Bulletin de veille
Polyexpositions chimie-chimie
N°5 – août-septembre 2024

Objectif : la polyexposition homogène agents chimiques/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

- 16 juillet. Metabolon Inc. le leader mondial des solutions métabolomiques, élargit sa bibliothèque pour inclure 70 pesticides, faisant progresser les connaissances sur les exposomes humains grâce à la métabolomique Metabolon Expands Library to Include 70 Pesticides, Advancing Human Exposome Insights through Metabolomics - BioSpace
  Communiqué sur PRNewswire : Metabolon Expands Library to Include 70 Pesticides, Advancing Human Exposome Insights through Metabolomics (prnewswire.com)
- 19 juillet. cnrs.fr. La Mission pour les initiatives transverses et interdisciplinaires (MITI) a pour objectif de promouvoir, animer et coordonner l'interdisciplinarité au CNRS, et en particulier l'interaction entre ses dix instituts. Dans ce cadre, elle lance en 2025 l'appel à projets « Exposome » AAP Exposome - MITI (cnrs.fr)
- Extrait de PARC Newsletter spring-summer 2024 :
  - Monitoring human exposure to chemicals: PARC Aligned Studies | Parc (eu-parc.eu)
  - PARC explores the use of Mixture Assessment Factor (MAF) to enhance regulatory mixture risk assessment | Parc (eu-parc.eu)

- 16 septembre. Fondation du Forum sur l'emballage alimentaire. « Nombreuses preuves de l'existence de produits chimiques liés à l'emballage chez l'homme. ». Widespread evidence for packaging-related che | EurekAlert!
- 16 septembre : Santé publique France et l'Anses lancent le 16 septembre 2024 la première phase de l'enquête Albane qui permettra d'évaluer en continu la santé de la population française, l'exposition aux substances chimiques et de mieux connaître leurs liens avec l'alimentation et l'environnement. Plus d'info sur https://www.anses.fr/fr/content/albane-actualite
- 30 septembre : Le projet EPHOR explore le développement et l'application d'outils et de méthodes d'exposome pour évaluer l'impact du travail sur la santé. Le projet EPHOR organisera deux ateliers avec le réseau PEROSH les 30 et 31 octobre à ce sujet. Plus d'infos sur : https://perosh.eu/event/ephor-perosh-workshops-on-30-and-31-october-2024/

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Biomonitoring, outils, modèles, machine learning pour les multi-expositions chimiques.

Wu, M., Zhao, Z., Wu, W., Cai, G.
Detection of volatile organic compounds by membrane interface probe: Multiphase numerical model for in-situ test evaluation.
Computers and Geotechnics 2024; Vol. 173, September 2024, 106491.

Membrane interface probe (MIP) is a widely used device for evaluating volatile organic compounds (VOCs) insitu. However, its results are often regarded to be qualitative. In this paper, we present a sophisticated numerical model for refined evaluation of the in-situ test results. Our multi-phase and multi-component model is based on the mixture theory for porous media. The numerical model is validated by our own model test on a hollow soil column. Parametric studies are performed to study the effect of contaminant concentration, testing temperature, soil porosity, thermal conductivity of dry soil, and soil intrinsic permeability on MIP test. A simplified model is then proposed based on the numerical simulations. The proposed model effectively characterizes the MIP testing process, providing a solid theoretical foundation for the in-situ evaluation of VOCs.
https://doi.org/10.1016/j.compgeo.2024.106491

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Mosquera, R., Perez Vergara, I. G., Contreras-Pacheco, O. E.
A model based on PDCA and data mining approach for the prevention of occupational accidents in the plumbing activity in the construction sector.
Work-a Journal of Prevention Assessment & Rehabilitation 2024; Vol. 78 (2) p 399-410.

BACKGROUND: Occupational accidents in the plumbing activity in the construction sector in developing countries have high rates of work absenteeism. The productivity of enterprises is heavily influenced by it.
OBJECTIVE: To propose a model based on the Plan, Do, Check, and Act cycle and data mining for the prevention of occupational accidents in the plumbing activity in the construction sector.
METHODS: This cross-sectional study was administered on a total of 200 male technical workers in plumbing. It considers biological, biomechanical, chemical, and, physical risk factors. Three data mining algorithms were compared: Logistic Regression, Naive Bayes, and Decision Trees, classifying the occurrences occupational accident. The model was validated considering 20% of the data collected, maintaining the same proportion between accidents and non-accidents. The model was applied to data collected from the last 17 years of occupational accidents in the plumbing activity in a Colombian construction company. RESULTS: The results showed that, in 90.5% of the cases, the decision tree classifier (J48) correctly identified the possible cases of occupational accidents with the biological, chemical, and, biomechanical, risk factors training variables applied in the model.
CONCLUSION: The results of this study are promising in that the model is efficient in predicting the occurrence of an occupational accident in the plumbing activity in the construction sector. For the accidents identified and the associated causes, a plan of measures to mitigate the risk of occupational accidents is proposed.
https://doi.org/10.3233/wor-230112

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Esu, C. O., Pyo, J., Cho, K.
Machine learning-derived dose-response relationships considering interactions in mixtures: Applications to the oxidative potential of particulate matter.
Journal of Hazardous Materials 2024; Vol. 475, 15 August 2024, 134864.

Conventional environmental health research is primarily focused on isolated chemical exposures, neglecting the complex interactions between multiple pollutants that may synergistically or antagonistically influence toxicity, thereby posing unexpected health risks.
In this study, we address this knowledge gap by introducing an explainable machine learning (ML) approach with Feature Localized Intercept Transformed-Shapley Additive Explanations (FLIT-SHAP) designed to extract the dose-response relationships of specific pollutants in mixtures. In contrast to traditional SHAP, FLIT-SHAP can localize the global intercept to elucidate mixture effects, which is crucial for understanding the oxidative potential (OP) of ambient particulate matter (PM). Assessing multipollutant OP using FLIT-SHAP revealed both synergistic (55-63 %) and antagonistic (25-42 %) effects in laboratory-controlled OP data, but an antagonistic (33-66 %; lower OP) effect in ambient PM. Notably, the FLITSHAP approach demonstrated higher prediction accuracy (R2 = 0.99) compared to the additive model (R2 = 0.89) when evaluated against real-world PM samples. Quinones, such as phenanthrenequinone, play a more significant role in PM2.5 than previously recognized.
Through this study, we highlighted the potential of FLITSHAP to enhance toxicity predictions and aid decision-making in the field of environmental health.
https://doi.org/10.1016/j.jhazmat.2024.134864

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Nian, M., Braun, G., Escher, B. I., Fang, M.
Toxicological Study of Human Exposure to Mixtures of Chemicals: Challenges and Approaches.
Environmental Science & Technology Letters 2024; Vol. 11 (8) p 773-782.

Humans are exposed to highly diverse mixtures of complex and often unknown compositions, which may adversely impact their health. There is a lack of guidance on how to design toxicological studies of chemical mixtures.
This paper aims to evaluate the weaknesses and strengths of chemical mixture studies and to propose the practical design of mixture effect studies including chemical selection, dosing considerations, and

determination of toxicological mechanisms of mixtures. The design of mixture effect studies should be optimized to yield relevant information on real-life mixture effects (1) by selecting appropriate chemicals based on the association between chemical effects and diseases using information from epidemiological studies and "chemical-disease" associations from toxicological databases and/or animal studies; (2) by testing mixture ratios and concentrations derived from biomonitoring data; (3) by evolving from binary mixtures and those with a low number of components to complex and diverse mixtures with as many components as practically possible; (4) by applying multiomics and high-throughput screening approaches to increase the number of testable individual chemicals and mixture scenarios; and (5) by implementing computational mixture models in the experiment planning phase and to interpret the outcomes to examine the toxicological mechanisms of "multiple exposure-multiple targets". We urge to move mixture investigation from answering academic questions such as mixture interaction models at high effect and concentration levels to mixture scenarios that are relevant for today's human exposure, i.e., low concentration, low effect but high complexity mixtures.
https://doi.org/10.1021/acs.estlett.4c00393

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Limbu, S., Glasgow, E., Block, T., Dakshanamurthy, S.
A Machine-Learning-Driven Pathophysiology-Based New Approach Method for the Dose-Dependent Assessment of Hazardous Chemical Mixtures and Experimental Validations.
Toxics 2024; Vol. 12 (7), 481

Environmental chemicals, such as PFAS, exist as mixtures and are frequently encountered at varying concentrations, which can lead to serious health effects, such as cancer. Therefore, understanding the dose-dependent toxicity of chemical mixtures is essential for health risk assessment. However, comprehensive methods to assess toxicity and identify the mechanisms of these harmful mixtures are currently absent. In this study, the dose-dependent toxicity assessments of chemical mixtures are performed in three methodologically distinct phases. In the first phase, we evaluated our machine-learning method (AI-HNN) and pathophysiology method (CPTM) for predicting toxicity. In the second phase, we integrated AI-HNN and CPTM to establish a comprehensive new approach method (NAM) framework called AI-CPTM that is targeted at refining prediction accuracy and providing a comprehensive understanding of toxicity mechanisms. The third phase involved experimental validations of the AI-CPTM predictions. Initially, we developed binary, multiclass classification, and regression models to predict binary, categorical toxicity, and toxic potencies using nearly a thousand experimental mixtures. This empirical dataset was expanded with assumption-based virtual mixtures, compensating for the lack of experimental data and broadening the scope of the dataset. For comparison, we also developed machine-learning models based on RF, Bagging, AdaBoost, SVR, GB, KR, DT, KN, and Consensus methods. The AI-HNN achieved overall accuracies of over 80%, with the AUC exceeding 90%. In the final phase, we demonstrated the superior performance and predictive capability of AI-CPTM, including for PFAS mixtures and their interaction effects, through rigorous literature and statistical validations, along with experimental dose-response zebrafish-embryo toxicity assays. Overall, the AI-CPTM approach significantly improves upon the limitations of standalone AI models, showing extensive enhancements in identifying toxic chemicals and mixtures and their mechanisms. This study is the first to develop a hybrid NAM that integrates AI with a pathophysiology method to comprehensively predict chemical-mixture toxicity, carcinogenicity, and mechanisms.
https://doi.org/10.3390/toxics12070481

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Kim, H. R., Kim, J. W., Lee, J.-H., Kim, Y., Lim, J., Baek, Y.-W*., et al.*
Toxicological evidence integration to confirm the biological plausibility of the association between humidifier disinfectant exposure and respiratory diseases using the AEP-AOP framework.
Epidemiology and health 2024; Vol., p e2024060.

Objectives: Exposure to humidifier disinfectants has been linked to respiratory diseases, including

interstitial lung disease, asthma, and pneumonia. Consequently, numerous toxicological studies have explored respiratory damage as both a necessary and sufficient condition for these diseases. We systematically reviewed and integrated evidence from toxicological studies by applying the evidence integration method established in previous research to confirm the biological plausibility of the association between exposure and disease.
Methods: We conducted a literature search focusing on polyhexamethylene guanidine phosphate (PHMG) and chloromethylisothiazolinone/methylisothiazolinone (CMIT/MIT), the primary ingredients in humidifier disinfectants. We selected relevant studies based on their quality and the population, exposure, comparator, outcome (PECO) statements. These studies were categorized into 3 lines of evidence: hazard information, animal studies, and mechanistic studies. Based on a systematic review, we integrated the evidence to develop an aggregate exposure pathway-adverse outcome pathway (AEP-AOP) model for respiratory damage. The reliability and relevance of our findings were assessed by comparing them with the hypothesized pathogenic mechanisms of respiratory diseases.
Results: The integration of each AEP-AOP component for PHMG and CMIT/MIT led to the development of an AEP-AOP model, wherein disinfectants released from humidifiers in aerosol or gaseous form reached target sites, causing respiratory damage through molecular initiating events and key events. The model demonstrated high reliability and relevance to the pathogenesis of respiratory diseases.
Conclusion: The AEP-AOP model developed in this study provides strong evidence that exposure to humidifier disinfectants causes respiratory diseases. This model demonstrates the pathways leading to respiratory damage, a hallmark of these conditions.
https://doi.org/10.4178/epih.e2024060

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Amini, P., Okeme, J. O.
Tear Fluid as a Matrix for Biomonitoring Environmental and Chemical Exposures.
Current Environmental Health Reports 2024; Vol. 11 (3) p 340-355.

