

# Bulletin Board

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## CONTACT US

subscribers@chemwatch.net  
tel +61 3 9572 4700  
fax +61 3 9572 4777

1227 Glen Huntly Rd  
Glen Huntly  
Victoria 3163 Australia

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## CHEMICAL EFFECTS

**Endocrine disruptors: Challenges and future directions in epidemiologic research**

2021-08-27

Public concern about the impact of endocrine disrupting chemicals (EDCs) on both humans and the environment is growing steadily. Epidemiologic research provides key information towards our understanding of the relationship between environmental exposures like EDCs and human health outcomes. Intended for researchers in disciplines complementary to epidemiology, this paper highlights the importance and challenges of epidemiologic research in order to present the key elements pertaining to the design and interpretation of an epidemiologic study on EDCs. The conduct of observational studies on EDCs derives from a thoughtful research question, which will help determine the subsequent methodological choices surrounding the careful selection of the study population (including the comparison group), the adequate ascertainment of exposure(s) and outcome(s) of interest, and the application of methodological and statistical concepts more specific to epidemiology. The interpretation of epidemiologic results may be arduous due to the latency occurring between EDC exposure and certain outcome(s), the complexity in capturing EDC exposure(s), and traditional methodological and statistical issues that also deserve consideration (e.g., confounding, effect modification, non-monotonic responses). Moving forward, we strongly advocate for an integrative approach of expertise in the fields of epidemiology, exposure science, risk assessment and toxicology to adequately study the health risks associated with EDCs while tackling their challenges.

Authors: V Ho, L Pelland-St-Pierre, S Gravel, M F Bouchard, M-A Verner, F Labrèche

Full Source: Environmental research 2021 Aug 27;204(Pt A):111969. doi: 10.1016/j.envres.2021.111969.

**Systemic toxicity induced by topical application of heptafluorobutyric acid (PFBA) in a murine model**

2021-08-30

Heptafluorobutyric acid (PFBA) is a synthetic chemical belonging to the per- and polyfluoroalkyl substances (PFAS) group that includes over 5000 chemicals incorporated into numerous products. PFBA is a short-chain PFAS (C4) labeled as a safer alternative to legacy PFAS which have been

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linked to numerous health effects. Despite the high potential for dermal exposure, occupationally and environmentally, dermal exposure studies are lacking. Using a murine model, this study analyzed serum chemistries, histology, immune phenotyping, and gene expression to evaluate the systemic toxicity of sub-chronic dermal PFBA 15-day (15% v/v or 375 mg/kg/dose) or 28-day (3.75-7.5% v/v or 93.8-187.5 mg/kg/dose) exposures. PFBA exposure produced significant increases in liver and kidney weights and altered serum chemistries (all exposure levels). Immune-cell phenotyping identified significant increases in draining lymph node B-cells (15%) and CD11b + cells (3.75-15%) and skin T-cells (3.75-15%) and neutrophils (7.5-15%). Histopathological and gene expression changes were observed in both the liver and skin after dermal PFBA exposure. The findings indicate PFBA induces liver toxicity and alterations of PPAR target genes, suggesting a role of a PPAR pathway. These results demonstrate that sustained dermal exposure to PFBA induces systemic effects and raise concerns of short-chain PFAS being promoted as safer alternatives.

Authors: Lisa M Weatherly, Hillary L Shane, Ewa Lukomska, Rachel Baur, Stacey E Anderson

Full Source: Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 2021 Aug 30;156:112528. doi: 10.1016/j.fct.2021.112528.

## ENVIRONMENTAL RESEARCH

**Differences in marine megafauna in vitro sensitivity highlights the need for species-specific chemical risk assessments**

2021-08-20

Sea turtles, dolphins and dugongs can be exposed to large mixtures of contaminants due to the proximity of foraging locations to anthropogenic inputs. Differences in accumulation and effect result in differences of chemical risk to these species. However, little is known about the effect of contaminants in marine wildlife. Cell-based, or in vitro, exposure experiments offer an ethical alternative to investigate the effect of contaminants in wildlife. Data from in vitro studies can then be placed in an environmental context, by using screening risk assessments, comparing effect data with accumulation data from the literature, to identify risk to populations of marine wildlife. Cytotoxicity of Cr6+, Cd2+, Hg2+, 4,4'-DDE, and PFNA were investigated in primary skin fibroblasts of green turtles,

