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CHEMICAL EFFECTS

EF24 exerts cytotoxicity against NSCLC via inducing ROS accumulation

2021-10-12

Background: The role of Diphenyldifluoroketone (EF24), a synthetic analogue of curcumin with noteworthy antitumor potential, remains unclear in non-small cell lung cancer (NSCLC). Herein, the inhibitory effect of EF24 on NSCLC and its mechanism were studied.

Methods: Cytotoxicity was measured by MTT assay, colony formation assay and xenograft model. Cell apoptosis and reactive oxygen species (ROS) level were quantified by flow cytometer. Protein level was detected by western blot assay. Mitochondria and autophagosomes were observed using transmission electron microscope and confocal microscopy.

Results: In-vitro, EF24 significantly induced proliferation inhibition, apoptosis, mitochondrial fission and autophagy of NSCLC cell lines. These cytotoxic effects were significantly attenuated by two reactive oxygen species (ROS) scavengers, indicating its anti-cancer effects largely depend on ROS accumulation. In-vivo, EF24 inhibited tumor growth in a dose-dependent manner. Moreover, no pathological changes of heart, lung, spleen, kidney and liver of mice were observed. Collectively, EF24 induced ROS accumulation, in turn activates cell apoptosis, and then exerts its cytotoxicity on NSCLC cells. Conclusions: The results showed that EF24 exerted cytotoxicity against NSCLC via ROS accumulation. Thus, EF24 might serve as a potential anti-cancer agent for the treatment of NSCLC.

Authors: Minghui Chang, Ming Shang, Fang Yuan, Wei Guo, Cuijuan Wang
Full Source: Cancer cell international 2021 Oct 12;21(1):531. doi: 10.1186/s12935-021-02240-z.

Recent progress and perspectives on the mechanisms underlying Asbestos toxicity

2021-10-12

Most cases of mesothelioma are known to result from exposure to asbestos fibers in the environment or occupational ambient air. The following questions regarding asbestos toxicity remain partially unanswered: (i) why asbestos entering the alveoli during respiration exerts toxicity in the pleura; and (ii) how asbestos causes mesothelioma, even though human mesothelial cells are easily killed upon exposure to asbestos. As for the latter question, it is now thought that the frustrated

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phagocytosis of asbestos fibers by macrophages prolongs inflammatory responses and gives rise to a "mutagenic microenvironment" around mesothelial cells, resulting in their malignant transformation. Based on epidemiological and genetic studies, a carcinogenic model has been proposed in which BRCA1-associated protein 1 mutations are able to suppress cell death in mesothelial cells and increase genomic instability in the mutagenic microenvironment. This leads to additional mutations, such as CDKN2A [p16], NF2, TP53, LATS2, and SETD2, which are associated with mesothelioma carcinogenesis. Regarding the former question, the receptors involved in the intracellular uptake of asbestos and the mechanism of transfer of inhaled asbestos from the alveoli to the pleura are yet to be elucidated. Further studies using live-cell imaging techniques will be critical to fully understanding the mechanisms underlying asbestos toxicity.

Authors: Akio Kuroda

Full Source: Genes and environment : the official journal of the Japanese Environmental Mutagen Society 2021 Oct 12;43(1):46. doi: 10.1186/s41021-021-00215-0.

Type 2 diabetes mellitus potentiates acute acrylonitrile toxicity: Potentiation reduction by phenethyl isothiocyanate

2021-10-13

Acrylonitrile (AN) is a known animal carcinogen and suspected human carcinogen. Recently, occupational exposure to AN has considerably increased. Previously, we demonstrated that streptozotocin-induced diabetes potentiates AN-induced acute toxicity in rats and that the induced cytochrome P450 2E1 (CYP2E1) is responsible for this effect. In the present study, we examined whether induction of CYP2E1 is also the underlying mechanism for the potentiation of AN-induced acute toxicity in type 2 diabetes in db/db mice. The effect of phenethyl isothiocyanate (PEITC) in reducing potentiation was also investigated. The mice were randomly divided into the normal control, diabetic control, AN, diabetes + AN, PEITC + AN, and diabetes + PEITC + AN groups. PEITC (40 mg/kg) was orally administered to rats for 3 days, and 1 h after the last PEITC gavage, 45 mg/kg AN was intraperitoneally injected. Time to death was observed. The CYP2E1 level and enzymatic activity, cytochrome c oxidase (CCO) activity, and reactive oxygen species (ROS) levels were measured. The survival rate was decreased in AN-treated db/db mice compared with that in AN-treated wild-type mice. The hepatic CYP2E1 level and enzymatic activity remained unaltered in db/db mice. Phenethyl isothiocyanate

