

Bulletin Board

Contents

DEC. 16, 2022

(click on page numbers for links)

CHEMICAL EFFECTS

Toxicity Assessment of [177Lu]Lu-iFAP/iPSMA Nanoparticles Prepared under GMP-Compliant Radiopharmaceutical Processes.....	3
Health Risk Assessment Based on Exposure to Chemicals in Air.....	4

ENVIRONMENTAL RESEARCH

Geochemical Contamination, Speciation, and Bioaccessibility of Trace Metals in Road Dust of a Megacity (Guangzhou) in Southern China: Implications for Human Health.....	5
Uptake, Translocation, and Fate of Carcinogenic Aristolochic Acid in Typical Vegetables in Soil-Plant Systems.....	6

PHARMACEUTICAL/TOXICOLOGY

Mercury Contamination in Fish and Its Effects on the Health of Pregnant Women and Their Fetuses, and Guidance for Fish Consumption-A Narrative Review.....	6
Exposure to Bisphenol A Substitutes, Bisphenol S and Bisphenol F, and Its Association with Developing Obesity and Diabetes Mellitus: A Narrative Review.....	7

OCCUPATIONAL

Top-Down Preparation of Nanoquartz for Toxicological Investigations.....	8
Exposure to chemical agents in the Spanish construction sector: A risk assumed and accepted by workers.....	9
Low-level Occupational Exposure to BTEX and Dyschromatopsia: A Systematic Review and Meta-analysis.....	10
Asbestos Exposure and Severity of COVID-19.....	10

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Bulletin Board

Technical

DEC. 16, 2022

CHEMICAL EFFECTS

Toxicity Assessment of [177Lu]Lu-iFAP/iPSMA Nanoparticles Prepared under GMP-Compliant Radiopharmaceutical Processes

2022-11-25

The fibroblast activation protein (FAP) is heavily expressed in fibroblasts associated with the tumor microenvironment, while the prostate-specific membrane antigen (PSMA) is expressed in the neovasculature of malignant angiogenic processes. Previously, we reported that [177Lu]lutetium sesquioxide-iFAP/iPSMA nanoparticles ([177Lu]Lu-iFAP/iPSMA) inhibit HCT116 tumor progression in mice. Understanding the toxicity of [177Lu]Lu-iFAP/iPSMA in healthy tissues, as well as at the tissue and cellular level in pathological settings, is essential to demonstrate the nanosystem safety for treating patients. It is equally important to demonstrate that [177Lu]Lu-iFAP/iPSMA can be prepared under good manufacturing practices (GMP) with reproducible pharmaceutical-grade quality characteristics. This research aimed to prepare [177Lu]Lu-iFAP/iPSMA under GMP-compliant radiopharmaceutical processes and evaluate its toxicity in cell cultures and murine biological systems under pathological environments. [177Lu]Lu₂O₃ nanoparticles were formulated as radiocolloidal solutions with FAP and PSMA inhibitor ligands (iFAP and iPSMA), sodium citrate, and gelatin, followed by heating at 121 °C (103-kPa pressure) for 15 min. Three consecutive batches were manufactured. The final product was analyzed according to conventional pharmacopeial methods. The Lu content in the formulations was determined by X-ray fluorescence. [177Lu]Lu-iFAP/iPSMA performance in cancer cells was evaluated in vitro by immunofluorescence. Histopathological toxicity in healthy and tumor tissues was assessed in HCT116 tumor-bearing mice. Immunohistochemical assays were performed to corroborate FAP and PSMA tumor expression. Acute genotoxicity was evaluated using the micronuclei assay. The results showed that the batches manufactured under GMP conditions were reproducible. Radiocolloidal solutions were sterile and free of bacterial endotoxins, with radionuclidic and radiochemical purity greater than 99%. The lutetium content was 0.10 ± 0.02 mg/mL (0.9 GBq/mg). Significant inhibition of cell proliferation in vitro and in tumors was observed due to the accumulation of nanoparticles in the fibroblasts (FAP+) and neovasculature (PSMA+) of the tumor microenvironment. No histopathological damage was detected in healthy tissues. The data obtained in this research provide new evidence on the

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Bulletin Board

Technical

DEC. 16, 2022

selective toxicity to malignant tumors and the absence of histological changes in healthy tissues after intravenous injection of [177Lu]Lu-iFAP/iPSMA in mammalian hosts. The easy preparation under GMP conditions and the toxicity features provide the added value needed for [177Lu]Lu-iFAP/iPSMA clinical translation.

