# Bulletin de veille
# Polyexpositions chimie-chimie
# N°1 - décembre 2023 - janvier 2024

<u>Objectif</u> : 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.*

## Sommaire

# Généralités

1. Tulpain Anne-Laure
**Comment aborder l'exposome professionnel pour mieux prévenir les risques des travailleurs ?**
In: actuEL HSE. 15/11/2023.

Ce concept a tout son intérêt pour appréhender la complexité des polyexpositions en milieu de travail. Il permet d'élargir les niveaux d'analyse des expositions et donc de l'évaluation des risques sanitaires et ainsi de promouvoir une approche plus globale et intégrée de la prévention sur le lieu de travail.
https://actuel-hse.fr/content/comment-aborder-lexposome-professionnel-pour-mieux-prevenir-les-risques-des-travailleurs

*********************************************

2. Tulpain Anne-Laure
**Les polyexpositions chimiques : le point**.
In: actuEL HSE. 02/11/2023.

Le 12 octobre dernier, l'INRS a organisé une journée technique sur les polyexpositions au travail. Dans la plupart des situations de travail, les salariés sont exposés à plusieurs risques. Nous faisons le point sur les polyexpositions à plusieurs substances chimiques.
https://actuel-hse.fr/content/les-polyexpositions-chimiques-le-point

************************************

3. Grady, S. K., Dojcsak, L., Harville, E. W., Wallace, M. E., Vilda, D., Donneyong, M. M.*, et al.*
**Seminar: Scalable Preprocessing Tools for Exposomic Data Analysis.**
Environmental health perspectives 2023; Vol. 131 (12) p 124201.

BACKGROUND: The exposome serves as a popular framework in which to study exposures from chemical and nonchemical stressors across the life course and the differing roles that these exposures can play in human health. As a result, data relevant to the exposome have been used as a resource in the quest to untangle complicated health trajectories and help connect the dots from exposures to adverse outcome pathways. OBJECTIVES: The primary aim of this methods seminar is to clarify and review preprocessing techniques critical for accurate and effective external exposomic data analysis. Scalability is emphasized through an application of highly innovative combinatorial techniques coupled with more traditional statistical strategies. The Public Health Exposome is used as an archetypical model. The novelty and innovation of this seminar's focus stem from its methodical, comprehensive treatment of preprocessing and its demonstration of the positive effects preprocessing can have on downstream analytics. DISCUSSION: State-of-the-art technologies are described for data harmonization and to mitigate noise, which can stymie downstream interpretation, and to select key exposomic features, without which analytics may lose focus. A main task is the reduction of multicollinearity, a particularly formidable problem that frequently arises from repeated measurements of similar events taken at various times and from multiple sources. Empirical results highlight the effectiveness of a carefully planned preprocessing workflow as demonstrated in the context of more highly concentrated variable lists, improved correlational distributions, and enhanced downstream analytics for latent relationship discovery. The nascent field of exposome science can be characterized by the need to analyze and interpret a complex confluence of highly inhomogeneous spatial and temporal data, which may present formidable challenges to even the most powerful analytical tools. A systematic approach to preprocessing can therefore provide an essential first step in the application of modern computer and data science methods.

https://doi.org/10.1289/ehp12901

************************************

4. Battais P. ; Jacquenet S.; Lechene S.; Duquenne P.; Battais F.

**Actualités sur les polyexpositions dans les fromageries : agents chimiques et biologiques en présence et caractérisation des allergènes à risque pour les salariés.**
Revue française d'allergologie, vol. 63, n° 6, octobre 2023, 9 p., ill., bibliogr. (En français)

L'exposition aux bioaérosols a été associée à plusieurs effets sur la santé, affectant en particulier le système respiratoire provoquant notamment des pathologies de type allergique, dans divers secteurs d'activité. La complexité de la composition en allergènes aéroportés d'origine biologique, susceptibles de se trouver dans l'ensemble des industries agro-alimentaires, est trop élevée pour être traitée en une seule approche. Cette revue se concentre donc sur les entreprises fromagères pour lesquelles des allergies professionnelles ont été rapportées et pourraient concerner plusieurs milliers de salariés. Elle a pour objectif de donner les dernières actualités sur les polyexpositions dans les fromageries, notamment en ce qui concerne les agents chimiques ainsi que les agents biologiques et le risque allergique qu'ils représentent pour les travailleurs de ce secteur.

Lien vers l'article : https://doi.org/10.1016/j.reval.2023.103689

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

5. Lamarque, V., Swierczynski, G., Verdun-Esquer, C., Léger, C., Canal-Raffin, M., Garrigou, A., et al.
**Exposition professionnelle aux médicaments anticancéreux : vers la prise en compte de l'activité pour repenser les actions de prévention.**
Archives des Maladies Professionnelles et de l'Environnement 2024; Vol. 85 (1) 101945.

Résumé Malgré les efforts réalisés en prévention pour réduire l'exposition professionnelle aux médicaments anticancéreux (MAC), ce problème reste d'actualité. La littérature à ce sujet pointe le besoin de caractériser et d'évaluer les risques et les dangers et de former les professionnels. Grâce à l'ergotoxicologie, mêlant des prélèvements d'essuyages de mains et des entretiens d'autoconfrontation, nous chercherons à savoir comment la poly-exposition et les moyens de protection associés se manifestent dans l'activité des soignants. Les essuyages de mains, réalisés avant/après des actions déterminées comme potentiellement exposantes, montrent la présence de MAC sur l'ensemble des prélèvements (n=20). La molécule manipulée le jour du prélèvement ne se retrouve que sur 25 % des prélèvements. Deux prélèvements (sur 9) montrent une augmentation du niveau de contamination des mains après une action potentiellement exposante. Les données d'entretiens montrent que malgré le manque de formation, les soignants sont capables d'identifier des sources et des espaces d'exposition potentielle. Nos résultats ne montrent qu'une partie de l'énigme de l'exposition aux MAC et ne permettent pas, encore, de la caractériser. Néanmoins, ils montrent des déterminants de la contamination à différents niveaux de l'activité qu'il reste à approfondir. Aussi, nos résultats nous laissent penser que, par nos méthodes, les soignants sont rentrés dans une « zone potentielle de développement », où une partie de leurs connaissances sur les risques biologiques pourraient leur servir de ressources pour mieux gérer le risque chimique et penser une prévention propre aux spécificités des MAC. En effet, au vu, des voies d'exposition et des modes de transmission des contaminations aux risques biologiques, les actions de protection développées pour ce risque pourraient permettre l'élaboration d'une nouvelle forme d'intervention pour les MAC. Cette dernière considèrerait les soignants comme agissant face aux poly-expositions et producteurs de leurs actions de protection, qui vont au-delà des équipements de protection prescrits. Summary Despite preventive efforts to reduce occupational exposure to antineoplastic drugs (ADs), the problem remains. The literature on the subject points to the need to characterize, assess and train professionals. In this article, using ergotoxicology as a tool, we will look at how multiple exposures to multiple nuisances and the associated protective measures arise in the work of healthcare workers, by means of hand-wiping samples and self-confrontation interviews. Hand wiping carried out before and after actions identified as potentially exposing, revealed the presence of ADs in all samples (n=20). The compound handled on the sampling day was found in only 25% of the samples. Only two samples (out of 9) showed an increase in the level of hand contamination after a potentially exposing action. Although these data have helped to reveal

part of the enigma of exposure to ADs, they do not yet allow us to characterize it. Nonetheless, our methods have enabled us to identify the determinants of contamination at different activity levels, which still need to be examined in greater depth in the rest of the prevention project. The interview data show that, despite a lack of training, carers can identify potential sources and areas of exposure. Our results lead us to believe that our methods have enabled carers to enter a "zone of proximal development", where their knowledge of biological risks could serve as a resource for better chemical risk management. These data also show that carers take action on a daily basis in the face of multiple exposures, and produce protective measures that go beyond the prescribed protective equipment. Given the routes of exposure and modes of transmission of biological risk contamination, the protective actions developed for this risk could contribute to the development of a new form of intervention for ADs.

https://doi.org/10.1016/j.admp.2023.101945

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

6.  Dervilly, G., Bourdeau, M., Pruvost-Couvreur, M., Severin, I., Platel, A., Chagnon, M. C., *et al.*
**Cocktails of endocrine disruptors in the different diets of French consumers.**
Environment international 2024; Vol. 183, p 108408.