PurposeExposures to hazardous chemicals have been linked to many detrimental health effects and it is therefore critical to have effective biomonitoring methods to better evaluate key environmental exposures that increase the risk of chronic disease and death. Traditional biomonitoring utilizing blood and urine is limited due to the specialized skills and invasiveness of collecting these fluid samples.
This systematic review focuses on tear fluid, which is largely under-researched, as a promising complementary matrix to the traditional fluids used for biomonitoring. The objective is to evaluate the practicability of using human tear fluid for biomonitoring environmental exposures, highlighting potential pitfalls and opportunities. Recent FindingTear fluid biomonitoring represents a promising method for assessing exposures because it can be collected with minimal invasiveness and tears contain exposure markers from both the external and internal environments. Tear fluid uniquely interfaces with the external environment at the air-tear interface, providing a surface for airborne chemicals to diffuse into the ocular environment and interact with biomolecules. Tear fluid also contains molecules from the internal environment that have travelled from the blood to tears by crossing the blood-tear barrier. This review demonstrates that tear fluid can be used to identify hazardous chemicals from the external environment and differentiate exposure groups.
This review provides a critical analysis of the current state of knowledge in tear-based biomonitoring, drawing attention to how the minimal invasiveness of collection and ease of analysis can increase access to exposure assessment. Tear fluid analysis will become acceptable for routine use as more individual and inter lab studies focus on broadly identifying and quantifying exposure markers in tears, helping improve our understanding of the factors that influence the reliability of tear biomonitoring and moving towards the standardization of tear fluid collection and analysis methods.
https://doi.org/10.1007/s40572-024-00454-7

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Song, G., Liu, X., Lei, K., Li, T., Li, W., Chen, D.

ExpoNano: A Strategy Based on Hyper-Cross-Linked Polymers Achieves Urinary Exposome Assessment for Biomonitoring.
Environmental science & technology 2024; Vol. 58 (32) p 14088-14097.

Urinary analysis of exogenous and endogenous molecules constitutes an efficient, noninvasive approach to evaluate human health status. However, the exposome characterization of urinary molecules remains extremely challenging with current techniques. Herein, we develop an ExpoNano strategy based on hyper-cross-linked polymers (HCPs) to achieve ultrahigh-throughput measurement of exo/endogenous molecules in urine. The strategy includes a simple trapping-detrapping procedure (15 min) with HCPs in enzymatically treated urine, followed by mass spectrometer determination. Molecules that can be determined by ExpoNano have a wide range of molecular weight (75-837 Da) and Log Kow (octanol-water partition coefficient; -9.86 to 10.56). The HCPs can be repeatedly used five times without decreasing the trapping efficiency. Application of ExpoNano in a biomonitoring study revealed a total of 63 environmental chemicals detected in >50% of the urine pools collected from Chinese adults living in 13 cities, with a median concentration of 0.026-47 ng/mL, while nontargeted analysis detected an additional 243 exogenous molecules. Targeted and nontargeted analysis also detected 926 endogenous molecules in pooled urine. Collectively, the ExpoNano strategy demonstrates unique advantages over traditional urine analysis approaches, including a wide range of analytes, satisfactory trapping efficiency, high simplicity and reusability, and extremely reduced time demand and financial cost.
https://doi.org/10.1021/acs.est.4c01146

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Baesu, A., Feng, Y.-L.
Development of a robust non-targeted analysis approach for fast identification of endocrine disruptors and their metabolites in human urine for exposure assessment.
Chemosphere 2024; Vol. 363 p 142754-142754.

Endocrine disrupting chemicals are of concern because of possible human health effects, thus they are frequently included in biomonitoring studies. Current analytical methods are focused on known chemicals and are incapable of identifying or quantifying other unknown chemicals and their metabolites. Non-targeted analysis (NTA) methods are advantageous since they allow for broad chemical screening, which provides a more comprehensive characterization of human chemical exposure, and can allow elucidation of metabolic pathways for unknown chemicals. There are still many challenges associated with NTA, which can impact the results obtained. The chemical space, i.e., the group of known and possible compounds within the scope of the method, must clearly be defined based on the sample preparation, as this is critical in identifying chemicals with confidence. Data acquisition modes and mobile phase additives used with liquid chromatography coupled to high-resolution mass-spectrometry can affect the chemicals ionized and structural identification based on the spectral quality. In this study, a sample preparation method was developed using a novel clean-up approach with CarbonS cartridges, for endocrine-disrupting chemicals in urine, including new bisphenol A analogues and benzophenone-based UV filters, like methyl bis (4-hydroxyphenyl acetate). The study showed that data dependent acquisition (DDA) had a lower identification rate (40%) at low spiking levels, i.e., 1ng/mL, compared to data independent acquisition (DIA) (57%), when Compound Discoverer was used. In DDA, more compounds were identified using Compound Discoverer, with an identification rate of 95% when ammonium acetate was compared to acetic acid (82%) as a mobile phase additive. TraceFinder software had an identification rate of 53% at 1ng/mL spiking level using the DDA data, compared to 40% using the DIA data. Using the developed method, 2,4 bisphenol F was identified for the first time in urine samples. The results show how NTA can provide human exposure information for risk assessment and regulatory action but standardized reporting of procedures is needed to ensure study results are reproducible and accurate. His Majesty the King in Right of Canada, as represented by the Minister of Health, 2024.
https://doi.org/10.1016/j.chemosphere.2024.142754

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Marín-Sáez, J., Hernández-Mesa, M., Cano-Sancho, G., García-Campaña, A. M.
Analytical challenges and opportunities in the study of endocrine disrupting chemicals within an exposomics framework.
Talanta 2024; Vol. 279, p 126616.

Exposomics aims to measure human exposures throughout the lifespan and the changes they produce in the human body. Exposome-scale studies have significant potential to understand the interplay of environmental factors with complex multifactorial diseases widespread in our society and whose origin remain unclear. In this framework, the study of the chemical exposome aims to cover all chemical exposures and their effects in human health but, today, this goal still seems unfeasible or at least very challenging, which makes the exposome for now only a concept. Furthermore, the study of the chemical exposome faces several methodological challenges such as moving from specific targeted methodologies towards high-throughput multitargeted and non-targeted approaches, guaranteeing the availability and quality of biological samples to obtain quality analytical data, standardization of applied analytical methodologies, as well as the statistical assignment of increasingly complex datasets, or the identification of (un)known analytes. This review discusses the various steps involved in applying the exposome concept from an analytical perspective. It provides an overview of the wide variety of existing analytical methods and instruments, highlighting their complementarity to develop combined analytical strategies to advance towards the chemical exposome characterization. In addition, this review focuses on endocrine disrupting chemicals (EDCs) to show how studying even a minor part of the chemical exposome represents a great challenge. Analytical strategies applied in an exposomics context have shown great potential to elucidate the role of EDCs in health outcomes. However, translating innovative methods into etiological research and chemical risk assessment will require a multidisciplinary effort. Unlike other review articles focused on exposomics, this review offers a holistic view from the perspective of analytical chemistry and discuss the entire analytical workflow to finally obtain valuable results.
https://doi.org/10.1016/j.talanta.2024.126616

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Poddalgoda, D., Macey, K., Chander, N., Jayawardene, I., Sitland, B., Mohr, S., Hancock, S.
A review of Health Canada's progress on human biomonitoring-based risk assessments and the path forward.
Toxicology Letters 2024; Vol. 399, p 19-24.

Since the launch of the Chemicals Management Plan (CMP) in 2006, Health Canada has initiated screening-level risk assessments (RAs) of approximately 4300 priority substances under the Canadian Environmental Protection Act, 1999 (CEPA). With the availability of nationally representative human biomonitoring (HBM) data, over 300 of these substances were assessed using HBM-based RA approaches. Qualitative and quantitative HBM-based RA approaches for the regulatory risk assessment of the general population of Canada were developed to increase the efficiency of screening the potential health risk of CMP priority substances. To support HBM-based RAs, several biomonitoring equivalents (BE) were derived to interpret HBM data. For some CMP substances, Health Canada conducted cumulative risk assessments of chemical mixtures using HBM data as measures of exposure. In 2023, CEPA was amended to include the assessment of populations who may be disproportionately impacted (vulnerable populations) and the cumulative effects of multiple chemicals. Going forward, Health Canada is exploring modern approaches in HBM-based RAs, including biomarkers of effect and non-traditional biomarkers (e.g., hair, nails) to address CEPA amendments. This manuscript will discuss Health Canada's progress in HBM-based RAs, and the possible path forward in using HBM data to strengthen human health risk assessments.
https://doi.org/10.1016/j.toxlet.2024.07.001

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Zhang, H., Wang, J., Zhang, K., Shi, J., Gao, Y., Zheng, J.*, et al.*
Association between heavy metals exposure and persistent infections: the mediating role of immune function.
Frontiers in public health 2024; Vol. 12 p 1367644.

Introduction: Persistent infections caused by certain viruses and parasites have been associated with multiple diseases and substantial mortality. Heavy metals are ubiquitous environmental pollutants with immunosuppressive properties. This study aimed to determine whether heavy metals exposure suppress the immune system, thereby increasing the susceptibility to persistent infections. Methods: Using data from NHANES 1999-2016, we explored the associations between heavy metals exposure and persistent infections: Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Hepatitis C Virus (HCV), Herpes Simplex Virus Type-1 (HSV-1), Toxoplasma gondii (T. gondii), and Toxocara canis and Toxocara cati (Toxocara spp.) by performing logistic regression, weighted quantile sum (WQS) and Bayesian kernel machine regression (BKMR) models. Mediation analysis was used to determine the mediating role of host immune function in these associations. Results: Logistic regression analysis revealed positive associations between multiple heavy metals and the increased risk of persistent infections. In WQS models, the heavy metals mixture was associated with increased risks of several persistent infections: CMV (OR: 1.58; 95% CI: 1.17, 2.14), HCV (OR: 2.94; 95% CI: 1.68, 5.16), HSV-1 (OR: 1.25; 95% CI: 1.11, 1.42), T. gondii (OR: 1.97; 95% CI: 1.41, 2.76), and Toxocara spp. (OR: 1.76; 95% CI: 1.16, 2.66). BKMR models further confirmed the combined effects of heavy metals mixture and also identified the individual effect of arsenic, cadmium, and lead. On mediation analysis, the systemic immune inflammation index, which reflects the host's immune status, mediated 12.14% of the association of mixed heavy metals exposure with HSV-1 infection. Discussion: The findings of this study revealed that heavy metals exposure may increase susceptibility to persistent infections, with the host's immune status potentially mediating this relationship. Reducing exposure to heavy metals may have preventive implications for persistent infections, and further prospective studies are needed to confirm these findings.
https://doi.org/10.3389/fpubh.2024.1367644

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Nguyen, H. D.
Interactions Between Heavy Metal Mixtures and Kidney Function: Gender-Stratified Analyses.
Exposure and Health 2024; Vol. 16 (3) p 821-836.