Authors: Tania Hernández-Jiménez, Pedro Cruz-Nova, Alejandra Ancira-Cortez, Brenda Gibbens-Bandala, Nancy Lara-Almazán, Blanca Ocampo-García, Clara Santos-Cuevas, Enrique Morales-Avila, Guillermina Ferro-Flores

Full Source: *Nanomaterials* (Basel, Switzerland) 2022 Nov 25;12(23):4181. doi: 10.3390/nano12234181.

Health Risk Assessment Based on Exposure to Chemicals in Air

2022-11-28

Few studies have investigated personal exposure concentrations of not only some volatile organic compounds but also more types of chemicals including acidic gases and acrolein. We measured the personal exposure concentrations of 35 chemicals including these chemicals in indoor and outdoor air in Chiba-shi, Japan, for 7 days in summer and winter to assess the associated health risks in 22 people. The personal exposure concentrations of nitrogen dioxide were higher in winter than in summer, and those of formaldehyde, p-dichlorobenzene, and tetradecane were higher in summer than in winter. The personal exposure concentrations were mostly equal to or lower than the concentrations in indoor air, contrary to the results of a lot of previous studies. The high-risk chemicals based on personal exposure concentrations were identified as acrolein (max. 0.43 µg/m³), benzene (max. 3.1 µg/m³), and hexane (max. 220 µg/m³) in summer, and acrolein (max. 0.31 µg/m³), nitrogen dioxide (max. 320 µg/m³), benzene (max. 5.2 µg/m³), formic acid (max. 70 µg/m³), and hexane (max. 290 µg/m³) in winter. In addition, we estimated personal exposure concentrations according to the time spent at home and the chemical concentrations in indoor and outdoor air. We found that the estimated concentrations of some participants largely differed from the measured ones indicating that it is difficult to estimate personal exposure concentrations based on only these data.

Authors: Hironari Sakamoto, Shigehisa Uchiyama, Ayana Sato, Tomohiko Isobe, Naoki Kunugita, Hironao Ogura, Shoji F Nakayama

Full Source: *International journal of environmental research and public health* 2022 Nov 28;19(23):15813. doi: 10.3390/ijerph192315813.

Few studies have investigated personal exposure concentrations of not only some volatile organic compounds but also more types of chemicals including acidic gases and acrolein.

ENVIRONMENTAL RESEARCH

Geochemical Contamination, Speciation, and Bioaccessibility of Trace Metals in Road Dust of a Megacity (Guangzhou) in Southern China: Implications for Human Health

2022-11-29

Road dust has been severely contaminated by trace metals and has become a major health risk to urban residents. However, there is a lack of information on bioaccessible trace metals in road dust, which is necessary for an accurate health risk assessment. In this study, we collected road dust samples from industrial areas, traffic intersections, and agricultural fields from a megacity (Guangzhou), China, and conducted a geochemical enrichment, speciation, and bioaccessibility-based health risk assessment of trace metals. In comparison with local soil background values, the results revealed a significant accumulation of trace metals, including Zn, Cd, Cu, and Pb in the road dust, which is considered moderate to heavy pollution. Sequential extraction indicated that most trace metals in the road dust were primarily composed of a Fe/Mn oxide-bound fraction, carbonate-bound fraction, and residual fraction, while the dominant fraction was the organic matter-bound fraction of Cu, and the residual fractions of As, Cr, and Ni. The in vitro gastrointestinal (IVG) method revealed that high percentages of Zn, Cd, Cu, and As were bioaccessible, suggesting the possible dissolution of trace metals from adsorbed and carbonate-associated fractions in road dust exposed to the biological fluid matrix. The IVG bioaccessibility-based concentration largely decreased the noncarcinogenic health risk to a negligible level. Nevertheless, the entire population is still exposed to the cumulative probability of a carcinogenic risk, which is primarily contributed to by As, Cd, Cr, and Pb. Future identification of the exact sources of these toxic metals would be helpful for the appropriate management of urban road dust contamination.

