

## Contents

CHEMWATCH

(click on page numbers for links)

### ENVIRONMENTAL RESEARCH

Evaluating the Effect of Honey Bee ( <i>Apis mellifera</i> ) Queen Reproductive State on Pheromone-Mediated Interactions with Male Drone Bees.....	3
A microarray-based comparative analysis of gene expression profiles in thyroid glands in amphibian metamorphosis: differences in effects between chemical exposure and food restriction .....	3
Sources, toxicity, and remediation of mercury: an essence review.....	4
Ferritin RNA interference inhibits the formation of iron granules in the trophocytes of worker honey bees ( <i>Apis mellifera</i> ) .....	5
Brominated flame retardants and perfluoroalkyl substances in landfill leachate from Ireland .....	6

### MEDICAL RESEARCH

Metallic air pollutants and breast cancer heterogeneity .....	7
High-throughput identification of the sensitivities of an <i>Escherichia coli</i> $\Delta$ recA mutant strain to various chemical compounds .....	8
Predictions of genotoxic potential, mode of action, molecular targets, and potency via a tiered multiflow <sup>®</sup> assay data analysis strategy...	8
Ecology of the cardiovascular system: Part II - A focus on non-air related pollutants.....	9
Taurine protects against myelin damage of sciatic nerve in diabetic peripheral neuropathy rats by controlling apoptosis of schwann cells via NGF/Akt/GSK3 $\beta$ pathway .....	10

### OCCUPATIONAL RESEARCH

Occupational exposure to formaldehyde and early biomarkers of cancer risk, immunotoxicity and susceptibility .....	11
Functional, inflammatory and interstitial impairment due to artificial stone dust ultrafine particles exposure.....	12
Severe Silicosis in Engineered Stone Fabrication Workers - California, Colorado, Texas, and Washington, 2017-2019 .....	13
Role of asbestos clearance in explaining long-term risk of pleural and peritoneal cancer: a pooled analysis of cohort studies .....	14
Heme oxygenase 1 polymorphism, occupational vapor, gas, dust, and fume exposure and chronic obstructive pulmonary disease in a Danish population-based study .....	15

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## Contents

CHEMWATCH

### PUBLIC HEALTH RESEARCH

Urinary levels of phthalate metabolites and their association with lifestyle behaviours in Chinese adolescents and young adults.....	16
Prenatal and early postnatal phthalate exposure and child neurodevelopment at age of 7 years - Polish Mother and Child Cohort ....	17
When Are Adverse Outcome Pathways and Associated Assays “Fit for Purpose” for Regulatory Decision-Making and Management of Chemicals? .....	18
There are good clinical, scientific, and social reasons to strengthen links between biomedical and environmental research.....	19
A comparison of endocrine disruption potential of nonylphenol ethoxylate, vanillin ethoxylate, 4-n-nonylphenol and vanillin in vitro .....	19

## Technical

### CHEMWATCH

#### ENVIRONMENTAL RESEARCH

##### Evaluating the Effect of Honey Bee (*Apis mellifera*) Queen Reproductive State on Pheromone-Mediated Interactions with Male Drone Bees

2019-10-22

Honey bee (*Apis mellifera*) queens produce pheromones responsible for mediating both male mating behaviour and many critical facets of worker social organisation within their colony. These pheromones are dynamic multi-component blends, allowing the communication of detailed information. Indeed, variation in the queen's mating and reproductive state is associated with significant changes in her pheromone profiles, and these different pheromone profiles elicit different behavioural and physiological responses in female workers. In the present study, the authors evaluated behavioural responses of male drones to the chemical blends produced by two exocrine glands in queens, and determine if the blends and responses are altered by the queen's mating and reproductive state. The authors find that drone attraction to the chemical blends of mandibular glands produced by mated, laying queens versus virgin queens is reduced, suggesting that the queens produce a reliable signal of their mating receptivity. Interestingly, while the chemical blends of mating, laying queens and virgins queens largely overlap, mated, laying queens produce a greater number of chemicals and greater quantities of certain chemicals than virgin queens, suggesting that these chemicals may serve to inhibit behavioural responses of drones to mated, laying queens. Thus, our results highlight the importance of considering chemical cues and signals that serve to both stimulate and inhibit behavioural responses during social interactions in animals.

Authors: Villar G, Hefetz A, Grozinger CM.

Full Source: *Journal of Chemical Ecology*. 2019 Jul;45(7):588-597. doi: 10.1007/s10886-019-01086-0. Epub 2019 Jul 24.

Honey bee (*Apis mellifera*) queens produce pheromones responsible for mediating both male mating behaviour and many critical facets of worker social organisation within their colony.

##### A microarray-based comparative analysis of gene expression profiles in thyroid glands in amphibian metamorphosis: differences in effects between chemical exposure and food restriction

2019-10-22

Tadpoles during metamorphosis are sensitive to chemical exposure as shown in the amphibian metamorphosis assay, which is a method to

detect effects of chemicals on the functions of hypothalamus-pituitary-thyroid axis. The present study reports existence of different modes of action between pyriproxyfen (PYR) and 6-propyl-2-thiouracil (PTU) under different feeding conditions based on gene expression profiles (transcriptomics) in the thyroid glands of tadpoles of the African clawed frog, *Xenopus laevis*. PTU and PYR were exposed to the tadpoles during metamorphosis under normal (fed groups, both of PTU and PRY) and restricted feeding (fasted groups, PTU only) conditions; and effects were compared to control groups. Delayed development based on decreased Nieuwkoop and Faber developmental stage number without any histopathological changes was observed in the control of restricted feeding (control-fasted) group, and the PYR group with reduced food consumption. Clear developmental retardation with typical thyroid histopathological changes was observed in the PTU groups. To find clusters of all samples based on their similarity of expression patterns, hierarchical clustering analysis using selected gene probes was conducted. It revealed gene profiles from samples of the PYR group were quite similar to those of the control-fasted group, followed by the control group with normal feeding (control-fed). The results suggest that key events in the thyroid glands of tadpoles induced by PYR should be quite similar to those of control-fasted, and quite different from those of the PTU groups. Our findings demonstrated the usefulness of transcriptomics, which enabled recognition of the different modes of actions.