Little is known about the effects of mixed heavy metals on estimated glomerular filtration rate (eGFR) and the molecular mechanisms involved in mixed heavy metal-caused progressive renal failure. Thus, we aimed to examine the relationship between combined heavy metals (cadmium, lead, and mercury) and eGFR using current statistical approaches. We then explored the main molecular processes implicated in the pathophysiology of progressive renal failure induced by combined heavy metals. We found that mixed heavy metals, especially lead, were positively associated with decreased eGFR using quantile g-computation, weighted quantile sum, and Bayesian kernel machine regression method. Furthermore, the levels of reduced eGFR related to combined heavy metals in females were more likely to be higher than in males, as consistently identified across all approaches. Serum heavy metal threshold levels in relation to eGFR were also analyzed. In silico research observed that combined heavy metals altered eleven genes implicated in the development of progressive renal failure. Between these genes, physical interactions accounted for about half of the interactions. At the molecular level, progressive renal failure induced by combined heavy metals was related to altered antioxidant activities and inflammatory responses. Key miRNAs (hsa-miR-26b-5p and hsa-miR-124-3p) and their sponges related to progressive renal failure were also described. Our findings imply that more research should be done to determine the impact of extended combined heavy metal exposure on juveniles' renal function and the risks of developing progressive renal

failure. Furthermore, further measures to prevent exposure to heavy metals are required to lower the prevalence of progressive renal failure, with a particular emphasis on females and lead exposure. Lastly, with regard to progressive renal failure development, the effects of combined heavy metals on common genes, critical miRNAs, sponges, and molecular pathways should be given special consideration.
https://doi.org/10.1007/s12403-023-00594-5

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Dai, Y., Duan, S., Wang, R., He, P., Zhang, Z., Li, M., *et al.*
Associations between multiple urinary metals and metabolic syndrome: Exploring the mediating role of liver function in Chinese community-dwelling elderly.
Journal of Trace Elements in Medicine and Biology 2024 September ; Vol. 85, 127472

Background: Multiple metals exposure has been revealed to be related to metabolic syndrome (MetS). However, the associations and interactions between multiple metals exposure and MetS are remains controversial, and the potential mechanism of the above-mentioned is still unclear. Methods: The associations between urinary metals and the MetS were analyzed by multivariable logistic regression model and restricted cubic spline (RCS). Bayesian kernel machine regression (BKMR) model and quantile-based g-computation (qgcomp) were applied to explore the mixed exposure and interaction effect of metals. Mediation analysis was used to explore the role of liver function. Results: In the single metal model, multiple metals were significantly associated with MetS. RCS analysis further verified the associations between 8 metals and MetS. BKMR model and qgcomp showed that zinc (Zn), iron (Fe), and tellurium (Te) were the main factors affecting the overall effect. In addition, mediation analysis indicated that serum alanine aminotransferase (ALT) mediated 21.54% and 13.29% in the associations of vanadium (V) and Zn with the risk of MetS, respectively. Conclusions: Elevated urinary concentration of Zn, V, Te, copper (Cu), molybdenum (Mo), and thallium (Tl) were related to the increased risk of MetS. Conversely, Fe and selenium (Se) may be protective factors for MetS in mixed exposure. Liver function may play a key role in the association of V and Zn exposure with MetS.
https://doi.org/10.1016/j.jtemb.2024.127472

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Pan, S., Niu, Y., Duan, S., Zhao, D., Wang, Q., Dong, Z., *et al.*
Uric acid mediates the relationship between mixed heavy metal exposure and renal function in older adult people.
Frontiers in Public Health 2024 July; Vol. 12.

Background Population aging is a pivotal trend observed globally, and the exposure to heavy metals can exacerbate the aging process and lead to kidney damage. However, the impact of combined heavy metal exposure on renal function among older individuals remains elusive. Our study employs machine learning techniques to delve into the effects and underlying mechanisms of mixed exposure to heavy metals on the renal function of the aging population.
Methods This study extracted comprehensive data from the National Health and Nutrition Examination Survey (NHANES) conducted between 2015 and 2020. A total of 3,175 participants aged 60 years and above, with complete information on six metals - lead, cadmium, manganese, cobalt, mercury, and selenium, along with relevant covariates, were included in the study. To assess the impact of single or mixed metal exposure on the renal function of older adult individuals, various statistical techniques were employed: multiple logistic regression, weighted quantitative sum (WQS) regression, Bayesian kernel machine regression (BKMR), and mediation effects analysis.
Results Multiple logistic regression revealed that selenium and manganese were protective factors for chronic kidney disease (CKD). Cobalt was a risk factor for CKD. High concentrations of lead, cadmium, and cobalt were risk factors for urinary albumin creatinine ratio (ACR). WQS analyses revealed that mixed metal exposure was positively correlated with estimated glomerular filtration rate (eGFR) but negatively correlated with CKD. Selenium and manganese can neutralize the effects of other metals on eGFR. Mixed

metal exposure was positively correlated with ACR, with lead and cadmium having a substantial effect. Mediation analysis showed that uric acid (UA) had a mediating effect of 9.7% and -19.7% in the association between mixed metals exposure and proteinuria and CKD, respectively.
Conclusion The impact of heavy metals on renal function in the older adult differs from that of adolescents and adults. This study suggests that elevated levels of mixed metals exposure are linked to proteinuria and CKD, with UA serving as a mediating factor.
https://doi.org/10.3389/fpubh.2024.1403878

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Wang, Y., Wang, Y., Li, R., Ni, B., Chen, R., Huang, Y.*, et al.*
Low-grade systemic inflammation links heavy metal exposures to mortality: A multi-metal inflammatory index approach.
Science of the Total Environment 2024 October; Vol. 947, 174537.

Certain heavy metals have been correlated to an elevated risk of inflammation-related diseases and mortality. Nevertheless, the intricate relationships between metal exposure, inflammation and mortality remain unknown. We included 3741 adults with measurements of ten urinary heavy metals in the National Health and Nutritional Examination Survey (NHANES) 2005-2010, followed up to December 31, 2019. Low-grade systemic inflammation was evaluated by various markers, including C-reactive protein (CRP) and ratios derived from regular blood tests. We assessed associations between heavy metal and all-cause mortality using multivariate COX regressions. Then we assessed the mediation effect of low-grade systemic inflammation on the associations via Sobel Test. To gauge the systemic inflammatory potential of the multi-metal mixture and its correlation with all- cause mortality, a Metal Mixture Inflammatory Index (MMII) was developed using reduced rank regression (RRR) models. The association between MMII and all-cause mortality was explored via multivariate COX regressions. Cadmium, antimony and uranium displayed positive associations with mortality, with hazard ratios (HR) ranging from 1.18 to 1.46 (all P-(FDR) < 0.05). Mediation analyses revealed that the associations between specific heavy metals (cadmium and antimony) and mortality risk were slightly mediated by the low-grade systemic inflammation markers, with mediation proportions ranging from 3.11 % to 5.38 % (all P < 0.05). MMII, the weighted sum of 9 heavy metals, significantly predicted platelet-to-lymphocyte ratio (PLR) and CRP (beta = 0.10 and 1.16, all P < 0.05), was positively associated with mortality risk (HR 1.28, 95 % CI 1.14 to 1.43). Exposure to heavy metals might increase all-cause mortality, partly mediated by low-grade systemic inflammation. MMII, designed to assess the potential systemic inflammatory effects of exposure to multiple heavy metals, was closely related to the all-cause mortality risk. This study introduces MMII as an approach to evaluating co-exposure and its potential health effects comprehensively.
https://doi.org/10.1016/j.scitotenv.2024.174537

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Sun, X., Deng, Y., Fang, L., Ni, M., Wang, X., Zhang, T.*, et al.*
Association of Exposure to Heavy Metal Mixtures with Systemic Immune-Inflammation Index Among US Adults in NHANES 2011-2016.
Biological Trace Element Research 2024; Vol. 202 (7) p 3005-3017.

In reality, people are often co-exposed to multiple heavy metals; however, current research has focused on the association between individual heavy metals and inflammation. Therefore, it is more relevant to explore the combined effects of multiple heavy metal exposure on inflammation. The study included data from the National Health and Nutrition Examination Survey (NHANES), 2011-2016. The systemic immune-inflammation index (SII) was used to reflect systemic immune-inflammation status. In this study, single variable models were used to assess the linear and non-linear relationships between single heavy metal exposures and SII. To analyze the combined effect of mixed heavy metals exposure on SII, we constructed three statistical models, including weighted quantile sum (WQS) regression, quantile-based g computation (qgcomp), and Bayesian kernel machine regression (BKMR). The single-exposure analysis found positive

associations between multiple heavy metals and SII, while mercury in blood was negatively associated with SII, and U-shaped correlations were observed between blood lead, urine barium and strontium, and SII. In the WQS model, SII increased significantly with increasing concentrations of mixed heavy metals, while consistent results in the qgcomp model, but not statistically significant. In the BKMR model, exposure to heavy metal mixtures was positively associated with SII, with mercury, cadmium, and cobalt in urine contributing the most to the mixed exposure. In addition, synergistic and antagonistic effects between heavy metals on increasing SII were found in our study.
In summary, our results reveal that combined exposure to multiple heavy metals is positively associated with SII in the US adults.
https://doi.org/10.1007/s12011-023-03901-y

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Ibrahimou, B., Hasan, K. T., Burchfield, S., Salihu, H., Zhu, Y., Dagne, G.*, et al.*
Assessing the Risk of Heart Attack: A Bayesian Kernel Machine Regression Analysis of Heavy Metal Mixtures.
Research square 2024; preprint.

Background: The assessment of heavy metals' effects on human health is frequently limited to investigating one metal or a group of related metals. The effect of heavy metals mixture on heart attack is unknown.
Methods: This study applied the Bayesian kernel machine regression model (BKMR) to the 2011-2016 National Health and Nutrition Examination Survey (NHANES) data to investigate the association between heavy metal mixture exposure with heart attack. 2972 participants over the age of 20 were included in the study.
Results: Results indicate that heart attack patients have higher levels of cadmium and lead in the blood and cadmium, cobalt, and tin in the urine, while having lower levels of mercury, manganese, and selenium in the blood and manganese, barium, tungsten, and strontium in the urine. The estimated risk of heart attack showed a negative association of 0.0030 units when all the metals were at their 25th percentile compared to their 50th percentile and a positive association of 0.0285 units when all the metals were at their 75th percentile compared to their 50th percentile. The results suggest that heavy metal exposure, especially cadmium and lead, may increase the risk of heart attacks.
Conclusions: This study suggests a possible association between heavy metal mixture exposure and heart attack and, additionally, demonstrates how the BKMR model can be used to investigate new combinations of exposures in future studies.
https://doi.org/10.21203/rs.3.rs-4456611/v1

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Gao, Y., Wang, Y., Lan, X., Guo, J., Ma, N., Yuan, Y.*, et al.*
Association between mixed metal exposure and stroke risk in Shanxi Province: a case-control study.
Ecotoxicology and Environmental Safety 2024 September; Vol. 282, 116765

Background: Stroke is the second leading cause of death for all human beings and poses a serious threat to human health. Environmental exposure to a mixture of metals may be associated with the occurrence and development of stroke, but the evidence in the Chinese population is not yet conclusive.
Objectives: This study evaluated the association between stroke risk and 13 metals
Methods: Metal concentrations in whole blood samples from 100 stroke cases and 100 controls were measured by ICP-MS. The cumulative impact of mixed metal on stroke risk was investigated by using three statistical models, BKMR, WQS and QGC.
Results: The case group had higher concentrations of Mg, Mn, Zn, Se, Sn, and Pb than the control group ($p<0.05$). BKMR model indicated a correlation between the risk of stroke and exposure to mixed metals. WQS model showed that Mg (27.2 %), Se (25.1 %) and Sn (14.8 %) were positively correlated with stroke risk (OR=1.53; 95 %CI: 1.03-2.37, p=0.013). The QGC model showed that Mg (49.2 %) was positively correlated with stroke risk, while Ti (31.7 %) was negatively correlated with stroke risk. Conclusions: Mg

may be the largest contributor to the cumulative effect of mixed metal exposure on stroke risk, and the interaction between metals requires more attention. These findings could provide scientific basis for effectively preventing stroke by managing metals in the environment.
https://doi.org/10.1016/j.ecoenv.2024.116765

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Wu, L., Lu, X., Zhang, S., Zhong, Y., Gao, H., Tao, F.-B., Wu, X.
Co-exposure effects of urinary polycyclic aromatic hydrocarbons and metals on lung function: mediating role of systematic inflammation.
BMC Pulmonary Medicine August 2024; Vol. 24, Article number: 386

Background : Polycyclic aromatic hydrocarbons (PAHs) and metals were associated with decreased lung function, but co-exposure effects and underlying mechanism remained unknown.
Methods : Among 1,123 adults from National Health and Nutrition Examination Survey 2011-2012, 10 urinary PAHs, 11 urinary metals, and peripheral white blood cell (WBC) count were determined, and 5 lung function indices were measured. Least absolute shrinkage and selection operator, Bayesian kernel machine regression, and quantile-based g-computation were used to estimate co-exposure effects on lung function. Mediation analysis was used to explore mediating role of WBC.
Results : These models demonstrated that PAHs and metals were significantly associated with lung function impairment. Bayesian kernel machine regression models showed that comparing to all chemicals fixed at median level, forced expiratory volume in 1 s (FEV1)/forced vital capacity, peak expiratory flow, and forced expiratory flow between 25 and 75% decreased by 1.31% (95% CI: 0.72%, 1.91%), 231.62 (43.45, 419.78) mL/s, and 131.64 (37.54, 225.74) mL/s respectively, when all chemicals were at 75th percentile. In the quantile-based g-computation, each quartile increase in mixture was associated with 104.35 (95% CI: 40.67, 168.02) mL, 1.16% (2.11%, 22.40%), 294.90 (78.37, 511.43) mL/s, 168.44 (41.66, 295.22) mL/s decrease in the FEV1, FEV1/forced vital capacity, peak expiratory flow, and forced expiratory flow between 25% and 75%, respectively. 2-Hydroxyphenanthrene, 3-Hydroxyfluorene, and cadmium were leading contributors to the above associations. WBC mediated 8.22%-23.90% of association between PAHs and lung function.
Conclusions : Co-exposure of PAHs and metals impairs lung function, and WBC could partially mediate this relationship. Our findings elucidate co-exposure effects of environmental mixtures on respiratory health and underlying mechanisms, suggesting that focusing on highly prioritized toxicants would effectively attenuate adverse effects.
https://doi.org/10.1186/s12890-024-03173-9

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Ge, X., He, J., Zheng, Y., Wang, Q., Cheng, H., Bao, Y.*, et al.*
Association of Blood Metals and Metal Mixtures with the Myocardial Enzyme Profile: An Occupational Population-Based Study in China.
Biological Trace Element Research 2024; preprint.

