with cobalt and chromium.
Methods Using full-thickness skin from stillborn piglets, in vitro experiments were conducted to assess retention of metals in skin at conditions mimicking intense hand hygiene practices. Treatment of skin with varying concentrations of sodium lauryl sulphate (SLS), to impair its barrier integrity was assessed. This was followed by exposure of treated and untreated skin to the metals, that were dissolved in Milli-Q water, 0.5% SLS, and ethanol respectively. Results Results showed that pre-treatment with 5% SLS impaired the skin barrier with regards to the measure of trans epidermal water loss (TEWL). Metal amounts retained in the skin were generally higher in treated than untreated skin. The highest amounts of metal retained in skin were observed for exposure to nickel in ethanol. Co-exposure to nickel, cobalt, and chromium in 0.5% SLS resulted in the highest amounts of total metal retention.
Conclusions The in vitro findings highlight the increased risk of metal retention in skin due to an impaired barrier. The SLS concentration used in the current study corresponds to those used in many hand hygiene products. Hence, occupational settings with frequent exposure to water, soap and disinfectants need to consider protective measures not only for the irritant exposures themselves but also simultaneous exposure to allergenic metals.
https://doi.org/10.1186/s12995-024-00442-5

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Wang, J., Wang, W., Zheng, G., Shi, F., Wu, S., Zhang, Y.
**Associations of mixed metals exposure with cognitive impairment risk: a cross-sectional study in Chinese adults.**
Postgraduate Medical Journal 2024; Vol.
Associations between exposure to single metals and cognitive impairment or related outcomes have been reported in many previous studies. However, co-exposure to more than one metal is common situation. In recent years, studies on the effects of exposure to multiple metals on cognitive impairment or related outcomes have increased, but remain very limited, with a focus on populations with occupational exposure to metals, children, and adolescents. The potential relationships between exposure to metal mixtures and risk of cognitive impairment in adults remain to be clarified.
To determine the associations between blood metal mixtures and cognitive impairment risk. Inductively coupled plasma mass spectrometry (ICP-MS) was utilized to detect the blood levels of lead (Pb), iron (Fe), copper (Cu), calcium (Ca), magnesium (Mg), and zinc (Zn). Multivariable logistic regression and Bayesian kernel machine regression (BKMR) models were employed to assess the relationships of exposure to these blood metal mixtures with the risk of cognitive impairment. It was found that four metals (Pb, Fe, Cu, and Mg) were positively correlated with cognitive impairment in each single metal model. The association of Pb

and Cu remained significant after adjusting for these six metals, with the odds ratios (95% confidence intervals) in the highest quartiles of 9.51 (4.41–20.54, p-trend <0.01) and 4.87 (2.17–10.95, p-trend <0.01), respectively.
The BKMR models indicated that co-exposure levels of Ca, Cu, Fe, Mg, Pb, and Zn were related to increased risk of cognitive impairment at ≥25th percentile compared with median, and Pb and Cu mainly contributed to the joint effect. In addition, the interaction effects of Mg and Pb/Pb and Cu on the risk of cognitive impairment were observed. Co-exposure of six metals (Pb, Fe, Cu, Ca, Mg, and Zn) increased the risk of cognitive impairment in Chinese adults, with Pb and Cu likely to have greater impact. Potential interaction effects of Mg and Pb, Pb and Cu on the risk of cognitive impairment may exist. What is already known on this subject—Co-exposure to a mixture of six metals (lead [Pb], iron, copper [Cu], calcium, magnesium, zinc) is associated with an increased risk of cognitive impairment in Chinese adults. Pb and Cu appear to have a greater impact on cognitive impairment risk among the metals studied.What the study adds—The study employs advanced Bayesian Kernel Machine Regression modeling to assess the joint and interactive effects of metal mixtures on cognitive function.How the research might affect research, practice or policy—The findings highlight the importance of considering the combined impact of environmental metal exposures in the development of public health strategies to prevent cognitive decline.
https://doi.org/10.1093/postmj/qgae154

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Wang, Y., Qiao, M., Yang, H., Chen, Y., Jiao, B., Liu, S.*, et al.*
**Investigating the relationship of co-exposure to multiple metals with chronic kidney disease: An integrated perspective from epidemiology and adverse outcome pathways.**
Journal of hazardous materials 2024; Vol. 480, p 135844.
Systematic studies on the associations between co-exposure to multiple metals and chronic kidney disease (CKD), as well as the underlying mechanisms, remain insufficient. This study aimed to provide a comprehensive perspective on the risk of CKD induced by multiple metal co-exposures through the integration of occupational epidemiology and adverse outcome pathway (AOP). The study participants included 401 male mine workers whose blood metal, beta2-microglobulin (beta2-MG), and cystatin C (Cys-C) levels were measured. Generalized linear models (GLMs), quantile g-computation models (qgcomp), least absolute shrinkage and selection operator (LASSO), and bayesian kernel machine regression (BKMR) were utilized to identify critical nephrotoxic metals. The mean concentrations of lead, cadmium, mercury, arsenic, and manganese were 191.93, 3.92, 4.66, 3.11, 11.35, and 16.33g/L, respectively. GLM, LASSO, qgcomp, and BKMR models consistently identified lead, cadmium, mercury, and arsenic as the primary contributors to kidney toxicity. Based on our epidemiological analysis, we used a computational toxicology method to construct a chemical-genetic-phenotype-disease network (CGPDN) from the Comparative Toxicogenomics Database (CTD), DisGeNET, and GeneCard databases, and further linked key events (KEs) related to kidney toxicity from the AOP-Wiki and PubMed databases. Finally, an AOP framework of multiple metals was constructed by integrating the common molecular initiating events (reactive oxygen species) and KEs (MAPK signaling pathway, oxidative stress, mitochondrial dysfunction, DNA damage, inflammation, hypertension, cell death, and kidney toxicity). This is the first AOP network to elucidate the internal association between multiple metal co-exposures and CKD, providing a crucial basis for the risk assessment of multiple metal co-exposures.
https://doi.org/10.1016/j.jhazmat.2024.135844

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Wei, N., Sanders, A. P., Wang, J., Buchanich, J. M.
**Assessing the Impact of Metal and PFAS Exposure on Chronic Kidney Disease: An NHANES data Analysis.**
Dissertation/Thesis 2024

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Wei, Y., Zhang, Y., Ji, Q., Yang, S., Yang, F.
**Association of per- and polyfluoroalkylated substances/heavy metals and bone health in children and adolescents.**
Frontiers in Public Health 2024; Vol. 12

Background : Research on the correlation between exposure to per- and polyfluoroalkylated substances (PFASs)/heavy metals and bone health during childhood and adolescence is limited. Considering their role as endocrine disruptors, we examined relationships of six PFASs and three heavy metals with bone mineral density (BMD) in children and adolescents using representative samples from the National Health and Nutrition Examination Survey (NHANES).
Methods : The study included 622 participants aged 12–19. The relationship between single pollutant and lumbar spine and total BMD was studied using linear regression analyses. Additionally, Bayesian Kernel Machine Regression (BKMR) models were applied to assess the joint effects of multiple PFASs and heavy metals exposure on the lumbar spine and total BMD.
Results : Statistically significant differences were noted in the serum concentrations of perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), blood lead (Pb), and blood manganese (Mn) between male and female participants (all <italic>p</italic> < 0.05). Single-exposure studies have shown that Mn was negatively correlated with lumbar spine BMD and total BMD. Multivariate linear regression models revealed that, in the male group, total bone density decreased as the blood PFOA levels [95% CI = (−0.031, −0.001), <italic>p</italic> = 0.040] and blood manganese levels [95% CI = (−0.009, −0.002), <italic>p</italic> = 0.004] increased. Similarly, lumbar spine bone density decreased as the blood manganese levels [95% CI = (−0.011, −0.002), <italic>p</italic> = 0.009] increased. In the female group, total bone density decreased as the serum PFNA levels [95% CI = (−0.039, 0.000), <italic>p</italic> = 0.048] increased. As shown in the BKMR model, the joint effects of pollutant mixtures, including Mn, were negatively associated with both the lumbar spine and total BMD. Among the pollutants analyzed, Mn appeared to be the primary contributor to this negative association.
Conclusion : This study suggests that exposure to certain PFASs and heavy metals may be associated with poor bone health. Childhood and adolescence are crucial stages for bone development, and improper exposure to PFASs and heavy metals during these stages could potentially jeopardize future bone health, consequently raising the risk of osteoporosis in adulthood.
https://doi.org/10.3389/fpubh.2024.1431001

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Zhu, Z., Wang, Y., Wang, Y., Fu, M., Luo, X., Wang, G.*, et al.*
**The association of mixed multi-metal exposure with sleep duration and self-reported sleep disorder: A subgroup analysis from the National Health and Nutrition Examination Survey (NHANES)☆.**
Environmental Pollution 2024; Vol. 361, 15 November 2024, 124798
Sleep disorders significantly affect sleep duration and constitute a major public health issue. However, the relationship between metal exposure and sleep is not fully elucidated. This study utilized publicly available data from the National Health and Nutrition Examination Survey (NHANES) to measure blood concentrations of seven metals-copper (Cu), zinc (Zn), selenium (Se), manganese (Mn), mercury (Hg), cadmium (Cd), and lead (Pb)-in a cohort of 4263 American adults. The relationship between metal exposure and self-reported sleep duration and sleep disorder risk was analyzed using single exposure models like logistic and linear regression and mixedexposure models such as weighted quantile sum (WQS) regression and Bayesian kernel machine regression (BKMR).
The results indicated an absence of statistically significant findings in the single exposure model. In contrast, the mixed exposure model revealed a positive correlation between selenium levels and the risk of sleep disorders across the entire population. A "U-shaped" association was identified between copper levels and the risk of sleep disorders in males, females, and individuals aged 60 and above. Moreover, a positive trend was observed between manganese levels and the risk of sleep disorders in individuals aged 60 and above. Additionally, elevated concentrations of metal mixtures were significantly associated with reduced sleep duration among females. Sensitivity analyses corroborated these findings.
In conclusion, within the context of metal mixtures, selenium may be a risk factor for sleep disorders in the general population. Manganese may be a unique risk factor in older adults. Copper levels have a "U" shaped link to sleep disorder risk in specific population subgroups. Finally, the accumulation of blood metal mixtures in females, mainly due to lead and mercury, may reduce sleep duration. Further research is necessary to validate these findings.
https://doi.org/10.1016/j.envpol.2024.124798

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## 3. Biomarqueurs – polyexpositions chimiques

Chen, Y., Li, Y., Gu, W., Liu, S., Wang, Y., Jiao, B., et al.