With a view to identifying main endocrine disruptors (ED) mixtures to which French consumers are exposed through food, their main diets were modelled using an adapted dimension reduction method. Seven specific diets could be modelled for adults while only one overall diet was considered for children aged 3-17 years. The knowledge of the contamination levels of 78 known or suspected endocrine disrupting compounds in the foods constituting these diets, collected in the frame of the second French Total Diet Study, made it possible to explore the mixtures of EDs to which consumers are exposed. We have thus shown that the ED substances most present in mass concentration are comparable for the whole population, whatever the diet considered. However, a second approach made it possible to highlight, for a given diet, the substances whose exposure is statistically higher than in the diet of the general population. Thus, significantly different ED mixtures could be established for each diet. For example, diets with a high proportion of animal-based foods induce significantly higher exposures to some persistent organic pollutants (e.g., PCDD/F, brominated flame retardants), whereas these exposures are lower for Mediterranean-type diet. On the other hand, the latter, richer in fruits and vegetables, is the one for which pesticides represent a specific signature. These results now pave the way for studying the specific effects of these cocktails of endocrine disruptors, each of which is representative of a type of chronic exposure linked to specific diets.

https://doi.org/10.1016/j.envint.2023.108408

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

7.  Olsson, A., Bouaoun, L., Schuz, J., Vermeulen, R., Behrens, T., Ge, C., *et al.*
**Lung Cancer Risks Associated with Occupational Exposure to Pairs of Five Lung Carcinogens: Results from a Pooled Analysis of Case-Control Studies (SYNERGY).**
Environmental health perspectives 2024; Vol. 132 (1) p 17005-1-17005-10.

BACKGROUND: While much research has been done to identify individual workplace lung carcinogens, little is known about joint effects on risk when workers are exposed to multiple agents. OBJECTIVES: We investigated the pairwise joint effects of occupational exposures to asbestos, respirable crystalline silica, metals (i.e., nickel, chromium-VI), and polycyclic aromatic hydrocarbons (PAH) on lung cancer risk, overall and by major histologic subtype, while accounting for cigarette smoking. METHODS: In the international 14-center SYNERGY project, occupational exposures were assigned to 16,901 lung cancer cases and 20,965 control subjects using a quantitative job-exposure matrix (SYN-JEM). Odds ratios (ORs) and 95% confidence intervals (CIs) were computed for ever vs. never exposure using logistic regression models stratified by sex and adjusted for study center, age, and smoking habits. Joint effects among pairs of agents were assessed

on multiplicative and additive scales, the latter by calculating the relative excess risk due to interaction (RERI). RESULTS: All pairwise joint effects of lung carcinogens in men were associated with an increased risk of lung cancer. However, asbestos/metals and metals/PAH resulted in less than additive effects; while the chromium-VI/silica pair showed marginally synergistic effect in relation to adenocarcinoma (RERI: 0.24; CI: 0.02, 0.46; p = 0.05). In women, several pairwise joint effects were observed for small cell lung cancer including exposure to PAH/silica (OR = 5.12; CI: 1.77, 8.48), and to asbestos/silica (OR = 4.32; CI: 1.35, 7.29), where exposure to PAH/silica resulted in a synergistic effect (RERI: 3.45; CI: 0.10, 6.8). DISCUSSION: Small or no deviation from additive or multiplicative effects was observed, but co-exposure to the selected lung carcinogens resulted generally in higher risk than exposure to individual agents, highlighting the importance to reduce and control exposure to carcinogens in workplaces and the general environment.

https://doi.org/10.1289/ehp13380

**********************************


# Approche métabolomique et exposome


8.  Balcells, C., Xu, Y., Gil-Solsona, R., Maitre, L., Gago-Ferrero, P., Keun, H. C.
**Blurred lines: Crossing the boundaries between the chemical exposome and the metabolome.**
Current opinion in chemical biology 2023; Vol. 78 : 102407.

The aetiology of every human disease lies in a combination of genetic and environmental factors, each contributing in varying proportions. While genomics investigates the former, a comparable holistic paradigm was proposed for environmental exposures in 2005, marking the onset of exposome research. Since then, the exposome definition has broadened to include a wide array of physical, chemical, and psychosocial factors that interact with the human body and potentially alter the epigenome, the transcriptome, the proteome, and the metabolome. The chemical exposome, deeply intertwined with the metabolome, includes all small molecules originating from diet as well as pharmaceuticals, personal care and consumer products, or pollutants in air and water. The set of techniques to interrogate these exposures, primarily mass spectrometry and nuclear magnetic resonance spectroscopy, are also extensively used in metabolomics. Recent advances in untargeted metabolomics using high resolution mass spectrometry have paved the way for the development of methods able to provide in depth characterisation of both the internal chemical exposome and the endogenous metabolome simultaneously. Herein we review the available tools, databases, and workflows currently available for such work, and discuss how these can bridge the gap between the study of the metabolome and the exposome.

https://doi.org/10.1016/j.cbpa.2023.102407

*********************************************


9.  Alcolea, J. A., Donat-Vargas, C., Chatziioannou, A. C., Keski-Rahkonen, P., Robinot, N., Molina, A. J.*, et al.*
**Metabolomic Signatures of Exposure to Nitrate and Trihalomethanes in Drinking Water and Colorectal Cancer Risk in a Spanish Multicentric Study (MCC-Spain).**
Environmental Science & Technology 2023; Vol. 57 (48), p:19316-19329.

We investigated the metabolomic profile associated with exposure to trihalomethanes (THMs) and nitrate in drinking water and with colorectal cancer risk in 296 cases and 295 controls from the Multi Case-Control Spain project. Untargeted metabolomic analysis was conducted in blood samples using ultrahigh-performance liquid chromatography-quadrupole time-of-flight mass spectrometry. A variety of univariate and multivariate association analyses were conducted after data quality control, normalization, and imputation. Linear

regression and partial least-squares analyses were conducted for chloroform, brominated THMs, total THMs, and nitrate among controls and for case-control status, together with a N-integration model discriminating colorectal cancer cases from controls through interrogation of correlations between the exposure variables and the metabolomic features. Results revealed a total of 568 metabolomic features associated with at least one water contaminant or colorectal cancer. Annotated metabolites and pathway analysis suggest a number of pathways as potentially involved in the link between exposure to these water contaminants and colorectal cancer, including nicotinamide, cytochrome P-450, and tyrosine metabolism. These findings provide insights into the underlying biological mechanisms and potential biomarkers associated with water contaminant exposure and colorectal cancer risk. Further research in this area is needed to better understand the causal relationship and the public health implications.

https://doi.org/10.1021/acs.est.3c05814

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*


10.Dong, Y., Cai, D., Liu, C., Zhao, S., Wang, L.
**Combined cytotoxicity of phthalate esters on HepG2 cells: A comprehensive analysis of transcriptomics and metabolomics.**
Food and Chemical Toxicology 2023; Vol. 180, 114034

Phthalate esters (PAEs), widely used as plasticizers, may pose a potential environmental and human hazard. The aim of this study was to compare the cytotoxicity of di(2-ethylhexyl) phthalates (DEHP) and dibutyl phthalate (DBP)) after their exposure to HepG2 cells alone or in combination. HepG2 cells treated with individual/combined DEHP and DBP at a dose of 10-2 M for 24 h were selected for metabolome and transcriptome analysis. The results demonstrated that exposure to the mixtures of DEHP and DBP caused enhanced or reduced toxic effects regarding 8 pathways with 1065 downregulated genes and 643 upregulated genes, in comparison with those of single chemicals. The combined toxicity of mixture revealed both synergistic and antagonistic interactions between DEHP and DBP. Besides, combined exposure to DEHP and DBP promoted TCA cycle, pyrimidine, and purine metabolism, while an antagonistic effect on fatty acid derangement should require further investigation. To summarize, our results suggest that DEHP exposed alone or combined with DBP caused a variety of metabolic disorders, and the type of combination effects varied among metabolic pathways.