Authors: Ose K, Yamada F, Ohara A, Suzuki N, Fukuda T, Miyamoto M, Sumida K.

Full Source: *Journal of Applied Toxicology*. 2019 Jul;39(7):1030-1042. doi: 10.1002/jat.3791. Epub 2019 Mar 18.

This review aims to summarise the sources of Hg, its combined effects on the ecosystem, and its remediation in the environment.

### Sources, toxicity, and remediation of mercury: an essence review

2019-10-22

Mercury (Hg) is a pollutant that poses a global threat, and it was listed as one of the ten leading 'chemicals of concern' by the World Health Organization in 2017. This review aims to summarise the sources of Hg, its combined effects on the ecosystem, and its remediation in the environment. The flow of Hg from coal to fly ash (FA), soil, and plants has become a serious concern. Hg chemically binds to sulphur-containing components in coal during coal formation. Coal combustion in thermal power plants is the major anthropogenic source of Hg in the environment. Hg is taken up by plant roots from contaminated soil and transferred to the stem and aerial parts. Through bioaccumulation in the plant system,

Hg moves into the food chain, resulting in potential health and ecological risks. The world average Hg concentrations reported in coal and FA are 0.01-1 and 0.62 mg/kg, respectively. The mass of Hg accumulated globally in the soil is estimated to be 250-1000 Gg. Several techniques have been applied to remove or minimise elevated levels of Hg from FA, soil, and water (soil washing, selective catalytic reduction, wet flue gas desulphurization, stabilisation, adsorption, thermal treatment, electro-remediation, and phytoremediation). Adsorbents such as activated carbon and carbon nanotubes have been used for Hg removal. The application of phytoremediation techniques has been proven as a promising approach in the removal of Hg from contaminated soil. Plant species such as *Brassica juncea* are potential candidates for Hg removal from soil.

Authors: Raj D, Maiti SK.

Full Source: Environmental Monitoring & Assessment. 2019 Aug 15;191(9):566. doi: 10.1007/s10661-019-7743-2.

### Ferritin RNA interference inhibits the formation of iron granules in the trophocytes of worker honey bees (*Apis mellifera*)

2019-10-22

Iron granules containing superparamagnetic magnetite act as magnetoreceptor for magnetoreception in honey bees. Biomineralisation of iron granules occurs in the iron deposition vesicles of trophocytes and requires the participation of actin, myosin, ferritin2, and ATP synthase. The mechanism of magnetoreception in honey bees can be explored by suppressing the formation of iron granules. Toward this goal, the authors injected double-stranded RNA of ferritin2 and ferritin1 into newly emerged worker honey bees to knock down these genes via RNA interference. It was confirmed that mRNA and protein production of the ferritins was inhibited, leading to immature iron granules. Downregulating ferritin2 and ferritin1, moreover, leads to different deposition morphology of 7.5-nm diameter iron particles, indicating that the two genes play different roles in the formation of iron granules in worker honey bees.

Authors: Hsu CY, Lo HF, Mutti NS, Amdam GV.

Full Source: Science Reports. 2019 Aug 15;9(1):10098. doi: 10.1038/s41598-019-45107-0.

Iron granules containing superparamagnetic magnetite act as magnetoreceptor for magnetoreception in honey bees.

### Brominated flame retardants and perfluoroalkyl substances in landfill leachate from Ireland

2019-10-22

Between June and November 2017, leachate samples were collected from 40 landfills across the Republic of Ireland. Concentrations of perfluoroalkyl substances (PFASs), polybrominated diphenyl ethers (PBDEs), and hexabromocyclododecane (HBCDD) determined in these samples were within the range previously reported in other countries. Average concentrations of PFASs exceeded those of PBDEs and HBCDD; likely due to the higher water solubility of PFASs. Log-transformed concentrations of BDEs-47, 100, 153, and 183, as well as perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorobutane sulfonate (PFBS) were significantly ( $p < 0.05$ ) higher in leachate from newer, lined landfills than in samples from unlined landfills. These higher concentrations in lined landfills are likely related to the fact that lined landfills are found to retain organic matter leading to a higher organic content of leachate from such landfills. This is evidenced by the significant ( $p < 0.05$ ) correlation between log-transformed concentrations in leachate of most of the same contaminants and those of chemical oxygen demand (COD). Concentrations of the less water-soluble, higher molecular weight BDE-209 were not correlated with leachate COD, nor landfill age or the presence of a landfill liner. This suggests that the presence of BDE-209 in landfill leachate is driven more by physical abrasion of particles and fibres from waste articles, than dissolution into the aqueous phase. The higher concentrations of some PFASs and PBDEs in leachate from lined landfills present a challenge with respect to leachate disposal, when leachate is sent to wastewater treatment plants that do not necessarily have mechanisms in place to remove or destroy these chemicals prior to discharge into the environment. Moreover, the presence of these persistent organic chemicals in leachate from unlined landfills raises concerns about releases to the environment including groundwater over the lifetime of such landfills and beyond.

Authors: Harrad S, Drage DS, Sharkey M, Berresheim H.

