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Food Safety Briefs

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Caffeine

Coffee, Caffeine, and Health Outcomes: An Umbrella Review

Grosso G, Godos J, Galvano F, Giovannucci EL. *Annu Rev Nutr.* 2017 Aug 21;37:131–156. Article Link

Significance: An umbrella review of caffeine and various health outcomes indicated probable decreased risk of several cancers, cardiovascular disease and mortality, Parkinson's disease, and type II diabetes and a rise in blood pressure.

To evaluate the associations between coffee and caffeine consumption and various health outcomes, we performed an umbrella review of the evidence from meta-analyses of observational studies and randomized controlled trials (RCTs). Of the 59 unique outcomes examined in the selected 112 meta-analyses of observational studies, coffee was associated with a probable decreased risk of breast, colorectal, colon, endometrial, and prostate cancers; cardiovascular disease and mortality; Parkinson's disease; and type-2 diabetes. Of the 14 unique outcomes examined in the 20 selected meta-analyses of observational studies, caffeine was associated with a probable decreased risk of Parkinson's disease and type-2 diabetes and an increased risk of pregnancy loss. Of the 12 unique acute outcomes examined in the selected 9 meta-analyses of RCTs, coffee was associated with a rise in serum lipids, but this result was affected by significant heterogeneity, and caffeine was associated with a rise in blood pressure. Given the spectrum of conditions studied and the robustness of many of the results, these findings indicate that coffee can be part of a healthful diet.

Maternal Caffeine Consumption During Pregnancy and Behavioral Disorders in 11-Year-Old Offspring: A Danish National Birth Cohort Study

Hvolgaard Mikkelsen S, Obel C, Olsen J, Niclasen J, Bech BH. *J Pediatr.* 2017 Oct;189:120–127.e1. Article Link

Significance: Analysis of data from 47,491 children enrolled in the Danish National Birth Cohort indicated that high maternal caffeine consumption from coffee and tea at 15 weeks of gestation was associated with behavioral disorders in 11-year-old offspring.

OBJECTIVE: To examine the association between maternal caffeine consumption from coffee and tea during pregnancy and offspring behavioral disorders. STUDY DESIGN: We studied 47 491 children enrolled in the Danish National Birth Cohort between 1996 and 2002. Data on maternal coffee and tea consumption was collected at 15 and 30 weeks of gestation. When the child was 11 years old, the Strength and Difficulties Questionnaire was filled in by children, parents, and teachers. We estimated risk ratios (RRs) for offspring behavioral disorders. RESULTS: At 15 weeks of gestation 3% and 4% of the pregnant women consumed ≥8 cups/d of coffee or tea, respectively. Maternal coffee consumption ≥8 cups/d at 15 weeks of gestation was associated with increased risk of hyperactivity-inattention disorder (RR 1.47; 95% CI 1.18-1.83), conduct-oppositional disorders (RR 1.22; 95% CI 1.01-1.48), and any psychiatric disorder (RR 1.23; 95% CI 1.08-1.40). Maternal tea consumption ≥8 cups/d at 15 weeks of gestation was associated with increased risk of anxiety-depressive disorders (RR 1.28; 95% CI 1.09-1.52) and any psychiatric disorder (RR 1.24; 95% CI 1.11-1.40). An increased risk of hyperactivity-inattention disorder was observed with increasing daily caffeine consumption at 15 weeks of gestation. CONCLUSION: High maternal caffeine consumption from coffee and tea at 15 weeks of gestation was associated with behavioral disorders in 11-year-old offspring. We hypothesize that caffeine exposure may affect the fetal brain and program for behavioral disorders later in life. The fetal brain seems to be more sensitive to caffeine exposure at 15 weeks of pregnancy compared with 30 weeks of gestation.