Authors: Fei Tang, Zhi Li, Yanping Zhao, Jia Sun, Jianteng Sun, Zhenghui Liu, Tangfu Xiao, Jinli Cui

Full Source: International journal of environmental research and public health 2022 Nov 29;19(23):15942. doi: 10.3390/ijerph192315942.

Road dust has been severely contaminated by trace metals and has become a major health risk to urban residents.

Uptake, Translocation, and Fate of Carcinogenic Aristolochic Acid in Typical Vegetables in Soil-Plant Systems

2022-11-27

When Aristolochia plants wilt and decay, aristolochic acids (AAs) are released into the soil, causing soil contamination. It has been demonstrated that aristolochic acid can be accumulated and enriched in crops through plant uptake. However, there is a lack of systematic studies on the migration and accumulation of AAs in a realistic simulated soil environment. In this study, Aristolochia herbal extracts were mixed with soil for growing three typical vegetables: lettuce, celery, and tomato. The contents of AAs in the above-mentioned plants were determined by an established highly sensitive LC-MS/MS method to study the migration and accumulation of AAs. We found that AAs in the soil can be transferred and accumulated in plants. AAs first entered the roots, which were more likely to accumulate AAs, and partially entered the above-ground parts. This further confirms that AAs can enter the food chain through plants and can have serious effects on human health. It was also shown that plants with vigorous growth and a large size absorbed AAs from the soil at a faster rate. The more AAs present in the soil, the more they accumulated in the plant.

Authors: Jinghe Zhang, Yinan Wang, Changhong Wang, Kan Li, Weifang Tang, Jing Sun, Xikui Wang

Full Source: Molecules (Basel, Switzerland) 2022 Nov 27;27(23):8271. doi: 10.3390/molecules27238271.

When Aristolochia plants wilt and decay, aristolochic acids (AAs) are released into the soil, causing soil contamination.

PHARMACEUTICAL/TOXICOLOGY

Mercury Contamination in Fish and Its Effects on the Health of Pregnant Women and Their Fetuses, and Guidance for Fish Consumption-A Narrative Review

2022-11-29

As a principal source of long-chain omega-3 fatty acids (3FAs), which provide vital health benefits, fish consumption also comes with the additional benefit of being rich in diverse nutrients (e.g., vitamins and selenium, high in proteins and low in saturated fats, etc.). The consumption of fish and other seafood products has been significantly promoted universally, given that fish is an important part of a healthy diet. However, many documents indicate that fish may also be a potential source of exposure to chemical pollutants, especially mercury (Hg) (one of the top ten chemicals or groups of chemicals of concern worldwide),

Bulletin Board

Technical

DEC. 16, 2022

and this is a grave concern for many consumers, especially pregnant women, as this could affect their fetuses. In this review, the definition of Hg and its forms and mode of entrance into fish are introduced in detail and, moreover, the bio-accumulation of Hg in fish and its toxicity and action mechanisms on fish and humans, especially considering the health of pregnant women and their fetuses after the daily intake of fish, are also reviewed. Finally, some feasible and constructive suggestions and guidelines are recommended for the specific group of pregnant women for the consumption of balanced and appropriate fish diets in a rational manner.

Authors: Bojian Chen, Shiyuan Dong

Full Source: International journal of environmental research and public health 2022 Nov 29;19(23):15929. doi: 10.3390/ijerph192315929.

Exposure to Bisphenol A Substitutes, Bisphenol S and Bisphenol F, and Its Association with Developing Obesity and Diabetes Mellitus: A Narrative Review

2022-11-29

Bisphenol A, a well-known endocrine-disrupting chemical, has been replaced with its analogs bisphenol S (BPS) and bisphenol F (BPF) over the last decade due to health concerns. BPS and BPF are present in relatively high concentrations in different products, such as food products, personal care products, and sales receipts. Both BPS and BPF have similar structural and chemical properties to BPA; therefore, considerable scientific efforts have investigated the safety of their exposure. In this review, we summarize the findings of relevant epidemiological studies investigating the association between urinary concentrations of BPS and/or BPF with the incidence of obesity or diabetes. The results showed that BPS and BPF were detected in many urinary samples at median concentrations ranging from 0.03 to 0.4 $\mu\text{g}\cdot\text{L}^{-1}$. At this exposure level, BPS median urinary concentrations (0.4 $\mu\text{g}\cdot\text{L}^{-1}$) were associated with the development of obesity. At a lower exposure level (0.1-0.03 $\mu\text{g}\cdot\text{L}^{-1}$), two studies showed an association with developing diabetes. For BPF exposure, only one study showed an association with obesity. However, most of the reported studies only assessed BPS exposure levels. Furthermore, we also summarize the findings of experimental studies in vivo and in vitro regarding our aim; results support the possible obesogenic effects/metabolic disorders mediated by BPS and/or BPF exposure. Unexpectedly, BPS may promote worse obesogenic effects than BPA. In addition, the possible mode of action underlying the obesogenic effects of BPS might be attributed to various pathophysiological mechanisms, including