**The key metabolic signatures and biomarkers of polycyclic aromatic hydrocarbon-induced blood glucose elevation in chinese individuals exposed to diesel engine exhaust.**

Ecotoxicology and Environmental Safety 2024; Vol. 179,p

Due to the complexity of environmental exposure factors and the low levels of exposure in the general population, identifying the key environmental factors associated with diabetes and understanding their potential mechanisms present significant challenges. This study aimed to identify key polycyclic aromatic hydrocarbons (PAHs) contributing to increased fasting blood glucose (FBG) concentrations and to explore their potential metabolic mechanisms. We recruited a highly PAH-exposed diesel engine exhaust testing population and healthy controls. Our findings found a positive association between FBG concentrations and PAH metabolites, identifying 1-OHNa, 2-OHPh, and 9-OHPh as major contributors to the rise in FBG concentrations induced by PAH mixtures. Specifically, each 10 % increase in 1-OHNa, 2-OHPh, and 9-OHPh concentrations led to increases in FBG concentrations of 0.201 %, 0.261 %, and 0.268 %, respectively. Targeted metabolomics analysis revealed significant alterations in metabolic pathways among those exposed to high levels of PAHs, including sirtuin signaling, asparagine metabolism, and proline metabolism pathway. Toxic function analysis highlighted differential metabolites involved in various dysglycemia-related conditions, such as cardiac arrhythmia and renal damage. Mediation analysis revealed that 2-aminooctanoic acid mediated the FBG elevation induced by 2-OHPh, while 2-hydroxyphenylacetic acid and hypoxanthine acted as partial suppressors. Notably, 2-aminooctanoic acid was identified as a crucial intermediary metabolic biomarker, mediating significant portions of the associations between the multiple different structures of OH-PAHs and elevated FBG concentrations, accounting for 16.73 %, 10.84 %, 10.00 %, and 11.90 % of these effects for 1-OHPyr, 2-OHFlu, the sum concentrations of 2- and 9-OHPh, and the sum concentrations of total OH-PAHs, respectively. Overall, our study explored the potential metabolic mechanisms underlying the elevated FBG induced by PAHs and identified 2-aminooctanoic acid as a pivotal metabolic biomarker, presenting a potential target for intervention.

https://doi.org/10.1016/j.ecoenv.2024.116997

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Chen, Y., Wang, Y., Delgado, D. H., Yu, H., Zhao, T., Fang, M., Huan, T.

**Constructing HairDB to facilitate exposome research using human hair.**

Environment International 2024; Vol. 193

This study introduces HairDB, an online database serving as a comprehensive repository of hair-related chemicals for exposome research. HairDB was created via an integrative approach. It first extracted 4,184 unique hairrelated chemicals through text mining of over 34 million PubMed abstracts and 5.2 million PubMed Central articles, followed by manual data checking. HairDB also applied an artificial intelligence-enabled search to discover organic aerosol biomarkers in literature. A set of 768 chemicals used in hair-related products was then curated through a combination of manual searches and data extraction from the Cosmetic Ingredient Database (CosIng) of the European Union. From manually reading review papers, 29 organic aerosol biomarkers were extracted. Furthermore, 3,679 known exposure chemicals extracted from the Toxin and Toxin Target Database (T3DB) were incorporated in HairDB to represent the possible environmental exposures detected on hair surfaces. The comprehensive set of chemicals captured in HairDB represents the current knowledge of what can be found in and on hair. HairDB was constructed as a user-friendly web interface, allowing easy exploration of hairrelated chemicals and tailored for annotating mass spectrometry-based hair exposomics data. The development of HairDB marks an important step forward in using hair as a biological matrix for chemical exposure measurement, facilitating the adoption of hair for exposome research. HairDB is publicly available at https://www. hairdb.ca/.

https://doi.org/10.1016/j.envint.2024.109077

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Ryck, E. D., Hoornaert, E. M., Buntinx, Y., Verscheure, E., Schlünssen, V., Stierum, R., et al.

**P23-12 Use of minimally invasive matrices for characterization of biomarkers in occupational exposome studies.**

Toxicology Letters 2024; Vol. 399, p S344.

https:// doi.org/10.1016/j.toxlet.2024.07.820

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## 4. Multi-expositions pesticides, herbicides

Adeyele, E. I., Ayanyemi, E. O., Akomolafe, R. O., Sesan, O. O., Aladesanmi, O. T., Adetutu, A. O.

**Assessment of the toxic influence of locally formulated pesticides on hepatic and renal biomarkers in male Wistar rats.**

Toxicology research 2024; Vol. 13 (5), tfae157.

Background: There is growing concern of the potential damage to vital organs after long term exposure to locally formulated pesticides in rural area of Nigeria. This study was designed to assessed the effects of the individual chemical compound and their combination on the kidney and liver of rats' model. Methodology: Fifty-four rats divided into six groups and three sub-groups were exposed to 25, 50 and 75% dose of each of the pesticide's LD50 for 4h at 3days interval in an inhalation chamber for 28days. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TOT_BIL), creatinine and urea assay showed significant increase at the aforementioned doses in comparison to the control group. The red blood cell counts, hematocrit and hemoglobin concentrations were significantly altered in the rats administered varying doses of the pesticides when compared with the control. Similar result was obtained for the differential white blood cell counts. Histopathological examinations of the liver tissue of rats showed infiltrated sinusoids, traces of karypyknosis, vacuolar degeneration and microvesicular steatosis while that of the renal tissue showed glomeruli atrophy leading to widened Bowman's spaces as well as few shrunken glomeruli and varied level of degenerative tubular changes to tubular necrosis. Conclusion: This study established that individual pesticides and their mixture is toxic to the liver and kidney, as evidenced by the elevated markers of renal and liver functions and distortion of the structure of both organs as revealed by their photomicrographs. Therefore, it is a matter of public health significance to regularly monitor pesticide residues in foods and humans in order to assess the food safety risk and population exposure to pesticides.

https://doi.org/10.1093/toxres/tfae157

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Alcala, C. S., Armendariz-Arnez, C., Mora, A. M., Rodriguez-Zamora, M. G., Bradman, A., Fuhrimann, S.*, et al.*

**Association of pesticide exposure with respiratory health outcomes and rhinitis in avocado farmworkers from Michoacan, Mexico.**

The Science of the total environment 2024; Vol. 945, p 173855.

BACKGROUND: A growing literature suggests associations between occupational pesticide exposure and respiratory health. In this study, we aimed to examine the association of exposure to insecticides, fungicides, and herbicides, individually and as a mixture, with respiratory health outcomes and rhinitis in avocado farmworkers from Michoacan, Mexico.

MATERIAL AND METHODS: We conducted a cross-sectional study of 105 avocado farmworkers between May and August 2021. We quantified 12 insecticide, fungicide, and herbicide metabolites in urine samples collected during two study visits (8-10weeks apart). We collected survey data on self-reported pesticide use during the 12months prior to the baseline survey and estimated annual exposure-intensity scores (EIS) using a semi-quantitative exposure algorithm. We also assessed respiratory symptoms, including wheezing, chest tightness, wheezing after exercise, and night cough. We used generalized linear regression models to examine associations of individual urinary metabolite concentrations and annual EIS with respiratory health

outcomes and rhinitis. Mixture effects were assessed using Bayesian Weighted Quantile Sum (BWQS) regression.
RESULTS: After adjusting for multiple comparisons, we observed mostly null associations of individual pesticide metabolite concentrations and annual EIS with the outcomes of interest. However, in BWQS analyses, we found evidence of a mixture association of urinary pesticide metabolites with increased odds of night cough (OR: 5.34, 95% CrI: 1.67, 20.62). Pyrethroid metabolites 3-phenoxybenzoic acid and cis- and trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid were the main contributors to this association (43%).
CONCLUSIONS: Our findings indicate that exposure to a mixture of pesticides, particularly pyrethroid insecticides, may be associated with night cough in avocado farmworkers.
https://doi.org/10.1016/j.scitotenv.2024.173855

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Fang, G., Hasi, W., Lin, X., Han, S.
**Automated identification of pesticide mixtures via machine learning analysis of TLC-SERS spectra.**
Journal of Hazardous Materials 2024; Vol. 474
Identification of components in pesticide mixtures has been a major challenge in spectral analysis. In this paper, we assembled monolayer Ag nanoparticles on Thin -layer chromatography (TLC) plates to prepare TLC-Ag substrates with mixture separation and surface -enhanced Raman scattering (SERS) detection. Spectral scans were performed along the longitudinal direction of the TLC-Ag substrate to generate SERS spectra of all target analytes on the TLC plate. Convolutional neural network classification and spectral angle similarity machine learning algorithms were used to identify pesticide information from the TLC-SERS spectra. It was shown that the proposed automated spectral analysis method successfully classified five categories, including four pesticides (thiram, triadimefon, benzimidazole, thiamethoxam) as well as a blank TLC-Ag data control. The location of each pesticide on the TLC plate was determined by the intersection of the information curves of the two algorithms with 100 % accuracy. Therefore, this method is expected to help regulators understand the residues of mixed pesticides in agricultural products and reduce the potential risk of agricultural products to human health and the environment.
https://doi.org/10.1016/j.jhazmat.2024.134814

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Hippert, J., Talibov, M., Morlais, F., Brugioni, M., Perrier, S., Baldi, I., *et al.*
**Identification of pesticide mixtures to which French agricultural workers and farm-owners are exposed: Results from the Agriculture and Cancer (AGRICAN) cohort study.**
The Science of the total environment 2024; Vol. 955 p 176607.
Farmers, particularly in Europe, are exposed to multiple pesticides during their working life. Such exposures can cause adverse health outcomes. We aimed to identify the main pesticide mixtures to which French agricultural workers are exposed and to classify farmers into clusters based on their mixture exposure profile. The AGRICAN cohort includes farm-owners and farm workers enrolled from 2005 to 2007, with information on exact years of beginning and end of pesticide use on 11 crops and five livestock. We estimated duration of exposure to 390 pesticides identified with the PESTIMAT crop-exposure matrix for 16,905 male pesticide users from 1950 to 2009. We used a Sparse Non-negative Matrix Under-approximation to identify the main pesticide mixtures based on exposure duration, and then applied hierarchical agglomerative clustering to classify farmers sharing similar profiles of co-exposure to the mixtures. SNMU suggested 6 optimal numbers of mixtures (4, 7, 11, 15, 27, 38) explaining from 29 to 91% of total variance. We selected 27 mixtures. Mixtures contained between four to 22 pesticides and mostly concerned the use of pesticides on wheat/barley, vineyards, corn, fruit and vegetables or on multiple crops together. We selected 11 clusters composed of 395 to 4521 farmers. Some had a higher proportion of individuals working on specific crops (as vineyard or corn), while others were characterized by the diversity of crops (cluster 8:"Permanent crops, potatoes and tobacco"). This is the first study to identify pesticide mixtures in farmers and to classify them into clusters based on their mixture exposure profiles. The next step will be to study the associations between pesticide mixtures and health outcomes such as prostate cancer in AGRICAN.
https://doi.org/10.1016/j.scitotenv.2024.176607