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alleviated AN-induced acute toxicity in db/db mice as evident in the increased survival rate, restored CCO activity, and decreased ROS level in both the liver and brain. The study results suggested that CYP2E1 may not be responsible for the sensitivity to AN-induced acute toxicity in db/db mice and that PEITC reduced the potentiation of AN-induced acute toxicity in db/db mice.

Authors: Jie Zhou, Xueyu Zhu, Ying Dong, Bobo Yang, Rongzhu Lu, Guangwei Xing, Suhua Wang, Fang Li

Full Source: Toxicology and industrial health 2021 Oct

13;7482337211048583. doi: 10.1177/07482337211048583.

Cytotoxicity of mancozeb on Sertoli-germ cell co-culture system: Role of MAPK signaling pathway

2021-10-13

Mancozeb (MZB) is a worldwide fungicide for the management of fungal diseases in agriculture and industrial contexts. Human exposure occurs by consuming contaminated plants, drinking water, and occupational exposure. There are reports on MZB's reprotoxicity such as testicular structure damage, sperm abnormalities, and decrease in sperm parameters (number, viability, and motility), but its molecular mechanism on apoptosis in testis remains limited. To investigate the molecular mechanisms involved in male reprotoxicity induced by MZB, we used primary cultures of mouse Sertoli-germ cells. Cells were exposed to MZB (1.5, 2.5, and 3.5 μ M) for 3 h to evaluate viability by 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) assay, reactive oxygen species (ROS) generation, and oxidative stress parameters (lipid peroxidation). Cell death and mitogen-activated protein kinase (MAPK) signaling were measured in these cells using flow cytometry and western blotting. In addition, some groups were exposed to N-acetylcysteine (NAC, 5 mM) in the form of co-treatment with MZB. Mancozeb reduced viability and increased the level of intracellular ROS, p38 and c-Jun N-terminal kinases (JNK) MAPK proteins phosphorylation, and apoptotic cell death, which could be blocked by NAC as an inhibitor of oxidative stress. The present study indicated for the first time the toxic manifestations of MZB on the Sertoli-germ cell co-culture. Redox imbalance and p38 and JNK signaling

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pathway activation might play critical roles in MZB-induced apoptosis in the male reproductive system.

Authors: Mohaddeseh Mohammadi-Sardoo, Ali Mandegary, Seyed Nouredin Nematollahi-Mahani, Mahshid Moballegh Nasery, Mohammad Nabiuni, Bagher Amirheidari

Full Source: Toxicology and industrial health 2021 Oct

13;7482337211044028. doi: 10.1177/07482337211044028.

ENVIRONMENTAL RESEARCH

Associations between persistent organic pollutants and endometriosis: A multiblock approach integrating metabolic and cytokine profiling

2021-10-11

Humans are exposed daily to complex mixtures of chemical pollutants through their environment and diet, some of which have the potential to disrupt the bodies' natural endocrine functions and contribute to reproductive diseases like endometriosis. Increasing epidemiological and experimental evidence supports the association between endometriosis and certain persistent organic pollutants (POPs) like dioxins; however, little is known about the underlying linking mechanisms. The main objective of this study is to proof the methodological applicability and discovery potential of integrating ultra-trace mass spectrometry (MS) profiling of POP biomarkers and endogenous biomarker profiling (MS metabolomics and cytokines) in a case-control study for the etiological research of endometriosis. The approach is applied in a pilot clinical-based study conducted in France where women with and without surgically confirmed endometriosis were recruited. Serum samples were analysed with high-resolution MS for about 30 polychlorinated biphenyls (PCBs), organochlorinated pesticides and perfluoroalkyl substances (PFAS). About 600 serum metabolites and lipids were identified with targeted metabolomics using tandem MS with the Biocrates MxP® Quant 500 Kit. A panel of 4 pro-inflammatory cytokines were analysed using ELISA-based 4-PLEX analyser. Statistical analysis included a battery of variable selection approaches, multivariate logistic regression for single-chemical associations, Bayesian kernel machine regressions (BKMR) to identify mixture effects of POPs and a multiblock approach to identify shared biomarker signatures among high risk clusters. The results showed the positive associations between some POPs and endometriosis risk,