Full Source: Science of the Total Environment. 2019 Aug 6; 695:133810. doi: 10.1016/j.scitotenv.2019.133810. [Epub ahead of print]

Between June and November 2017, leachate samples were collected from 40 landfills across the Republic of Ireland.

### MEDICAL RESEARCH

#### Metallic air pollutants and breast cancer heterogeneity

2019-10-22

Emerging evidence suggests airborne metals may be associated with breast cancer risk. However, breast cancer is heterogeneous and associations with heavy metals vary by subtype. Heavy metals possess both carcinogenic and xenoestrogenic properties which may be related to different tumour aetiologies. Therefore, in this study, the authors tested for aetiologic heterogeneity, using a case-series approach, to determine whether associations between residential airborne metal concentrations and breast cancer differed by tumour subtype. Between 2005 and 2008, the authors enrolled incident breast cancer cases into the Breast Cancer Care in Chicago study. Tumour estrogen and progesterone receptors status was determined by medical record abstraction and confirmed immunohistochemically (N = 696; 147 ER/PR-negative). The 2002 USEPA's National Air Toxics Assessment census-tract estimates of metal concentrations (antimony, arsenic, beryllium, cadmium, chromium, cobalt, lead, manganese, mercury, nickel and selenium) were matched to participants' residences of the same year. Adjusted logistic regression models were used to examine whether the airborne heavy metal associations differed by tumour ER/PR status. Principal component analysis was performed to assess associations by metal co-exposures. Comparing the highest and lowest quintiles, higher concentrations of antimony (odds ratio[OR]: 1.8, 95% confidence interval[CI]: 0.9, 3.7, P-trend: 0.05), cadmium (OR: 2.3, 95% CI: 1.2, 4.4, P-trend: 0.04) and cobalt (OR: 2.0, 95% CI: 0.9, 4.4, P-trend: 0.04) were associated with ER/PR-negative breast cancer. Mixture analysis using principal components suggested co-exposures to multiple airborne heavy metals may drive associations with tumour receptor status. Among women diagnosed with breast cancer, metallic air pollutants were associated with increased odds of developing ER/PR-negative breast cancer.

Authors: Kresovich JK, Erdal S, Chen HY, Gann PH, Argos M, Rauscher GH.  
Full Source: Environ Res. 2019 Oct; 177:108639. doi: 10.1016/j.envres.2019.108639. Epub 2019 Aug 8.

In this study, the authors performed high-throughput screening to determine the minimum inhibitory concentrations (MICs) of 217 chemicals in the wild-type MDS42 and the  $\Delta$ recA mutant strains of *Escherichia coli*.

### High-throughput identification of the sensitivities of an *Escherichia coli* $\Delta$ recA mutant strain to various chemical compounds

2019-10-22

Antibiotic resistance is considered a global threat to public health. Adaptive resistance mutations and the acquisition of resistance genes by horizontal gene transfer are known to be facilitated by the RecA-dependent SOS response during antibiotic treatment, making RecA inhibitors promising agents for the prevention of antibiotic resistance. However, the impact of RecA inactivation on antibiotic sensitivities remains unclear. Therefore, in this study, the authors performed high-throughput screening to determine the minimum inhibitory concentrations (MICs) of 217 chemicals, including both antibiotics and toxic chemicals of unknown drug action, in the wild-type MDS42 and the  $\Delta$ recA mutant strains of *Escherichia coli*. The  $\Delta$ recA mutant showed increased sensitivity to DNA-damaging agents, DNA replication inhibitors, and chromate stress, as well as to other chemicals, such as S-(2-aminoethyl)-L-cysteine, L-histidine, ruthenium red, D-penicillamine, carbonyl cyanide 3-chlorophenylhydrazone (CCCP), cerulenin, and L-cysteine. Microarray analysis showed further that the  $\Delta$ recA mutant had lower expressions of *glnK*, *nac*, and *glnLG*, which encode nitrogen assimilation regulators, as well as *amtB*, which encodes an ammonium transporter, compared with the wild type. These findings suggest that the  $\Delta$ recA mutation affects not only the SOS response but also amino acid metabolism.

Authors: Maeda T, Horinouchi T, Sakata N, Sakai A, Furusawa C.

Full Source: *Journal of Antibiotics* (Tokyo). 2019 Jul; 72(7):566-573. doi: 10.1038/s41429-019-0160-5. Epub 2019 Feb 21.

### Predictions of genotoxic potential, mode of action, molecular targets, and potency via a tiered multiflow<sup>®</sup> assay data analysis strategy

2019-10-22

The in vitro MultiFlow<sup>®</sup> DNA Damage Assay multiplexes  $\gamma$ H2AX, p53, phospho-histone H3, and polyploidization biomarkers into a single flow cytometric analysis. The current report describes a tiered sequential data analysis strategy based on data generated from exposure of human TK6 cells to a previously described 85 chemical training set and a new pharmaceutical-centric test set (n=40). In each case, exposure was continuous over a range of closely spaced concentrations, and cell aliquots

The current report describes a tiered sequential data analysis strategy based on data generated from exposure of human TK6 cells to a previously described 85 chemical training set and a new pharmaceutical-centric test set

were removed for analysis following 4 and 24 hr of treatment. The first data analysis step focused on chemicals' genotoxic potential, and for this purpose, the authors evaluated the performance of a machine learning (ML) ensemble, a rubric that considered fold increases in biomarkers against global evaluation factors (GEFs), and a hybrid strategy that considered ML and GEFs. This first tier further used ML output and/or GEFs to classify genotoxic activity as clastogenic and/or aneugenic. Test set results demonstrated the generalisability of the first tier, with particularly good performance from the ML ensemble: 35/40 (88%) concordance with a priori genotoxicity expectations and 21/24 (88%) agreement with expected mode of action (MoA). A second tier applied unsupervised hierarchical clustering to the biomarker response data, and these analyses were found to group certain chemicals, especially aneugens, according to their molecular targets. Finally, a third-tier utilised benchmark dose analyses and MultiFlow biomarker responses to rank genotoxic potency. The relevance of these rankings is supported by the strong agreement found between benchmark dose values derived from MultiFlow biomarkers compared to those generated from parallel in vitro micronucleus analyses. Collectively, the results suggest that a tiered MultiFlow data analysis pipeline is capable of rapidly and effectively identifying genotoxic hazards while providing additional information that is useful for modern risk assessments-MoA, molecular targets, and potency.