To investigate a cross-sectional association between blood metal mixture and myocardial enzyme profile, we quantified creatine kinase (CK), creatine kinase-MB (CK-MB), lactate dehydrogenase (LD), alpha-hydroxybutyrate dehydrogenase (alpha-HBD), and aspartate transaminase (AST) levels among participants from the manganese-exposed workers healthy cohort (MEWHC) (n = 544). The levels of 22 metals in blood cells were determined using inductively coupled plasma mass spectrometry. The least absolute shrinkage and selection operator (LASSO) penalized regression model was utilized for screening metals. The exposure-response relationship between specific metal and myocardial enzyme profile was identified by general linear regression and restricted cubic spline analyses. The overall effect and interactions were evaluated using Bayesian kernel machine regression (BKMR). Manganese was linearly and positively associated with CK (P-overall = 0.019, Pnon-linearity = 0.307), dominating the positive overall effect of mixture exposure (manganese, arsenic, and rubidium) on CK level. Calcium and zinc were linearly and negatively associated with LD levels (P-overall < 0.05, Pnon-linearity > 0.05), and asserted dominance in the negative overall effect

of metal mixtures (rubidium, molybdenum, zinc, nickel, cobalt, calcium, and magnesium) on LD level. Interestingly, we observed a U-shaped dose-response relationship of molybdenum with LD level (P-overall < 0.001, Pnon-linearity = 0.015), an interaction between age and calcium on LD level (P-interation = 0.041), and an interaction between smoking and molybdenum on LD level (P-interation = 0.035).
Our study provides evidence that metal mixture exposure affects the myocardial enzyme profile. Additional investigation is required to confirm these associations, and to reveal the fundamental mechanisms involved.
https://doi.org/10.1007/s12011-024-04316-z

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Wei, J., Liu, R., Yang, Z., Liu, H., Wang, Y., Zhang, J.*, et al.*
Association of metals and bisphenols exposure with lipid profiles and dyslipidemia in Chinese adults: Independent, combined and interactive effects.
The Science of the total environment 2024 October; Vol. 946 p 174315-174315.

BACKGROUND: Although studies have assessed the association of metals and bisphenols with lipid metabolism, the observed results have been controversial, and limited knowledge exists about the combined and interactive effects of metals and bisphenols exposure on lipid metabolism.
METHODS: Plasma metals and serum bisphenols concentrations were evaluated in 888 participants. Multiple linear regression and logistic regression models were conducted to assess individual associations of 18 metals and 3 bisphenols with 5 lipid profiles and dyslipidemia risk, respectively. The dose-response relationships of targeted contaminants with lipid profiles and dyslipidemia risk were captured by applying a restriction cubic spline (RCS) function. The bayesian kernel machine regression (BKMR) model was used to assess the overall effects of metals and bisphenols mixture on lipid profiles and dyslipidemia risk. The interactive effects of targeted contaminants on interested outcomes were explored by constructing an interaction model.
RESULTS: Single-contaminant analyses revealed that exposure to iron (Fe), nickel (Ni), copper (Cu), arsenic (As), selenium (Se), strontium (Sr), and tin (Sn) was associated with elevated lipid levels. Cobalt (Co) showed a negative association with high density lipoprotein cholesterol (HDL-C). Bisphenol A (BPA) and bisphenol AF (BPAF) were associated with decreased HDL-C levels, with nonlinear associations observed. Vanadium (V), lead (Pb), and silver (Ag) displayed U-shaped dose-response relationships with most lipid profiles. Multi-contaminant analyses indicated positive trends between contaminants mixture and total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), and non-high-density lipoprotein cholesterol (non-HDL-C). The interaction analyses showed that Se-Fe exhibited synergistic effects on LDL-C and non-HDL-C, and Se-Sn showed a synergistic effect on HDL-C. CONCLUSIONS: Our study suggested that exposure to metals and bisphenols was associated with changes in lipid levels, and demonstrated their combined and interactive effects.
https://doi.org/10.1016/j.scitotenv.2024.174315

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Martinez-Morata, I., Schilling, K., Glabonjat, R. A., Domingo-Relloso, A., Mayer, M., Mcgraw, K. E.*, et al.*
Association of Urinary Metals With Cardiovascular Disease Incidence and All-Cause Mortality in the Multi-Ethnic Study of Atherosclerosis (MESA).
Circulation 2024; Vol. 150 (10), p 758-769.

BACKGROUND: Exposure to metals has been associated with cardiovascular disease (CVD) end points and mortality, yet prospective evidence is limited beyond arsenic, cadmium, and lead. In this study, we assessed the prospective association of urinary metals with incident CVD and all-cause mortality in a racially diverse population of US adults from MESA (the Multi-Ethnic Study of Atherosclerosis). METHODS: We included 6599 participants (mean [SD] age, 62.1 [10.2] years; 53% female) with urinary metals available at baseline (2000 to 2001) and followed through December 2019. We used Cox proportional hazards models to estimate the adjusted hazard ratio and 95% CI of CVD and all-cause mortality by baseline urinary levels of

cadmium, tungsten, and uranium (nonessential metals), and cobalt, copper, and zinc (essential metals). The joint association of the 6 metals as a mixture and the corresponding 10-year survival probability was calculated using Cox Elastic-Net.
RESULTS: During follow-up, 1162 participants developed CVD, and 1844 participants died. In models adjusted by behavioral and clinical indicators, the hazard ratios (95% CI) for incident CVD and all-cause mortality comparing the highest with the lowest quartile were, respectively: 1.25 (1.03, 1.53) and 1.68 (1.43, 1.96) for cadmium; 1.20 (1.01, 1.42) and 1.16 (1.01, 1.33) for tungsten; 1.32 (1.08, 1.62) and 1.32 (1.12, 1.56) for uranium; 1.24 (1.03, 1.48) and 1.37 (1.19, 1.58) for cobalt; 1.42 (1.18, 1.70) and 1.50 (1.29, 1.74) for copper; and 1.21 (1.01, 1.45) and 1.38 (1.20, 1.59) for zinc. A positive linear dose-response was identified for cadmium and copper with both end points. The adjusted hazard ratios (95% CI) for an interquartile range (IQR) increase in the mixture of these 6 urinary metals and the corresponding 10-year survival probability difference (95% CI) were 1.29 (1.11, 1.56) and -1.1% (-2.0, -0.05) for incident CVD and 1.66 (1.47, 1.91) and -2.0% (-2.6, -1.5) for all-cause mortality.
CONCLUSIONS: This epidemiological study in US adults indicates that urinary metal levels are associated with increased CVD risk and mortality. These findings can inform the development of novel preventive strategies to improve cardiovascular health.
https://doi.org/10.1161/circulationaha.124.069414

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Sun, Y., Mao, Q., Zhou, D., Tian, J., Du, H., Yu, Q.*, et al.*
Associations of multiple blood metals with cardiac structure and function: A cross-sectional study in a CAD population.
Environmental Pollution November 2024; Vol. 360, 124718

Coronary artery disease (CAD) is often accompanied by abnormal cardiac structure and function, leading to an increased prognostic risk. However, less is known about the associations of mixed metals with abnormal cardiac structure and function in CAD patients. Here, we aimed to investigate the associations of exposure to metal mixtures with cardiac structure and function and potential interactions in a CAD population. We conducted a cross-sectional study from Southwest China that included 1555 CAD patients. The blood concentrations of 14 metals were measured via inductively coupled plasma spectrometry. CAD was defined as at least one vessel having stenosis >= 50% the vessel diameter. Echocardiography was used for cardiac structural and functional measurements. Bayesian kernel machine regression was applied to explore the overall effect, metal weight, and dose effect. Linear regression analysis was used to analyze the effects of single metals, metal-metal interactions and metal-traditional interactions.
Finally, we found that the negative associations of mixed metals with cardiac structure was significant when the levels of all metals were below the 60th percentile. For cardiac function, changes in metals from 50th to 75th were associated with 0.954% and 0.683% decrease in left ventricular ejection fraction and left ventricular fractional shortening, respectively. Negative associations of copper and manganese with cardiac structure and function, whereas positive associations of titanium, selenium and molybdenum with several parameters were found. Antagonistic interactions between copper and tin and between selenium and several metals (manganese, copper and aluminum) (all P-interaction terms < 0.05) were found.
In conclusion, mixed metal exposure was negatively associated with cardiac structure and function in CAD patients. The main metals contributing to this negative associations were copper and manganese. Selenium or tin supplementation may reduce the adverse associations of copper and manganese with cardiac structure and function.
https://doi.org/10.1016/j.envpol.2024.124718

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Jian, L. Y., Hui, R. J., Xiu, W. X., Sheng, C. J., Li Dong, Q., Mei, L. Q.*, et al.*
Correlation between Combined Urinary Metal Exposure and Grip Strength under Three Statistical Models: A Cross-sectional Study in Rural Guangxi.
Biomedical and Environmental Sciences 2024; Vol. 37 (1) p 3-18.