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Li, T., Wu, X., Zheng, L., Cheng, Y., Zhao, L., Chen, Z.
**Quantitative tracing of typical herbicides and their metabolites in sorghum agrosystems for fate tendency and cumulative risk.**
Food chemistry 2024; Vol. 464 (Pt 1),p 141638.
Elucidating the combined exposure of agrochemicals is essential for safeguarding human health and agroecosystem safety. A rapid and high-sensitivity UHPLC-MS/MS method was developed for simultaneous quantification of nine compounds in sorghum by an assembly-line optimization process with a limit of quantitation of 0.001mg/kg. The concentration variation of atrazine, quinclorac, fluroxypyr-meptyl and metabolites was reflected by terminal magnitudes of ≤0.0665mg/kg. Additionally, atrazine was dealkylated to deethyl atrazine and desethyl desisopropyl atrazine at concentrations of 0.0014-0.0058mg/kg during the sorghum harvest. Acceptable health hazardous of atrazine and quinclorac for all life cycle populations were comparatively assessed via deterministic and probabilistic models, in which atrazine gained an 83.55% share of cumulative dietary risks. Rural residents had significantly higher risks than urban residents, and children were the most sensitive group. Despite the low health risks, combined exposure to herbicides and their metabolites should be continuously stressed, given their cumulative amplification effects.
https://doi.org/10.1016/j.foodchem.2024.141638

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Lozano-Paniagua, D., Parron, T., Alarcon, R., Requena, M., Lacasana, M., Hernandez, A. F.
**A Th2-type immune response and low-grade systemic inflammatory reaction as potential immunotoxic effects in intensive agriculture farmers exposed to pesticides.**
Science of the Total Environment 2024; Vol. 938
Pesticides are chemicals widely used in agriculture to keep crops healthy and prevent them from being destroyed by pests, thus contributing to a sustainable food and feed production. However, long-term exposure to these compounds may be harmful to human health as they can affect the function of various organs systems, including the immune system. There is growing evidence that pesticides may increase the risk of developing immune-based diseases and inflammation. This study assessed whether greenhouse farmers occupationally exposed to pesticides presented alterations in immunoregulatory proteins, used as surrogate biomarkers of immune function. The study population consisted of 175 greenhouse workers occupationally exposed to pesticides and 91 non-exposed controls. Serum levels of 27 cytokines, chemokines and growth factors were measured using a magnetic beadbased immunoassay in a subpopulation of 111 greenhouse workers and 79 non-exposed controls. Since analytical determinations were performed in two periods of the same crop season with different use of pesticides (period of high and low pesticide exposure), linear mixed models for repeated measures were used to optimize statistical inference. The increase in IL-13, IL-4 and IL-6 observed in greenhouse workers compared to controls, and in the period of high exposure to pesticides relative to that of low exposure, suggest an altered Th1/Th2 balance towards the Th2 response. This finding points to a type-2 inflammation commonly presented as allergic inflammation, which has often been reported in farm-workers and in which pesticide exposure is considered a risk factor. Furthermore, the increase in IL-1 beta and VEGF, mediators of inflammation and angiogenesis, may suggest a low-grade systemic inflammation that might underlie chronic pathological conditions linked to pesticide exposure.
https://doi.org/10.1016/j.scitotenv.2024.173545

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## 5. Polyexpositions chimiques chez l'homme

Tagne-Fotso, R., Riou, M., Saoudi, A., Zeghnoun, A., Frederiksen, H., Berman, T., et al.

**Exposure to bisphenol A in European women from 2007 to 2014 using human biomonitoring data – The European Joint Programme HBM4EU.**

Environment International 2024; Vol. 190, p 108912.

Background Bisphenol A (BPA; or 4,4'-isopropylidenediphenol) is an endocrine disrupting chemical. It was widely used in a variety of plastic-based manufactured products for several years. The European Food Safety Authority (EFSA) recently reduced the Tolerable Daily Intake (TDI) for BPA by 20,000 times due to concerns about immune-toxicity.

Objective We used human biomonitoring (HBM) data to investigate the general level of BPA exposure from 2007 to 2014 of European women aged 18–73 years (n = 4,226) and its determinants.

Methods Fifteen studies from 12 countries (Austria, Belgium, Denmark, France, Germany, Greece, Israel, Luxembourg, Slovenia, Spain, Sweden, and the United Kingdom) were included in the BPA Study protocol developed within the European Joint Programme HBM4EU. Seventy variables related to the BPA exposure were collected through a rigorous post-harmonization process. Linear mixed regression models were used to investigate the determinants of total urine BPA in the combined population.

Results Total BPA was quantified in 85–100 % of women in 14 out of 15 contributing studies. Only the Austrian PBAT study (Western Europe), which had a limit of quantification 2.5 to 25-fold higher than the other studies (LOQ=2.5 µg/L), found total BPA in less than 5 % of the urine samples analyzed. The geometric mean (GM) of total urine BPA ranged from 0.77 to 2.47 µg/L among the contributing studies. The lowest GM of total BPA was observed in France (Western Europe) from the ELFE subset (GM=0.77 µg/L (0.98 µg/g creatinine), n = 1741), and the highest levels were found in Belgium (Western Europe) and Greece (Southern Europe), from DEMOCOPHES (GM=2.47 µg/L (2.26 µg/g creatinine), n = 129) and HELIX-RHEA (GM=2.47 µg/L (2.44 µg/g creatinine), n = 194) subsets, respectively. One hundred percent of women in 14 out of 15 data collections in this study exceeded the health-based human biomonitoring guidance value for the general population (HBM-GVGenPop) of 0.0115 µg total BPA/L urine derived from the updated EFSA's BPA TDI. Variables related to the measurement of total urine BPA and those related to the main socio-demographic characteristics (age, height, weight, education, smoking status) were collected in almost all studies, while several variables related to BPA exposure factors were not gathered in most of the original studies (consumption of beverages contained in plastic bottles, consumption of canned food or beverages, consumption of food in contact with plastic packaging, use of plastic film or plastic containers for food, having a plastic floor covering in the house, use of thermal paper…). No clear determinants of total urine BPA concentrations among European women were found. A broader range of data planned for collection in the original questionnaires of the contributing studies would have resulted in a more thorough investigation of the determinants of BPA exposure in European women.

Conclusion This study highlights the urgent need for action to further reduce exposure to BPA to protect the population, as is already the case in the European Union. The study also underscores the importance of pre-harmonizing HBM design and data for producing comparable data and interpretable results at a European-wide level, and to increase HBM uptake by regulatory agencies.

https://doi.org/https://doi.org/10.1016/j.envint.2024.108912

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Qian, C., Bai, L., Wang, W., Luo, Y., Li, J., Wang, Y.

**Occurrences and migration characteristics of photoinitiators in paper food packaging: Implication for human exposure.**

Journal of Environmental Sciences 2024; Vol.

Photoinitiators (PIs), as an important component of UV inks, are widely used in the printing of paper food packaging. Nevertheless, there is limited information concerning the identification of PIs in food packaging and their potential migration rules under natural storage condition. In this study, 23 target PIs detected in paper food packaging were dominated by benzophenones (BZPs), followed by amine co-initiators (ACIs), thioxanthones (TXs) and phosphine oxides (POs). The concentration of ΣPIs ranged between 48.3 and 1.11 × 105 ng/g. Meanwhile, the concentration of ΣPIs were found to be significantly higher in Corrugated paper compared to Polyethylene (PE) coated paper, Composite paper and White card paper. Benzophenone (BP) was found as the dominant PI congener in Corrugated paper, with the concentration ranging from 923-3.66 × 104 ng/g. The migration quantity of ΣPIs increased in a time-dependent manner in the first 13 days and then eventually reached equilibrium. Low temperatures had a certain inhibitory effect on the migration of PIs from paper packaging to food. Under high exposure scenario, the EDIs of ΣPIs for children,

adolescents, and adults were 31.4 ng/(kg bw·day), 17.2 ng/(kg bw·day), and 14.4 ng/(kg bw·day), respectively, all of which did not exceed the reference dose, indicating that dietary intake of PIs does not pose any health risks to the human body.

https://doi.org/https://doi.org/10.1016/j.jes.2024.09.021

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Palmqvist, T., Lopez-Riego, M., Bucher, M., Oestreicher, U., Pojtinger, S., Giesen, U., et al.

**Biological effectiveness of combined exposure to neutrons and gamma radiation applied in two orders of sequence: Relevance for biological dosimetry after nuclear emergencies.**

Radiation Medicine and Protection 2024; Vol.

Objective After a nuclear detonation, people will be exposed to varying mixtures of neutrons and gamma radiation and the biological effectiveness of mixed beams is not well known. Additionally, it is not known how far both radiation types interact, a question that is relevant for generating calibration curves for the purpose of biological dosimetry. The objective of this study was to investigate the potential impact of two different combinations of neutron and gamma radiation on gene expression and dicentric chromosomes in peripheral blood mononuclear cells (PBMC).

Methods Whole blood from 3 human donors was exposed to neutrons with an energy spectrum similar to that of the Hiroshima uranium bomb, to gamma radiation from a 60Co source and to a 50:50 combination of both radiations, given in two orders of sequence. In all cases the total doses were 0.5, 0.75 and 1.0 Gy. Dicentric chromosomes were analyzed by light microscopy and the expression of six known radiation-responsive genes BBC3, CDKN1A, FDXR, GADD45A, MDM2, and XPC were analyzed by RT-qPCR.

Results Per unit dose, exposure to neutrons lead to a higher level of dicentrics and gene expression as compared to gamma radiation. Dose-response relationships for both endpoints were linear, allowing calculating the expected outcome of combined exposure by arithmetic. For dicentric chromosomes, the RBE values for 60Co→neutrons, neutrons→60Co and neutrons were 4.05, 3.62 and 7.30 respectively. For gene expression the RBE values were gene-specific, but showed values in the range of 1.14–3.01 for 60Co→neutrons, 1.33–2.68 for neutrons→60Co and 1.39–3.91 for neutrons.

Conclusions The results demonstrate that combined exposure to neutrons and gamma radiation, regardless of the order of sequence, leads to an additive response at both endpoints. This indicates that calibration curves for mixed beams can be constructed from dose response relationships of the single beam components.

https://doi.org/https://doi.org/10.1016/j.radmp.2024.10.004

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Braun, G., Herberth, G., Krauss, M., König, M., Wojtysiak, N., Zenclussen, A. C., Escher, B. I.

**Neurotoxic mixture effects of chemicals extracted from blood of pregnant women.**

Science 2024; Vol. 386 (6719),p 301-309.