Authors: Dertinger SD, Kraynak AR, Wheeldon RP, Bernacki DT, Bryce SM, Hall N, Bemis JC, Galloway SM, Escobar PA, Johnson GE.

Full Source: Environmental Molecular Mutagenesis. 2019 Jul;60(6):513-533. doi: 10.1002/em.22274. Epub 2019 Feb 27.

In the present study, the authors aim to address the cardiovascular effects of noise, food pollutants, radiation, and some other emerging environmental factors.

### Ecology of the cardiovascular system: Part II - A focus on non-air related pollutants

2019-10-22

An integrated exposomic view of the relation between environment and cardiovascular health should consider the effects of both air and non-air related environmental stressors. Cardiovascular impacts of ambient air temperature, indoor and outdoor air pollution were recently reviewed. In the present study, the authors aim to address the cardiovascular effects of noise, food pollutants, radiation, and some other emerging environmental factors. Road traffic noise exposure is associated with increased risk of premature arteriosclerosis, coronary artery disease, and stroke. Numerous studies report an increased prevalence of hypertension in people exposed to noise, especially while sleeping. Sleep disturbances generated by

nocturnal noise are followed by a neuroendocrine stress response. Some oxidative and inflammatory endothelial reactions are observed during experimental session of noise exposure. Moreover, throughout the alimentation, the cardiovascular system is exposed to persistent organic pollutants (POPs) as dioxins or pesticides, and plastic associated chemicals (PACs), such as bisphenol A. Epidemiological studies show positive associations of exposures to POPs and PACs with diabetes, arteriosclerosis and cardiovascular disease incidence. POPs and PACs share some abilities to interact with nuclear receptors activating different pathways leading to oxidative stress, insulin resistance and angiotensin potentiation. Regarding radiation, survivors of nuclear explosion have an excess risk of cardiovascular disease. Dose-effect relationships remain debated, but an increased cardiovascular risk at low dose of radiation exposure may be of concern. Some emerging environmental factors like electromagnetic fields, greenspace and light exposure may also require further attention. Non-air related environmental stressors also play an important role in the burden of cardiovascular disease. Specific methodologies should be developed to assess the interactions between air and non-air related pollutants.

Argacha JF, Mizukami T, Bourdrel T, Bind MA.

Full Source: Trends in Cardiovascular Medicine. 2019 Jul;29(5):274-282. doi: 10.1016/j.tcm.2018.09.003. Epub 2018 Sep 8.

### Taurine protects against myelin damage of sciatic nerve in diabetic peripheral neuropathy rats by controlling apoptosis of schwann cells via NGF/Akt/GSK3 $\beta$ pathway

2019-10-22

Diabetic peripheral neuropathy is a common complication of Type 2 Diabetes and its main pathological feature is myelin sheath damage of peripheral nerve that was induced by Schwann cells (SCs) apoptosis. Increasing evidence suggested that taurine might play a role in improving DPN because of its ability to prevent SCs apoptosis. In this study, the authors explored the effect of taurine on preventing SCs apoptosis and its underlying mechanism. Sprague Dawley rats were treated with streptozotocin to establish the diabetes model. Rats were randomly divided into control, diabetes, taurine treatment (as giving 0.5%, 1% and 2% taurine in drinking water) groups. RSC96 cell (a rat SCs line) was used for intervention experiments in vitro. Results showed that taurine significantly corrected morphology of damaged myelin sheath and inhibited SCs apoptosis in sciatic nerve of diabetic rats. Moreover, taurine prevented apoptosis of RSC96 cells exposed to high

In this study, the authors explored the effect of taurine on preventing Schwann cells apoptosis and its underlying mechanism.

glucose. Mechanistically, taurine up-regulated NGF expression and phosphorylation levels of Akt and GSK3 $\beta$ , while, blocking activation of NGF and phosphorylation of Akt and GSK3 $\beta$  increased apoptosis of high glucose-exposed RSC96 cells with taurine supplement. These results revealed taurine improved the myelin sheath damage of sciatic nerve in diabetic rats by controlling SCs apoptosis via NGF/Akt/GSK3 $\beta$  signalling pathways, which provides some clues that taurine might be effective and feasible candidate for the treatment of DPN.

Authors: Li K, Shi X, Luo M, Inam-U-Llah, Wu P, Zhang M, Zhang C, Li Q, Wang Y, Piao F.