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Bulletin Board

Technical

DEC. 16, 2022

estrogenic or androgenic activities, alterations in the gene expression of critical adipogenesis-related markers, and induction of oxidative stress and an inflammatory state. Furthermore, susceptibility to the adverse effects of BPS may be altered by sex differences according to the results of both epidemiological and experimental studies. However, the possible mode of action underlying these sex differences is still unclear. In conclusion, exposure to BPS or BPF may promote the development of obesity and diabetes. Future approaches are highly needed to assess the safety of BPS and BPF regarding their potential effects in promoting metabolic disturbances. Other studies in different populations and settings are highly suggested.

Authors: Hend F Alharbi, Raya Algonaiman, Rana Alduwayghiri, Thamer Aljutaily, Reham M Algheshairy, Abdulkarim S Almutairi, Razan M Alharbi, Leena A Alfurayh, Amjad A Alshahwan, Amjad F Alsadun, Hassan Barakat
Full Source: International journal of environmental research and public health 2022 Nov 29;19(23):15918. doi: 10.3390/ijerph192315918.

OCCUPATIONAL

Top-Down Preparation of Nanoquartz for Toxicological Investigations

2022-12-06

Occupational exposure to quartz dust is associated with fatal diseases. Quartz dusts generated by mechanical fracturing are characterized by a broad range of micrometric to nanometric particles. The contribution of this nanometric fraction to the overall toxicity of quartz is still largely unexplored, primarily because of the strong electrostatic adhesion forces that prevent isolation of the nanofraction. Furthermore, fractured silica dust exhibits special surface features, namely nearly free silanols (NFS), which impart a membranolytic activity to quartz. Nanoquartz can be synthesized via bottom-up methods, but the surface chemistry of such crystals strongly differs from that of nanoparticles resulting from fracturing. Here, we report a top-down milling procedure to obtain a nanometric quartz that shares the key surface properties relevant to toxicity with fractured quartz. The ball milling was optimized by coupling the dry and wet milling steps, using water as a dispersing agent, and varying the milling times and rotational speeds. Nanoquartz with a strong tendency to form submicrometric agglomerates was obtained. The deagglomeration with surfactants or simulated body fluids was negligible. Partial lattice amorphization and a bimodal crystallite domain size were observed. A moderate membranolytic activity, which correlated with the

Occupational exposure to quartz dust is associated with fatal diseases.

Bulletin Board

Technical

DEC. 16, 2022

number of NFS, signaled coherence with the previous toxicological data. A membranolytic nanoquartz for toxicological investigations was obtained.

Authors: Chiara Bellomo, Cristina Pavan, Gianluca Fiore, Guillermo Escolano-Casado, Lorenzo Mino, Francesco Turci

Full Source: International journal of molecular sciences 2022 Dec 6;23(23):15425. doi: 10.3390/ijms232315425.

Exposure to chemical agents in the Spanish construction sector: A risk assumed and accepted by workers

2022-12-08

Background: The weak preventive culture among workers in the construction sector leads to the underestimation of risks posed by the presence or handling of chemical agents on-site and, consequently, harms workers' health.

Objective: The objectives of this paper are to classify exposure to chemical agents present or used on-site, determine workers' perception of said agents and establish the influence that socio-demographic variables have on chemical agent exposure and the perception of such exposure. Methods: A total of 490 workers in the Spanish construction sector participated in this study. The data were gathered through a self-administered questionnaire that explored socio-demographic characteristics, the degree of exposure to chemical agents, attitudes toward exposure and the prevention of consequences. The underlying dimensions of perception were researched using an adapted version of the questionnaire used by the Paul Slovic group to apply the psychometric paradigm.

