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CHEMICAL EFFECTS

Combined toxicity of endocrine-disrupting chemicals: A review

2021-03-15

The combined toxicological assessment provides a realistic approach for hazard evaluation of chemical cocktails that co-existed in the environment. This review provides a holistic insight into the studies highlighting the mixture toxicity of the endocrine-disrupting chemicals (EDCs), especially focusing on the screening of biochemical pathways and other toxicogenetic endpoints. Reviewed literature showed that numerous multiplexed toxicogenomic techniques were applied to determine reproductive effects in vertebrates, but limited studies were found in non-mammalian species after mixture chemical exposure. Further, we found that the experimental design and concentration selection are the two important parameters in mixture toxicity studies that should be time- and cost-effective, highly precise, and environmentally relevant. A summary of EDC mixtures affecting the thyroid axis, estrogen axis, androgen axis, growth stress, and immune system via in vivo bioassays was also presented. It is interesting to mention that majority of estrogenic effects of the mixtures were sex-dependent, particularly observed in male fish as compared to female fish. Further, the androgen axis was perturbed with serious malformations in male rat testis (epididymal or gubernacular lesions, and deciduous spermatids). Also, transgenerational epigenetic effects were promoted in the F3 and F4 generations in the form of DNA methylation epimutations in sperm, increasing polycystic ovaries and reducing the offspring. Similarly, increased oxidative stress, high antioxidant enzymatic activities, disturbed estrous cycle, and decreased steroidogenesis were the commonly found effects after acute or chronic exposure to EDC mixtures. Importantly, the concentration addition (CA) and independent action (IA) models became more prevalent and suitable predictive models to unveil the prominence of synergistic estrogenic and anti-androgenic effects of chemical mixtures. More importantly, this review encompasses the research challenges and gaps in the existing knowledge and specific future research perspectives on combined toxicity.

Authors: Naima Hamid, Muhammad Junaid, De-Sheng Pei

Full Source: Ecotoxicology and environmental safety 2021 Mar 15;215:112136. doi: 10.1016/j.ecoenv.2021.112136.

The combined toxicological assessment provides a realistic approach for hazard evaluation of chemical cocktails that co-existed in the environment.

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Experimental Approaches for Characterizing the Endocrine-Disrupting Effects of Environmental Chemicals in Fish

2021-02-25

Increasing industrial and agricultural activities have led to a disturbing increase of pollutant discharges into the environment. Most of these pollutants can induce short-term, sustained or delayed impacts on developmental, physiological, and behavioral processes that are often regulated by the endocrine system in vertebrates, including fish, thus they are termed endocrine-disrupting chemicals (EDCs). Physiological impacts resulting from the exposure of these vertebrates to EDCs include abnormalities in growth and reproductive development, as many of the prevalent chemicals are capable of binding the receptors to sex steroid hormones. The approaches employed to investigate the action and impact of EDCs is largely dependent on the specific life history and habitat of each species, and the type of chemical that organisms are exposed to. Aquatic vertebrates, such as fish, are among the first organisms to be affected by waterborne EDCs, an attribute that has justified their wide-spread use as sentinel species. Many fish species are exposed to these chemicals in the wild, for either short or prolonged periods as larvae, adults, or both, thus, studies are typically designed to focus on either acute or chronic exposure at distinct developmental stages. The aim of this review is to provide an overview of the approaches and experimental methods commonly used to characterize the effects of some of the environmentally prevalent and emerging EDCs, including 17 β -ethinylestradiol, nonylphenol, BPA, phthalates, and arsenic; and the pervasive and potential carriers of EDCs, microplastics, on reproduction and growth. In vivo and in vitro studies are designed and employed to elucidate the direct effects of EDCs at the organismal and cellular levels, respectively. In silico approaches, on the other hand, comprise computational methods that have been more recently applied with the potential to replace extensive in vitro screening of EDCs. These approaches are discussed in light of model species, age and duration of EDC exposure.

Authors: Fritzie T Celino-Brady, Darren T Lerner, Andre P Seale

Full Source: Frontiers in endocrinology 2021 Feb 25;11:619361. doi: 10.3389/fendo.2020.619361.

Increasing industrial and agricultural activities have led to a disturbing increase of pollutant discharges into the environment.