Full Source: Experimental Cell Research. 2019 Aug 12:111557. doi: 10.1016/j.yexcr.2019.111557. [Epub ahead of print]

## OCCUPATIONAL RESEARCH

### Occupational exposure to formaldehyde and early biomarkers of cancer risk, immunotoxicity and susceptibility

2019-10-22

Formaldehyde (FA) is a high-volume production chemical manufactured worldwide to which many people are exposed to both environmentally and occupationally. FA was recently reclassified as a human carcinogen. Several epidemiological studies have revealed an increased risk of cancer development among workers exposed to FA. Although FA genotoxicity was confirmed in a variety of experimental systems, data from human studies are conflicting. The aim of the present study was to evaluate the occupational exposure to FA in a multistage approach relating the exposure with different biomarkers (dose and effect) and individual susceptibility. Air monitoring was performed to estimate the level of exposure to FA during shift work. Eighty-five workers from hospital anatomy-pathology laboratories exposed to FA and 87 controls were tested for cytogenetic alterations in lymphocytes (micronucleus, MN; sister-chromatid exchange, SCE) and T-cell receptor (TCR) mutation assay. The frequency of MN in exfoliated buccal cells, a first contact tissue was also assessed. Percentages of different lymphocyte subpopulations were selected as immunotoxicity biomarkers. The level of formic acid in urine was investigated as a potential biomarker of internal dose. The effects of polymorphic genes of xenobiotic metabolising enzymes and DNA repair enzymes on the endpoints studied were determined. The mean level of FA exposure was  $0.38 \pm 0.03$  ppm. MN (in lymphocytes and buccal cells)

The aim of the present study was to evaluate the occupational exposure to FA in a multistage approach relating the exposure with different biomarkers (dose and effect) and individual susceptibility.

and SCE were significantly increased in FA-exposed workers compared to controls. MN frequency positively correlated with FA levels of exposure and duration. Significant alterations in the percentage of T cytotoxic lymphocytes, NK cells and B lymphocytes were found between groups. Polymorphisms in CYP2E1, GSTP1 and FANCA genes were associated with increased genetic damage in FA-exposed subjects. The obtained information may provide new important data to be used by health and safety care programs and by governmental agencies responsible for setting the acceptable levels for occupational exposure to FA.

Authors: Costa S, Costa C, Madureira J, Valdiglesias V, Teixeira-Gomes A, Guedes de Pinho P, Laffon B, Teixeira JP.

Full Source: Environmental Research. 2019 Sep 14;179(Pt A):108740. doi: 10.1016/j.envres.2019.108740. [Epub ahead of print]

### Functional, inflammatory and interstitial impairment due to artificial stone dust ultrafine particles exposure

2019-10-22

Artificial stone dust (ASD) contains high levels of ultrafine particles (UFP <1 µm) which penetrate deeply into the lungs. This study aimed to demonstrate the direct effect of UFP in the lungs of ASD-exposed workers on functional inflammatory and imaging parameters.

**METHODS:** 68 workers with up to 20 years of ASD exposure at the workplace were recruited from small enterprises throughout the country and compared with 48 non-exposed individuals. Pulmonary function test (PFT), CT, induced sputum (IS) and cytokine analyses were performed by conventional methods. The CT scans were evaluated for features indicative of silicosis in three zones of each lung. UFP were quantitated by the NanoSight LM20 system (NanoSight, Salisbury) using the Nanoparticle Tracking Analysis. Interleukin (IL)-6, IL-8 and tumour necrosis factor alpha (TNF-α) levels were measured by Luminex (R&D Systems). Thirty-four patients had CT scores between 0 and 42, and 29 of them were diagnosed with silicosis. Content of the UFP retrieved from IS supernatants correlated negatively with the PFT results (total lung capacity  $r=-0.347$ ,  $p=0.011$ ; forced expiratory volume in 1 s  $r=-0.299$ ,  $p=0.046$ ; diffusion lung carbon monoxide in a single breath  $r=-0.425$ ,  $p=0.004$ ) and with the CT score ( $r=0.378$ ,  $p=0.023$ ), and with the inflammatory cytokines IL-8 ( $r=0.336$ ,  $p=0.024$ ), IL-6 ( $r=0.294$ ,  $p=0.065$ ) and TNF-α ( $r=0.409$ ,  $p=0.007$ ). Raw material of ASD was left to sedimentate in water for <15 min, and 50% of the floating particles were UFP. A cut-off of  $8 \times 10^6$  UFP/mL in IS samples had a sensitivity of 77% to predict pulmonary disease. This is the first demonstration of an association between UFP-related decreased PFT

This study aimed to demonstrate the direct effect of ultra-fine particles in the lungs of ASD-exposed workers on functional inflammatory and imaging parameters.

results, worsening of CT findings and elevation of inflammatory cytokines, which may be attributed to high-dose inhalation of UFP of ASD at the workplace.

Authors: Ophir N, Bar Shai A, Korenstein R, Kramer MR, Fireman E.

Full Source: Occupational & Environmental Medicine. 2019 Sep 27. pii: oemed-2019-105711. doi: 10.1136/oemed-2019-105711. [Epub ahead of print]

### Severe Silicosis in Engineered Stone Fabrication Workers - California, Colorado, Texas, and Washington, 2017-2019

2019-10-22

Silicosis is an incurable occupational lung disease caused by inhaling particles of respirable crystalline silica. These particles trigger inflammation and fibrosis in the lungs, leading to progressive, irreversible, and potentially disabling disease. Silica exposure is also associated with increased risk for lung infection (notably, tuberculosis), lung cancer, emphysema, autoimmune diseases, and kidney disease (1). Because quartz, a type of crystalline silica, is commonly found in stone, workers who cut, polish, or grind stone materials can be exposed to silica dust. Recently, silicosis outbreaks have been reported in several countries among workers who cut and finish stone slabs for countertops, a process known as stone fabrication (2-5). Most worked with engineered stone, a manufactured, quartz-based composite material that can contain >90% crystalline silica (6). This study describes 18 cases of silicosis, including the first two fatalities reported in the United States, among workers in the stone fabrication industry in California, Colorado, Texas, and Washington. Several patients had severe progressive disease, and some had associated autoimmune diseases and latent tuberculosis infection. Cases were identified through independent investigations in each state and confirmed based on computed tomography (CT) scan of the chest or lung biopsy findings. Silica dust exposure reduction and effective regulatory enforcement, along with enhanced workplace medical and public health surveillance, are urgently needed to address the emerging public health threat of silicosis in the stone fabrication industry.