Human biomonitoring studies typically capture only a small and unknown fraction of the entire chemical universe. We combined chemical analysis with a high-throughput in vitro assay for neurotoxicity to capture complex mixtures of organic chemicals in blood. Plasma samples of 624 pregnant women from the German LiNA cohort were extracted with a nonselective extraction method for organic chemicals. 294 of >1000 target analytes were detected and quantified. Many of the detected chemicals as well as the whole extracts interfered with neurite development. Experimental testing of simulated complex mixtures of detected chemicals in the neurotoxicity assay confirmed additive mixture effects at concentrations less than individual chemicals' effect thresholds. The use of high-throughput target screening combined with bioassays has the potential to improve human biomonitoring and provide a new approach to including mixture effects in epidemiological studies. Exposure to exogenous chemicals can influence human health, particularly during critical periods such as pregnancy. Braun et al. used high-resolution mass spectrometry and an in vitro assay to identify chemicals in the blood of pregnant women from Germany and characterized the individual and mixed neurotoxicity effects. Chemicals attributed to industry and consumer goods were the major drivers of the neurotoxic effects in mixtures. This work demonstrates the power of

comprehensive monitoring to inform human chemical exposure and help guide risk assessment. —Michael A. Funk and Iyinoluwa Sofowora

https://doi.org/doi:10.1126/science.adq0336

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Du, X., Xu, X., Yu, H., Du, Z., Wu, Y., Qian, K., et al.

**Thyrotoxic Effects of Mixed Exposure to Perfluorinated Compounds: Integrating Population-Based, Toxicogenomic, Animal, and Cellular Evidence to Elucidate Molecular Mechanisms and Identify Potential Effector Targets.**

Environmental science & technology 2024; Vol. 58 (41), p 18177-18189.

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are emerging environmental endocrine disruptors that may adversely affect the human endocrine system, particularly the thyroid gland, the largest endocrine gland in the human body.

An epidemiologic survey was conducted involving 318 community residents in Shanghai, China, to assess PFAS exposure levels. The relationship between PFAS exposure and five thyroid function indicators was analyzed using Bayesian Kernel Regression (BKMR) and Weighted Quantile Sum Regression (WQS). Ten effector genes related to PFAS and thyroid diseases were identified through the Comparative Toxicogenomics Database (CTD) for bioinformatics analysis and pathways involved were explored through mediation analysis. In vivo validation of these effector genes was conducted using PCR, complemented by in vitro cellular experiments involving transcriptome sequencing and the construction of animal models to simulate mixed PFAS exposure in the general population. Mixed PFAS exposure was found to impact thyroid health primarily through pathways related to lipid metabolism in toxicogenomic studies and resulted in the upregulation of key genes associated with lipid metabolism in animal models. Our results demonstrate that PFAS exposure could affect the expression of lipid metabolism pathways through the modulation of transcription factors, contributing to the development of thyroid disease.

https://doi.org/10.1021/acs.est.4c06287

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Kim, Y., Jong-Hyeop, O., Cho, H., Ye, S.

**Recognized cases of amyotrophic lateral sclerosis in automobile workers by the Korean Epidemiologic Investigation Evaluation Committee.**

Annals of Occupational and Environmental Medicine 2024; Vol. 36,

Background: Three automobile company workers (one from Factory D and two from Factory E) were diagnosed with amyotrophic lateral sclerosis. The Korean Epidemiologic Investigation and Evaluation Committee determined that there is considerable scientific evidence supporting the association between amyotrophic lateral sclerosis and combined exposure to heavy metals, organic solvents, and diesel exhaust at the manufacturing plant.

Case presentation: Patient A, who primarily engaged in engine processing and completed vehicle inspection at Factory D, was exposed to considerable amounts of heavy metals and organic solvents during medium- and large-engine processing, welding, and painting for over 23 years. Additionally, the patient was likely exposed to diesel exhaust for 33 years from forklifts delivering engines in the workshop. Patients B and C, who were responsible for engine assembly, ignition testing, and engine shipment at Factory E since around 1990, were exposed to lead and benzene from gasoline during engine ignition tests in the engine department for 15 and 16 years, respectively. They also encountered welding fumes, heavy metals, and organic solvents during welding and painting tasks. In addition, Patients B and C were continuously exposed to diesel exhaust from logistics vehicles on standby during work hours for 25 and 30 years, respectively.

Conclusions: Although the specific level of lead exposure causing amyotrophic lateral sclerosis remains undetermined, numerous studies have consistently reported a relationship between lead exposure and disease development. Limited evidence suggests that exposure to organic solvents and diesel exhaust may increase the risk of amyotrophic lateral sclerosis. Therefore, the Epidemiological Investigation and Evaluation Committee concluded that the three patients' work-related exposure to heavy metals, organic

solvents, and diesel exhaust is significantly supported by scientific evidence as a cause of their amyotrophic lateral sclerosis.

https://doi.org/10.35371/aoem.2024.36.e28

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Li, T., Wu, X., Zheng, L., Cheng, Y., Zhao, L., Chen, Z.

**Quantitative tracing of typical herbicides and their metabolites in sorghum agrosystems for fate tendency and cumulative risk.**

Food chemistry 2024; Vol. 464 (Pt 1), p 141638-141638.

Elucidating the combined exposure of agrochemicals is essential for safeguarding human health and agroecosystem safety. A rapid and high-sensitivity UHPLC-MS/MS method was developed for simultaneous quantification of nine compounds in sorghum by an assembly-line optimization process with a limit of quantitation of 0.001mg/kg. The concentration variation of atrazine, quinclorac, fluroxypyr-meptyl and metabolites was reflected by terminal magnitudes of ≤0.0665mg/kg. Additionally, atrazine was dealkylated to deethyl atrazine and desethyl desisopropyl atrazine at concentrations of 0.0014-0.0058mg/kg during the sorghum harvest. Acceptable health hazardous of atrazine and quinclorac for all life cycle populations were comparatively assessed via deterministic and probabilistic models, in which atrazine gained an 83.55% share of cumulative dietary risks. Rural residents had significantly higher risks than urban residents, and children were the most sensitive group. Despite the low health risks, combined exposure to herbicides and their metabolites should be continuously stressed, given their cumulative amplification effects.

https://doi.org/10.1016/j.foodchem.2024.141638

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Fontana, L., Stabile, L., Caracci, E., Chaillon, A., Ait-Ikhlef, K., Buonanno, G.

**Filovirus outbreak responses and occupational health effects of chlorine spraying in healthcare workers: a systematic review and meta-analysis of alternative disinfectants and application methods.**

MedRxiv : the preprint server for health sciences 2024; Vol.

Objective: In the context of filovirus outbreaks, chlorine spraying has been the standard for infection prevention and control. Due to potential occupational health risks, public health institutions now recommend wiping, which is labor-intensive and may increase the risk of heat stress for healthcare workers wearing personal protective equipment. This systematic review and meta-analysis quantified the health effects of occupational exposure to chlorine-based products compared to other disinfectants, and the effects of spraying compared to general disinfection tasks (GDTs) like wiping and mopping, in healthcare settings. Data sources design and eligibility criteria: MEDLINE, Scopus, and ScienceDirect were searched for studies addressing the association between exposure to disinfectants applied by different application methods and occupational diseases in healthcare settings. Risk of bias was assessed by two independent reviewers using a validated tool.

Data extraction and synthesis: Two reviewers independently screened and performed data extraction and synthesis. A third reviewer resolved disagreements. Meta-analyses were conducted using fixed- and random-effects models based on the Higgins I2 statistic. Results: 30 studies investigating chlorine-based products (7,123 participants), glutaraldehyde (6,256 participants), peracetic acid, acetic acid and hydrogen peroxide (4,728 participants), quaternary ammonium compounds (QACs) (9,270 participants), use of spray (4,568 participants) and GDTs (3,480 participants) were included. Most had a cross-sectional design and high risk of bias. Meta-analysis indicates a significant association between respiratory conditions and exposure to chlorine-based products (OR 1.71, 95%CI 1.41-2.08), glutaraldehyde (OR 1.44, 95%CI 1.14-1.81), QACs (OR 1.30, 95%CI 1.06-1.60), use of spray (OR 2.25, 95%CI 1.61-3.14) and GDTs (OR 2.20, 95%CI 1.66-2.90). The relative odds ratio (ROR) of respiratory conditions for chlorine-based products compared to QACs was 0.76 (95%CI 0.62-0.94). The ROR for the use of spray compared to GDTs was 0.98 (95%CI 0.74-1.29). Strengths include evaluating respiratory health risks of disinfectants, applying a validated tool, using both fixed- and random-effects models, and comparing pooled effect sizes. Limitations include high risk of

bias for the majority of included articles, varying confounder adjustments, underreported non-respiratory outcomes, and unspecified disinfectants and PPE use for spray and GDTs articles.

Conclusion: Chlorine-based disinfectants significantly increase respiratory risk compared to QACs. Sprays and general disinfection tasks present similar risks. Our findings advocate for using less hazardous products like QACs, rather than banning sprays in filovirus outbreak responses to enhance disinfection safety. Prospero registration number: CRD42023479363.

https://doi.org/10.1101/2024.09.18.24313940

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Geueke, B., Parkinson, L. V., Groh, K. J., Kassotis, C. D., Maffini, M. V., Martin, O. V., et al.

**Evidence for widespread human exposure to food contact chemicals.**

Journal of Exposure Science and Environmental Epidemiology 2024; Vol.

Background: Over 1800 food contact chemicals (FCCs) are known to migrate from food contact articles used to store, process, package, and serve foodstuffs. Many of these FCCs have hazard properties of concern, and still others have never been tested for toxicity. Humans are known to be exposed to FCCs via foods, but the full extent of human exposure to all FCCs is unknown.

Objective: To close this important knowledge gap, we conducted a systematic overview of FCCs that have been monitored and detected in human biomonitoring studies according to a previously published protocol. Methods: We first compared the more than 14,000 known FCCs to five biomonitoring programs and three metabolome/exposome databases. In a second step, we prioritized FCCs that have been frequently detected in food contact materials and systematically mapped the available evidence for their presence in humans.

Results: For 25% of the known FCCs (3601), we found evidence for their presence in humans. This includes 194 FCCs from human biomonitoring programs, with 80 of these having hazard properties of high concern. Of the 3528 FCCs included in metabolome/exposome databases, most are from the Blood Exposome Database. We found evidence for the presence in humans for 63 of the 175 prioritized FCCs included in the systematic evidence map, and 59 of the prioritized FCCs lack hazard data.

Significance: Notwithstanding that there are also other sources of exposure for many FCCs, these data will help to prioritize FCCs of concern by linking information on migration and biomonitoring. Our results on FCCs monitored in humans are available as an interactive dashboard (FCChumon) to enable policymakers, public health researchers, and food industry decision-makers to make food contact materials and articles safer, reduce human exposure to hazardous FCCs and improve public health.

Impact statement : We present systematically compiled evidence on human exposure to 3601 food contact chemicals (FCCs) and highlight FCCs that are of concern because of their known hazard properties. Further, we identify relevant data gaps for FCCs found in food contact materials and foods. This article improves the understanding of food contact materials' contribution to chemical exposure for the human population and highlights opportunities for improving public health.

https://doi.org/10.1038/s41370-024-00718-2

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Ki, N., Shin, S., Choi, J., Shim, S., Byeon, S.