https://doi.org/10.1016/j.fct.2023.114034

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*


11. Xiao, Z., Li, Q., Wang, Z., Zhang, H.
**Single- and combined-phthalate exposures are associated with biological ageing among adults.**
Ecotoxicology and Environmental Safety 2023; Vol. 268, p

Background: Previous research has emphasized the effects of lifestyle and genetics on ageing. However, the association between exposure to phthalates, which are extensively used in cosmetics and personal care products, and ageing is still unclear. Method: Data for 4711 subjects from the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2010 were incorporated in the present study. The acceleration of the Klemera-Doubal method-biological age (KDM-BA) and phenotypic Age (PhenoAge) were measured by the composite of 13 biomarkers. Multiplelinear and weighted-quantile sum (WQS) regression models were constructed to explore the relationships of single- and combined-phthalate exposures, as indicated by urinary phthalate metabolites, with KDM-BA and PhenoAge. A generalized additive model (GAM) was fitted to explore the potential nonlinear relationships among the above variables. Results: Except for mono-(carboxynonyl), all urinary phthalate metabolites were associated with biological ageing, with correlation coefficients ranging from 0.241 to 0.526; however, mono-ethyl presented a negative correlation. The WQS models revealed mixed effects of combined urinary phthalate metabolites on ageing, with a 0.22-year ((95 % CI) 0.09, 0.32) increase

in KDM-BA acceleration and a 0.27-year ((95 % CI) 0.13, 0.37) increase in PhenoAge acceleration for each decile increase in urinary phthalate metabolites. Moreover, MCPP, MEOHP, and MBzP seemed to be the top three phthalates in terms of biological ageing, with weights of 33.3 % and 32.2 %, 29.2 % and 17.2 %, and 21.5 % and 30.1 % in KDM-BA and PhenoAge acceleration, respectively. Conclusion: Single-phthalate exposure was mostly associated with the ageing process, and combined-phthalate exposure presented mixed effects on biological ageing, emphasizing phthalate exposure as a significant risk factor for ageing.

https://doi.org/10.1016/j.ecoenv.2023.115715

**********************************

12.   Dumas, T., Gomez, E., Boccard, J., Ramirez, G., Armengaud, J., Escande, A*., et al.*
**Mixture effects of pharmaceuticals carbamazepine, diclofenac and venlafaxine on *Mytilus galloprovincialis* mussel probed by metabolomics and proteogenomics combined approach.**
Science of the Total Environment 2024; Vol. 907 : 168015

Exposure to single molecules under laboratory conditions has led to a better understanding of the mechanisms of action (MeOAs) and effects of pharmaceutical active compounds (PhACs) on non-target organisms. However, not taking the co-occurrence of contaminants in the environment and their possible interactions into account may lead to underestimation of their impacts. In this study, we combined untargeted metabolomics and proteoge-nomics approaches to assess the mixture effects of diclofenac, carbamazepine and venlafaxine on marine mussels (Mytilus galloprovincialis). Our multi-omics approach and datafusion strategy highlighted how such xenobiotic cocktails induce important cellular changes that can be harmful to marine bivalves. This response is mainly characterized by energy metabolism disruption, fatty acid degradation, protein synthesis and degradation, and the induction of endoplasmic reticulum stress and oxidative stress. The known MeOAs and molecular signatures of PhACs were taken into consideration to gain insight into the mixture effects, thereby revealing a potential additive effect. Multi-omics approaches on mussels as sentinels offer a comprehensive overview of molecular and cellular responses triggered by exposure to contaminant mixtures, even at environmental concentrations.

https://doi.org/10.1016/j.scitotenv.2023.168015

**********************************

13.   Gu, Y., Zheng, S., Huang, C., Cao, X., Liu, P., Zhuang, Y*., et al.*
**Microbial colony sequencing combined with metabolomics revealed the effects of chronic hexavalent chromium and nickel combined exposure on intestinal inflammation in mice.**
Science of The Total Environment 2024; Vol., p 169853.

The pollution and toxic effects of hexavalent chromium [Cr(VI)] and divalent nickel [Ni(II)] have become worldwide public health issues. However, the potential detailed effects of chronic combined Cr(VI) and Ni exposure on colonic inflammation in mice have not been reported. In this study, 16S rDNA sequencing, metabolomics data analysis, qPCR and other related experimental techniques were used to comprehensively explore the mechanism of toxic damage and the inflammatory response of the colon in mice under the co-toxicity of chronic hexavalent chromium and nickel. The results showed that long-term exposure to Cr(VI) and/or Ni resulted in an imbalance of trace elements in the colon of mice with significant inflammatory infiltration of tissues. Moreover, Cr(VI) and/or Ni poisoning upregulated the expression levels of IL-6, IL-18, IL-1β, TNF-α, IFN-γ, JAK2 and STAT3 mRNA, and downregulated IL-10 mRNA, which was highly consistent with the trend in protein expression. Combined with multiomics analysis, Cr(VI) and/or Ni could change the α diversity and β diversity of the gut microbiota and induce significant differential changes in metabolites such as Pyroglu-Glu-Lys, Val-Asp-Arg, stearidonic acid, and 20-hydroxyarachidonic acid. They are also associated with disorders of important metabolic pathways such as lipid metabolism and amino acid metabolism. Correlation analysis revealed that there was a significant correlation between gut microbes and metabolites

(P < 0.05). In summary, based on the advantages of comprehensive analysis of high-throughput sequencing sets, these results suggest that chronic exposure to Cr(VI) and Ni in combination can cause microbial flora imbalances, induce metabolic disorders, and subsequently cause colonic damage in mice. These data provide new insights into the toxicology and molecular mechanisms of Cr(VI) and Ni.

https://www.sciencedirect.com/science/article/pii/S0048969723084851
https://doi.org/https://doi.org/10.1016/j.scitotenv.2023.169853

**********************************

# Biomonitoring, modèles maths et stats

14.  Bollati, V., Biganzoli, E. M., Carugno, M.
**What if ... ? A new hypothesis to approach the relationship between environmental stimuli, biological features, and health.**
Heliyon 2023; Vol. 9 (12), e22985

The "exposome" covers all disease determinants across a lifetime. Many exposome factors could induce epigenetic changes, especially in DNA methylation. Yet, the role of these modifications in disease development remains partly understood. Although the possible relationship among the exposome factors, epigenetic modifications, and health/disease has been investigated extensively, all previous studies start from the assumption that epigenetic changes are always detrimental to (or represent an adverse effect on) the health of the affected individual. We hereby propose a new approach to investigate these modifications, and their possible relation with human health, in the context of the exposome. Our hypothesis is based on the possibility that some environmentally-induced changes are plastic entities, responding physiologically to the environment to allow individual adaptation. Briefly, after evaluating the association between environmental exposure and the variation of a given biological parameter through regression models, we use the estimated regression function to predict values for each study subject. We then calculated the relative percent difference (PD) between the measured (i.e., observed) biological parameter and the predicted (i.e., expected) from the model. Notably, we have tested our hypothesis using two distinct models, specifically focusing on LINE-1 methylation and extracellular vesicles (EVs). We hypothesize that the greater the difference between the observed and the expected, the greater the inability of the subject to adapt to external stimuli.

https://doi.org/10.1016/j.heliyon.2023.e22985

**********************************

15.  Hu, C.-W., Chang, Y.-J., Chang, W.-H., Cooke, M. S., Chen, Y.-R., Chao, M.-R.
**A Novel Adductomics Workflow Incorporating « FeatureHunter » Software: Rapid Detection of Nucleic Acid Modifications for Studying the Exposome.**
Environmental Science & Technology 2023; Vol. 58 (1), p 75-89.