Authors: Rose C, Heinzerling A, Patel K, Sack C, Wolff J, Zell-Baran L, Weissman D, Hall E, Sooriash R, McCarthy RB, Bojes H, Korotzer B, Flattery J, Weinberg JL, Potocko J, Jones KD, Reeb-Whitaker CK, Reul NK, LaSee CR, Materna BL, Raghu G, Harrison R.

Full Source: MMWR Morbidity and Mortality Weekly Report. 2019 Sep 27;68(38):813-818. doi: 10.15585/mmwr.mm6838a1.

This study describes 18 cases of silicosis, including the first two fatalities reported in the United States, among workers in the stone fabrication industry in California, Colorado, Texas, and Washington.

### Role of asbestos clearance in explaining long-term risk of pleural and peritoneal cancer: a pooled analysis of cohort studies

2019-10-22

Models based on the multistage theory of cancer predict that rates of malignant mesothelioma continuously increase with time since first exposure (TSFE) to asbestos, even after the end of external exposure. However, recent epidemiological studies suggest that mesothelioma rates level off many years after first exposure to asbestos. A gradual clearance of asbestos from the lungs has been suggested as a possible explanation for this phenomenon. The authors analysed long-term trends of pleural and peritoneal cancer mortality in subjects exposed to asbestos to evaluate whether such trends were consistent with the clearance hypothesis. Data from a pool of 43 Italian asbestos cohorts (51 801 subjects) was used. The role of asbestos clearance was explored using the traditional mesothelioma multistage model, generalised to include a term representing elimination of fibres over time. Rates of pleural cancer increased until 40 years of TSFE, but remained stable thereafter. On the other hand, we observed a monotonic increase of peritoneal cancer with TSFE. The model taking into account asbestos clearance fitted the data better than the traditional one for pleural ( $p=0.004$ ) but not for peritoneal ( $p=0.09$ ) cancer. Rates of pleural cancer do not increase indefinitely after the exposure to asbestos, but eventually reach a plateau. This trend is well described by a model accounting for a gradual elimination of the asbestos fibres. These results are relevant for the prediction of future rates of mesothelioma and in asbestos litigations.

Authors: Barone-Adesi F, Ferrante D, Chellini E, Merler E, Pavone V, Silvestri S, Miligi L, Gorini G, Bressan V, Girardi P, Ancona L, Romeo E, Luberto F, Sala O, Scarnato C, Menegozzo S, Oddone E, Tunesi S, Perticaroli P, Pettinari A, Cuccaro F, Curti S, Baldassarre A, Cena T, Angelini A, Marinaccio A, Mirabelli D, Musti M, Pirastu R, Ranucci A, Magnani C; Working Group.

Collaborators: Ballarin MN, Bisceglia L, Brentisci C, Cortini B, Mattioli S, Gangemi M, Giofrè F, Legittimo P, Mangone L, Marinelli F, Marinilli P, Nannavecchia AM, Panato C, Roncaglia F, Storchi C, Stura A, Vicentini M, Verdi S.

Full Source: Occupational & Environmental Medicine. 2019 Sep;76(9):611-616. doi: 10.1136/oemed-2019-105779.

The authors analysed long-term trends of pleural and peritoneal cancer mortality in subjects exposed to asbestos to evaluate whether such trends were consistent with the clearance hypothesis.

### Heme oxygenase 1 polymorphism, occupational vapor, gas, dust, and fume exposure and chronic obstructive pulmonary disease in a Danish population-based study

2019-10-22

The number of dinucleotide repeats (GT) modulate expression of heme oxygenase 1 (HMOX1), a stress response gene. Multiple repeats might affect chronic obstructive pulmonary disease (COPD) susceptibility. This study aimed to investigate the association of this polymorphism with COPD and its interaction with occupational exposures (vapor, gas, dust, or fumes). This population-based cross-sectional study included 4703 Danes, aged 45-84 years. HMOX1 (GT) was genotyped and grouped as short:  $\leq 26$ , medium: 27-32 and long:  $\geq 33$  alleles. COPD was defined by the lower limit of normal (2.5<sup>th</sup> FEV 1/FVC and FEV 1 centiles). Occupational exposure was defined as ever exposed to vapor, gas, dust, or fume in expert-selected jobs. Associations were analysed by adjusted mixed logistic regression. The population included 6% with COPD, 48% who had smoked  $\geq 10$  pack-years, and 46% with occupational exposure. HMOX1 was genotyped in 4423 participants. The adjusted odds ratio (OR) for the association between HMOX1 long allele and COPD was 1.75 [95% confidence interval (CI) 1.18-2.60]. An interaction was evident between HMOX1 long allele and occupational exposure, OR 2.38 (95% CI 1.04-5.46), versus HMOX1 short/medium without exposure. Analyses were replicated in another cohort, aged 20-44 years, N=1168, including 3% with COPD, 25% who had smoked  $\geq 10$  pack-years and 20% with occupational exposure. No associations were seen between COPD and HMOX1 long allele here. Conclusions Long alleles in HMOX1 alone and in interaction with occupational exposure seem to be associated with COPD. Failure to replicate data may be due to premature age for COPD development and low occupational exposure prevalence. We propose this long allele may be a genetic contributor to the COPD pathogenesis.