**Chemical Substance Exposure of Some Cleaning Workers in Korea: Focusing on Inhalation Exposure.**

Applied Sciences-Basel 2024; Vol. 14 (17)

This study aimed to prevent health damage caused by chemical exposure among cleaning workers who use cleaning agents and disinfectants in facility management and kitchen areas. We analyzed 5 years of measurement data (2016-2020) for cleaning workers across various industries in Korea, and conducted an exposure survey and health risk assessment for the two most frequently measured substances (i.e., 2-butoxyethanol and sodium hydroxide) and representative substances generated by their combined use (i.e., chlorine and chloroform).

The findings indicate that when chlorine was generated by mixing hypochlorite-based disinfectants (e.g., bleach) with acidic cleaners containing substances such as nitric, hydrochloric, or citric acid, the risk index for chlorine gas (based on the 95th percentile exposure values) was 5.65 in the facility management cleaning industry, exceeding the acceptable threshold of 1.

Because of the high usage and exposure frequency of cleaning and disinfecting agents and the common practice of mixing multiple products to enhance cleaning efficacy, it is necessary to manage hazardous risk factors by providing education on appropriate working methods, supplying personal protective equipment, and installing ventilation systems for these workers. Further research on the health risk assessment of combined chemical use is needed.

https://doi.org/10.3390/app14177533

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Maddalon, A., Pierzchalski, A., Krause, J. L., Bauer, M., Finckh, S., Brack, W., et al.

**Impact of chemical mixtures from wastewater treatment plant effluents on human immune cell activation: An effect-based analysis.**

Science of the Total Environment 2024; Vol. 906

Background: Humans are exposed to many different chemicals on a daily basis, mostly as chemical mixtures, usually from food, consumer products and the environment. Wastewater treatment plant effluent contains mixtures of chemicals that have been discarded or excreted by humans and not removed by water treatment. These effluents contribute directly to water pollution, they are used in agriculture and may affect human health. The possible effect of such chemical mixtures on the immune system has not been characterized. Objective: The aim of this study was to investigate the effect of extracts obtained from four European wastewater treatment plant effluents on human primary immune cell activation. Methods: Immune cells were exposed to the effluent extracts and modulation of cell activation was performed by multi-parameter flow cytometry. Messenger-RNA (mRNA) expression of genes related to immune system and hormone receptors was measured by RT-PCR. Results: The exposure of immune cells to these extracts, containing 339 detected chemicals, significantly reduced the activation of human lymphocytes, mainly affecting T helper and mucosal-associated invariant T cells. In addition, basophil activation was also altered upon mixture exposure. Concerning mRNA expression, we observed that 12 transcripts were down-regulated by at least one extract while 11 were up-regulated. Correlation analyses between the analyzed immune parameters and the concentration of chemicals in the WWTP extracts, highlighted the most immunomodulatory chemicals. Discussion: Our results suggest that the mixture of chemicals present in the effluents of wastewater treatment plants could be considered as immunosuppressive, due to their ability to interfere with the activation of immune cells, a process of utmost importance for the functionality of the immune system. The combined approach of immune effect-based analysis and chemical content analysis used in our study provides a useful tool for inves-tigating the effect of environmental mixtures on the human immune response.

https://doi.org/10.1016/j.scitotenv.2023.167495

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West, M., Brown, S., Noth, E., Domitrovich, J., Dubose, K. N.

**A review of occupational exposures to carcinogens among wildland firefighters.**

Journal of Occupational and Environmental Hygiene 2024; Vol. 21 (10), p 741-764.

Wildfires can negatively impact the health and well-being of wildland firefighters through a variety of exposure pathways. Many studies have measured acute health effects from occupational exposure to pollutants in wildfire smoke; however, research specifically examining cancer risks from exposure to carcinogens is limited.

This review aimed to better understand cancer risk in this occupation by assessing the existing evidence of exposures and summarizing measured concentrations of carcinogens among wildland firefighters. A systematic search was conducted to identify scientific papers using the following databases: Medline(OVID), Embase(OVID), PsycINFO(OVID), Cochrane Library, CINAHL(EBSCOHost), EconLit(EBSCOHost), Scopus, Agricultural and Environmental Science Collect(ProQuest), and NIOSHTIC-2.

Forty-nine papers were identified that met eligibility criteria. Across the papers, 31 carcinogens were identified and quantified using a variety of assessment methods. Papers measured particulate matter (N = 26), polycyclic aromatic hydrocarbons (N = 12), volatile organic compounds (N = 14), crystalline silica (N = 5), black carbon (N = 4), asbestos (N = 3), radionuclides (N = 7), and metals (N = 2). Most papers measured inhalation exposures through traditional air sampling methods, but a subset of exposures to polycyclic aromatic hydrocarbons (N = 8), as well as heavy metals (N = 1), were measured through urinary biomarkers and naphthalene was measured using dermal wipe samples (N = 2). Although the heterogeneity of exposure assessment methods made direct comparison of concentrations difficult, the papers provide consistent evidence that wildland firefighters are regularly exposed to carcinogens. All wildland fire personnel should continue to implement recommended mitigation strategies and support new mitigations to reduce exposure to carcinogens on the job.
https://doi.org/10.1080/15459624.2024.238853

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## 6. Expositions multiples aux polluants ambiants, VOCs

Thongsak, N., Chitapanarux, T., Chotirosniramit, A., Chakrabandhu, S., Traisathit, P., Nakharutai, N.*, et al.*
**Air pollutants and primary liver cancer mortality: a cohort study in crop-burning activities and forest fires area.**
Frontiers in Public Health 2024; Vol. 12,
Introduction : Northern Thailand experiences high levels of air pollution in the dry season due to agricultural waste burning and forest fires. Some air pollutants can enter the bloodstream, and the liver has the role of detoxifying these along with other harmful substances. In this study, we assessed the effects of long-term exposure to air pollutants on liver cancer mortality in this area. Methods : A cohort of 10,859 primary liver cancer patients diagnosed between 2003 and 2018 and followed up to the end of 2020 were included in the study. Extended time-varying covariates of the annually averaged pollutant concentrations updated each year were utilized. The associations between air pollutants and mortality risk were examined by using a Cox proportional hazard model. Results : Metastatic cancer stage had the highest adjusted hazard ratio (aHR) of 3.57 (95% confidence interval (CI):3.23–3.95). Being male (aHR = 1.10; 95% CI: 1.04–1.15), over 60 years old (aHR = 1.16; 95% CI: 1.11–1.21), having a history of smoking (aHR = 1.16; 95%CI: 1.11–1.22), and being exposed to a time-updated local concentration of PM<sub>2.5</sub> of 40 µg/m<sup>3</sup> (aHR = 1.10; 95% CI: 1.05–1.15) increased the mortality risk. Conclusion : We found that air pollution is one of several detrimental factors on the mortality risk of liver cancer
https://doi.org/10.3389/fpubh.2024.1389760
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Zheng, K., Yang, D., Qi, W., He, X., Qu, S., Chu, L.*, et al.*
**Air pollutant exposure is associated with visual trajectories and visual impairment in children.**
Journal of Hazardous Materials 2024; Vol. 480, p 135842.
Air pollution is associated with vision loss in children, but the relationship with vision trajectories has not been explored. The study was conducted as a prospective cohort in 16 districts of Shanghai from 2021 to 2023, involving 5612 children with complete survey data. Each child underwent 3–4 eye tests, including unaided visual acuity and computerized refraction. Children's air pollutant exposure levels (PM2.5, PM10, O3, SO2, NO2, and CO) were assessed using school addresses and examination dates. Latent class mixture modeling was used to identify the trajectories of changes in vision-related measurements in children. Multinomial logistic regression and Cox proportional hazards regression were used to examine the association of air pollutant exposure and visual trajectories, as well as visual impairment outcomes. The study identified three trajectory categories for children's unaided visual acuity, spherical equivalent, and four trajectory categories for axial length. Increased levels of PM2.5, PM10, O3, and SO2 exposure are associated with an increased risk of categorizing vision-related measurements into the "poor" category trajectory in children. Increased exposure to PM2.5, O3, and NO2 was associated with an increased risk of

visual impairment outcomes in children with normal vision at baseline, and the effect was more significant in female and older children.
https://doi.org/https://doi.org/10.1016/j.jhazmat.2024.135842

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Yang, J., Zhang, X., Liu, Z., Yang, C., Li, S., Zhou, H., Gao, Z.
**The impact of emerging contaminants exposure on human health effects: A review of organoid assessment models.**
Chemical Engineering Journal 2024; Vol. 498, p 155882.
With the development of industrialization and modernization, the exposure risk of emerging contaminants in the environment has inevitably increased. However, compared with traditional pollutants, little is known about the adverse effects of trace emerging contaminants exposure on human health. At present, most of the existing exposure assessment models remain at the cellular level and animal level, but due to species differences, it is difficult to fully deduce to the human level. As an in vitro model based on tissue-engineering cells, organoids have the cell type and structure of the corresponding human organs and show some similar functions. Organoid models can overcome the shortcomings of cell experiments and simulate the complex environment in vivo, and are gradually widely used in emerging contaminants exposure assessment. This review introduces the advantages and characteristics of organoids and organoid exposure assessment models. The research status, current limitations, and application prospects of organoid models in exposure assessment of emerging contaminants are summarized. This study aims to promote the in-depth development of organoid applications and provide new ideas for exposure assessment and toxicity mechanism research of emerging contaminants.
https://doi.org/https://doi.org/10.1016/j.cej.2024.155882

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Fowler, C. H., Reuben, A., Stapleton, H. M., Hoffman, K., Herkert, N., Barakat, L., Gaffrey, M. S.
**Children's exposure to chemical contaminants: Demographic disparities and associations with the developing basal ganglia.**
Environmental Research 2024; Vol. 263, p 119990.
Children are regularly exposed to chemical contaminants that may influence brain development. However, relatively little is known about how these contaminants impact the developing human brain. Here, we combined silicone wristband exposure assessments with neuroimaging for the first time to examine how chemical contaminant mixtures are associated with the developing basal ganglia—a brain region key for the healthy development of emotion, reward, and motor processing, and which may be particularly susceptible to contaminant harm. Further, we examined demographic disparities in exposures to clarify which children were at highest risk for any contaminant-associated neurobiological changes. Participants included 62 community children (average age 7.00 years, 53% female, 66% White) who underwent structural neuroimaging to provide data on their basal ganglia structure and wore a silicone wristband for seven days to track their chemical contaminant exposure. 45 chemical contaminants—including phthalates and their alternatives, brominated flame retardants, organophosphate esters, pesticides, polycyclic aromatic hydrocarbons, and polychlorinated biphenyls—were detected in over 75% of wristbands. Notable demographic disparities in exposure were present, such that Non-White and lower-income children were more exposed to several contaminants. Exposure to chemical contaminant mixtures was not associated with overall basal ganglia volume; however, two organophosphate esters (2IPPDPP and 4IPPDPP) were both associated with a larger globus pallidus, a basal ganglia sub-region. Results highlight demographic disparities in exposure and suggest possible risks to a brain region key for healthy emotional development.
https://doi.org/https://doi.org/10.1016/j.envres.2024.119990

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Zhu, Y., Ju, Y., Wang, M., Wu, R.