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loggerhead turtles, hawksbill turtles, dugongs, Burrunan dolphins, and common bottlenose dolphins. The general order of toxicity for all species was  $Hg^{2+} > Cr^{6+} > Cd^{2+} > 4,4\text{-DDE} > PFNA$ , and significant differences in cytotoxicity were found between species for  $Cr^{6+}$ ,  $Cd^{2+}$  and PFNA. For  $Cd^{2+}$ , in particular, cells from turtle species were less sensitive than mammalian species, and dugong cells were by far the most sensitive. The results from the cytotoxicity assay were then used in combination with published data on tissue contaminant concentrations to calculate risk quotients for identifying populations of each species most at risk from these chemicals. Cr, Cd and Hg were identified as posing risk in all six species. Dugongs were particularly at risk from Cd accumulation and dolphin species were particularly at risk from Hg accumulation. These results demonstrate the importance of using species-specific effect and accumulation data for developing chemical risk assessments and can be used to inform managers of priority contaminants, species, or populations. Development of additional in vitro endpoints, and improving links between in vitro and in vivo effects, would further improve this approach to understanding chemical risk in marine megafauna.

Authors: Kimberly A Finlayson, Jason P van de Merwe

Full Source: Aquatic toxicology (Amsterdam, Netherlands) 2021 Aug 20;239:105939. doi: 10.1016/j.aquatox.2021.105939.

### Morphological and biochemical responses of *Macrotyloma uniflorum* (Lam.) Verdc. to allelopathic effects of *Mikania micrantha* Kunth extracts

2021-08-17

Yield loss due to noxious weeds is one among several reasons for the reduced economy for the developing countries. Impacts of one such weed i.e. *Mikania micrantha* were investigated on the rate of seed germination, growth, biomass, photosynthetic pigments, total soluble protein, phenolics and proline content of leaves of *Macrotyloma uniflorum* (an important pulse). In a completely randomized setup, control and four concentrations (10 mg/ml, 50 mg/ml, 100 mg/ml and 200 mg/ml) of the aqueous leaf extracts of *M. micrantha* were tested on the seeds of *M. uniflorum*. The extracts inhibited germination, growth, biomass, chlorophyll, carotenoid and protein contents. The protein content of *M. uniflorum* decreased to 8.48 mg/g at 200 mg/ml. Similarly, shoot length and root length were also decreased up to 5.11 cm and 0.85 cm respectively and water content increased with the increasing concentration of weed extracts. The leaf extracts resulted in an increase in the phenolics (19.66 mg) and proline (24.49 mg) content of the crop plant. The preliminary study

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indicated that the aqueous leaf extracts of weed plant resulted in negative or detrimental impact on growth and physiology of the plant and this might be due to the release of secondary metabolites. The present investigation may further lead to the identification of certain secondary metabolites or allelo-chemicals that may have an important agricultural application for sustainability and may enhance the level of crop protection against several other harmful plant species.

Authors: Pallavi Jali, Ipsita Priyadarsini Samal, Sameer Jena, Gyanranjan Mahalik

Full Source: Heliyon 2021 Aug 17;7(8):e07822. doi: 10.1016/j.heliyon.2021.e07822.

### Estimating the release of chemical substances from consumer products, textiles and pharmaceuticals to wastewater

2021-08-25

Chemical emissions from households originate from a wide range of sources and results in highly diverse mixtures. This makes traditional monitoring based on analytical chemistry challenging, especially for compounds that appear in low concentrations. We therefore developed a method for predicting emissions of chemicals from households into wastewater, relying on consumption patterns from multiple data sources. The method was then used to predict the emissions of chemical preparations, chemicals leaching from textiles and prescription pharmaceuticals in Sweden. In total we predicted emissions of 2007 chemicals with a combined emission of 62,659 tonnes per year - or 18 g/person and day. Of the emitted chemicals, 2.0% (w/w) were either classified as hazardous to the environment or were both persistent and mobile. We also show that chemical emissions come from a wide range of uses and that the total emission of any individual chemical is determined primarily by its use pattern, not by the total amount used. This emphasizes the need for continuous updates and additional knowledge generation both on emission factors and excretion rates as well as a need for improved reporting on the intended use of individual chemicals. Finally, we scrutinize the model and its uncertainty and suggest areas that need improvement to increase the accuracy of future emission modelling. We conclude that emission modelling can help guide environmental monitoring and provide

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input into management strategies aimed at reducing the environmental effect caused by hazardous chemicals.

Authors: M Gustavsson, S Molander, T Backhaus, E Kristiansson  
Full Source: Chemosphere 2021 Aug 25;287(Pt 1):131854. doi: 10.1016/j.chemosphere.2021.131854.