Exposure to the physicochemical agents that interact with nucleic acids (NA) may lead to modification of DNA and RNA (i.e., NA modifications), which have been associated with various diseases, including cancer. The emerging field of NA adductomics aims to identify both known and unknown NA modifications, some of which may also be associated with proteins. One of the main challenges for adductomics is the processing of massive and complex data generated by high-resolution tandem mass spectrometry (HR-MS/MS). To address this, we have developed a software called "FeatureHunter", which provides the automated extraction, annotation, and classification of different types of key NA modifications based on the MS and MS/MS spectra acquired by HR-MS/MS, using a user-defined feature list. The capability and effectiveness of FeatureHunter was demonstrated by analyzing various NA modifications induced by formaldehyde or chlorambucil in mixtures of calf thymus

DNA, yeast RNA and proteins, and by analyzing the NA modifications present in the pooled urines of smokers and nonsmokers. The incorporation of FeatureHunter into the NA adductomics workflow offers a powerful tool for the identification and classification of various types of NA modifications induced by reactive chemicals in complex biological samples, providing a valuable resource for studying the exposome.

https://doi.org/10.1021/acs.est.3c04674

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

16. Kwon, D., Simon, S. L., Hoffman, F. O., Pfeiffer, R. M.
**Frequentist model averaging for analysis of dose-response in epidemiologic studies with complex exposure uncertainty.**
PloS one 2023; Vol. 18 (12), p e0290498-e0290498.

In epidemiologic studies, association estimates of an exposure with disease outcomes are often biased when the uncertainties of exposure are ignored. Consequently, corresponding confidence intervals (CIs) will not have correct coverage. This issue is particularly problematic when exposures must be reconstructed from physical measurements, for example, for environmental or occupational radiation doses that were received by a study population for which radiation doses cannot be measured directly. To incorporate complex uncertainties in reconstructed exposures, the two-dimensional Monte Carlo (2DMC) dose estimation method has been proposed and used in various dose reconstruction efforts. The 2DMC method generates multiple exposure realizations from dosimetry models that incorporate various sources of errors to reflect the uncertainty of the dose distribution as well as the uncertainties in individual doses in the exposed population. Traditional measurement-error model approaches, typically based on using mean doses in the dose-exposure analysis, do not fully account exposure uncertainties. A recently developed statistical approach that overcomes many of these limitations by analyzing multiple exposure realizations in relation to disease risk is Bayesian model averaging (BMA). The analytic advantage of the BMA is its ability to better accommodate complex exposure uncertainty in the risk estimation, but a practical. Drawback is its significant computational complexity.
In this present paper, we propose a novel frequentist model averaging (FMA) approach which has all the analytical advantages of the BMA method but is much simpler to implement and computationally faster. We show in simulations that, like BMA, FMA yields 95% confidence intervals for association parameters that close to 95% coverage rate. In simulations, the FMA has shorter length of CIs than those of another frequentist approach, the corrected information matrix (CIM) method. We illustrate the similarities in performance of BMA and FMA from a study of exposures from radioactive fallout in Kazakhstan.

https://doi.org/10.1371/journal.pone.0290498

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

17. Warembourg, C., Anguita-Ruiz, A., Siroux, V., Slama, R., Vrijheid, M., Richiardi, L., Basagana, X.
**Statistical Approaches to Study Exposome-Health Associations in the Context of Repeated Exposure Data: A Simulation Study.**
Environmental Science & Technology 2023; Vol. 57 (43), p 16232-16243.

The exposome concept aims to consider all environmental stressors simultaneously. The dimension of the data and the correlation that may exist between exposures lead to various statistical challenges. Some methodological studies have provided insight regarding the efficiency of specific modeling approaches in the context of exposome data assessed once for each subject. However, few studies have considered the situation in which environmental exposures are assessed repeatedly. Here, we conduct a simulation study to compare the performance of statistical approaches to assess exposome-health associations in the context of multiple exposure variables. Different scenarios were tested, assuming different types and numbers of exposure-outcome causal relationships. An application study using real data collected within the INMA mother-child cohort (Spain) is also presented. In the simulation experiment, assessed methods showed varying performance

across scenarios, making it challenging to recommend a one-size-fits-all strategy. Generally, methods such as sparse partial least-squares and the deletion-substitution-addition algorithm tended to outperform the other tested methods (ExWAS, Elastic-Net, DLNM, or sNPLS). Notably, as the number of true predictors increased, the performance of all methods declined. The absence of a clearly superior approach underscores the additional challenges posed by repeated exposome data, such as the presence of more complex correlation structures and interdependencies between variables, and highlights that careful consideration is essential when selecting the appropriate statistical method. In this regard, we provide recommendations based on the expected scenario. Given the heightened risk of reporting false positive or negative associations when applying these techniques to repeated exposome data, we advise interpreting the results with caution, particularly in compromised contexts such as those with a limited sample size.

https://doi.org/10.1021/acs.est.3c04805

**********************************

18.   Lallmahomed, A., Mercier, F., Costet, N., Fillol, C., Bonvallot, N., Le Bot, B.
**Characterization of organic contaminants in hair for biomonitoring purposes.**
Environment international 2024; Vol. 183, 108419.

Biological monitoring is one way to assess human exposure to contaminants. Blood and urine are often used as biological matrices, but hair is an innovative and effective tool for quantifying more biomarkers over a wider exposure window. In order to improve the use of hair in exposure assessment, this article identifies relevant compounds in the literature to investigate hair contamination. Statistical analysis was performed to correlate the physical-chemical properties of the relevant compounds and their concentration levels in hair. Phthalates, pyrethroids and organophosphate flame retardants were chosen for further study of the interpretation of hair measurements for exposure assessment. No significant correlation was found between the average concentration levels in the literature and the physical-chemical properties of the selected compounds. This work also explores the properties of hair and the analytical process that may impact the quantification of organic contaminants in hair. The sample preparation method (sampling, storage, washing) were also studied and adaptations were suggested to improve the existing methods.

https://doi.org/10.1016/j.envint.2024.108419

**********************************

19.   Musatadi, M., Baciero-Hernandez, I., Prieto, A., Olivares, M., Etxebarria, N., Zuloaga, O.
**Development and evaluation of a comprehensive workflow for suspect screening of exposome-related xenobiotics and phase II metabolites in diverse human biofluids.**
Chemosphere 2024; Vol. 351 : 141221.

Suspect and non-target screening (SNTS) methods are being promoted in order to decode the human exposome since a wide chemical space can be analysed in a diversity of human biofluids. However, SNTS approaches in the exposomics field are infra-studied in comparison to environmental or food monitoring studies. In this work, a comprehensive suspect screening workflow was developed to annotate exposome-related xenobiotics and phase II metabolites in diverse human biofluids. Precisely, human urine, breast milk, saliva and ovarian follicular fluid were employed as samples and analysed by means of ultra-high performance liquid chromatography coupled with high resolution tandem mass spectrometry (UHPLC-HRMS/MS). To automate the workflow, the "peak rating" parameter implemented in Compound Discoverer 3.3.2 was optimized to avoid time-consuming manual revision of chromatographic peaks. In addition, the presence of endogenous molecules that might interfere with the annotation of xenobiotics was carefully studied as the employment of inclusion and exclusion suspect lists. To evaluate the workflow, limits of identification (LOIs) and type I and II errors (i.e., false positives and negatives, respectively) were calculated in both standard solutions and spiked biofluids using 161 xenobiotics and 22 metabolites. For 80.3 % of the suspects, LOIs below