Authors: Würtz ET, Brasch-Andersen C, Steffensen R, Hansen JG, Malling TH, Schlünssen V, Omland Ø.

Authors: Scandinavian Journal of Work, Environment & Health. 2019 Aug 11. pii: 3846. doi: 10.5271/sjweh.3846. [Epub ahead of print]

This study aimed to investigate the association of this polymorphism with COPD and its interaction with occupational exposures

### PUBLIC HEALTH RESEARCH

#### Urinary levels of phthalate metabolites and their association with lifestyle behaviours in Chinese adolescents and young adults

2019-10-22

Adolescence and young adulthood are critical periods of human growth and development. Phthalates are environmental endocrine disruptors, and their health hazards in adolescents and young adults cannot be ignored. This study was undertaken to assess phthalate exposure and determine the associations between lifestyle behaviours and phthalate metabolite levels in Chinese adolescents and young adults. Four hundred and seventy-eight adolescents and young adults aged 16-20 years were included in this study. The levels of mono-ethyl phthalate (MEP), mono-butyl phthalate (MBP), mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) and mono-(2-carboxymethyl)-hexyl phthalate (MCMHP) in the subjects' urine were measured by high-performance liquid chromatography-tandem mass spectrometry. The estimated daily intake (EDI) and hazard index (HI) of phthalates were calculated based on urinary metabolite levels. Relevant information on the subjects was collected via questionnaires. The associations between phthalate metabolite levels and lifestyle behaviours were examined using the independent-sample t-test, Mann-Whitney test and multiple linear regression. In this study, the detection rates of all seven metabolites were >98%. The highest median metabolite concentration was MBP, which was 43.00 µg/L (33.11 µg/g creatinine). The highest median EDI was for di-(2-ethylhexyl) phthalate (DEHP), which was 2.40 µg/kg-bw/day (volume-based) and 1.51 µg/kg-bw/day (creatinine-based). 2.7% (volume-based) and 1.0% (creatinine-based) of the subjects showed excessive HITDI (HI of the tolerable daily intake) values, which indicated the cumulative risk of anti-androgenic effects. Furthermore, factors significantly associated with phthalate metabolite levels included the use of plastic food packages (DEHP metabolites), physical exercise (MEOHP), the frequency of fast food consumption (MBP), and the frequency of skin care cosmetics and colour cosmetics use (MEP). The results suggest that Chinese adolescents and young adults are widely

This study was undertaken to assess phthalate exposure and determine the associations between lifestyle behaviours and phthalate metabolite levels in Chinese adolescents and young adults.

exposed to phthalates and their metabolite levels are influenced by lifestyle behaviours.

Authors: Ding S, Zhang Z, Chen Y, Qi W, Zhang Y, Xu Q, Liu H, Zhang T, Zhao Y, Han X, Song X, Zhao T, Ye L.

Full Source: Ecotoxicology & Environmental Safety. 2019 Nov 15; 183:109541. doi: 10.1016/j.ecoenv.2019.109541. Epub 2019 Aug 13.

### Prenatal and early postnatal phthalate exposure and child neurodevelopment at age of 7 years - Polish Mother and Child Cohort

2019-10-22

Phthalates are among the most frequently investigated environmental chemicals influencing children's health and particularly their neuropsychological development. However, the reported effects of these compounds on child behaviour, cognitive and psychomotor outcomes are not fully consistent. The aim of this study is to evaluate the associations between prenatal and early postnatal phthalate exposures and child neurodevelopment at age of 7 years. A total of 134 mother-child pairs from Polish Mother and Child Cohort (REPRO\_PL) constitute the basis for current analysis. Eleven phthalate metabolites were measured in urine samples collected from mothers in the 3rd trimester of pregnancy and from children at the age of 2 years. Child neuropsychological development at early school age (7 years) was assessed by both the Strengths and Difficulties Questionnaire (SDQ) filled by mothers and the Polish adaptation of the Intelligence and Development Scales (IDS) performed by psychologists. Mono-ethyl phthalate (MEP) concentration during pregnancy was significantly associated with increased risk of peer relationship problems in SDQ (OR = 2.7,  $p = 0.03$ ). The results of the IDS analyses focused on child's cognitive and psychomotor development are not fully conclusive. Negative associations were evident between some phthalates in early childhood period and fluid intelligence and cognition (MEP:  $\beta = -5.2$ ;  $p = 0.006$ ;  $\beta = -4.2$ ;  $p = 0.006$ ; mono-n-butyl phthalate (MnBP):  $\beta = -4.9$ ;  $p = 0.03$ ;  $\beta = -4.0$ ;  $p = 0.03$ ; respectively), while positive associations have been found in the prenatal period (mono-2-ethyl-5-oxo-hexyl phthalate (oxo-MEHP):  $\beta = 3.6$ ;  $p = 0.03$  for fluid intelligence;  $\beta = 2.9$ ;  $p = 0.03$  for cognition). Further studies are required in order to elucidate

The aim of this study is to evaluate the associations between prenatal and early postnatal phthalate exposures and child neurodevelopment at age of 7 years.

which are the most critical periods of phthalate exposure on children's neurodevelopmental outcomes.

Authors: Jankowska A, Polańska K, Hanke W, Wesołowska E, Ligocka D, Waszkowska M, Stańczak A, Tartaglione AM, Mirabella F, Chiarotti F, Garí M, Calamandrei G.

Full Source: Environmental Research. 2019 Oct; 177:108626. doi: 10.1016/j.envres.2019.108626. Epub 2019 Aug 5.

### When Are Adverse Outcome Pathways and Associated Assays "Fit for Purpose" for Regulatory Decision-Making and Management of Chemicals?