**Depressive symptoms mediate the relationship between blood volatile organic compounds exposure and short sleep duration among US adults.**

Journal of Environmental Sciences 2024; Vol.,p

The associations of volatile organic compounds (VOCs) exposure with short sleep duration (SSD) have rarely been studied. We aimed to evaluate the correlation between VOC exposure and SSD risk, while also exploring the potential mediating influence of depressive symptoms. Blood concentrations of seven VOCs, namely benzene, toluene, ethylbenzene, m-/p-xylene, o-xylene, styrene (collectively known as BTEXS), and 1,4-dichlorobenzene, were analyzed in 2905 U.S. adults. Weighted logistic regression, quantile-based g-computation (QGC), and weighted quantile sum (WQS) regression were employed to investigate associations between selected VOCs and SSD risk. Mediation analyses were conducted to explore the potential mediating effects of depressive symptoms on these relationships. Increased blood levels of BTEXS were positively correlated with SSD risk, with odds ratios (OR) ranging from 1.130 to 1.212 (all $P < 0.05$). A nonlinear association between toluene concentration and SSD risk was observed (P for nonlinearity = 0.028). Both QGC and WQS analyses indicated a positive association between co-exposure to VOCs and SSD, with styrene showing the highest positive weights (QGC: OR = 1.313, 95 % confidence interval (CI): 1.038–1.660; WQS: OR = 1.386, 95 % CI: 1.110–1.731). Furthermore, BTEXS exposure was positively linked to depressive symptoms, which in turn were significantly associated with SSD risk. Mediation analyses revealed that depressive symptoms partially mediated the relationships between individual and mixed VOCs and SSD risk, with mediation proportions ranging from 15.87 % to 20.54 % (all $P < 0.05$). These findings indicated that exposure to VOCs increased SSD risk, with depressive symptoms playing a partial mediating role.

https://doi.org/https://doi.org/10.1016/j.jes.2024.09.009

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Zhou, H., Cui, Z., Di, D., Chen, Z., Zhang, X., Ling, D., Wang, Q.

**Connecting volatile organic compounds exposure to osteoporosis risk via oxidative stress based on adverse outcome pathway methodology.**

Journal of Environmental Sciences 2024; Vol., p

Existing evidence has demonstrated the association between exposure to volatile organic compounds (VOCs) and osteoporosis (OP) risk, but the underlying mechanistic framework remains unclear. This study aimed to explore potential pathways using adverse outcome pathway (AOP) analysis, and evidence this association in middle-to-old-aged American adults using the updated National Health and Nutrition Examination Survey data. Multivariable-adjusted general linear and weighted quantile sum models were employed to analyze associations of VOC metabolites (VOCMs), representing internal VOCs exposure levels, with OP-related phenotypes. An AOP framework based on network analysis was developed by extracting target genes and phenotypes. Among 3555 American adults aged ≥ 40 years (539 OP participants), we found that increasing urinary 3- and 4-methylhippuric acid, N-acetyl-S-(n-propyl)-l-cysteine (BPMA), and N-acetyl-S-(3-hydroxypropyl)-l-cysteine were associated with elevated OP odds with odds ratios (ORs) (95 % confidence intervals, 95 % CIs) being 1.254 (1.016 to 1.548), 1.182 (1.014 to 1.377), and 1.244 (1.029 to 1.505), respectively, per standard deviation. Urinary BPMA and N-acetyl-S-(2-cyanoethyl)-l-cysteine were inversely associated with lumbar spine bone mineral density (BMD), while urinary N-acetyl-S-(2-hydroxypropyl)-l-cysteine was positively associated with hip BMD. Additionally, OP odds increased by 46.0 % (95 % CI: 3.9 % to 105.1 %) per quartile increment in the VOC mixture. AOP analysis identified 53 target genes and 9 target phenotypes, and 5 of 9 target phenotypes were oxidative stress (OS)-related. Literature and the “AOP 482” framework implied the core role of OS in the VOC exposure and prevalent OP association, with the interleukin-6 as the molecular initiating event. Our findings provided a theoretical basis for further investigation.

https://doi.org/https://doi.org/10.1016/j.jes.2024.09.010

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Fang, P., Zhang, J.-J., Lu, Z.-Q., Li, S., Xia, D.-L., Xu, Q.*, et al.*

**Effects of single and combined urinary polycyclic aromatic hydrocarbon effects on lung function in the U.S. adult population.**

BMC Public Health 2024; Vol. 24 (1),p 2778.

The impact of polycyclic aromatic hydrocarbons (PAHs) on lung function has garnered attention, but studies mostly focus on individual effect. This study investigates urinary PAH metabolites as biomarkers of exposure and assesses the relationships between single and combined exposures to nine urinary PAH metabolites and lung function in adults.

https://doi.org/10.1186/s12889-024-20267-5

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Verzola, D., Rumeo, N., Alberti, S., Loiacono, F., La Maestra, S., Passalacqua, M.*, et al.*

**Coexposure to microplastic and Bisphenol A exhacerbates damage to human kidney proximal tubular cells.**

Heliyon 2024; Vol. 10 (20),p

Microplastics (MPs) accumulate in tissues, including kidney tissue, while Bisphenol A (BPA) is a plasticizer of particular concern. At present, the combined effects of MPs and BPA are unexplored in human renal cells. Therefore, we exposed a proximal tubular cell line (PTECs) to polyethylene (PE)-MPs and BPA, both separately and in combination. When co-exposed, cells showed a significantly reduced cell viability (MTT test) and a pronounced pro-oxidant (MDA levels, NRF2 and NOX4 expression by Western blot) and pro-inflammatory response (IL1?, CCL/CCR2 and CCL/CCR5 mRNAs by RT-PCR), compared to those treated with a single compound. In addition, heat shock protein (HSP90), a chaperone involved in multiple cellular functions, was reduced (by Western Blot and immunocytochemistry), while aryl hydrocarbon receptor (AHR) expression, a transcription factor which binds environmental ligands, was increased (RT-PCR and immunofluorescence). Our research can contribute to the study of the nephrotoxic effects of pollutants and MPs and shed new light on the combined effects of BPA and PE-MPs.

https://doi.org/10.1016/j.heliyon.2024.e39426

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Cao, Q., Song, Y., Huan, C., Jia, Z., Gao, Q., Ma, X.*, et al.*

**Biological aging mediates the association between volatile organic compounds and cardiovascular disease.**

BMC public health 2024; Vol. 24 (1),p 2928-2928.

BACKGROUND: Evidence for the relationship between individual and combined volatile organic compounds (VOCs) and cardiovascular disease (CVD) is limited. Besides, the mediating role of biological aging (BA) has not been studied. Therefore, this study aimed to examine the association between VOCs and CVD risk and to explore the mediating effects of BA. METHODS: Logistic regression models were used to investigate the relationships of metabolites of volatile organic compounds (mVOCs) and BA with CVD. In addition, weighted quantile sum (WQS) regression, adaptive elastic networks, and Environmental Risk Score (AENET-ERS) were utilized to assess overall associations of mixed VOCs co-exposure with CVD. Mediation analyses were used to identify potential mediating effects of BA. RESULTS: In the single-pollutant model, CYMA was shown to be associated with an increased risk of CVD. Additionally, we identified significantly positive associations between the WQS index and CVD (odds ratio (OR)=1.292, 95% confidence interval (CI): 1.006, 1.660), and DHBMA had the greatest contribution for CVD (0.246). Furthermore, the AENET-ERS results showed that 8 mVOCs were significantly associated with CVD, and ERS was related to an elevated risk of CVD (OR=1.538, 95%CI: 1.255, 1.884). Three BA indicators mediated the association of the mVOCs mixture with CVD, with mediating effect proportions of 11.32%, 34.34%, and 7.92%, respectively. CONCLUSION: The risk of CVD was found to increase with both individual and combined exposure to VOCs. BA mediates the positive effects of VOCs on CVD, suggesting that this pathway may be one of the mechanisms of CVD.

https://doi.org/10.1186/s12889-024-20349-4

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Chen, Z., Yang, T., Zhou, R., Yang, C., Huang, Q., Cheng, S.

**Impact of polyfluoroalkyl chemicals and volatile organic compounds exposure on lung function of American adults.**

Environmental pollution (Barking, Essex : 1987) 2024; Vol. 363 (Pt 1) p 125152-125152.

BACKGROUND: Environmental chemicals, such as Perfluoroalkyl and polyfluoroalkyl substances (PFAS) and volatile organic compounds (VOCs), and the association between the combined exposure of these chemicals and human lung function remains unclear. This study aimed to explore the effects of mixed exposure to PFAS and VOCs on lung function in the general population of the United States and investigate their potential mechanisms. METHODS: Data from 30442 respondents were selected for analysis during the US National Health and Nutrition Examination Survey (NHANES) database from 2007 to 2012. Linear models, weighted quantile (WQS) regression, quantile g calculation (QGC), and Bayesian kernel machine regression (BKMR) were used to evaluate the contribution of individual components. Moreover, the interactions between substances in the dose-response relationship mixture of multiple environmental chemical exposures and lung function were also evaluated. The Benjamini-Hochberg method was used to correct multiple tests. FINDINGS: Univariate analysis showed that nitromethane was negatively correlated with FEV1 (beta =-0.052), FVC (beta =-0.056), and PEF (beta =-0.065), while perfluorohexanesulfonic acid was positively associated with FEV1 (beta=0.026), FVC (beta=0.024), FEF25-75% (beta=0.012), and PEF (beta=0.029). Multivariate analysis showed that chloroform and perfluorohexane sulfonic acid were positively associated with lung function (P <0.05), and perfluorohexane sulfonic acid contributed the most. Nitromethane and perfluorodecanoic acid were negatively associated with lung function (P < 0.05), and perfluorodecanoic acid contributed the highest weight in the negative direction. When all chemicals were in the 50th percentile, the environmental chemical mixture had no significant consistent effect or dose-response on lung function. There were interactions among various environmental chemicals within the mixture except for 2-N-methyl-PFOSA acetate and bromodichloromethane. INTERPRETATION: These results suggest that environmental mixture exposure is associated with abnormal lung function in American adults, and the interaction of various substances in the mixture affects its physiological and chemical effects.

https://doi.org/10.1016/j.envpol.2024.125152

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Huang, P.-C., Lin, T.-Y., Wu, C.-C., Lo, Y.-T. C., Lin, W.-Y., Huang, H.-B.