15ng/mL were achieved. In terms of type I errors, only two cases were identified in standards and spiked samples. Regarding type II errors, the 7.7 % errors accounted in standards increased to 17.4 % in real samples. Lastly, the use of an inclusion list for endogens was favoured since it avoided 18.7 % of potential type I errors, while the exclusion list caused 7.2 % of type II errors despite making the annotation workflow less time-consuming.

https://doi.org/10.1016/j.chemosphere.2024.141221

**********************************

20.  Xu, S., Sun, M.
**The interpretable machine learning model associated with metal mixtures to identify hypertension via EMR mining method.**
Journal of clinical hypertension (Greenwich, Conn.) 2024; pre-publication

There are limited data available regarding the connection between hypertension and heavy metal exposure. The authors intend to establish an interpretable machine learning (ML) model with high efficiency and robustness that identifies hypertension based on heavy metal exposure. Our datasets were obtained from the US National Health and Nutrition Examination Survey (NHANES, 2013-2020.3). The authors developed 5 ML models for hypertension identification by heavy metal exposure, and tested them by 10 discrimination characteristics. Further, the authors chose the optimally performing model after parameter adjustment by Genetic Algorithm (GA) for identification. Finally, in order to visualize the model's ability to make decisions, the authors used SHapley Additive exPlanation (SHAP) and Local Interpretable Model-Agnostic Explanations (LIME) algorithm to illustrate the features. The study included 19368 participants in total. A best-performing eXtreme Gradient Boosting (XGB) with GA for hypertension identification by 16 heavy metals was selected (AUC: 0.774; 95% CI: 0.772-0.776; accuracy: 87.7%). According to SHAP values, Barium (0.02), Cadmium (0.017), Lead (0.017), Antimony (0.008), Tin (0.007), Manganese (0.006), Thallium (0.004), Tungsten (0.004) in urine, and Lead (0.048), Mercury (0.035), Selenium (0.05), Manganese (0.007) in blood positively influenced the model, while Cadmium (-0.001) in urine negatively influenced the model. Study participants' hypertension associated with heavy metal exposure was identified by an efficient, robust, and interpretable GA-XGB model with SHAP and LIME. Barium, Cadmium, Lead, Antimony, Tin, Manganese, Thallium, Tungsten in urine, and Lead, Mercury, Selenium, Manganese in blood are positively correlated with hypertension, while Cadmium in blood is negatively correlated with hypertension.

https://doi.org/10.1111/jch.14768

**********************************

21.  Owolabi, I. O., Siwarak, K., Greer, B., Rajkovic, A., Dall'asta, C., Karoonuthaisiri, N.*, et al.*
**Applications of Mycotoxin Biomarkers in Human Biomonitoring for Exposome-Health Studies: Past, Present, and Future.**
Exposure and Health 2023; pre-publication

This publication reviews the state-of-the-art human biological monitoring (HBM) of mycotoxin biomarkers in breast milk, plasma, serum, and whole blood samples with a focus on the past two decades (2000-2011 and 2011-2021). Three aspects have been analyzed and summarized: (a) the biomarkers detected and their levels found, (b) the analytical methodologies developed and employed, and (c) the exposome concept and the significance of omics tools. From the literature reviewed, aflatoxins (AFs) and ochratoxin A (OTA) in human breast milk, plasma and serum were the most widely studied mycotoxin biomarkers for HBM. Regarding analytical methodologies, a clear increase in the development and implementation of mass spectrometry methods for simultaneous determination of multiple mycotoxins was observed. For this purpose, use of liquid chromatography (LC) methodologies, especially when coupled with tandem mass spectrometry (MS/MS) or high-resolution mass spectrometry (HRMS) has grown substantially and are now

the methods of choice. A high percentage of the samples analyzed for various mycotoxins in the literature reviewed were found to contain biomarkers, demonstrating a combination of targeted sampling and high levels of human exposure to mycotoxins within the target populations. Also, most HBM investigations only examined exposure to one or a few mycotoxins at a given period. Human exposome studies undertake a wider evaluation of the exposure as part of epidemiological studies through the discovery of novel biomarkers that exist as potential indicators of environmental influences on human health. However, guidelines are required for analytical method validation, as well as algorithms to establish the relationship between the levels of biomarkers detected in human biofluids and mycotoxin intake.

https://doi.org/10.1007/s12403-023-00595-4

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

22. Chen, Y.-C., Hsu, J.-F., Chang, C.-W., Li, S.-W., Yang, Y.-C., Chao, M.-R*., et al.*
**Connecting chemical exposome to human health using high-resolution mass spectrometry-based biomonitoring: Recent advances and future perspectives.**
Mass Spectrometry Reviews 2023; Vol. 42 (6) p 2466-2486.

Compared with the rapid advances in genomics leading to broad understanding of human disease, the linkage between chemical exposome and diseases is still under investigation. High-resolution mass spectrometry (HRMS) is expected to accelerate the process via relatively accurate and precise biomonitoring of human exposome. This review covers recent advancements in biomonitoring of exposed environmental chemicals (chemical exposome) using HRMS described in the 124 articles that resulted from a systematic literature search on Medline and Web of Science databases. The analytical strategic aspects, including the selection of specimens, sample preparation, instrumentation, untargeted versus targeted analysis, and workflows for MS-based biomonitoring to explore the environmental chemical space of human exposome, are deliberated. Applications of HRMS in human exposome investigation are presented by biomonitoring (1) exposed chemical compounds and their biotransformation products; (2) DNA/protein adducts; and (3) endogenous compound perturbations. Challenges and future perspectives are also discussed.

https://doi.org/10.1002/mas.21805

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

23. Bury, D., Weber, T., Ebert, K. E., Zuelz, S., Bruening, T., Koch, H. M., Kolossa-Gehring, M.
**Increasing exposure to the UV filters octocrylene and 2-ethylhexyl salicylate in Germany from 1996 to 2020: Human biomonitoring in 24-h urine samples of the German Environmental Specimen Bank (ESB).**
Environment International 2023; Vol. 182 108334

The UV filters octocrylene (OC) and 2-ethylhexyl salicylate (EHS) are commonly used in sunscreens and frequently detected in environmental media. However, knowledge on human exposures is scarce. In this human biomonitoring (HBM) study, we analyzed concentrations of exposure biomarkers specific to OC (CPAA, DOCCA, 5OH-OC) and EHS (5OH-EHS, 5oxo-EHS, 5cx-EPS) in 24-h urine samples (n = 420) from the German Environmental Specimen Bank (ESB). These samples were collected from German students (20-29 years; 30 males/30 females per year) between 1996 and 2020 (4-year intervals; collection in winter). We found continuously increasing OC and EHS exposures (Jonckheere-Terpstra; $p < 0.001$) documented by very few to no samples with concentrations of the most sensitive biomarkers CPAA and 5cx-EPS above the limit of quantification (LOQ) in 1996 (5 % and 0 %, respectively) and reaching 100 % and 93 % above the LOQ in 2016, with median concentrations of 4.79 and 0.071 µg/L, respectively. In 2020, biomarker concentrations slightly decreased to 3.12 µg/L CPAA (97 %>LOQ) and 0.060 µg/L 5cx-EPS (88 %>LOQ). This general trend was confirmed by the other biomarkers, however at lower detection rates. Based on metabolite excretion in the 24-h urine samples and human toxicokinetic data, we calculated maximum daily intakes (DI) of 17 µg

/ (kg bw * d) OC and 59 µg / (kg bw * d) EHS. Based on a derived no-effect level (DNEL) of 0.8 mg/ (kg bw * d), the OC exposures of individuals in our study did not indicate any health risk. Similarly, for EHS all biomarker concentrations were well below the HBM-I values of 12 µg /L 5OH-EHS and 11 µg /L 5cx-EPS. Our data proves the general applicability of specific OC and EHS metabolites for HBM in the general population and shows clearly increasing exposures. Higher (co-)exposures must be expected in populations with increased sunscreen use such as (summer) vacationers, children and outdoor workers.