Nanotechnology

Perspectives from the NanoSafety Modelling Cluster on the Validation Criteria for (Q)SAR Models Used in Nanotechnology

Puzyn T, Jeliazkova N, Sarimveis H, Marchese Robinson RL, Lobaskin V, Rallo R, et al. *Food Chem Toxicol.* 2017 Sep 21. doi: 10.1016/j.fct.2017.09.037. Article Link

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Significance: This paper interprets and expands the guidance for the well-known "OECD Principles for the Validation, for Regulatory Purposes, of (Q)SAR Models."

Nanotechnology and the production of nanomaterials have been expanding rapidly in recent years. Since many types of engineered nanoparticles are suspected to be toxic to living organisms and to have a negative impact on the environment, the process of designing new nanoparticles and their applications must be accompanied by a thorough risk analysis. (Quantitative) Structure-Activity Relationship ([Q]SAR) modelling creates promising options among the available methods for the risk assessment. These in silico models can be used to predict a variety of properties, including the toxicity of newly designed nanoparticles. However, (Q)SAR models must be appropriately validated to ensure the clarity, consistency and reliability of predictions. This paper is a joint initiative from recently completed European research projects focused on developing (Q)SAR methodology for nanomaterials. The aim was to interpret and expand the guidance for the well-known "OECD Principles for the Validation, for Regulatory Purposes, of (Q)SAR Models", with reference to nano-(Q)SAR, and present our opinions on the criteria to be fulfilled for models developed for nanoparticles.

Acute Oral Toxicity Study of Magnesium Oxide Nanoparticles and Microparticles in Female Albino Wistar Rats

Mangalampalli B, Dumala N, Grover P. *Regul Toxicol Pharmacol*. 2017 Nov;90:170–184. Article Link

Significance: Results of this study revealed that the acute oral exposure to high doses of MgO nanoparticles produced significant ($p < 0.01$) DNA damage and biochemical alterations in female Wistar rats.

Advancements in nanotechnology have led to the development of the nanomedicine, which involves nanodevices for diagnostic and therapeutic purposes. A key requirement for the successful use of the nanoparticles (NPs) in biomedical applications is their good dispensability, colloidal stability in biological media, internalization efficiency, and low toxicity. Therefore, toxicological profiling is necessary to understand the mechanism of NPs and microparticles (MPs). MgO NPs have attracted wide scientific interest due to ease of synthesis, chemical stability and unique properties. However, their toxic effects on humans should also be of concern with the increased applications of nano MgO. The present study was aimed to assess the toxicological potential of MgO NPs in comparison to their micron counterparts in female Wistar rats. Toxicity was evaluated using genotoxicity, histological, biochemical, antioxidant and biodistribution parameters post administration of MgO particles to rats through oral route. The results obtained from the investigation revealed that the acute exposure to the high doses of MgO NPs produced significant ($p < 0.01$) DNA damage and biochemical alterations. Antioxidant assays revealed prominent oxidative stress at the high dose level for both the particles. Toxicokinetic analysis showed significant levels of Mg accumulation in the liver and kidney tissues apart from urine and feces. Further, mechanistic investigational reports are warranted to document safe exposure levels and health implications post exposure to high levels of NPs.

Food Packaging

Scientific Challenges in the Risk Assessment of Food Contact Materials

Muncke J, Backhaus T, Geueke B, Maffini MV, Martin OV, Myers JP, et al. *Environ Health Perspect*. 2017 Sep 11;125(9): 095001. Article Link

Significance: Reviewing the regulatory requirements for risk assessment of food contact materials in the United States and Europe, the authors conclude that current regulations are insufficient for addressing chemical exposures from food contact materials.