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Gut microbiota-mediated pesticide toxicity in humans: Methodological issues and challenges in the risk assessment of pesticides

2021-05

Many in vivo and in vitro studies have shown that pesticides can disrupt the functioning of gut microbiota (GM), which can lead to many diseases in humans. While the tests developed by the Organization of Economic Cooperation and Development (OECD) are expected to capture most apical effects resulting from GM disruptions, exclusion of GM in the risk assessment might mischaracterize hazards or overestimate/underestimate risks, especially when extrapolating results from one species to another species or population with a substantially different GM. On the other hand, direct assessment of GM-mediated effects may face challenges in identifying hazards, since not all GM perturbations will lead to human adverse effects. In this regard, reliable and validated biomarkers for common GM-mediated adverse effects may be very useful in the identification of GM-mediated pesticide toxicity. Nevertheless, proving causality of GM-mediated effects will need modifications of Bradford Hill criteria as well as Koch's postulates, which are more suitable for the "one-pathogen" paradigm. Furthermore, risk assessment of GM-mediated effects may require pesticide toxicokinetics along the gut, possibly through modeling, and the establishment of the involvement of GM in the mechanism of action (MOA) of the pesticide. Risk assessment of GM mediated effects also requires the standardization of experimental approaches as well as the establishment of microbial reference communities, since variations exist among GM in human populations.

Authors: Wells Utembe, Arox Wadson Kamng'ona

Full Source: Chemosphere 2021 May;271:129817. doi: 10.1016/j.chemosphere.2021.129817.

Toxicity, residue and risk assessment of tetraniliprole in soil-earthworm microcosms

2021-04-15

Maize seed treatment with chemicals to control underground pests is a common agricultural practice, but inappropriate use of insecticides poses a considerable threat to plant development and soil nontarget organisms. In this study, the availability of tetraniliprole seed dressing to control the black cutworm *Agrotis ipsilon* (Lepidoptera: Noctuidae) in the maize seeding stage and its safety to earthworms (*Eisenia fetida*) were investigated. The selective toxicity (ST) of tetraniliprole between

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E. fetida and *A. ipsilon* was greater than 4000. No significant adverse effect of tetraniliprole seed treatment on the germination of maize seeds was observed at concentrations of 2.4-9.6 g a.i. /kg seed. Compared with the untreated control, seed treatment with tetraniliprole at 9.6 g a.i. /kg seed greatly reduced the percentage of damaged plants from 88.73% to 26.67%, and achieved the highest control effect of 69.91%. Tetraniliprole of 2.4 g a.i. /kg seed can effectively inhibit *A. ipsilon* until 14 days after seed germination, with the lowest mortality rate of 44.44%. During the entire exposure period, the maximum residual concentration of tetraniliprole detected in the soil (5.86 mg/kg) was considerably lower than the LC50 value of tetraniliprole to *E. fetida* (>4000 mg/kg). According to the low-tier risk assessment, the highest risk quotient (RQ) of tetraniliprole seed treatment to earthworms at test concentrations was 2.8×10^{-3} , which was evaluated as acceptable. This study provided data support for tetraniliprole seed treatment to control underground pests in maize fields.

Authors: Dicheng Ma, Song Yang, Jiangong Jiang, Jiamei Zhu, Beixing Li, Wei Mu, Daolong Dou, Feng Liu

Full Source: Ecotoxicology and environmental safety 2021 Apr 15;213:112061. doi: 10.1016/j.ecoenv.2021.112061.

ENVIRONMENTAL RESEARCH**Interdisciplinary Data Science to Advance Environmental Health Research and Improve Birth Outcomes**

2021-03-15

Rates of preterm birth and low birthweight continue to rise in the United States and pose a significant public health problem. Although a variety of environmental exposures are known to contribute to these and other adverse birth outcomes, there has been a limited success in developing policies to prevent these outcomes. A better characterization of the complexities between multiple exposures and their biological responses can provide the evidence needed to inform public health policy and strengthen preventative population-level interventions. In order to achieve this, we encourage the establishment of an interdisciplinary data science framework that integrates epidemiology, toxicology and bioinformatics with biomarker-based research to better define how population-level exposures contribute to these adverse birth outcomes. The proposed interdisciplinary research framework would 1) facilitate data-driven analyses using existing data from health registries and environmental monitoring programs; 2) develop novel algorithms with the ability to predict which exposures are

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driving, in this case, adverse birth outcomes in simultaneous exposures; and 3) refine biomarker-based research, ultimately leading to new policies and interventions to reduce the incidence of adverse birth outcomes.

Authors: Jeanette A Stingone, Sofia Triantafillou, Alexandra Larsen, Jay P Kitt, Gary M Shaw, Judit Marsillach

Full Source: Environmental research 2021 Mar 15;111019. doi: 10.1016/j.envres.2021.111019.