https://doi.org/10.1016/j.envint.2023.108334

**********************************

## Expositions Metals-Metals

24.   Qin, L., Liu, Q., Zhang, T., Tang, X., Mo, X., Liang, Y.*, et al.*
**Association Between Combined Polymetallic Exposure and Osteoporosis.**
Biological Trace Element Research 2023; PrePrint

Combined polymetallic exposure may be an influential factor in osteoporosis. This study aimed to explore the association between polymetallic combined exposure and osteoporosis. A total of 2115 participants were included. Plasma concentrations of 22 metals were determined by inductively coupled plasma mass spectrometry. Osteoporosis was defined as a T <= - 2.5. The least absolute shrinkage and selection operator (LASSO) regression, binary logistics regression, and Bayesian kernel machine regression (BKMR) model were used to explore the association between plasma metals and osteoporosis. LASSO regression showed that 10 metals were associated with osteoporosis in the total population (magnesium, calcium, manganese, nickel, cobalt, arsenic, selenium, rubidium, cadmium, aluminum) and women (magnesium, calcium, molybdenum, nickel, cobalt, arsenic, selenium, rubidium, cadmium, aluminum), and four metals associated with men (magnesium, cobalt, aluminum, iron). Logistics regression showed that in total population, magnesium (ORQ3 = 0.653, 95% CI = 0.446-0.954) was negatively correlated with osteoporosis, while aluminum (ORQ2 = 1.569, 95% CI = 1.095-2.248, ORQ4 = 1.616, 95% CI = 1.109-2.354) and cadmium (ORQ4 = 1.989, 95% CI = 1.379-2.870) were positively correlated; in women, magnesium (ORQ3 = 0.579, 95% CI = 0.379-0.883) was negatively correlated with osteoporosis, while aluminum (ORQ2 = 1.563, 95% CI = 1.051-2.326, ORQ4 = 1.543, 95% CI = 1.024-2.326) and cadmium (ORQ3 = 1.482, 95% CI = 1.003-2.191, ORQ4 = 1.740, 95% CI = 1.167-2.596) were positively correlated. BKMR model showed that combined polymetallic exposure had an overall positive effect on osteoporosis, magnesium was negatively associated with osteoporosis, and cadmium, selenium, and aluminum were positively associated with osteoporosis. Metal mixtures in plasma were associated with osteoporosis risk. Magnesium may reduce the risk of osteoporosis, while cadmium, selenium, and aluminum may increase the risk of osteoporosis. Future studies needed to explore correlations and mechanisms.

https://doi.org/10.1007/s12011-023-04002-6

**********************************

25.   Zhu, J., Hu, S., Wang, S., Zhang, Y., Zhu, Q., Zhang, M., Shi, Z.
**Association between metal mixture exposure and abnormal glucose metabolism in multiple mixture exposure models: Evidence from NHANES 2015-2016.**
Current Research in Toxicology 2023; Vol. 5, 100141

Previous studies primarily focused on the single metal exposure and one-sided glucose metabolism disordered states, leading to conflicting results. Herein, we combined diabetes and prediabetes as abnormal glucose metabolism (AGM) to describe the effect of metal mixture exposure on it. Eligible data were obtained from the National Health and Nutrition Examination Survey (NHANES) 2015-2016. In the generalized linear model

(GLM), Cd (OR: 1.060, 95 %CI: 1.032-1.089, P value < 0.001) and Tl (OR: 1.039, 95 %CI: 1.004-1.075, P value = 0.031) exposure were positively associated with AGM. In the weighted quantile sum (WQS) regression model, the positive index was obviously associated with AGM (OR: 1.358, 95 %CI: 1.007-1.832, P value = 0.045). In the least absolute shrinkage and selection operator (LASSO) regression model, Cd and Tl were selected as the most contributors. In the Bayesian kernel machine regression (BKMR) model, the effect of co-exposure to metal mixture was associated with AGM, and Cd exposure showed a significantly positive trend. In conclusion, Cd and Tl exposure exhibited independent positive effects on AGM among metal mixture exposure, consistent with their effects on prediabetes.

https://doi.org/10.1016/j.crtox.2023.100141

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

26.  Gasull, M., Camargo, J., Pumarega, J., Henriquez-Hernandez, L. A., Campi, L., Zumbado, M.*, et al.*
**Blood concentrations of metals, essential trace elements, rare earth elements and other chemicals in the general adult population of Barcelona: Distribution and associated sociodemographic factors.**
Science of the Total Environment 2024; Vol. 909, 168502

Background: Very little information is available on the population distribution and on sociodemographic predictors of body concentrations of rare earth elements (REE) and other chemicals used in the manufacturing of high-tech devices.
Objectives: To analyze the distribution and associated sociodemographic factors of blood concentrations of chemical elements (including some metals, essential trace elements, rare earth elements and other minority elements) in a representative sample of the general population of Barcelona (Spain).
Methods: A sample of participants in the Barcelona Health Survey of 2016 (N = 240) were interviewed face-toface, gave blood, and underwent a physical exam. Concentrations of 50 chemical elements were analyzed by ICPMS in whole blood samples. Results: All 50 chemicals studied, including 26 REE and minority elements, were detected. Lead, silver, arsenic, cadmium, mercury, antimony, strontium, thallium and six essential trace elements were detected in more than 70% of the population. The most frequently detected REE and minority elements were europium (62%), thulium (56%), gold (41%), indium (31%), ruthenium (24%), and tantalum (20%). Less affluent occupational social classes had higher percentages of detection of some REE. Median concentrations of silver, arsenic, cadmium and mercury were: 0.091, 3.01, 0.309, and 3.33 ng/mL, respectively. Women had lower median concentrations than men of lead (1.47 vs. 2.04 mu g/dL, respectively), iron and zinc, and higher concentrations of copper and manganese. The influence of sociodemographic characteristics on chemical concentrations differed by sex. Conclusions: While well-known contaminants as lead, mercury, cadmium, or arsenic were detected in the majority of the population, numerous individuals had also detectable concentrations of chemicals as europium, indium, thulium, or gold. Sociodemographic and physical characteristics (sex, age, social class, weight change) influenced concentrations of some chemicals.

https://doi.org/10.1016/j.scitotenv.2023.168502

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

27.  Jiang, M., Zhao, H.
**Joint association of heavy metals and polycyclic aromatic hydrocarbons exposure with depression in adults.**
Environmental Research 2024; Vol. 242 : 117807

Background: Heavy metals (HMs) and polycyclic aromatic hydrocarbons (PAHs) represent significant components of environmental pollution, typically occurring as mixtures, raising concerns about their potential impact on human health. However, the combined effect of HMs and PAHs exposure on depression has not been explored. Methods: Leveraging National Health and Nutrition Examination Survey (NHANES) data spanning 2005 to 2016, we employ survey-weighted multiple logistic regression models to probe the interrelation between HMs, PAHs, and depression. This exploration is complemented by age and gender-

stratified analyses, as well as a determination of the dose-response linkage via restricted cubic spline regression. Furthermore, the combined impact of HMs and PAHs on depression was evaluated through a range of statistical methodologies. Results: The study encompasses 7732 adults. Our findings unveil notable associations, indicating the significant influence of cadmium (Cd), lead (Pb), and all six PAHs metabolites on depression. Moreover, mixed exposure to HMs and PAHs emerges as a substantial contributor to an augmented depression risk, with Cd, Pb, 1-hydroxynaphthalene (1-NAP), 2-hydroxyfluorene (2-FLU), and 1-hydroxypyrene (1-PYR) likely driving this positive relationship. Intriguingly, subgroup analyses highlight greater prominence of these connections among individuals aged 20-59 and among women. Furthermore, the results tentatively suggest a potential interplay between Cd and 2-NAP in relation to depression. Conclusion: This study posits that exposure to both individual and combined HMs and PAHs may be associated with an elevated risk of depression. Further prospective investigations are warranted to substantiate these findings.