2019-10-22

There have been increasing demands for chemical hazard and risk assessments in recent years. Chemical companies have expanded internal product stewardship initiatives, and jurisdictions have increased the regulatory requirements for the manufacture and sale of chemicals. There has also been a shift in chemical toxicity evaluations within the same time frame, with new methodologies being developed to improve chemical safety assessments for both human health and the environment. With increased needs for chemical assessments coupled with more diverse data streams from new technologies, regulators and others tasked with chemical management activities are faced with increasing workloads and more diverse types of data to consider. The Adverse Outcome Pathway (AOP) framework can be applied in different scenarios to integrate data and guide chemical assessment and management activities. In this study, scenarios of how AOPs can be used to guide chemical management decisions during research and development, chemical registration, and subsequent regulatory activities such as prioritisation and risk assessment are considered. Furthermore, specific criteria (e.g., the type and level of AOP complexity, confidence in the AOP, as well as external review and assay validation) are proposed to examine whether AOPs and associated tools are fit for purpose when applied in different contexts. Certain toxicity pathways are recommended as priority areas for AOP research and development, and the continued use of AOPs and defined approaches in regulatory activities are recommended. Furthermore, a call for increased outreach, education, and enhanced use of AOP databases is proposed to increase their utility in chemicals management.

Authors: Coady K, Browne P, Embry M, Hill T, Leinala E, Steeger T, Maślankiewicz L, Hutchinson T.

Full Source: Integrated Environmental Assessment & Management. 2019 Jul;15(4):633-647. doi: 10.1002/ieam.4153. Epub 2019 Jul 17.

The Adverse Outcome Pathway (AOP) framework can be applied in different scenarios to integrate data and guide chemical assessment and management activities.

### There are good clinical, scientific, and social reasons to strengthen links between biomedical and environmental research

2019-10-22

Clinical epidemiology rarely addresses biological, clinical, epidemiological, environmental, economic, and other social and scientific issues posed by environmental chemical contaminants such as endocrine-disrupting chemicals. There is a considerable gap between research and practice in clinical medicine and in environmental health. Organisations often fail to appreciate the human and economic costs of the diseases that environmental chemical contaminants contribute to cause. Also, the relative lack of attention to environmental causes of disease by researchers in medicine and clinical epidemiology cannot be explained just on scientific grounds. Many scientists have shown the virtues of integrative research. Knowledge on the causes of disease is often secondary in clinical practice, but in other instances, to help patients, clinicians tackle causes of diseases. We can better address how environmental contaminants influence negatively not just the occurrence of disease but its course. To do so, we can generate better evidence and strengthen the social conversation on environmental influences on all dimensions of health and disease.

Authors: Porta M, Vandenberg LN.

Full Source: Journal of Clinical Epidemiology. 2019 Jul; 111:124-126. doi: 10.1016/j.jclinepi.2019.03.009. Epub 2019 Mar 21.

### A comparison of endocrine disruption potential of nonylphenol ethoxylate, vanillin ethoxylate, 4-n-nonylphenol and vanillin in vitro

2019-10-22

The widely used surfactant nonylphenol ethoxylate (NPEO) and its raw material 4-n-nonylphenol (4-n-NP), as well as its degradation products, are recognised as endocrine disrupting chemicals. The USA Environmental Protection Agency (EPA) released an assessment that looked for safe alternatives to NPEO. Vanillin ethoxylate (VAEO) is a novel substitute for NPEO and is quite similar to NPEO in structure; there is a risk that it has similar endocrine disrupting effects to NPEO. However, their effects on various nuclear hormone receptors have not been thoroughly examined. In this study, the effects of NPEO, VAEO, 4-n-NP and Vanillin on the oestrogen receptor  $\alpha$  (ER $\alpha$ ), androgen receptor (AR), thyroid hormone receptor (TR), retinoic X receptor  $\beta$  (RXR $\beta$ ) and oestrogen-related receptor

Clinical epidemiology rarely addresses biological, clinical, epidemiological, environmental, economic, and other social and scientific issues posed by environmental chemical contaminants such as endocrine-disrupting chemicals.

## Technical

### CHEMWATCH

$\gamma$  (ERR $\gamma$ ) were determined and compared using a battery of recombined yeast strains expressing  $\beta$ -galactosidase. The results showed that NPEO and 4-n-NP acted as significant antagonists of ER, AR, TR and ERR $\gamma$ . In addition, 4-n-NP also had antagonistic activity toward RXR $\beta$ . Moreover, VAEO was shown to be a very weak antagonist of TR and ERR $\gamma$ , and Vanillin had no interaction with any nuclear receptors. For the first time, it was found that NPEO had AR, TR and ERR $\gamma$  antagonistic effects and that 4-n-NP was an antagonist of RXR $\beta$ . The in vitro data indicated that NPEO, 4-n-NP and VAEO have the potential to act as endocrine disruptors involving more than one nuclear hormone receptor, but VAEO has much lower endocrine disrupting potential than NPEO. Thus, it is critical to find safe substitutes for NPEO and a substitute of NPEO with structural analogues should be carried out with caution. Furthermore, to look for preferable alternatives for NPEO, more in vivo and in vitro studies of the alternatives concerning endocrine disruption are needed, especially in vitro studies need to involve various target points, not only focus on their effects on ER but also take other nuclear hormone receptor pathways into consideration.

Authors: Ji X, Li N, Yuan S, Zhou X, Ding F, Rao K, Ma M, Wang Z.

Full Source: Ecotoxicology & Environmental Safety. 2019 Jul 15; 175:208-214. doi: 10.1016/j.ecoenv.2019.03.060. Epub 2019 Mar 19.