**Relationship between phthalate exposure and kidney function in Taiwanese adults as determined through covariate-adjusted standardization and cumulative risk assessment.**

Ecotoxicology and Environmental Safety 2024; Vol. 285

Few studies have investigated the associations between phthalate exposure and kidney function indicators in adults by simultaneously performing covariate-adjusted creatinine standardization, cumulative risk assessment, and mixture analysis. Thus, we applied these methods simultaneously to investigate the aforementioned associations in an adult population. This cross-sectional study analyzed data (N = 839) from a community-based arm of the Taiwan Biobank. The levels of 10 urinary phthalate metabolites were measured and calculated as the sum of the molar concentrations of the dibutyl phthalate metabolite (Sigma DBPm) and di(2-ethylhexyl) phthalate (DEHP) metabolite (Sigma DEHPm). The hazard index (HI) and daily intake (DI) were estimated by measuring the urinary levels of the phthalate metabolite. Kidney function biomarkers were assessed by measuring the following: blood urea nitrogen (BUN), uric acid, the albumin-to-creatinine ratio (ACR), and the estimated glomerular filtration rate (eGFR). Generalized linear models were implemented to examine the associations between exposure to individual phthalates, HI scores, and kidney function biomarkers. We also employed Bayesian kernel machine regression (BKMR) to analyze the relationships between exposure to various combinations of phthalates and kidney function. Sigma DEHPm levels were significantly and positively associated with BUN and ACR levels, and Sigma DBPm levels were positively associated with ACR levels. In addition, eGFR was negatively associated with Sigma DBPm and Sigma DEHPm levels. In the BKMR model, a mixture of 10 phthalate metabolites was significantly associated with BUN, uric acid, ACR, and eGFR results. Higher DIDEHP and higher DIDnBP values were significantly associated with lower eGFRs and higher ACRs, respectively. Higher DIDiBP and DIDEP values were significantly associated with higher uric acid levels. A higher HI was significantly associated with lower

eGFRs and higher ACRs. Our results suggest that exposure to environmental phthalates is associated with impaired kidney function in Taiwanese adults.
https://doi.org/10.1016/j.ecoenv.2024.117091

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O'donnell, C., Campbell, E. J., Mccormick, S., Anenberg, S. C.
**Prenatal exposure to air pollution and maternal and fetal thyroid function: a systematic review of the epidemiological evidence.**
Environmental Health 2024; Vol. 23 (1),p
Background : Exposure to ambient air pollution is a top risk factor contributing to the global burden of disease. Pregnant persons and their developing fetuses are particularly susceptible to adverse health outcomes associated with air pollution exposures. During pregnancy, the thyroid plays a critical role in fetal development, producing thyroid hormones that are associated with brain development. Our objective is to systematically review recent literature that investigates how prenatal exposure to air pollution affects maternal and fetal thyroid function. Methods : Following the Navigation Guide Framework, we systematically reviewed peer-reviewed journal articles that examined prenatal exposures to air pollution and outcomes related to maternal and fetal thyroid function, evaluated the risk of bias for individual studies, and synthesized the overall quality and strength of the evidence. Results : We found 19 studies that collected data on pregnancy exposure windows spanning preconception to full term from 1999 to 2020 across nine countries. Exposure to fine particulate matter (PM2.5) was most frequently and significantly positively associated with fetal/neonatal thyroid hormone concentrations, and inversely associated with maternal thyroid hormone concentrations. To a lesser extent, traffic-related air pollutants, such as nitrogen dioxide (NO2) had significant effects on fetal/neonatal thyroid function but no significant effects on maternal thyroid function. However, the body of literature is challenged by risk of bias in exposure assessment methods and in the evaluation of confounding variables, and there is an inconsistency amongst effect estimates. Thus, using the definitions provided by the objective Navigation Guide Framework, we have concluded that there is limited, low quality evidence pertaining to the effects of prenatal air pollution exposure on maternal and fetal thyroid function.ConclusionTo improve the quality of the body of evidence, future research should seek to enhance exposure assessment methods by integrating personal monitoring and high-quality exposure data (e.g., using spatiotemporally resolved satellite observations and statistical modeling) and outcome assessment methods by measuring a range of thyroid hormones throughout the course of pregnancy.
https://doi.org/10.1186/s12940-024-01116-9

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Pan, S., Li, Z., Rubbo, B., Quon-Chow, V., Chen, J. C., Baumert, B. O.*, et al.*
**Applications of mixture methods in epidemiological studies investigating the health impact of persistent organic pollutants exposures: a scoping review.**
Journal of Exposure Science and Environmental Epidemiology 2024; Vol.
BackgroundPersistent organic pollutants (POPs) are environmental chemicals characterized by long half-lives in nature and human bodies, posing significant health risks. The concept of the exposome, encompassing all lifetime environmental exposures, underscores the importance of studying POP as mixtures rather than in isolation. The increasing body of evidence on the health impacts of POP mixtures necessitates the proper application of statistical methods.ObjectivesWe aimed to summarize studies on the overall effects of POP mixtures, identify patterns in applications of mixture methods-statistical methods for investigating the association of mixtures-and highlight current challenges in synthesizing epidemiologic evidence of POP mixtures on health effects as illustrated through a case study.MethodsWe conducted a systematic literature search on PubMed and Embase for epidemiological studies published between January 2011 and April 2023.ResultsWe included 240 studies that met our eligibility criteria. 126 studies focused on per- and polyfluoroalkyl substances (PFAS) mixtures only, while 40 analyzed three or more classes of POPs in mixture analyses. We identified 23 unique mixture methods used to estimate the overall effects of POP mixtures, with Bayesian Kernel Machine Regression (BKMR), a type of response-surface modeling, being the most common. Additionally, 22.9% of studies used a combination of methods, including response-surface modeling, index modeling, dimension reduction, and latent variable models.

The most extensively explored health outcome category was body weight and birth sizes (n = 43), and neurological outcomes (n = 41). In the case study of PFAS mixtures and birth weight, 12 studies showed negative associations, while 4 showed null results, and 2 showed positive associations. Impact StatementThis scoping review consolidates the existing literature on the overall effects of POP mixtures using statistical methods. By providing a comprehensive overview, our study illuminates the present landscape of knowledge in this field and underscores the methodological hurdles prevalent in epidemiological studies focused on POP mixtures. Through this analysis, we aim to steer future research directions, fostering a more nuanced comprehension of the intricate dynamics involved in assessing the health effects of POP mixtures. Our work stands as a significant contribution to the ongoing exploration of the chemical exposome.
https://doi.org/10.1038/s41370-024-00717-3

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Salamanca-Fernandez, E., Espin-Moreno, L., Olivas-Martinez, A., Perez-Cantero, A., Martin-Rodriguez, J. L., Poyatos, R. M.*, et al.*
**Associations between Urinary Phthalate Metabolites with BDNF and Behavioral Function among European Children from Five HBM4EU Aligned Studies.**
Toxics 2024; Vol. 12 (9),p
Based on toxicological evidence, children's exposure to phthalates may contribute to altered neurodevelopment and abnormal regulation of brain-derived neurotrophic factor (BDNF). We analyzed data from five aligned studies of the Human Biomonitoring for Europe (HBM4EU) project. Ten phthalate metabolites and protein BDNF levels were measured in the urine samples of 1148 children aged 6-12 years from Italy (NACII-IT cohort), Slovakia (PCB-SK cohort), Hungary (InAirQ-HU cohort) and Norway (NEBII-NO). Serum BDNF was also available in 124 Slovenian children (CRP-SLO cohort). Children's total, externalizing and internalizing behavioral problems were assessed using the Child Behavior Checklist at 7 years of age (only available in the NACII-IT cohort). Adjusted linear and negative binomial regression models were fitted, together with weighted quantile sum (WQS) regression models to assess phthalate mixture associations. Results showed that, in boys but not girls of the NACII-IT cohort, each natural-log-unit increase in mono-n-butyl phthalate (MnBP) and Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) was cross-sectionally associated with higher externalizing problems [incidence rate ratio (IRR): 1.20; 95% CI: 1.02, 1.42 and 1.26; 95% CI: 1.03, 1.55, respectively].
A suggestive mixture association with externalizing problems was also observed per each tertile mixture increase in the whole population (WQS-IRR = 1.15; 95% CI: 0.97, 1.36) and boys (IRR = 1.20; 95% CI: 0.96, 1.49). In NACII-IT, PCB-SK, InAirQ-HU and NEBII-NO cohorts together, urinary phthalate metabolites were strongly associated with higher urinary BDNF levels, with WQS regression confirming a mixture association in the whole population (percent change (PC) = 25.9%; 95% CI: 17.6, 34.7), in girls (PC = 18.6%; 95% CI: 7.92, 30.5) and mainly among boys (PC = 36.0%; 95% CI: 24.3, 48.9). Among CRP-SLO boys, each natural-log-unit increase in & sum; DINCH concentration was associated with lower serum BDNF levels (PC: -8.8%; 95% CI: -16.7, -0.3). In the NACII-IT cohort, each natural-log-unit increase in urinary BDNF levels predicted worse internalizing scores among all children (IRR: 1.15; 95% CI: 1.00, 1.32). Results suggest that (1) children's exposure to di-n-butyl phthalate (DnBP) and di(2-ethylhexyl) phthalate (DEHP) metabolites is associated with more externalizing problems in boys, (2) higher exposure to DINCH may associate with lower systemic BDNF levels in boys, (3) higher phthalate exposure is associated with higher urinary BDNF concentrations (although caution is needed since the possibility of a "urine concentration bias" that could also explain these associations in noncausal terms was identified) and (4) higher urinary BDNF concentrations may predict internalizing problems.
Given this is the first study to examine the relationship between phthalate metabolite exposure and BDNF biomarkers, future studies are needed to validate the observed associations.
https://doi.org/10.3390/toxics12090642

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Sellaro, F., Pernetti, R., Oddone, E.
**Early biological effects in outdoor workers exposed to urban air pollution: A systematic review.**
Environmental pollution (Barking, Essex : 1987) 2024; Vol. 362, p 124985.
Urban outdoor workers (OWs), identified as professionals spending most of their working shifts in an urban environment, are exposed for at least 8h/day to traffic air pollution, leading to potential health risks. This paper reports the results of a systematic review aimed at identifying the potential health outcomes of exposure to air pollutants for OWs, focusing mainly on police officers, drivers and street vendors. Health outcomes were analysed in terms of early biological effects quantified with specific measured indicators. The main inclusion criterion was the assessment of at least one early biological effect (genetic and epigenetic damage/alterations, inflammation or oxidative stress indicators, or hormonal imbalance) in a population of OWs exposed to urban air pollution. By applying the PRISMA workflow, 82 papers were included in this study. The results showed that the measured pollutant concentrations were significantly below the current occupational limit values, while exceeds the indications of WHO for urban air pollution. This exposure led to significant alterations of biological markers in OWs with respect to non-exposed subjects. In particular, OWs presented an increased frequency of micronuclei and DNA adducts as the main DNA alterations, while police officers (a category of highly exposed OWs) showed hormonal alterations affecting mainly the hypothalamic-pituitary-gonadal axis. Concerning oxidative stress and inflammation, all the analysed matrices (i.e. blood, sputum, urine and lachrymal fluids) showed increased indices for OWs respect to non-exposed groups. Therefore, the evaluation of effect biomarkers to detect early alterations provides crucial information for supporting the occupational risk management of OWs and, at broader level, allows for an insight of the early-stage health outcomes due to urban air pollution.
https://doi.org/10.1016/j.envpol.2024.124985