### Cadmium exposure induces osteoporosis through cellular senescence, associated with activation of NF- $\kappa$ B pathway and mitochondrial dysfunction

2021-08-24

Cadmium (Cd) is a heavy metal toxicant as a common pollutant derived from many agricultural and industrial sources. The absorption of Cd takes place primarily through Cd-contaminated food and water and, to a significant extent, via inhalation of Cd-contaminated air and cigarette smoking. Epidemiological data suggest that occupational or environmental exposure to Cd increases the health risk for osteoporosis and spontaneous fracture such as itai-itai disease. However, the direct effects and underlying mechanism(s) of Cd exposure on bone damage are largely unknown. We used primary bone marrow-derived mesenchymal stromal cells (BMMSCs) and found that Cd significantly induced BMMSC cellular senescence through over-activation of NF- $\kappa$ B signaling pathway. Increased cell senescence was determined by production of senescence-associated secretory phenotype (SASP), cell cycle arrest and upregulation of p21/p53/p16INK4a protein expression. Additionally, Cd impaired osteogenic differentiation and increased adipogenesis of BMMSCs, and significantly induced cellular senescence-associated defects such as mitochondrial dysfunction and DNA damage. Sprague-Dawley (SD) rats were chronically exposed to Cd to verify that Cd significantly increased adipocyte number, and decreased mineralization tissues of bone marrow in vivo. Interestingly, we observed that Cd exposure remarkably retarded bone repair and regeneration after operation of skull defect. Notably, pretreatment of melatonin is able to partially prevent Cd-induced some senescence-associated defects of BMMSCs including mitochondrial dysfunction and DNA damage. Although Cd activated mammalian target of rapamycin (mTOR) pathway, rapamycin only partially ameliorated Cd-induced cell apoptosis rather than cellular senescence phenotypes of BMMSCs. In addition, a selective NF- $\kappa$ B inhibitor moderately alleviated Cd-caused the senescence-related defects of the BMMSCs. The study shed light on the

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action and mechanism of Cd on osteoporosis and bone ageing, and may provide a novel option to ameliorate the harmful effects of Cd exposure.

Authors: Huigen Luo, Renjie Gu, Huiya Ouyang, Lihong Wang, Shanwei Shi, Yuna Ji, Baicheng Bao, Guiqing Liao, Baoshan Xu  
Full Source: Environmental pollution (Barking, Essex : 1987) 2021 Aug 24;290:118043. doi: 10.1016/j.envpol.2021.118043.

### OCCUPATIONAL

#### Development of Updated RfD and RfC Values for Medium Carbon Range Aromatic and Aliphatic Total Petroleum Hydrocarbon Fractions

2021-09-01

Using total petroleum hydrocarbon (TPH) measurements as a tool for assessing potential human health risks associated with exposures to petroleum products in the environment poses unique challenges, as TPH represents highly variable and complex mixtures containing hundreds of individual chemicals with wide-ranging chemical and physical properties. Current risk assessment practice generally involves analysis of environmental samples for various TPH fractions and summation of risk across those fractions. The United States Environmental Protection Agency (USEPA) derived provisional toxicity criteria for low, medium, and high carbon range aromatic and aliphatic hydrocarbon fractions over a decade ago. These criteria have been used, in whole or in part, to derive risk-based cleanup levels for TPH contamination in soil and groundwater. Herein, we evaluate and update oral and inhalation toxicity criteria for two of these fractions-medium carbon range aromatics and aliphatics-using, where applicable, newer data, updated modeling techniques, and new/alternative analyses of certain endpoints, human relevance, and uncertainty. The results of the analyses support an ~10-fold increase in the USEPA provisional reference concentration (p-RfC) values from 0.1 mg/m<sup>3</sup> to 1 mg/m<sup>3</sup> for both medium carbon range aromatics (different uncertainty factor) and aliphatics (new study and different judgement of toxicity data from existing study). Compared to the USEPA provisional oral reference dose (p-RfD) values for the medium carbon range aromatics and aliphatics of 0.03 mg/kg-day and 0.01 mg/kg-day, respectively, the present analyses suggest the RfD for medium carbon range aromatics could be increased >6.6-fold to 0.2 mg/kg-day (updated modeling and different uncertainty factors), and the RfD for medium carbon range aliphatics could be increased ~20-fold to 0.2 mg/kg-day (new study).

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These updated toxicity criteria could be used by regulatory agencies to re-evaluate risk-based screening levels or by risk managers to support cleanup levels for medium carbon range aromatics and aliphatics, while still ensuring adequate health protection.

Authors: Chad M Thompson, Virunya S Bhat, Greg Brorby, Laurie C Haws  
Full Source: Journal of the Air & Waste Management Association (1995) 2021 Sep 1. doi: 10.1080/10962247.2021.1974123.