https://doi.org/10.1016/j.envres.2023.117807


\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*


28.   Kou, Z., Tran, F., Dai, W.
**Heavy metals, oxidative stress, and the role of AhR signaling.**
Toxicology and Applied Pharmacology 2024; Vol. 482, p

The Aryl Hydrocarbon Receptor (AhR) is a ligand-activated transcriptional factor pivotal in responding to environmental stress and maintaining cellular homeostasis. Exposure to specific xenobiotics or industrial compounds in the environment activates AhR and its subsequent signaling, inducing oxidative stress and related toxicity. Past research has also identified and characterized several classes of endogenous ligands, particularly some tryptophan (Trp) metabolic/catabolic products, that act as AhR agonists, influencing a variety of physiological and pathological states, including the modulation of immune responses and cell death. Heavy metals, being non-essential elements in the human body, are generally perceived as toxic and hazardous, originating either naturally or from industrial activities. Emerging evidence indicates that heavy metals significantly influence AhR activation and its downstream signaling. This review consolidates current knowledge on the modulation of the AhR signaling pathway by heavy metals, explores the consequences of co-exposure to AhR ligands and heavy metals, and investigates the interplay between oxidative stress and AhR activation, focusing on the regulation of immune responses and ferroptosis.

https://doi.org/10.1016/j.taap.2023.116769


\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*


29.   Zheng, M., Yu, H., An, T., Shen, X.
**Association between urinary multiple metals and platelet-related parameters: A cross-sectional study in a metal-contaminated area of China.**
Environmental science and pollution research international 2024; 31 : 7828–7836

Previous works have shown that hematological system can be affected by exposure to lead; however, the effects of multiple metals on platelets remain elusive within the population from metal-contaminated areas. Hence, the study enrolled 609 participants, with 396 from a metal-exposed area and 213 from a control area. Platelet count (PLT), mean platelet volume (MPV), thrombocytocrit (PCT), platelet to large cell ratio (P-LCR), and platelet distribution width (PDW) were selected to evaluate platelet function. Stepwise regression and Lasso regression were utilized to identify the most influential metals. Moreover, the generalized linear model (GLM), Bayesian kernel machine regression (BKMR) models, and quantile g-computation were employed to estimate the individual or combined effects associations between 12 urinary metals and platelet indices. The results revealed all metals except vanadium, copper, strontium, and molybdenum were significantly higher in the exposed group. The GLM models indicated that urinary metals, including lead, antimony, and arsenic, exhibited associations with PLT, MPV, P-LCR, and PDW. Quantile g-computation and BKMR demonstrated

negative correlations between metal mixtures and MPV as well as PDW. In conclusion, the study highlights the associations between multiple metal exposures and platelet indices, suggesting that elevated levels of the metal mixture may impede platelet activation in the population in metal-contaminated areas.

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

30. Chen, H., Wang, M., Li, J.
**Exploring the association between two groups of metals with potentially opposing renal effects and renal function in middle-aged and older adults: Evidence from an explainable machine learning method.**
Ecotoxicology and Environmental Safety 2024; Vol. 269 : 115812

Background: Machine learning models have promising applications in capturing the complex relationship between mixtures of exposures and outcomes. Objective: Our study aimed at introducing an explainable machine learning (EML) model to assess the association between metal mixtures with potentially opposing renal effects and renal function in middle-aged and older adults. Methods: This study extracted data from two cycle years of the National Health and Nutrition Examination Survey (NHANES). Participants aged 45 years or older with complete data on six metals (lead, cadmium, manganese, mercury, and selenium) and related covariates were enrolled. The EML model was developed by the optimized machine learning model together with Shapley Additive exPlanations (SHAP) to assess the chronic kidney disease (CKD) risk with metal mixtures. The results from EML were further compared in detail with multiple logistic regression (MLR) and Bayesian kernel machine regression (BKMR). Results: After adjusting for included covariates, MLR pointed out the lead and arsenic were generally positively associated with CKD, but manganese had a negative association. In the BKMR analysis, each metal was found to have a non-linear association with the risk of CKD, and interactions can exist between metals, especially for arsenic and lead. The EML ranked the feature importance: lead, manganese, arsenic and selenium were close behind in importance after gender, age or BMI for participants with CKD. Strong interactions between mercury and lead, manganese and cadmium and arsenic and manganese were identified by partial dependence plot (PDP) of SHAP and bivariate exposure-response effect plots of BKMR. The EML model determined the "trigger point" at which the risk of CKD abruptly changed. Conclusion: Co-exposure to metals with different nephrotoxicity could have different joint association with renal function, and EML can be a powerful method for studying complex exposure mixtures.

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

# Expositions multiples aux polluants ambiants, et VOCs

31. Jiang, Z., Zhang, S., Gao, T., Chen, K., Liu, Y., Liu, Y.*, et al.*
**Co-exposure to multiple air pollutants, genetic susceptibility, and the risk of myocardial infarction onset: a cohort analysis of the UK Biobank participants.**
European Journal of Preventive Cardiology 2023; zwad384

Aims The relationship between the long-term joint exposure to ambient air pollution and incidence of myocardial infarction (MI) and modification by genetic susceptibility remain inconclusive.
Methods and results We analysed 329 189 UK Biobank participants without MI at baseline. Exposure concentrations to particulate matter (PM2.5 and PM10), nitrogen dioxide (NO2), and nitrogen oxides (NOx) were obtained. Air pollution score assessing the joint exposure was calculated, and its association with MI was evaluated via Cox model under the P value aggregation framework. Genetic susceptibility to MI was evaluated

by incorporating polygenic risk score (PRS) into models. Risk prediction models were also established. During a median follow-up of 13.4 years, 9993 participants developed MI. Per interquartile range increase of PM2.5, PM10, NO2, and NOx resulted in 74% [95% confidence intervals (CIs) 69%-79%], 67% (63%-72%), 46% (42%-49%), and 38% (35%-41%) higher risk of MI. Compared with the lowest quartile (Q1) of air pollution score, the multivariable adjusted hazard ratio (HR) (95%CIs) of Q4 (the highest cumulative air pollution) was 3.50 (3.29-3.72) for MI. Participants with the highest PRS and air pollution score possessed the highest risk of incident MI (HR = 4.88, 95%CIs 4.35-5.47). Integrating PRS, air pollution exposure, and traditional factors substantially improved risk prediction of MI.

Conclusion Long-term joint exposure to air pollutants including PM2.5, PM10, NO2, and NOx is substantially associated with increased risk of MI. Genetic susceptibility to MI strengthens such adverse joint association. Air pollutions together with genetic and traditional factors enhance the accuracy of MI risk prediction. Our study aimed to analyse the relationship between the long-term joint exposure to four ambient air pollutants and incidence of myocardial infarction (MI), and the modification role of genetic susceptibility. Four air pollutants (PM2.5, PM10, NO2, and NOx) were adversely associated with the incidence of MI as well as with its two subtypes including ST-segment-elevation myocardial infarction (STEMI) and non-ST-segment-elevation myocardial infarction (NSTEMI). Air pollution score representing co-exposure to multiple air pollutants was related to increased risk of incident MI, STEMI, and NSTEMI. Genetic susceptibility to MI strengthened the adverse association of co-exposure to air pollution with the risk of MI, STEMI, and NSTEMI.

https://doi.org/10.1093/eurjpc/zwad384

************************************

32.  Ramirez, D. M., Gutenkunst, S., Lothrop, N., Quijada, C., Chaires, M., Cortez, I., *et al.*
**What a mix! Volatile organic compounds and worker exposure in small business beauty salons in Tucson, Arizona.**
Frontiers in Public Health 2023; Vol. 11

Introduction Small business beauty salons have volatile organic compounds (VOCs) in their workplace air. VOCs are present as ingredients in beauty or hair products. They may also form because of chemical reactions, where thermal-styling elements accelerate the volatilization of these compounds. Uncertainties remain about the relationship between air pollutant concentrations and the variety of beauty salon activities in a work shift. Investigating these associations can help determine high-risk services, associated products, and at-risk workers.