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including the pesticide trans-nonachlor Odds Ratio (95% Confidence Interval) 3.38 (2.06-5.98), $p < 0.0001$ and PCB 114 OR (95% CI) 1.83 (1.17-2.93), $p = 0.009$. The BKMR approach showed a tendency of a positive cumulative effect of the mixture, however trans-nonachlor exhibited significant associations within the mixture and interacted with other PCBs, strengthening the effects at highest concentrations. Finally, the multiblock analysis, relating the various blocks of data, revealed a latent cluster of women with higher risk of endometrioma presenting higher concentrations of trans-nonachlor, PCB 114 and dioxin-like toxic equivalents from PCBs, together with an increased inflammatory profile (i.e. elevated interleukin-8 and monocyte chemoattractant protein-1). It was also highlighted a specific metabolic pattern characterized by dysregulation of bile acid homeostasis and lipase activity. Further research will be required with larger sample size to confirm these findings and gain insight on the underlying mechanisms between POPs and endometriosis.

Authors: Komodo Matta, Tiphaine Lefebvre, Evelyne Vigneau, Véronique Cariou, Philippe Marchand, Yann Guitton, Anne-Lise Royer, Stéphane Ploteau, Bruno Le Bizec, Jean-Philippe Antignac, German Cano-Sancho
Full Source: Environment international 2021 Oct 11;158:106926. doi: 10.1016/j.envint.2021.106926.

Exposure to environmental contaminants is associated with altered hepatic lipid metabolism in non-alcoholic fatty liver disease

2021-10-07

Background & aims: Recent experimental models and epidemiological studies suggest that specific environmental contaminants (ECs) contribute to the initiation and pathology of NAFLD. However, the underlying mechanisms linking EC exposure with NAFLD remain poorly understood and there is no data on their impact on the human liver metabolome. Herein, we hypothesized that exposure to ECs, particularly perfluorinated alkyl substances (PFAS), impacts liver metabolism, specifically bile acid metabolism.

Methods: In a well-characterized human NAFLD cohort of 105 individuals, we investigated the effects of EC exposure on liver metabolism. We characterized the liver (via biopsy) and circulating metabolomes using four mass spectrometry-based analytical platforms, and measured PFAS and other ECs in serum. We subsequently compared these results with an exposure study in a PPAR α -humanized mouse model. Results: PFAS exposure appears associated with perturbation of key hepatic metabolic pathways previously found altered in NAFLD, particularly as

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regards bile acid and lipid metabolism. We identified stronger associations between the liver metabolome, chemical exposure and NAFLD-associated clinical variables (liver fat content, HOMA-IR), in female subjects versus males. Specifically, we observed PFAS-associated up-regulation of bile acids, triacylglycerols and ceramides, and association between chemical exposure and dysregulated glucose metabolism in females. The murine exposure study further corroborated our findings, vis-à-vis a sex-specific association between PFAS exposure and NAFLD-associated lipid changes. Conclusions: Females may be more sensitive to the harmful impacts of PFAS. Lipid-related changes subsequent to PFAS exposure may be secondary to the interplay between PFAS and bile acid metabolism. Lay summary: There is increasing evidence that specific environmental contaminants such, as per- and polyfluoroalkyl substances (PFAS), contribute to the progression of non-alcoholic fatty liver disease (NAFLD). However, it is poorly understood how these chemicals impact human liver metabolism. Here we show that human exposure to PFAS impacts liver metabolic processes associated with NAFLD, and does so in a sexually-dimorphic manner.