Objective This study aimed to investigate the potential relationship between urinary metals copper (Cu), arsenic (As), strontium (Sr), barium (Ba), iron (Fe), lead (Pb) and manganese (Mn) and grip strength. Methods : We used linear regression models, quantile g-computation and Bayesian kernel machine regression (BKMR) to assess the relationship between metals and grip strength.
Results : In the multimetal linear regression, Cu (beta = -2.119), As (beta = -1.318), Sr (beta = -2.480), Ba (beta = 0.781), Fe (beta = 1.130) and Mn (beta = -0.404) were significantly correlated with grip strength ($P < 0.05$). The results of the quantile g-computation showed that the risk of occurrence of grip strength reduction was -1.007 (95% confidence interval: -1.362, -0.652; $P < 0.001$) when each quartile of the mixture of the seven metals was increased. Bayesian kernel function regression model analysis showed that mixtures of the seven metals had a negative overall effect on grip strength, with Cu, As and Sr being negatively associated with grip strength levels. In the total population, potential interactions were observed between As and Mn and between Cu and Mn (P-interactions of 0.003 and 0.018, respectively). Conclusion : In summary, this study suggests that combined exposure to metal mixtures is negatively associated with grip strength. Cu, Sr and As were negatively correlated with grip strength levels, and there were potential interactions between As and Mn and between Cu and Mn.
https://doi.org/10.3967/bes2024.002

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Obeng-Gyasi, E., Obeng-Gyasi, B.
Association of combined lead, cadmium, and mercury with systemic inflammation.
Frontiers in Public Health 2024; Vol. 12 p

Exposure to environmental metals has been increasingly associated with systemic inflammation, which is implicated in the pathogenesis of various chronic diseases, including those with neurodegenerative aspects. However, the complexity of exposure and response relationships, particularly for mixtures of metals, has not been fully elucidated.
Objective : This study aims to assess the individual and combined effects of lead, cadmium, and mercury exposure on systemic inflammation as measured by C-reactive protein (CRP) levels, using data from the National Health and Nutrition Examination Survey (NHANES) 2017-2018.
Methods : We employed Bayesian Kernel Machine Regression (BKMR) to analyze the NHANES 2017-2018 data, allowing for the evaluation of non-linear exposure-response functions and interactions between metals. Posterior Inclusion Probabilities (PIP) were calculated to determine the significance of each metal's contribution to CRP levels.
Results : The PIP results highlighted mercury's significant contribution to CRP levels (PIP = 1.000), followed by cadmium (PIP = 0.6456) and lead (PIP = 0.3528). Group PIP values confirmed the importance of considering the metals as a collective group in relation to CRP levels. Our BKMR analysis revealed non-linear relationships between metal exposures and CRP levels. Univariate analysis showed a flat relationship between lead and CRP, with cadmium having a positive relationship. Mercury exhibited a U-shaped association, indicating both low and high exposures as potential risk factors for increased inflammation. Bivariate analysis confirmed this relationship when contaminants were combined with lead and cadmium. Analysis of single-variable effects suggested that cadmium and lead are associated with higher values of the h function, a flexible function that takes multiple metals and combines them in a way that captures the complex and potentially nonlinear relationship between the metals and CRP. The overall exposure effect of all metals on CRP revealed that exposures below the 50th percentile exposure level are associated with an increase in CRP levels, while exposures above the 60th percentile are linked to a decrease in CRP levels.
Conclusions : Our findings suggest that exposure to environmental metals, particularly mercury, is associated with systemic inflammation. These results highlight the need for public health strategies that address the cumulative effects of metal exposure and reinforce the importance of using advanced statistical methods to understand the health impact of environmental contaminants. Future research should focus on the mechanistic pathways of metal-induced inflammation and longitudinal studies to ascertain the long-term effects of these exposures.
https://doi.org/10.3389/fpubh.2024.1385500

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Liao, G., Weng, X., Wang, F., Yu, Y. H. K., Arrandale, V. H., Chan, A. H.-S.*, et al.*
Urinary metals and their associations with DNA oxidative damage among e-waste recycling workers in Hong Kong.
Ecotoxicology and Environmental Safety 2024; Vol. 284, p 116872.

Recycling electronic waste (e-waste) poses risks of metal exposure, potentially leading to health impairments. However, no previous study has focused on this issue in Hong Kong. Therefore, from June 2021 to September 2022, this study collected urine samples from 101 e-waste workers and 100 office workers in Hong Kong to compare their urinary levels of metals using ICP-MS. Among the 15 included metals (with detection rates above the 70 % threshold), eight showed significantly higher urinary concentrations (unit: μg/g creatinine) in e-waste workers compared to office workers: Li (25.09 vs. 33.36), Mn (1.78 vs. 4.15), Ni (2.10 vs. 2.77), Cu (5.81 vs. 9.23), Zn (404.35 vs. 431.52), Sr (151.33 vs. 186.26), Tl (0.35 vs. 0.43), and Pb (0.69 vs. 1.16). E-waste workers in Hong Kong generally exhibited lower metal levels than those in developing regions but higher than their counterparts in developed areas. The urine level of 8-hydroxy-2-deoxyguanosine (8-OHdG) was determined by HPLC-MS/MS, and no significant difference was found between the two groups. Multiple linear regression models revealed no significant association between individual metal and urinary 8-OHdG concentrations. However, the metal mixture was identified to marginally elevate the 8-OHdG concentrations (1.12, 95 %CI: 0.04, 2.19) by quantile g-computation models, with Mn and Cd playing significant roles in such effect.
In conclusion, while the metal levels among Hong Kong e-waste workers compared favorably with their counterparts in other regions, their levels were higher than those of local office workers. This underscores the need for policymakers to prioritize attention to this unique industry.
https://doi.org/10.1016/j.ecoenv.2024.116872

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Li, P., Ma, J., Jiang, Y., Yang, X., Luo, Y., Tao, L.*, et al.*
Association between Mixed Heavy Metal Exposure and Arterial Stiffness, with Alkaline Phosphatase Identified as a Mediator.
Biological Trace Element Research 2024 September ; preprint.

Elevated arterial stiffness has been associated with exposure to heavy metals such as lead (Pb) and cadmium (Cd). However, the collective impact of multiple metals and the underlying mechanisms are not fully elucidated. The purpose of this study was to assess the combined effects of exposure to nine heavy metals on arterial stiffness and explore whether serum alkaline phosphatase (ALP) acts as a mediator in this relationship. In the retrospective analysis, data from 8,700 participants were retrieved from the National Health and Nutrition Examination Survey (NHANES) spanning from 1999 to 2018. Arterial stiffness was measured by estimated pulse wave velocity (ePWV). The cumulative impact of exposure to multiple metals was examined using adaptive elastic-net, environmental risk score, weighted quantile sum regression, and quantile g-computation. Additionally, mediation analysis was conducted to explore the potential mediating role of serum ALP. We found that combined exposure to multiple metals was consistently associated with elevated ePWV, with Ba, Pb, and Sb exhibiting the greatest contributions. Notably, serum ALP partially mediated the associations between individual (Pb, Sb) and mixed metal exposure with ePWV, with mediation proportions at 10.76% for Pb, 18.22% for Sb, and 11.07% for mixed metal exposure. In conclusion, this study demonstrates a clear association between exposure to heavy metals, either individually or in combination, and heightened arterial stiffness. Furthermore, the findings suggest that serum ALP activity may act as a mediator in these relationships.
https://doi.org/10.1007/s12011-024-04359-2

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Wang, Y., Wang, Y., Li, R., Ni, B., Chen, R., Huang, Y.*, et al.*
Low-grade systemic inflammation links heavy metal exposures to mortality: A multi-metal inflammatory index approach.
Science of The Total Environment 2024; Vol. 947 p 174537.

Certain heavy metals have been correlated to an elevated risk of inflammation-related diseases and mortality. Nevertheless, the intricate relationships between metal exposure, inflammation and mortality remain unknown. We included 3741 adults with measurements of ten urinary heavy metals in the National Health and Nutritional Examination Survey (NHANES) 2005–2010, followed up to December 31, 2019. Low-grade systemic inflammation was evaluated by various markers, including C-reactive protein (CRP) and ratios derived from regular blood tests. We assessed associations between heavy metal and all-cause mortality using multivariate COX regressions. Then we assessed the mediation effect of low-grade systemic inflammation on the associations via Sobel Test. To gauge the systemic inflammatory potential of the multi-metal mixture and its correlation with all-cause mortality, a Metal Mixture Inflammatory Index (MMII) was developed using reduced rank regression (RRR) models. The association between MMII and all-cause mortality was explored via multivariate COX regressions. Cadmium, antimony and uranium displayed positive associations with mortality, with hazard ratios (HR) ranging from 1.18 to 1.46 (all P-FDR < 0.05). Mediation analyses revealed that the associations between specific heavy metals (cadmium and antimony) and mortality risk were slightly mediated by the low-grade systemic inflammation markers, with mediation proportions ranging from 3.11 % to 5.38 % (all P < 0.05). MMII, the weighted sum of 9 heavy metals, significantly predicted platelet-to-lymphocyte ratio (PLR) and CRP (β = 0.10 and 1.16, all P < 0.05), was positively associated with mortality risk (HR 1.28, 95 % CI 1.14 to 1.43). Exposure to heavy metals might increase all-cause mortality, partly mediated by low-grade systemic inflammation. MMII, designed to assess the potential systemic inflammatory effects of exposure to multiple heavy metals, was closely related to the all-cause mortality risk. This study introduces MMII as an approach to evaluating co-exposure and its potential health effects comprehensively.
https://doi.org/10.1016/j.scitotenv.2024.174537

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Métabolites, biomarqueurs, et multi-expositions chimiques

Lai, Y., Koelmel, J. P., Walker, D. I., Price, E. J., Papazian, S., Manz, K. E.*, et al.*
High-Resolution Mass Spectrometry for Human Exposomics: Expanding Chemical Space Coverage.
Environmental science & technology 2024; Vol. 58 (29) p 12784-12822.

In the modern "omics" era, measurement of the human exposome is a critical missing link between genetic drivers and disease outcomes. High-resolution mass spectrometry (HRMS), routinely used in proteomics and metabolomics, has emerged as a leading technology to broadly profile chemical exposure agents and related biomolecules for accurate mass measurement, high sensitivity, rapid data acquisition, and increased resolution of chemical space. Non-targeted approaches are increasingly accessible, supporting a shift from conventional hypothesis-driven, quantitation-centric targeted analyses toward data-driven, hypothesis-generating chemical exposome-wide profiling.
However, HRMS-based exposomics encounters unique challenges. New analytical and computational infrastructures are needed to expand the analysis coverage through streamlined, scalable, and harmonized workflows and data pipelines that permit longitudinal chemical exposome tracking, retrospective validation, and multi-omics integration for meaningful health-oriented inferences.
In this article, we survey the literature on state-of-the-art HRMS-based technologies, review current analytical workflows and informatic pipelines, and provide an up-to-date reference on exposomic approaches for chemists, toxicologists, epidemiologists, care providers, and stakeholders in health sciences and medicine. We propose efforts to benchmark fit-for-purpose platforms for expanding coverage of chemical space, including gas/liquid chromatography-HRMS (GC-HRMS and LC-HRMS), and discuss

opportunities, challenges, and strategies to advance the burgeoning field of the exposome.
https://doi.org/10.1021/acs.est.4c01156

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Kwon, J.-Y., Kim, W. J., Cho, Y. M., Kim, B.-G., Lee, S., Rho, J. H.*, et al.*
Introduction to the Forensic Research via Omics Markers in Environmental Health Vulnerable Areas (FROM) study.
Epidemiology and health 2024; Vol., p e2024062-e2024062.

This research group (FROM) aimed to develop biomarkers for exposure to environmental hazards and diseases, assess environmental diseases, and apply and verify these biomarkers in environmentally vulnerable areas. Environmentally vulnerable areasincluding refineries, abandoned metal mines, coal-fired power plants, waste incinerators, cement factories, and areas with high exposure to particulate matteralong with control areas, were selected for epidemiological investigations.
A total of 1,157 adults, who had resided in these areas for over 10 years, were recruited between June 2021 and September 2023. Personal characteristics of the study participants were gathered through a survey. Biological samples, specifically blood and urine, were collected during the field investigations, separated under refrigerated conditions, and then transported to the laboratory for biomarker analysis. Analyses of heavy metals, environmental hazards, and adducts were conducted on these blood and urine samples. Additionally, omics analyses of epigenomes, proteomes, and metabolomes were performed using the blood samples. The biomarkers identified in this study will be utilized to assess the risk of environmental disease occurrence and to evaluate the impact on the health of residents in environmentally vulnerable areas, following the validation of diagnostic accuracy for these diseases.
https://doi.org/10.4178/epih.e2024062

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Carlin, D. J., Rider, C. V.
Combined Exposures and Mixtures Research: An Enduring NIEHS Priority.
Environmental health perspectives 2024; Vol. 132 (7) p 75001-75001.