Results: The levels of exposure to and handling of chemical agents found in the sample were high and moderate, respectively. The participants were found to have advanced knowledge about the effects of exposure, with the majority of the workers considering the probability of suffering a serious disease to be low. Statistically significant associations were found between the socio-demographic variables identified in the sample and the various exposure characteristics. A factor analysis performed on the underlying dimensions of perception provided a final version of the instrument comprising two factors.

Conclusion: Measures are needed to improve the preventive culture among workers in the construction sector and reinforce on-site preventive measures aimed at preventing or minimising the consequences of exposure to chemical agents.

Authors: Eduardo Simal, Joaquín Catalá, José M Arnal

Full Source: Work (Reading, Mass.) 2022 Dec 8. doi: 10.3233/WOR-211420.

Background: The weak preventive culture among workers in the construction sector leads to the underestimation of risks posed by the presence or handling of chemical agents on-site and, consequently, harms workers' health.

Bulletin Board

Technical

DEC. 16, 2022

Low-level Occupational Exposure to BTEX and Dyschromatopsia: A Systematic Review and Meta-analysis

2022-12-10

Purpose: The present study aimed to assess whether occupational exposure to low concentrations of benzene, toluene, ethyl benzene, and xylene (BTEX) is associated with color vision impairment.

Methods: We queried the PubMed, Scopus, Embase, Web of Science, and ProQuest as the main databases, as well as grey literature such as Google scholar. A random-effects model was used to assess relative risk. A funnel plot was created to assess publication bias. Meta-regression analysis was applied to identify variables that explain the between-study variation in the reported risk estimate.

Results: An overall standardized mean difference of 0.529 (95% CI:0.269, 0.788; $p < 0.0001$) was obtained in the random-effects model, which was corresponded to a medium-size effect. Duration and the levels of exposure to benzene, toluene, and xylene were the significant predictors of the magnitude of the combined risk estimate. Chronic exposures to low levels of BTEX was associated with dyschromatopsia determined by the color confusion index.

Conclusions: The impairments can occur even at exposures lower than the occupational exposure limits of BTEX. However, there are several flaws in the determination of workers' exposure, which did not allow to establish how low the level of these chemicals can cause color vision impairment.

Authors: Younes Sohrabi, Fatemeh Rahimian, Esmaeel Soleimani, Soheil Hassanipour

Full Source: International journal of occupational safety and ergonomics : JOSE 2022 Dec 10;1-29. doi: 10.1080/10803548.2022.2157543.

Purpose: The present study aimed to assess whether occupational exposure to low concentrations of benzene, toluene, ethyl benzene, and xylene (BTEX) is associated with color vision impairment.

Asbestos Exposure and Severity of COVID-19

2022-12-06

Background: The aim of this study was to analyse the relationship between occupational exposure to asbestos and the severity of SARS-CoV-2 infection.

Methods: We evaluated patients who survived admission in our centre for COVID-19 pneumonia. Demographic, analytical, and clinical variables were collected during admission. After discharge, a previously validated occupational exposure to asbestos questionnaire was administered. Spirometry, CO diffusion test, the 6-min walk test, and high-resolution chest CT were performed. Patients who required respiratory support (oxygen, CPAP, or NIV) were considered severe.

Bulletin Board

Technical

DEC. 16, 2022

Results: In total, 293 patients (mean age 54 + 13 years) were included. Occupational exposure to asbestos was detected in 67 (24%). Patients with occupational exposure to asbestos had a higher frequency of COVID-19 pneumonia requiring respiratory support (n = 52, 77.6%) than their unexposed peers (n = 139, 61.5%) (p = 0.015). Asbestos exposure was associated with COVID-19 severity in the univariate but not in the multivariate analysis. No differences were found regarding follow-up variables including spirometry and the DLCO diffusion, the 6-min walk test, and CT alterations.

Conclusions: In hospitalised patients with COVID-19 pneumonia, those with occupational exposure to asbestos more frequently needed respiratory support. However, an independent association between asbestos exposure and COVID-19 severity could not be confirmed.

Authors: Galo Granados, María Sáez-López, Cristina Aljama, Júlia Sampol, María-Jesús Cruz, Jaume Ferrer, Se-Covid-Team

Full Source: International journal of environmental research and public health 2022 Dec 6;19(23):16305. doi: 10.3390/ijerph192316305.