Authors: Partho Sen, Sami Qadri, Panu K Luukkonen, Oddny Ragnarsdottir, Aidan McGlinchey, Sirkku Jääntti, Anne Juuti, Johanna Arola, Jennifer J Schlezinger, Thomas F Webster, Matej Orešič, Hannele Yki-Järvinen, Tuulia Hyötyläinen

Full Source: Journal of hepatology 2021 Oct 7;S0168-8278(21)02104-8. doi: 10.1016/j.jhep.2021.09.039.

Trans-disciplinary diagnosis for an in-depth reform of regulatory expertise in the field of environmental toxicology and security

2021-01-25

Repeated health and environmental scandals, the loss of biodiversity and the recent burst of chronic diseases constantly remind us the inability of public authorities and risk assessment agencies to protect health and the environment. After reviewing the main shortcomings of our evaluation system of chemicals and new technologies, supported by some concrete examples, we develop a number of proposals to reform both the risk assessment agencies and the evaluation processes. We especially propose the establishment of an independent structure, a High Authority of Expertise, supervising, either at European level or at national level, all the evaluation agencies, and ensuring the transparency, the methodology and the deontology of the expertise. In addition to modifying the evaluation protocols, both in their nature and in their content, especially in order

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to adapt them to current pollutants such as endocrine disruptors, we propose a reform of the expertise processes based on transparency, contradiction, and greater democracy, including close collaboration between the institutional and scientific parties on the one hand and the whole civil society on the other. All the proposals we make are inspired by the desire to prevent, through appropriate mechanisms, the human, health, ecological, but also economic consequences of contemporary technological choices.

Authors: Joël Spiroux de Vendômois, Jean-Paul Bourdineaud, Arnaud Apoteker, Nicolas Defarge, Emilie Gaillard, Corinne Lepage, Jacques Testart, Christian Vélot

Full Source: Toxicological research 2021 Jan 25;37(4):405-419. doi: 10.1007/s43188-020-00075-w.

OCCUPATIONAL

Firefighter exposures to potential endocrine disrupting chemicals measured by military-style silicone dog tags

2021-10-11

Studies suggest that exposure to potential endocrine disrupting chemicals (pEDCs) may contribute to adverse health outcomes, but pEDC exposures among firefighters have not been fully characterized. Previously, we demonstrated the military-style silicone dog tag as a personal passive sampling device for assessing polycyclic aromatic hydrocarbon exposures among structural firefighters. This follow-up analysis examined the pEDC exposures based on department call volume, duty shift, and questionnaire variables. Structural firefighters (n = 56) were from one high and one low fire call volume department (Kansas City, MO metropolitan area) and wore separate dog tags while on- and off-duty (ndogtags = 110). The targeted 1530 analyte semi-quantitative screening method was conducted using gas chromatography mass spectrometry (npEDCs = 433). A total of 47 pEDCs were detected, and several less-frequently-detected pEDCs (<75%) were more commonly detected in off- compared to on-duty dog tags (conditional logistic regression). Of the 11 phthalates and fragrances detected most frequently (>75%), off-duty pEDC concentrations were strongly correlated (r = 0.31-0.82, p < 0.05), suggesting co-applications of phthalates and fragrances in consumer products. Questionnaire variables of "regular use of conventional cleaning products" and "fireplace in the home" were associated with select elevated pEDC concentrations by duty shift (paired t-test). This suggested researchers should include detailed

Studies suggest that exposure to potential endocrine disrupting chemicals (pEDCs) may contribute to adverse health outcomes, but pEDC exposures among firefighters have not been fully characterized.

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questions about consumer product use and home environment when examining personal pEDC exposures.

Authors: Carolyn M Poutasse, Christopher K Haddock, Walker S C Poston, Sara A Jahnke, Lane G Tidwell, Emily M Bonner, Peter D Hoffman, Kim A Anderson

Full Source: Environment international 2021 Oct 11;158:106914. doi: 10.1016/j.envint.2021.106914.

Capacity development and safety measures for health care workers exposed to COVID-19 in Bangladesh

2021-10-11

Background: The safety of health care workers (HCWs) in Bangladesh and the factors associated with getting COVID-19 have been infrequently studied. The aim of this study was to address this gap by assessing the capacity development and safety measures of HCWs in Bangladesh who have been exposed to COVID-19 and by identifying the factors associated with respondents' self-reported participation in capacity development trainings and their safety practices.