BACKGROUND: The National Institute of Environmental Health Sciences (NIEHS) continues to prioritize research to better understand the health effects resulting from exposure to mixtures of chemical and nonchemical stressors. Mixtures research activities over the last decade were informed by expert input during the development and deliberations of the 2011 NIEHS Workshop "Advancing Research on Mixtures: New Perspectives and Approaches for Predicting Adverse Human Health Effects." NIEHS mixtures research efforts since then have focused on key themes including a) prioritizing mixtures for study, b) translating mixtures data from in vitro and invivo studies, c) developing cross-disciplinary collaborations, d) informing component-based and whole-mixture assessment approaches, e) developing sufficient similarity methods to compare across complex mixtures, f) using systems-based approaches to evaluate mixtures, and g) focusing on management and integration of mixtures-related data.
OBJECTIVES: We aimed to describe NIEHS driven research on mixtures and combined exposures over the last decade and present areas for future attention.
RESULTS: Intramural and extramural mixtures research projects have incorporated a diverse array of chemicals (e.g., polycyclic aromatic hydrocarbons, botanicals, personal care products, wildfire emissions) and nonchemical stressors (e.g., socioeconomic factors, social adversity) and have focused on many diseases (e.g., breast cancer, atherosclerosis, immune disruption). We have made significant progress in certain areas, such as developing statistical methods for evaluating multiple chemical associations in epidemiology and building translational mixtures projects that include both in vitro and invivo models.
DISCUSSION: Moving forward, additional work is needed to improve mixtures data integration, elucidate interactions between chemical and nonchemical stressors, and resolve the geospatial and temporal nature of mixture exposures. Continued mixtures research will be critical to informing cumulative impact assessments and addressing complex challenges, such as environmental justice and climate change.

https://doi.org/10.1289/ehp14340

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Wu, L., Xin, Y., Zhang, J., Cui, F., Chen, T., Chen, L.*, et al.*
Metabolic signatures of population exposure to metal mixtures: A metabolome-wide association study.
Environmental Pollution 2024; Vol. 360 p

Numerous studies have explored the health impacts of individual metal exposures, yet the effects of metal mixtures on human endogenous metabolism remain largely unexplored. We aimed to assess the serum metabolic signatures of people exposed to metal mixtures. Serum and urine samples were collected from 186 workers at a steel factory in Anhui, China, in September 2019. Inductively coupled plasma mass spectrometry was used to analyze the concentrations of 23 metal elements. The serum metabolome was determined by liquid chromatography-mass spectrometry (LC-MS). A metabolome-wide association study (MWAS) was performed across the metal exposures and metabolism using quantile g-computation modeling. Pathway enrichment analysis was performed using MetaboAnalyst. We identified 226 metabolites associated with metal mixtures, primarily involving lipid metabolism (glycerophospholipids, sphingolipids), amino acid metabolism (arginine and proline, alanine, aspartate and glutamate metabolism) and caffeine metabolic pathways. Exposure to metal mixtures is mainly associated with alterations in lipid metabolism and amino acid metabolism, particularly in the glycerophospholipid and arginine and proline metabolism pathways.
https://doi.org/10.1016/j.envpol.2024.124673

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Fang, Y., Yin, W., He, C., Shen, Q., Xu, Y., Liu, C.*, et al.*
Adverse impact of phthalate and polycyclic aromatic hydrocarbon mixtures on birth outcomes: A metabolome Exposome-Wide association study.
Environmental pollution (Barking, Essex : 1987) 2024; Vol. 357 p 124460.

It has been well-investigating that individual phthalates (PAEs) or polycyclic aromatic hydrocarbons (PAHs) affect public health. However, there is still a gap that the mixture of PAEs and PAHs impacts birth outcomes. Through innovative methods for mixtures in epidemiology, we used a metabolome Exposome-Wide Association Study (mExWAS) to evaluate and explain the association between exposure to PAEs and PAHs mixtures and birth outcomes. Exposure to a higher level of PAEs and PAHs mixture was associated with lower birth weight (maximum cumulative effect: 143.5g) rather than gestational age. Mono(2-ethlyhexyl) phthalate (MEHP) (posterior inclusion probability, PIP=0.51), 9-hydroxyphenanthrene (9-OHPHE) (PIP=0.53), and 1-hydroxypyrene (1-OHPYR) (PIP=0.28) were identified as the most important compounds in the mixture. In mExWAS, we successfully annotated four overlapping metabolites associated with both MEHP/9-OHPHE/1-OHPYR and birth weight, including arginine, stearamide, Arg-Gln, and valine. Moreover, several lipid-related metabolism pathways, including fatty acid biosynthesis and degradation, alpha-linolenic acid, and linoleic acid metabolism, were disturbed. In summary, these findings may provide new insights into the underlying mechanisms by which PAE and PAHs affect fetal growth.
https://doi.org/10.1016/j.envpol.2024.124460

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Shen, J., Ji, X., Liang, J., Feng, X., Liu, X., Wang, Y.*, et al.*
Elevated Levels of Photoinitiators in Nail Salon Workers' Hand Wipes and Occupational Risk Estimation.
Environmental Science & Technology Letters 2024; Vol. p

Photoinitiators (PIs) are widely used as chemical additives in various commercial products, including nail polishes, leading to major concern with regard to occupational exposure. Herein, 27 PIs, including 12 benzophenones, 8 amine co-initiators, 3 thioxanthones, and 4 phosphine oxides, were analyzed in hand

wipes from nail salon workers and controls. Twenty-four PIs were identified in hand wipes collected from nail salon workers, with concentrations ranging from 133 to 5.06 × 104 ng/wipe (median: 4.26 × 103 ng/wipe), which were significantly higher than those of control workers (median: 59.4 ng/wipe). Particularly, 1-hydroxycyclohexylphenylketone (median: 1.27 × 103 ng/wipe) and 2,4,6-trimethylbenzoyldiphenylphosphine oxide (median: 2.20 × 103 ng/wipe) were the most abundant congeners in hand wipes of nail salon workers, respectively contributing 42% and 57% to the total PI concentrations. An artificial skin model experiment found that 3–30% of PIs on human skin could be absorbed by human bodies. The estimated daily intakes, based on median concentrations for nail salon workers via dermal and hand-to-mouth contacts, were 5.17 and 0.32 ng/kg bw/day, respectively, significantly higher than those of the general population. This is the first study investigating PIs on human hands, providing solid evidence of dermal exposure to PIs for nail salon workers and the general population.
https://doi.org/10.1021/acs.estlett.4c00469

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Expositions multiples aux polluants ambiants

Zhuang, Y., Li, L., Zhang, Y., Dai, F.
Associations of exposure to volatile organic compounds with sleep health and potential mediators: analysis of NHANES data.
Frontiers in Public Health 2024; Vol. 12, p

Objective The effect of environmental pollution on sleep has been widely studied, yet the relationship between exposure to volatile organic compounds (VOCs) and sleep health requires further exploration. We aimed to investigate the single and mixed effect of urinary VOC metabolites on sleep health and identify potential mediators.
Methods Data for this cross-sectional study was collected from the National Health and Nutrition Examination Surveys (NHANES) (2005-2006, 2011-2014). A weighted multivariate logistic regression was established to explore the associations of 16 VOCs with four sleep outcomes. Following the selection of important VOCs through the least absolute shrinkage and selection operator (LASSO) regression, principal component analyses (PCA), weight quantile sum (WQS), and Bayesian kernel machine regression (BKMR) analyses were conducted to explore the associations between exposure to single and mixed VOCs and sleep outcomes, as well as identify the most contributing components. A mediation analysis was performed to explore the potential effect of depression scores.
Results Of the 3,473 participants included in the study, a total of 618 were diagnosed with poor sleep patterns. In logistic regression analyses, 7, 10, 1, and 5 VOCs were significantly positively correlated with poor sleep patterns, abnormal sleep duration, trouble sleeping, and sleep disorders, respectively. The PCA analysis showed that PC1 was substantially linked to a higher risk of poor sleep patterns and its components. The WQS model revealed a positive association between VOC mixture of increased concentrations and poor sleep patterns [OR (95% CI): 1.285 (1.107, 1.493)], abnormal sleep duration [OR (95% CI): 1.154 (1.030, 1.295)], trouble sleeping [OR (95% CI): 1.236 (1.090, 1.403)] and sleep disorders [OR (95% CI): 1.378 (1.118, 1.705)]. The BKMR model found positive associations of the overall VOC exposure with poor sleep patterns, trouble sleeping, and sleep disorders. PCA, WQS, and BKMR models all confirmed the significant role of N-acetyl-S-(N-methylcarbamoyl)-l-cysteine (AMCC) in poor sleep patterns and its components. The depression score was a mediator between the positive VOC mixture index and the four sleep outcomes.
Conclusion Exposure to single and mixed VOCs negatively affected the sleep health of American population, with AMCC playing a significant role. The depression score was shown to mediate the associations of VOC mixtures with poor sleep patterns and its components.
https://doi.org/10.3389/fpubh.2024.1423771

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Hu, A., Li, R., Chen, G., Chen, S.
Impact of Respiratory Dust on Health: A Comparison Based on the Toxicity of PM2.5, Silica, and Nanosilica.
International Journal of Molecular Sciences 2024; Vol. 25 (14) p

Respiratory dust of different particle sizes in the environment causes diverse health effects when entering the human body and makes acute or chronic damage through multiple systems and organs. However, the precise toxic effects and potential mechanisms induced by dust of different particle sizes have not been systematically summarized. In this study, we described the sources and characteristics of three different particle sizes of dust: PM2.5 (<2.5 mu m), silica (<5 mu m), and nanosilica (<100 nm). Based on their respective characteristics, we further explored the main toxicity induced by silica, PM2.5, and nanosilica in vivo and in vitro. Furthermore, we evaluated the health implications of respiratory dust on the human body, and especially proposed potential synergistic effects, considering current studies.
In summary, this review summarized the health hazards and toxic mechanisms associated with respiratory dust of different particle sizes. It could provide new insights for investigating the synergistic effects of co-exposure to respiratory dust of different particle sizes in mixed environments.
https://doi.org/10.3390/ijms25147654

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Shi, Y., Zhao, L., Zheng, J., Ding, R., Li, K., Zhao, H.*, et al.*
End-of-life vehicle dismantling activity emits large quantities of phthalates and their alternatives: New insights on environmental sources and co-exposure risks.
Environment International 2024; Vol. 190 p

Automotive interiors have been identified as significant sources of various chemicals, yet their occupational hazards for end-of-life vehicle (ELV) dismantlers remain poorly characterized. Herein, eight classes of plasticizers, including 11 phthalates esters (PAEs) and 16 non-phthalates esters (NPAEs), were detected in dust samples from inside and outside ELV dismantling workshops. Moreover, indoor dust from ordinary households and university dormitories was compared. The indoor dust from the ELV dismantling workshops contained the highest concentrations of plasticizers (median: 594 mu g/g), followed by ordinary households (296 mu g/g), university dormitories (186 mu g/g), and outdoor dust (157 mu g/g). PAEs remained the dominant plasticizers, averaging 11.7-fold higher than their NPAE alternatives. Specifically, diisononyl phthalate and trioctyl trimellitate were notably elevated in workshop dust, being 15.5 and 4.78 times higher, respectively, than in ordinary household dust, potentially indicating their association with ELV dismantling activities. The estimated daily intake of occupational ELV dismantling workers was up to five times higher than that of the general population. Moreover, certain dominant NPAEs demonstrated nuclear receptor interference abilities comparable to typical PAEs, suggesting potential toxic effects. This study is the first to demonstrate that ELV dismantling activities contribute to the co-emission of PAEs and NPAEs, posing a substantial risk of exposure to workers, which warrants further investigation.
https://doi.org/10.1016/j.envint.2024.108933

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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 18814.