Seaweeds fast EDC bioremediation: Supporting evidence of EE2 and BPA degradation by the red seaweed *Gracilaria* sp., and a proposed model for the remedy of marine-borne phenol pollutants

2021-03-02

In the last few decades, Endocrine Disrupting Chemicals (EDCs) have taken significant roles in creating harmful effects to aquatic organisms. Many proposed treatment applications are time consuming, expensive and focus mainly on waste water treatment plants (WWTP), which are indeed a major aquatic polluting source. Nonetheless, the marine environment is the ultimate sink of many pollutants, e.g. EDCs, and has been largely neglected mainly due to the challenge in treating such salty and immense open natural ecosystems. In this study we describe the bromination and the yet unrepresented degradation process of high concentrations (5 mg/L) of phenolic EDCs, by the marine red macroalgae *Gracilaria* sp. As shown, 17β-Ethinylestradiol (EE2), a well-known contraceptive drug, and one of the most persistent phenol EDCs in the environment, was eliminated from both the medium and tissues of the macroalga, in addition to the degradation of all metabolites as verified by the nil estrogenic activity recorded in the medium. Validation of the proposed bromination-degradation route was reinforced by identifying Bisphenol A (BPA) brominated degradation products only, following 168H of incubation in the presence of *Gracilaria* sp. As demonstrated in this assay for EE2, BPA and finally for paracetamol, it is likely that the phenol scavenging activity is nonspecific and, thus, possibly even a wider scope of various other phenol-based pollutants might be treated in coastal waters. As far as we know, *Gracilaria* sp. is the only marine sessile organism able of degrading various phenol based pollutants. The worldwide distribution of many *Gracilaria* species and their wide aquaculture knowhow, suggest that bioremediation based on these

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seaweeds is a possible cost effective progressive solution to the treatment of a wide scope of phenols at the marine environment.

Authors: Peleg Astrahan, Leor Korzen, Marina Khanin, Yoav Sharoni, Álvaro Israel

Full Source: Environmental pollution (Barking, Essex : 1987) 2021 Mar 2;278:116853. doi: 10.1016/j.envpol.2021.116853.

OCCUPATIONAL

Distinct metabolic features in the plasma of patients with silicosis and dust-exposed workers in China: a case-control study

2021-03-17

Background: Silicosis is a progressive pneumoconiosis characterized by interstitial fibrosis following exposure to silica dust. The role of metabolic dysregulation in the pathogenesis of silicosis has not been investigated in detail. This study aimed to identify different metabolic features in the plasma of patients with silicosis and dust-exposed workers without silicosis in metabolomics studies.

Methods: Patients with silicosis, dust-exposed workers (DEWs) without silicosis and age-matched healthy controls were recruited in a case-control study. The metabolomics analyses by ultra-high performance liquid chromatography-mass spectrometry were conducted. Distinct metabolic features (DMFs) were identified in the pilot study and were validated in the validation study. The enriched signalling pathways of these DMFs were determined. The ability of DMFs to discriminate among the groups was analysed through receiver operating characteristic (ROC) curves. The correlations between DMFs and clinical features were also explored. Results: Twenty-nine DMFs and 9 DMFs were detected and had the same trend in the pilot study and the validation study in the plasma of the DEW and silicosis groups, respectively. Sphingolipid metabolism was the major metabolic pathway in the DEWs, and arginine and proline metabolism was associated with silicosis. Twenty DMFs in the DEWs and 3 DMFs in the patients with silicosis showed a discriminatory ability with ROC curve analysis. The abundance of kynurenine was higher in Stage III silicosis than in Stage I or Stage II silicosis. L-arginine and kynurenine were both negatively correlated with the percentage of forced vital capacity predicted in silicosis.

Conclusions: Distinct metabolic features in the plasma of DEWs and the patients with silicosis were found to be different. Sphingolipid metabolism

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and arginine and proline metabolism were identified as the major metabolic pathway in the DEW and silicosis groups, respectively. L-arginine and kynurenine were correlated with the severity of silicosis.

Authors: Changjiang Xue, Na Wu, Yali Fan, Jing Ma, Qiao Ye

Full Source: BMC pulmonary medicine 2021 Mar 17;21(1):91. doi:

10.1186/s12890-021-01462-1.

Reconstruction of the Korean Asbestos Job Exposure Matrix

2021-03

Background: A job-exposure matrix (JEM) is an important surrogate indicator to evaluate past exposure levels. Although a Korean asbestos JEM has been constructed previously, this JEM includes only a few industrial and occupational groups. This study aimed to reconstruct the JEM by integrating the latest organized data to improve its utility.

Methods: We used recent Korean standard industry and occupation codes and extracted 36 articles from a systematic literature review to initiate the reconstruction of the previous Korean asbestos JEM. The resulting data consisted of 141 combinations of industrial and occupational groups. Data from the Netherlands's JEM were also reviewed and categorized into 70 industrial and 117 occupational groups by matching with the Korean data. We also utilized Germany's data, which consisted of 10 industrial and 14 occupational groups.

Results: The reconstructed Korean asbestos JEM had 141 combinations of industries and occupations. The time periods are from the 1980s to the 2000s in 10-year intervals. Most of the data were distributed between the 1990s and the 2000s. Occupations with high exposure to asbestos included knitting and weaving machine operators, automobile mechanics or assemblers, ship mechanics or assemblers, mineral ore and stone products processing mechanics, and metal casting machine operators or mold makers.