Methods In this exploratory study, female community health workers recruited beauty salons from target zip codes in predominately Latino neighborhoods, including primarily Spanish-speaking small businesses. We collected salon chemical inventories, business characteristics, and participant activity logs to understand how chemicals and activities influence the total and specific VOC concentrations. We sampled personal total VOCs and specific VOCs from the same shop during the participant work shift. We also measured personal total VOCs for four work shifts per shop.

Results A linear mixed effects model of log VOCs on the fixed effect of activity and the random effects of salon and shift within the salon showed that the variance between salons explains over half (55%) of the total variance and is 4.1 times bigger than for shifts within salons. Summa canisters detected 31 specific VOCs, and hazard scores ranged between 0 and 4.3. 2-Propanol (isopropyl alcohol) was the only VOC detected in all shifts of all salons.

Discussion In this study, differences in VOC measurements were primarily between salons. These differences may result from differences in ventilation, services rendered, and product lines applied.

https://doi.org/10.3389/fpubh.2023.1300291

************************************

33. Tan, L., Liu, Y., Liu, J., Liu, Z., Shi, R.
**Associations of individual and mixture exposure to volatile organic compounds with metabolic syndrome and its components among US adults.**
Chemosphere 2024; Vol. 347 : 140683.

BACKGROUND: People are exposed to various volatile organic compounds (VOCs) in their environment. Our study aims to examine the links between VOCs exposure and metabolic syndrome (MetS) and its components, as well as identify critical VOCs. METHOD: In this study, we enrolled 8223 adults from the National Health and Nutrition Examination Survey (NHANES) and analyzed 15 kinds of urinary VOCs metabolites. The Spearman correlation model, generalized linear regression model, restricted cubic spline (RCS), weighted quantile sum (WQS) analysis, and Bayesian kernel machine regression (BKMR) were used to evaluate the association between individual VOC/VOCs mixture and MetS as well as its components. RESULTS: In generalized linear regression model, compared to the lowest quartile of urinary VOCs metabolites, the highest quartiles of urinary VOC metabolites were positively associated with MetS including N-Acetyl-S-(N-methylcarbamoyl)-l-cysteine (AMCC) (OR: 1.22, 95%CI: 1.00, 1.49), N-Acetyl-S-(2-carboxyethyl)-l-cysteine (CEMA) (OR: 1.71, 95%CI: 1.41, 2.07), N-Acetyl-S-(3-hydroxypropyl)-l-cysteine (3HPMA) (OR: 1.32, 95%CI: 1.11, 1.63), and N-Acetyl-S-(3-hydroxypropyl-1-methyl)-l-cysteine (HMPMA) (OR: 1.34, 95%CI: 1.09, 1.64). Consistent results were found in the dose-response relationship in RCS model. Results of WQS showed that VOCs mixture was positively associated with MetS (OR: 1.16, 95%CI: 1.06, 1.28), elevated WC (OR: 1.25, 95%CI: 1.13, 1.37), elevated FBG (OR: 1.24, 95%CI: 1.12, 1.37), elevated TG (OR: 1.34, 95%CI: 1.21, 1.49), and reduced HDL-C (OR: 1.20, 95%CI: 1.09, 1.33). However, the WQS index was negatively associated with elevated BP (OR: 0.81; 95%CI: 0.70, 0.94). BKMR analysis confirmed that the urinary VOCs mixture was positively associated with MetS, elevated WC, elevated TG, reduced HDL-C, elevated FBG, but negatively associated with elevated BP. CEMA was defined as the most heavily weighted chemical in the WQS and BKMR models. CONCLUSION: Our findings suggested that exposure to specific VOC or VOCs mixture is associated with the higher risk of MetS and its components, except for elevated BP.

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

34. Liu, Q., Fan, G., Bi, J., Qin, X., Fang, Q., Wu, M._, et al._
**Associations of polychlorinated biphenyls and organochlorine pesticides with metabolic dysfunction-associated fatty liver disease among Chinese adults: Effect modification by lifestyle.**
Environmental Research 2024; Vol. 240 part 2 : 117507

Exposure to environmental pollutants and unhealthy lifestyles are key risk factors for metabolic dysfunction associated fatty liver disease (MAFLD). While previous studies have suggested links between exposure to organochlorine pesticides (PCBs) and organochlorine pesticides (OCPs) and MAFLD, the results have been inconsistent. Furthermore, the combined effects of PCBs and OCPs on MAFLD and whether lifestyle factors can modify the associations remain unknown. Therefore, this study aimed to investigate the individual and joint effects of PCBs and OCPs on MAFLD and explore the potential modifying role of lifestyle. The study included 1923 participants from Wuhan, China. MAFLD was diagnosed based on ultrasonically diagnosed hepatic steatosis and the presence of overweight/obese, diabetes mellitus, or metabolic dysregulation. Healthy lifestyle score was determined by smoking, alcohol consumption, physical activity, and diet. Logistic regression and weighted quantile sum (WQS) were used to assess associations of individual and mixture of PCBs/OCPs with MAFLD. To explore the potential lifestyle modification, joint associations of PCBs/OCPs and lifestyle on MAFLD were conducted. Single-pollutant analysis showed positive associations of p,p '-DDE, beta-HCH, PCB-153, and PCB-180 with MAFLD, with ORs (95% CIs) of 1.18 (1.05, 1.33), 1.57 (1.20, 2.05), 1.45 (1.14, 1.83), and 1.42 (1.12, 1.80), respectively. WQS regression demonstrated a harmful effect of PCBs/OCPs mixture on MAFLD (OR = 1.73, 95% CI = 1.24, 2.43), with beta-HCH, p,p'-DDE, and PCB-180 being the major contributors. In the joint association analysis, participants with both high PCBs/OCPs exposure and unhealthy lifestyle have the highest odds of MAFLD. In conclusion, exposure to the mixture of PCBs and OCPs was positively correlated with MAFLD, and adopting a healthy lifestyle can mitigate the adverse impact.

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

35.   Tang, L., Liu, M., Tian, J.
**Volatile organic compounds exposure associated with depression among U.S. adults: Results from NHANES 2011-2020.**
Chemosphere 2024; Vol. 349 : 140690.

Volatile organic compounds (VOCs) are important contributors to air pollution. VOCs exposure was associated with various human diseases. Depression is one of the most prevalent mental disorders and poses a serious mental health burden. Although VOCs are neurotoxic and can damage the central nervous system, the association between VOCs exposure and depression remains obscure. Based on data from the National Health and Nutrition Examination Survey, we included 5676 adult individuals and 15 major components of urinary volatile organic compound metabolites (mVOCs). We comprehensively evaluated the potential association between each single urinary mVOC exposure and depressive symptoms using binary logistic and restricted cubic spline regression, whereas the weighted quantile sum regression and least absolute shrinkage and selection operator regression model were used to explore the mixture co-exposure association. The results indicated significantly higher mean concentrations of the 11 urinary mVOC components in the depression group than that in the non-depression group. And 12 mVOC components had a significantly positive association with depression. The overall effect of all 15 mVOCs components was also significantly positive. The corresponding odds ratio was 1.56 (95%CI: 1.2-2.03) in the categorical variable model and the regression coefficient was 0.36 (95%CI: 0.12-0.6) in the numerical variable model. Five urinary mVOCs (URXCYM, URXPHG, URX34M, URXMB3, and URXAMC) were identified as the most relevant components associated with depression, with 89.06% total weights in the categorical variable model and 89.39% in the numerical variable model. The mVOCs were the biomarkers of VOCs, their concentrations in urine could specifically represent the contents of their metabolic parents in the human body. Considering that the metabolic parents of the above five mVOCs were predominantly acrylonitrile, toluene, styrene, acrylamide, 1,3-Butadiene, and xylenes, our results further indicated that exposure to these VOCs was closely related to depression, and more attention should be paid to the mental health risks of VOCs exposure.