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 (64-386g/m3). The gaseous fraction was the most important contributor to the total mass fraction for both straight (322-2362g/m3) and water-based MWFs (101-699g/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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Hamroun, A., Genin, M., Glowacki, F., Sautenet, B., Leffondre, K., De Courreges, A.*, et al.*
Multiple air pollutant exposure is associated with higher risk of all-cause mortality in dialysis patients: a French registry-based nationwide study.
Frontiers in Public Health 2024; Vol. 12 p

Background Little is known about the effect of combined exposure to different air pollutants on mortality in dialysis patients. This study aimed to investigate the association of multiple exposures to air pollutants with all-cause and cause-specific death in dialysis patients.
Materials and methods This registry-based nationwide cohort study included 90,373 adult kidney failure patients initiating maintenance dialysis between 2012 and 2020 identified from the French REIN registry. Estimated mean annual municipality levels of PM2.5, PM10, and NO2 between 2009 and 2020 were combined in different composite air pollution scores to estimate each participant's exposure at the residential place one to 3 years before dialysis initiation. Adjusted cause-specific Cox proportional hazard models were used to estimate hazard ratios (HRs) per interquartile range (IQR) greater air pollution score. Effect measure modification was assessed for age, sex, dialysis care model, and baseline comorbidities.
Results Higher levels of the main air pollution score were associated with a greater rate of all-cause deaths (HR, 1.082 [95% confidence interval (CI), 1.057-1.104] per IQR increase), regardless of the exposure lag. This association was also confirmed in cause-specific analyses, most markedly for infectious mortality (HR, 1.686 [95% CI, 1.470-1.933]). Sensitivity analyses with alternative composite air pollution scores showed consistent findings. Subgroup analyses revealed a significantly stronger association among women and fewer comorbid patients.
Discussion Long-term multiple air pollutant exposure is associated with all-cause and cause-specific mortality among patients receiving maintenance dialysis, suggesting that air pollution may be a significant contributor to the increasing trend of CKD-attributable mortality worldwide.
https://doi.org/10.3389/fpubh.2024.1390999

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Hernandes, V. V., Warth, B.
Bridging Targeted (Zeno MRM-HR) and Untargeted (SWATH) LC-HRMS in a Single Run for Sensitive Exposomics.
Analytical Chemistry 2024; Vol. 96 (31) p 12710-12717.

Traditionally, chemical exposure has been assessed by low-resolution mass spectrometry via targeted approaches due to the typically extremely low concentration of such compounds in biological samples. Nevertheless, untargeted approaches are now becoming a promising tool for a broader investigation of the exposome, covering additional compounds, their biotransformation products, and possible metabolic

alterations (metabolomics). However, despite broad compound coverage, untargeted metabolomics still underperforms in ultratrace biomonitoring analysis.
To overcome these analytical limitations, we present the development of the first combined targeted/untargeted LC-MS method, merging MRM-HR and SWATH experiments in one analytical run, making use of Zeno technology for improved sensitivity. Multiple reaction monitoring transitions were optimized for 135 highly diverse toxicants including mycotoxins, plasticizers, PFAS, personal care products ingredients, and industrial side products as well as potentially beneficial xenobiotics such as phytohormones. As a proof of concept, standard reference materials of human plasma (SRM 1950) and serum (SRM 1958) were analyzed with both Zeno MRM-HR + SWATH and SWATH-only methodologies. Results demonstrated a significant increase in sensitivity represented by the detection of lower concentration levels in spiked SRM materials (mean value: 2.2 and 3 times lower concentrations for SRMs 1950 and 1958, respectively). Overall, the detection frequency was increased by 68% (19 to 32 positive detections) in the MRM-HR + SWATH mode compared to the SWATH-only. This work presents a promising avenue for addressing the outstanding key challenge in the small-molecule omics field: finding a balance between high sensitivity and broad chemical coverage. It was demonstrated for exposomic applications but might be transferred to lipidomics and metabolomics workflows.
https://doi.org/10.1021/acs.analchem.4c01630

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Ossai, I. C., Hamid, F. S., Aboudi-Mana, S. C., Hassan, A.
Ecotoxicological effects, human and animal health risks of pollution and exposure to waste engine oils: a review.
Environmental geochemistry and health 2024; Vol. 46 (10) p 416-416.

Waste engine oils are hazardous waste oils originating from the transportation sector and industrial heavy-duty machinery operations. Improper handling, disposal, and miscellaneous misuses cause significant air, soil, sediments, surface water, and groundwater pollution. Occupational exposure by prolonged and repeated contact poses direct or indirect health risks, resulting in short-term (acute) or long-term (chronic) toxicities. Soil pollution causes geotoxicity by disrupting the biocenosis and physicochemical properties of the soil, and phytotoxicity by impairing plant growth, physiology and metabolism. Surface water pollution impacts aquatic ecosystems and biodiversity. Air pollution from incineration causes the release of greenhouse gases creating global warming, noxious gases and particulate matter eliciting pulmonary disorders. The toxicity of waste engine oil is due to the total petroleum hydrocarbons (TPH) composition, including polycyclic aromatic hydrocarbons (PAHs), benzene, toluene, ethylbenzene, xylene (BTEX), polychlorinated biphenyls (PCBs) congeners, organometallic compounds, and toxic chemical additives. The paper aims to provide a comprehensive overview of the ecotoxicological effects, human and animal health toxicology and exposure to waste engine oils. It highlights the properties and functions of engine oil and describes waste engine oil generation, disposal and recycling. It provides intensive evaluations and descriptions of the toxicokinetics, metabolism, routes of exposure and toxicosis in human and animal studies based on toxicological, epidemiological and experimental studies. It emphasises the preventive measures in occupational exposure and recommends risk-based remediation techniques to mitigate environmental pollution. The review will assist in understanding the potential risks of waste engine oil with significant consideration of the public health benefits and importance.
https://doi.org/10.1007/s10653-024-02198-7

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Ma, T., Wang, X., He, W., Zhang, G., Shan, T., Song, X.*, et al.*
Expose to volatile organic compounds is associated with increased risk of depression: A cross-sectional study.
Journal of affective disorders 2024; Vol. 363 p 239-248.

With increasing prevalence rate of depression by years, more attention has been paid to the influence of

environmental pollutants on depression, but relationship between exposure to volatile organic compounds (VOCs) and depression is rarely studied. Therefore, this cross-sectional study use the National Center for Health Statistics (NHANES) database (2013-2016years) to explore association between exposure to multiple VOCs and depression in general population. Multiple linear and logistic regression models were used to analyze the association between urinary VOC metabolism (mVOCs) and depression. To further analyze effect of multiple mVOCs mixed exposure, Bayesian kernel machine regression (BKMR) models were performed. A total of 3240 participants and 16 mVOCs were included in the analysis. Results showed that 10 mVOCs exposure were positively correlated with depression by multiple linear and logistic regression models, especially CYMA and MHBMA3, which also showed significant positive association with depression in BKMR model. Mixed exposure of multiple mVOCs was significantly positively correlated with depression. Gender differences were existed in effects of some VOCs concentrations on depression. AAMA, CYMA and MA had significant positive correlations with depression by women, and DHBMA had significant positive correlations with depression by men. Hence, this study showed that exposing to VOCs might have negative impacts on depression, and impact of CYMA and MHBMA3 on depression may be more evident, which provide new ideas for prevention and control of depression. But further research and exploration are needed to clarify the mechanism and influence factors of this relationship, to demonstrate the reliability of these relationship.
https://doi.org/10.1016/j.jad.2024.07.028

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Jung, J.-Y., Park, S.-H., Moon, J.-E., Yoon, J.-H., Yoon, S.-W., Lee, C.-M.
Aggregate risk assessment for multi-route exposure to hazardous chemicals caused by chemical accidents, with a focus on toluene.
Asian Journal of Atmospheric Environment 2024; Vol. 18 (1),p

Chemical accidents significantly impact environmental and human health. However, studies investigating the impacts of such accidents have primarily focused on single-route exposures, potentially underestimating the extent of damage. This study aimed to conduct an aggregate risk assessment for multi-route exposure to hazardous chemicals to ensure systematic and rational management of the health impacts on residents exposed to chemical accidents, considering the behavior of a hazardous chemical from a chemical accident within environmental media. Drawing upon a real chemical accident that occurred in Siheung, Gyeonggi-do, in 2019, leakage of 500 L of toluene over an hour was assumed. Employing a multimedia environmental dynamics model, the time-dependent concentrations across various environmental media were calculated, and the average daily dose (ADD), hazard quotient (HQ), and hazard index (HI) for each exposure route included in the multi-route exposure assessment were derived. Health risks were deemed present if the calculated HQ and HI values exceeded the threshold of 1. The results indicated the highest ADD values among the 0-9 age group, with inhalation exposure registering the highest ADD across all exposure routes. However, no significant health risks were observed, with both HQ and HI values not exceeding 1. This aggregate risk assessment approach is proposed as an effective preliminary evaluation method for health impact assessments in areas affected by chemical accidents.
https://doi.org/10.1007/s44273-024-00039-8

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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 & Environmental Epidemiology 2024; Vol. p

Persistent 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.
https://doi.org/10.1038/s41370-024-00717-3

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Hof, M., De Baat, M. L., Noorda, J., Peijnenburg, W. J. G. M., Van Wezel, A. P., Oomen, A. G.
Informing the public about chemical mixtures in the local environment: Currently applied indicators in the Netherlands and ways forward.
Journal of Environmental Management 2024; Vol. 368 p 122108.

The current use of chemicals puts pressure on human and ecological health. Based on the Aarhus Convention, citizens have the right to have access to information on substances in their local environment. Providing this information is a major challenge, especially considering complex mixtures, as the current substance-by-substance risk assessment may not adequately address the risk of co-exposure to multiple substances. Here, we provide an overview of the currently available indicators in the Netherlands to explore current scientific possibilities to indicate the impacts of complex chemical mixtures in the environment on human health and ecology at the local scale. This is limited to impact estimates on freshwater species for 701 substances, impact estimates of four metals on soil organisms, and impacts on human health for particulate matter (PM10) and nitrogen dioxide (NO2) in air. The main limiting factors in developing and expanding these indicators to cover more compartments and substances are the availability of emission and concentration data of substances and dose-response relationships at the population (human health) or community (ecology) level. As ways forward, we propose; 1) developing cumulative assessment groups (CAGs) for substances on the European Pollutant Transfer and Release Register and Water Framework Directive substance lists, to enable the development of mixture indicators based on mixture risk assessment and concentration addition principles; 2) to gain insight into local mixtures by also applying these CAGs to emission data, which is available for soil and air for more substances than concentrations data; 3) the application of analytical non-target screening methods as well as effect-based methods for whole-mixture assessment.
https://doi.org/10.1016/j.jenvman.2024.122108

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Shen, Q., Liu, Y., Li, G., An, T.
A review of disrupted biological response associated with volatile organic compound exposure: Insight into identification of biomarkers.
Science of The Total Environment 2024; Vol. 948, p 174924.

Volatile organic compounds (VOCs) are widespread harmful atmospheric pollutants, which have long been concerned and elucidated to be one of the risks of acute and chronic diseases for human, such as leukemia and cancer. Although numerous scientific studies have documented the potential adverse outcomes caused by VOC exposure, the mechanisms which biological response pathways of these VOC disruption remain poorly understood. Therefore, the identification of biochemical markers associated with metabolism, health effects and diseases orientation can be an effective means of screening biological targets for VOC exposure, which provide evidences to the toxicity assessment of compounds. The current review aims to understand the mechanisms underlying VOCs-elicited adverse outcomes by charactering various types of biomarkers. VOCs-related biomarkers from three aspects were summarized through in vitro, animal and epidemiological studies. i) Unmetabolized and metabolized VOC biomarkers in human samples for assessing exposure characteristics in different communities; ii) Adverse endpoint effects related biomarkers, mainly including (anti)oxidative stress, inflammation response and DNA damage; iii) Omics-based molecular biomarkers alteration in gene, protein, lipid and metabolite aspects associated with biological signaling pathway disorders response to VOC exposure. Further research, advanced machine learning and

bioinformation approaches combined with experimental results are urgently needed to ascertain the selection of biomarkers and further illuminate toxic mechanisms of VOC exposure. Finally, VOCs-induced disease causes can be predicted with proven results.
https://doi.org/10.1016/j.scitotenv.2024.174924

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Yu, Y., Tang, Z., Huang, Y., Zhang, J., Wang, Y., Zhang, Y., Wang, Q.
Assessing long-term effects of gaseous air pollution exposure on mortality in the United States using a variant of difference-in-differences analysis.
Scientific Reports 2024; Vol. 14 (1), p 16220.