Conclusions: The reconstructed Korean asbestos JEM has expanded the type and duration of the occupational groups of the previous JEM and can serve as an important reference tool for evaluating asbestos exposure and designing compensation and prevention policies in Korea.

Authors: Dongmug Kang, Saemi Jung, Yun-Ji Kim, Juyoung Kim, Sangjun Choi, Se Yeong Kim, Youngki Kim

Full Source: Safety and health at work 2021 Mar;12(1):74-95. doi:

10.1016/j.shaw.2020.09.005.

Background: A job-exposure matrix (JEM) is an important surrogate indicator to evaluate past exposure levels.

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Chronic exposure to metal fume PM 2.5 on inflammation and stress hormone cortisol in shipyard workers: A repeat measurement study

2021-03-17

Particulate matter with an aerodynamic diameter of $\leq 2.5 \mu\text{m}$ (PM_{2.5}) has been linked to adverse health outcomes in welding workers. The objective of this study was to investigate associations of chronic exposure to metal fume PM_{2.5} in shipyard workers with health outcomes. A longitudinal study was conducted to determine the effects of metal fume PM_{2.5} on FeNO, urinary metals, urinary oxidative stress, inflammation, and stress hormones in workers. There were 20 office workers and 49 welding workers enrolled in this study who were followed-up for a second year. We observed that Fe, Zn, and Mn were abundant in PM_{2.5} to which welding workers were personally exposed, whereas PM_{2.5} to which office workers were personally exposed was dominated by Pb, Cu, and Zn. We observed in the first and/or second visits that urinary 8-iso-prostaglandin F₂- α (PGF₂ α) and 8-hydroxy-2'-deoxy guanosine (8-OHdG) were significantly increased by exposure. An increase in urinary interleukin (IL)-6 and decreases in urinary serotonin and cortisol were observed in the first and/or second visits after exposure. PM_{2.5} was associated with decreases in urinary 8-OHdG and cortisol among workers. Next, we observed that urinary Ni, Co, and Fe had significantly increased among workers after a year of exposure. Urinary metals were associated with decreases in urinary 8-iso-PGF₂ α and cortisol among workers. Urinary Ni, Cu, and Fe levels were associated with an increase in urinary IL-6 and a decrease in urinary cortisol among workers. In conclusion, chronic exposure to metal fume PM_{2.5} was associated with inflammation and a cortisol deficiency in shipyard workers, which could associate with adrenal glands dysfunction.

Authors: Ching-Huang Lai, Shu-Chuan Ho, Chih-Hong Pan, Wei-Liang Chen, Chung-Ching Wang, Che-Wi Liang, Chi-Yu Chien, Michael Riediker, Kai-Jen Chuang, Hsiao-Chi Chuang

Full Source: Ecotoxicology and environmental safety 2021 Mar 17;215:112144. doi: 10.1016/j.ecoenv.2021.112144.

Particulate matter with an aerodynamic diameter of $\leq 2.5 \mu\text{m}$ (PM_{2.5}) has been linked to adverse health outcomes in welding workers.

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PHARAMACEUTICAL/TOXICOLOGY

HPLC method development/validation and skin diffusion study of caffeine, methyl paraben and butyl paraben as skin-diffusing model drugs

2021-03-17

The focus of this research was to develop and validate a suitable HPLC method, which allows simultaneous determination of three proposed skin model penetrants to investigate the percutaneous diffusion behavior of their combination: caffeine, methyl paraben and butyl paraben. These penetrants were selected because they represent a wide range of lipophilicities. This model highlights the effect of combining penetrants of different molecular properties on their diffusion behavior through skin. The proposed method employed a gradient system that was systematically optimized for separation and quantification of the penetrants. The effect of the stationary phase (C18, C4 and cyano (CN)) was assessed with CN proven to be superior in terms of peak shape, retentivity and dynamic linear range. Significant differences in retention time, peak broadening, and quantifiability between different stationary phases could be demonstrated. The method was validated as per ICH guidelines Q2 (R1) with a satisfactory outcome. The method was successfully applied for real diffusion experiments, and revealed notable differences between the individual penetrants and their ternary mixture on transdermal permeation. The method could potentially be extended to determine these analytes in other related skin permeation investigations.

Authors: Randa S H Mansour, Imad I Hamdan, Mutaz S H Salem, Enam A Khalil, ALSayed A Sallam

Full Source: PloS one 2021 Mar 17;16(3):e0247879. doi: 10.1371/journal.pone.0247879.

The focus of this research was to develop and validate a suitable HPLC method, which allows simultaneous determination of three proposed skin model penetrants to investigate the percutaneous diffusion behavior of their combination: caffeine, methyl paraben and butyl paraben.