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Strand, D., Lundgren, B., Bergdahl, I. A., Martin, J. W., Karlsson, O.
**Personalized mixture toxicity testing: A proof-of-principle *in vitro* study evaluating the steroidogenic effects of reconstructed contaminant mixtures measured in blood of individual adults.**
Environment International 2024; Vol. 192
Chemical risk assessments typically focus on single substances, often overlooking real-world co-exposures to chemical mixtures. Mixture toxicology studies using representative mixtures can reveal potential chemical interactions, but these do not account for the unique chemical profiles that occur in the blood of diverse individuals.
Here we used the H295R steroidogenesis assay to screen personalized mixtures of 24 persistent organic pollutants (POPs) for cytotoxicity and endocrine disruption. Each mixture was reconstructed at a human exposure relevant concentration (1x), as well as at 10- and 100-fold higher concentration (10x, 100x) by acoustic liquid handling based on measured blood concentrations in a Swedish cohort. Among the twelve mixtures tested, nine mixtures decreased the cell viability by 4-18%, primarily at the highest concentration. While the median and maximum mixtures based on the whole study population induced no measurable effects on steroidogenesis at any concentration, the personalized mixture from an individual with the lowest total POPs concentration was the only mixture that affected estradiol synthesis (35% increase at the 100x concentration). Mixtures reconstructed from blood levels of three different individuals stimulated testosterone synthesis at the 1x (11-15%) and 10x concentrations (12-16%), but not at the 100x concentration. This proof-of-principle personalized toxicity study illustrates that population-based representative chemical mixtures may not adequately account for the toxicological risks posed to individuals. It highlights the importance of testing a range of real-world mixtures at relevant concentrations to explore potential interactions and non-monotonic effects. Further toxicological studies of personalized contaminant mixtures could improve chemical risk assessment and advance the understanding of human health, as chemical exposome data become increasingly available.
https://doi.org/10.1016/j.envint.2024.108991

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Teixeira, T., Almeida, L., Dias, I., Baptista, J. S., Santos, J., Vaz, M., Guedes, J.

**Occupational Chemical Exposure and Health Status of Wildland Firefighters at the Firefront: A Systematic Review.**

Safety 2024; Vol. 10 (3),p

Wildland firefighting represents a physically and mentally demanding endeavour fraught with various risk factors. The primary aim of this study is to delineate occupational chemical exposure within the firefighting work environment on the firefront and its implications for firefighters' health status. A systematic literature review was conducted utilising diverse keyword combinations across Scopus, Web of Science, Academic Search Complete, and ScienceDirect databases. Only English-language journal articles, real-world monitoring reports, and studies featuring samples of firefighters were considered for inclusion. Forty-one studies were analysed, with 26 focusing on firefighters' occupational exposure to chemical agents during wildland firefighting and 15 addressing the health impairments of wildland firefighting activities. Polycyclic aromatic hydrocarbons (PAHs), VOCs, and particulates emerged as the most prevalent chemical agents in the exposure profiles of frontline firefighters. They were shown to be the main incidents of cardiovascular disease, respiratory disease, and work-related cancer. The rigorous demands of wildland firefighting have been demonstrated to significantly impact firefighter health, resulting in a notable prevalence of fatalities and illnesses. Given that an elevated number of health issues are common in this occupation, adopting advanced assessment technologies is imperative.

https://doi.org/10.3390/safety10030060

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Duboeuf, M., Amadou, A., Coudon, T., Ramel-Delobel, M., Faure, E., Salizzoni, P.*, et al.*

**Long-term exposure to air pollution at residential and workplace addresses and breast cancer risk: A case-control study nested in the French E3N-Ge<acute accent>ne<acute accent>rations cohort from 1990 to 2011.**

European Journal of Cancer 2024; Vol. 210

Background: An increasing evidence links air pollution to breast cancer (BC) risk. Yet, pollutant exposure estimates at the workplace location in pollution exposure assessment have not been considered. Objectives: This study investigates the association between particulate matters (PM2.5, PM10) and nitrogen dioxide (NO2) atmospheric concentrations (1990-2011), at the women's residential and workplace locations, and BC risk.

Methods: This case-control study of 2419 BC cases and 2984 controls, was nested in the French prospective E3N cohort. The annual mean PM2.5, PM10 and NO2 concentrations were estimated using a Land Use Regression model (50 m x 50 m resolution) and assigned to the women's geocoded residential and workplace locations, from cohort recruitment to their index date (date of case diagnosis). Odds ratios (OR) and 95 % confidence intervals (CI) were estimated using multivariate logistic regression models.

Results: An increased BC risk was observed for a 10 mu g/m3 increase of the 1990-2011 average PM2.5 concentration estimates (OR=1.28; CI 1.00, 1.63). An increased risk was suggested for a 10 mu g/m3 increase for PM10 (OR=1.09; CI 0.92, 1.30) and NO2 (OR=1.05; CI 0.97, 1.13). No effect modification by menopausal status, nor difference by hormone receptor status were observed.

Discussion: This study is the first to estimate BC risk and long-term air pollutant exposure from both, residential and workplace location histories. Results suggest that residential PM2.5, PM10 and NO2 concentrations are strongly correlated with workplace ones, indicating that residential data may serve as proxy for overall exposure. Future studies should consider exposure during commuting.

https://doi.org/10.1016/j.ejca.2024.114293

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Bouredji, A., Lakhmi, R., Muresan-Paslaru, B., Pourchez, J., Forest, V.

**Exposure of RAW264.7 macrophages to exhaust emissions (gases and PAH) and non-exhaust emissions (tire particles) induces additive or synergistic TNF-α production depending on the tire particle size.**

Toxicology 2024; Vol. 509,p 153990.

Road traffic is a major contributor to air pollution and consequently negatively affects human health. Car pollution originates both from exhaust emissions (EE) and non-exhaust emissions (NEE, such as tire and brake wear particles, erosion of road surfaces and resuspension of road dust). While the toxicity of EE and NEE has been characterized separately, their combined effects are poorly documented. However, we are constantly exposed to a mixture of pollutants and their interactions should not be neglected as they may significantly impact their toxicological profile resulting in additive, synergistic or antagonistic effects.

To fill this gap, we investigated in vitro the combined toxicity of exhaust gases and benzo[a]pyrene (representative of EE) and tire particles (representative of NEE). Macrophages from the RAW264.7 cell line were exposed for 24 h to tire particles (TP) of variable size (6–113 µm), alone or in combination with exhaust gases (CO2, CO, NO, NO2) and benzo[a]pyrene (B[a]P) as an archetype of polycyclic aromatic hydrocarbon (PAH). The cell response was assessed in terms of cytotoxicity, proinflammatory response and oxidative stress. TP, gases and B[a]P, alone or in combination triggered neither cytotoxicity nor oxidative stress. On the contrary, a proinflammatory response was elicited with two different profiles depending on the size of the TP: TNF-α production was either slightly (with the finest TP) or strongly (with coarse TP) increased in the presence of gases and B[a]P, suggesting that the effects of TP, gases and B[a]P were either additive or synergistic, depending on TP size.

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**Impact of polyfluoroalkyl chemicals and volatile organic compounds exposure on lung function of American adults.**

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BACKGROUND: Environmental chemicals, such as Perfluoroalkyl and polyfluoroalkyl substances (PFAS) and volatile organic compounds (VOCs), and the association between the combined exposure of these chemicals and human lung function remains unclear. This study aimed to explore the effects of mixed exposure to PFAS and VOCs on lung function in the general population of the United States and investigate their potential mechanisms. METHODS: Data from 30442 respondents were selected for analysis during the US National Health and Nutrition Examination Survey (NHANES) database from 2007 to 2012. Linear models, weighted quantile (WQS) regression, quantile g calculation (QGC), and Bayesian kernel machine regression (BKMR) were used to evaluate the contribution of individual components. Moreover, the interactions between substances in the dose-response relationship mixture of multiple environmental chemical exposures and lung function were also evaluated. The Benjamini-Hochberg method was used to correct multiple tests. FINDINGS: Univariate analysis showed that nitromethane was negatively correlated with FEV1 (beta =-0.052), FVC (beta =-0.056), and PEF (beta =-0.065), while perfluorohexanesulfonic acid was positively associated with FEV1 (beta=0.026), FVC (beta=0.024), FEF25-75% (beta=0.012), and PEF (beta=0.029). Multivariate analysis showed that chloroform and perfluorohexane sulfonic acid were positively associated with lung function (P <0.05), and perfluorohexane sulfonic acid contributed the most. Nitromethane and perfluorodecanoic acid were negatively associated with lung function (P < 0.05), and perfluorodecanoic acid contributed the highest weight in the negative direction. When all chemicals were in the 50th percentile, the environmental chemical mixture had no significant consistent effect or dose-response on lung function. There were interactions among various environmental chemicals within the mixture except for 2-N-methyl-PFOSA acetate and bromodichloromethane. INTERPRETATION: These results suggest that environmental mixture exposure is associated with abnormal lung function in American adults, and the interaction of various substances in the mixture affects its physiological and chemical effects.

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**Biotoxicity of silver nanoparticles complicated by the co-existence of micro-/nano-plastics.**

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Silver nanoparticles (AgNP) and polystyrene (PS) plastics have been broadly utilized in various field, e.g., food storage, packaging materials, and medical therapies. However, investigation on the potential biotoxicity induced by the co-exposure to AgNP and PS plastics remains understudied. Thus, we performed this study to examine the toxicological profile of the co-exposure to AgNP and PS in mice. Biochemical and microbial characterizations were performed in mice receiving 90-day oral gavage feeding to examine the hepatotoxicity, neurotoxicity, inflammatory responses, gut microbial alterations. It has been found that the presence of plastic particles aggravates the toxicity of silver nanoparticle materials. Regardless of the plastic type and size, energy and choline metabolisms will be altered by the co-exposures. Moreover, microplastics may induce cell damage by modulating fatty acid peroxidation in unison with stimulating inflammatory responses. Due to the smaller size of nanoplastics, they may pass through blood-brain barrier to induce neuronal damage and increase vascular risks. Changes in the microbial functional abundances are sensitive to the microplastics doses. These results support the necessity of reducing the co-exposure between AgNP and multiscale plastics, and advocate further developments of biodegradable package materials to improve food safety.

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