Long-term mortality effects of particulate air pollution have been investigated in a causal analytic frame, while causal evidence for associations with gaseous air pollutants remains extensively lacking, especially for carbon monoxide (CO) and sulfur dioxide (SO2).
In this study, we estimated the causal relationship of long-term exposure to nitrogen dioxide (NO2), CO, SO2, and ozone (O3) with mortality. Utilizing the data from National Morbidity, Mortality, and Air Pollution Study, we applied a variant of difference-in-differences (DID) method with conditional Poisson regression and generalized weighted quantile sum regression (gWQS) to investigate the independent and joint effects. Independent exposures to NO2, CO, and SO2 were causally associated with increased risks of total, nonaccidental, and cardiovascular mortality, while no evident associations with O3 were identified in the entire population. In gWQS analyses, an interquartile range-equivalent increase in mixture exposure was associated with a relative risk of 1.067 (95% confidence interval: 1.010–1.126) for total mortality, 1.067 (1.009–1.128) for nonaccidental mortality, and 1.125 (1.060–1.193) for cardiovascular mortality, where NO2 was identified as the most significant contributor to the overall effect. This nationwide DID analysis provided causal evidence for independent and combined effects of NO2, CO, SO2, and O3 on increased mortality risks among the US general population.
https://doi.org/10.1038/s41598-024-66951-9

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Yang, B., Jia, Y., Yan, M., Zhao, X., Gu, Z., Qin, Y.*, et al.*
Moderate BMI accumulation modified associations between blood benzene, toluene, ethylbenzene and xylene (BTEX) and phenotypic aging: mediating roles of inflammation and oxidative stress.
Environmental pollution (Barking, Essex : 1987) 2024; Vol. 360 p 124669.

The associations between blood benzene, toluene, ethylbenzene, and xylenes (BTEX) and biological aging among general adults remain elusive. The present study comprised 5780 participants from the National Health and Nutrition Examination Survey 1999-2010. A novel measure of biological aging, phenotypic age acceleration (PhenoAge.Accel), derived from biochemical markers was calculated. Weighted generalized linear regression and weighted quantile sum regression (WQS) were utilized to assess the associations between BTEX components and mixed exposure, and PhenoAge.Accel. The mediating roles of systemic immune-inflammation index (SII) and oxidative stress indicators (serum bilirubin and gamma-glutamyl transferase), along with the modifying effects of body mass index (BMI) were also examined. In the single-exposure model, the highest quantile of blood benzene (b=0.89, 95%CI: 0.58 to 1.20), toluene (b=0.87, 95%CI: 0.52 to 1.20), and ethylbenzene (b=0.80, 95%CI: 0.46 to 1.10) was positively associated with PhenoAge.Accel compared to quantile 1. Mixed-exposure analyses revealed a consistent positive association between BTEX mixed exposure and PhenoAge.Accel (b=0.88, 95%CI: 0.56 to 1.20), primarily driven by benzene (92.78%). The association between BTEX and PhenoAge.Accel was found to be partially mediated by inflammation and oxidative stress indicators (ranging from 3.2% to 13.7%). Additionally, BMI negatively modified the association between BTEX mixed exposure and PhenoAge.Accel, with a threshold

identified at 36.2kg/m^2. Furthermore, BMI negatively moderated the direct effect of BTEX mixed exposure on PhenoAge.Accel in moderated mediation models, while positively modified the link between SII and PhenoAge.Accel in the indirect path (binteraction=0.04, 95%CI: 0.01 to 0.06). Overall, BTEX mixed exposure was associated with PhenoAge.Accel among US adults, with benzene may have reported most contribution, and inflammation and oxidative damage processes may partially explain this underlying mechanism. The study also highlighted the potential benefits of appropriate BMI increased. Additional large-scale cohort studies and experiments were necessary to substantiate these findings.
https://doi.org/10.1016/j.envpol.2024.124669

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He, R., Zhong, H., He, C., Li, H., Wang, Z., Zheng, J., *et al.*
Individual and mixture effects of BTEX occupational exposure with hematologic and hepatic profiles in petrochemical workers and the metabolic mechanism.
Journal of Environmental Sciences 2024; Vol. p

Evidence on the association of occupational exposure to benzene, toluene, ethylbenzene, and xylene (BTEX) with hematologic and hepatic profiles were equivocal, and few studies have investigated overall effect of BTEX mixtures. Herein, significant higher concentrations ($p < 0.05$) of hippuric acid, 1,2-dihydroxybenzene, mandelic acid, trans, trans-muconic acid and phenylglyoxylic acid were found in petrochemical workers than the controls, in accordance with higher levels of hematologic and hepatic profiles found in petrochemical workers ($p < 0.05$). Occupational exposure to individual BTEX was associated with elevated levels of white blood cell (WBC), lymphocyte (LYMPH), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT). Further, the Weighted Quantile Sum Regression model and Bayesian Kernel Machine Regression model consistently identified a positive association between BTEX mixture exposure and WBC, LYMPH, and GGT. Xylene was the primary contributor to increased WBC, LYMPH, and GGT levels. Furthermore, BTEX exposure resulting in the increased inflammation indices were mainly related to perturbations of sphingolipid metabolism, biosynthesis of unsaturated fatty acids, and primary bile acid biosynthesis. Whereas metabolites mediated the correlation between BTEX exposure and liver function indices were related to the perturbations of biosynthesis of unsaturated fatty acids, arachidonic acid metabolism, sphingolipid metabolism, primary bile acid biosynthesis, etc. Our findings revealed potential health risk of occupational exposure to BTEX and might help one to understand the link between BTEX exposure and hematologic and hepatic profiles.
https://doi.org/10.1016/j.jes.2024.06.021

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Multi-expositions aux particules de microplastiques, ou pesticides

Trenteseaux, C., Fontaine, K., Chatzidimitriou, E., Bouscaillou, W., Mienne, A., Sarda, X.
Cumulative dietary risk assessment for French consumers exposed to succinate dehydrogenase inhibitor pesticides.
Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 2024; Vol. 191 : p 114890.

Consumers are exposed to succinate dehydrogenase inhibitor (SDHI) pesticides through their diet. A cumulative dietary risk assessment for the French population has been performed with French monitoring data (2017-2021) and consumption data from INCA3. The calculation followed a two-tiered approach, using deterministic then probabilistic methods. It was carried out, using European health based guidance values (HBGV) derived for each active substance to characterise their toxicity. In Tier I, the calculated hazard index of 0.12 was below the threshold of 1 and in Tier II, the total margin of exposure at percentile 99.9 remains

above the trigger value of 100 (1798 [1631-2311]). In Tier II, the three main risk drivers identified at the upper tail of the distribution were strawberries-fluopyram (19.1%), peaches-fluopyram (14.1%) and table grapes-boscalid (10.5%). Finally, the impact of the major sources of uncertainties was qualitatively evaluated. All together, they were considered of low impact on the outcomes. This work demonstrates the absence of unacceptable chronic risk related to the cumulative exposure of SDHI for French consumers during the 2017-2021 period.
https://doi.org/10.1016/j.fct.2024.114890

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Liang, K. H., Colombijn, J. M. T., Verhaar, M. C., Ghannoum, M., Timmermans, E. J., Vernooij, R. W. M.
The general external exposome and the development or progression of chronic kidney disease: A systematic review and meta-analyses.
Environmental pollution (Barking, Essex : 1987) 2024; Vol. 358 p 124509.

The impact of environmental risk factors on chronic kidney disease (CKD) remains unclear. This systematic review aims to provide an overview of the literature on the association between the general external exposome and CKD development or progression. We searched MEDLINE and EMBASE for case-control or cohort studies, that investigated the association of the general external exposome with a change in eGFR or albuminuria, diagnosis or progression of CKD, or CKD-related mortality. The risk of bias of included studies was assessed using the Newcastle-Ottawa Scale. Summary effect estimates were calculated using random-effects meta-analyses. Most of the 66 included studies focused on air pollution (n=33), e.g. particulate matter (PM) and nitric oxides (NOx), and heavy metals (n=21) e.g. lead and cadmium. Few studies investigated chemicals (n=7) or built environmental factors (n=5). No articles on other environment factors such as noise, food supply, or urbanization were found. PM2.5 exposure was associated with an increased CKD and end-stage kidney disease incidence, but not with CKD-related mortality. There was mixed evidence regarding the association of NO2 and PM10 on CKD incidence. Exposure to heavy metals might be associated with an increased risk of adverse kidney outcomes, however, evidence was inconsistent. Studies on effects of chemicals or built environment on kidney outcomes were inconclusive.
In conclusion, prolonged exposure to PM2.5 is associated with an increased risk of CKD incidence and progression to kidney failure. Current studies predominantly investigate the exposure to air pollution and heavy metals, whereas chemicals and the built environment remains understudied. Substantial heterogeneity and mixed evidence were found across studies. Therefore, long-term high-quality studies are needed to elucidate the impact of exposure to chemicals or other (built) environmental factors and CKD.
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Deng, Y., Li, G., Xie, L., Li, X., Wu, Y., Zheng, J.*, et al.*
Associations of occupational exposure to micro-LiNiCoMnO2 particles with systemic inflammation and cardiac dysfunction in cathode material production for lithium batteries.
Environmental Pollution 2024; Vol. 359 p 124694.

Micro-LiNiCoMnO2 (MNCM), a cathode material with highest market share, has increasing demand with the growth of lithium battery industry. However, whether MNCM exposure brings adverse effects to workers remains unclear. This study aimed to explore the association between MNCM exposure with systemic inflammation and cardiac function. A cross-sectional study of 347 workers was undertaken from the MNCM production industry in Guangdong province, China in 2020. Metals in urine were measured using ICP-MS. The associations between metals, systemic inflammation, and cardiac function were appraised using a linear or logistic regression model. Bayesian kernel machine regression (BKMR) and generalized weighted quantile sum (gWQS) models were used to explore mixed metal exposures. The analysis of interaction and mediation was adopted to assess the role of inflammation in the relation between urinary metals and cardiac function.
We observed that the levels of lithium (Li) and cobalt (Co) were positively associated with systemic

inflammation and heart rate. The amount of Co contributed the highest weight on the increased systemic immune-inflammation index (SII) (59.8%), the system inflammation response index (SIRI) (44.3%), and heart rate (65.0%). Based on the mediation analysis, we estimated that SII mediated 32.3% and 20.9% of the associations between Li and Co with heart rate, and SIRI mediated 44.6% and 22.2% of the associations between Li and Co with heart rate, respectively. This study demonstrated for the first time that MNCM exposure increased the risk of workers' systemic inflammation and elevated heart rate, which were contributed by the excessive Li and Co exposure. Additionally, it indicates that systemic inflammation was a major mediator of the associations of Li and Co with cardiac function in MNCM production workers.
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Radivojevic, I., Stojilkovic, N., Antonijevic-Miljakovic, E., Dordevic, A. B., Baralic, K., Curcic, M., *et al.*
In silico attempt to reveal the link between cancer development and combined exposure to the maize herbicides: Glyphosate, nicosulfuron, S-metolachlor and terbuthylazine.
Science of the Total Environment November 2024; Vol. 949, 175187.

Pesticides are crucial for crop protection and have seen a 50 % increase in use in the last decade. Besides preventing significant crop losses their use has raised health concerns due to consumer exposure through residues in food and water. The toxicity data from individual components is often used to assess overall mixture toxicity, but uncertainty persists in understanding the behaviors of individual chemicals within these mixtures. Assessing the risk of pesticide mixture exposure remains challenging, potentially leading to overestimation or underestimation of toxicity.
This study aims to establish a possible link between exposure to a herbicide mixture and genotoxic effects, focusing on cancer development. Our analysis was focused on four herbicides glyphosate, nicosulfuron, Smetolachlor and terbuthylazine. To determine the link between genes associated with cancer development due to exposure to herbicide mixture, a CTD database tools were used. Through the ToppFun tool molecular function and biological process associated with genes common to the disease of interest and selected herbicides were evaluated. And finally, GeneMANIA was used in order to analyze the function and interaction between common genes of herbicide mixture. Among the 7 common genes for herbicide mixture and cancer development coexpression characteristics dominant at 65.41 %, 22.14 % of annotated genes shared the same pathway and 7.88 % showed co-localization. Among six target genes involved in genetic disease development co-expression was dominant at 87.34 colocalization at 8.03 % and shared protein domains at 4.52 %. Comprehensive molecular analyses, encompassing genomics, proteomics, and pathway analysis, are essential to unravel the specific mechanisms involved in the context of the studied mixture and its potential carcinogenic effects.
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