Methods: This cross-sectional study was based on an online survey of 811 HCWs working at 39 dedicated COVID-19 hospitals in Bangladesh. A pretested structured questionnaire consisting of questions related to respondents' characteristics, capacity development trainings and safety measures was administered. Binary logistic regressions were run to assess the association between explanatory and dependent variables. Results: Among the respondents, 58.1% had been engaged for at least 2 months in COVID-19 care, with 56.5% of them attending capacity development training on the use of personal protective equipment (PPE), 44.1% attending training on hand hygiene, and 35% attending training on respiratory hygiene and cough etiquette. Only 18.1% reported having read COVID-19-related guidelines. Approximately 50% of the respondents claimed that there was an inadequate supply of PPE for hospitals and HCWs. Almost 60% of the respondents feared a high possibility of becoming COVID-19-positive. Compared to physicians, support staff [odds ratio (OR) 4.37, 95% confidence interval (CI) 2.25-8.51] and medical technologists (OR 8.77, 95% CI 3.14-24.47) were more exhausted from working in COVID-19 care. Respondents with longer duty rosters were more exhausted, and those who were still receiving infection prevention and control (IPC) trainings were less exhausted (OR 0.54, 95% CI 0.34-0.86). Those who read COVID-19 guidelines perceived a lower risk of being infected by COVID-19 (OR 0.44, 95% CI 0.29-0.67). Compared to the respondents who strongly agreed that hospitals had a sufficient supply

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of PPE, others who disagreed (OR 2.68, 95% CI 1.31-5.51) and strongly disagreed (OR 5.05, 95% CI 2.15-11.89) had a higher apprehension of infection by COVID-19.

Conclusion: The findings indicated a need for necessary support, including continuous training, a reasonable duty roster, timely diagnosis of patients, and an adequate supply of quality PPE.

Authors: Tapan Kumar Nath, Alak Paul, Dwaipayan Sikdar, Janardan Mahanta, Sujat Paul, Md Robed Amin, Shahanara Chowdhury, Md Nur Hossain Bhuiyan, Md Abdur Rob, Abdur Rahim, Md Khairul Islam, Md Mohiuddin Sharif, Kannan Navaneetham

Full Source: BMC health services research 2021 Oct 11;21(1):1079. doi: 10.1186/s12913-021-07071-2.

PHARMACEUTICAL/TOXICOLOGY

Overview of the Mechanisms of Action of Selected Bisphenols and Perfluoroalkyl Chemicals on the Male Reproductive Axes

2021-09-27

Male fertility has been deteriorating worldwide for considerable time, with the greatest deterioration recorded mainly in the United States, Europe countries, and Australia. That is, especially in countries where an abundance of chemicals called endocrine disruptors has repeatedly been reported, both in the environment and in human matrices. Human exposure to persistent and non-persistent chemicals is ubiquitous and associated with endocrine-disrupting effects. This group of endocrine disrupting chemicals (EDC) can act as agonists or antagonists of hormone receptors and can thus significantly affect a number of physiological processes. It can even negatively affect human reproduction with an impact on the development of gonads and gametogenesis, fertilization, and the subsequent development of embryos. The negative effects of endocrine disruptors on sperm gametogenesis and male fertility in general have been investigated and repeatedly demonstrated in experimental and epidemiological studies. Male reproduction is affected by endocrine disruptors via their effect on testicular development, impact on estrogen and androgen receptors, potential epigenetic effect, production of reactive oxygen species or direct effect on spermatozoa and other cells of testicular tissue. Emerging scientific evidence suggests that the increasing incidence of male infertility is associated with the exposure to persistent and non-persistent endocrine-disrupting chemicals such as bisphenols

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and perfluoroalkyl chemicals (PFAS). These chemicals may impact men's fertility through various mechanisms. This study provides an overview of the mechanisms of action common to persistent (PFAS) and nonpersistent (bisphenols) EDC on male fertility.

Authors: Michal Jeřeta, Jana Navrátilová, Kateřina Franzová, Sandra Fialková, Bartořs Kempisty, Pavel Ventruba, Jana Āáková, Igor Crha

Full Source: Frontiers in genetics 2021 Sep 27;12:692897. doi: 10.3389/fgene.2021.692897.