### Prevalence of Breast Cancer in Female Physicians Performing Procedures With Significant Fluoroscopy Exposure: Survey

2021-08-31

Objective: The aim of this study was to assess self-reported breast cancer prevalence potentially associated with occupational radiation exposure from fluoroscopy-guided procedures in female physicians using current standard protection measures.

Methods: An institutional review board-approved survey was shared as a link to self-identified female physicians. We compared self-reported prevalence of breast cancer among women physicians with longer than 10 years of postfellowship practice in specialties with heavy fluoroscopy exposure versus specialties with low fluoroscopy exposure. We compared the distribution of breast cancer risk factors and personal radiation safety measures.

Results: A total of 303 women physicians participated in the survey. There were 8 (16%) of 49 from the first study group and 8 (18%) of 44 from the second study group who self-reported a diagnosis of breast cancer. There were no differences in the distribution of breast cancer risk factors between the 2 groups or prevalence of breast cancer ( $P = 0.81$ ).  
Conclusions: Self-reported breast cancer prevalence is similar between women physicians who are practicing fluoroscopically heavy and light medical specialties.

Authors: Bianca Biglione, Masoud Nakhaei, Barbara Hamilton, Meridith J Englander, Anahita Dua, Olga R Brook  
Full Source: Journal of computer assisted tomography 2021 Aug 31. doi: 10.1097/RCT.0000000000001186.

**Objective: The aim of this study was to assess self-reported breast cancer prevalence potentially associated with occupational radiation exposure from fluoroscopy-guided procedures in female physicians using current standard protection measures.**

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## PHARMACEUTICAL/TOXICOLOGY

### The effects of thirdhand smoke on reproductive health

2021-08-30

Tobacco smoke is an environmental pollutant that can cause follicle destruction and oocyte dysfunction. Thirdhand smoke (THS) is residual tobacco smoke existing in the environment long after cigarettes have been extinguished, which can react with other environmental compounds to produce secondary pollutants. THS contains a variety of toxic and harmful chemicals, such as nicotine and 1-(N-methyl-N-nitrosamino)-1-(3-pyridinyl)-4-butanol (NNA), a logical biomarker of THS exposure. The health hazards of THS exposure and its components have been researched in recent years. In this review, we have summarized research progress on the effects of THS exposure on organs in mice and humans especially on the reproductive system. This review may help evaluate the health risks of THS, in particular reproduction and offspring health. We hope this review will guide public health education on the dangers of THS exposure and promotion of healthy living habits.

Authors: Huage Liu, Hao Chen

Full Source: Journal of applied toxicology : JAT 2021 Aug 30. doi: 10.1002/jat.4227.

### phase1RMD: An R package for repeated measures dose-finding designs with novel toxicity and efficacy endpoints

2021-09-02

Traditional dose-finding designs are substantially inefficient for targeted agents and cancer immunotherapies by failing to incorporate efficacy signals, mild and moderate adverse events, and late, cumulative toxicities. However, the lack of user-friendly software is a barrier to the practical use of the novel phase I designs, despite their demonstrated superiority of traditional 3+3 designs. To overcome these barriers, we present an R package, phase1RMD, which provides a comprehensive implementation of novel designs with repeated toxicity measures and early efficacy. A novel phase I repeated measures design that used a continuous toxicity score from multiple treatment cycles was implemented. Furthermore, in studies where preliminary efficacy is evaluated, an adaptive, multi-stage design to identify the most efficacious dose with acceptable toxicity was demonstrated. Functions are provided to recommend the next dose based on the data collected in a phase I trial, as well as to assess trial characteristics given design parameters via simulations. The repeated measure designs accurately estimated both the magnitude and direction

**Tobacco smoke is an environmental pollutant that can cause follicle destruction and oocyte dysfunction.**

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of toxicity trends in late treatment cycles, and allocated more patients at therapeutic doses. The R package for implementing these designs is available from the Comprehensive R Archive Network. To our best knowledge, this is the first software that implement novel phase I dose-finding designs that simultaneously accounts for the multiple-grade toxicity events over multiple treatment cycles and a continuous early efficacy outcome. With the software published on CRAN, we will pursue the implementation of these designs in phase I trials in real-life settings.

Authors: Jun Yin, Yu Du, Rui Qin, Shihao Shen, Sumithra Mandrekar

Full Source: [PloS one 2021 Sep 2;16\(9\):e0256391](https://doi.org/10.1371/journal.pone.0256391). doi: 10.1371/journal.pone.0256391.