BACKGROUND: Food contact articles (FCAs) are manufactured from food contact materials (FCMs) that include plastics, paper, metal, glass, and printing inks. Chemicals can migrate from FCAs into food during storage, processing, and transportation. Food contact materials' safety is evaluated using chemical risk assessment (RA). Several challenges to the RA of FCAs exist. OBJECTIVES: We review regulatory requirements for RA of FCMs in the United States and Europe, identify gaps in RA, and highlight opportunities for improving the protection of public health. We intend to initiate a discussion in the wider scientific community to enhance the safety of food contact articles. DISCUSSION: Based on our evaluation of the evidence, we conclude that current regulations are insufficient for addressing chemical exposures from FCAs. RA currently focuses on monomers and additives used in the manufacture of products, but it does not cover all substances formed in the production processes. Several factors hamper effective RA for many FCMs, including a lack of information on chemical identity, inadequate assessment of hazardous properties, and missing exposure data. Companies make decisions about the safety of some food contact chemicals (FCCs) without review by public authorities. Some chemical migration limits cannot be enforced because analytical standards are unavailable. CONCLUSION: We think that exposures to hazardous substances migrating from FCAs require more attention. We recommend *a*) limiting the number and types of chemicals authorized for manufacture and *b*) developing novel approaches for assessing the safety of chemicals in FCAs, including unidentified chemicals that form during or after production.

Chemical Risk Assessment

Thresholds of Toxicological Concern for Cosmetics-Related Substances: New Database, Thresholds, and Enrichment of Chemical Space

Yang C, Barlow SM, Muldoon Jacobs KL, Vitcheva V, Boobis AR, Felter SP, et al. *Food Chem Toxicol.* 2017 Sep 1; 109(Pt 1):170–193. Article Link

Significance: This paper describes the creation of a new COSMOS TTC dataset.

A new dataset of cosmetics-related chemicals for the Threshold of Toxicological Concern (TTC) approach has been compiled, comprising 552 chemicals with 219, 40, and 293 chemicals in Cramer Classes I, II, and III, respectively. Data were integrated and curated to create a database of No-/Lowest-Observed-Adverse-Effect Level (NOAEL/LOAEL) values, from which the final COSMOS TTC dataset was developed. Criteria for study inclusion and NOAEL decisions were defined, and rigorous quality control was performed for study details and assignment of Cramer classes. From the final COSMOS TTC dataset, human exposure thresholds of 42 and 7.9 µg/kg-bw/day were derived for Cramer Classes I and III, respectively. The size of Cramer Class II was insufficient for derivation of a TTC value. The COSMOS TTC dataset was then federated with the dataset of Munro and colleagues, previously published in 1996, after updating the latter using the quality control processes for this project. This federated dataset expands the chemical space and provides more robust thresholds. The 966 substances in the federated database comprise 245, 49 and 672 chemicals in Cramer Classes I, II and III, respectively. The corresponding TTC values of 46, 6.2 and 2.3 µg/kg-bw/day are broadly similar to those of the original Munro dataset.

Health Risk Assessment of Heavy Metals via Dietary Intake of Five Pistachio (Pistacia vera L.) Cultivars Collected From Different Geographical Sites of Iran

Taghizadeh SF, Davarynejad G, Asili J, Nemati SH, Rezaee R, Goumenou M, et al. *Food Chem Toxicol.* 2017 Sep;107(Pt A):99–107. Article Link

Significance: Heavy metal concentrations in pistachios from four geographical regions of Iran do not pose a risk to consumers.

Pistachio is an important horticultural product and Iran is considered as a main pistachio producing country. Assessment of heavy metals in this export fruit is crucial for protecting public health against toxic heavy metals. The concentration of selected heavy metals in soil, water and five pistachio cultivars from four geographical regions of Iran were measured. Although none of the elements were detected in water irrigation, infield metal content in the soil had good correlation with that of pistachio. The highest amounts of Al, As, Co, Ni and Se were reported in samples collected from Sarakhs, Iran. Considering both cultivar and region effects on selected heavy metals concentration, Kaleghoochi cultivar from Sarakhs site showed the highest amount of Al, As, Ni and Se. The maximum concentration of Hg was found in Akbari cultivar collected from Damghan. In the Akbari and the Ahmad aghaei cultivars collected from Sarakhs and Damghan cultivation zones, respectively, the highest amount of Co were observed. Based on our results, the HI value for the consumers of Iranian pistachio was 0.066. It seems that the levels of heavy metals in these pistachio samples pose no risk to consumers.

Origin of the TTC Values for Compounds That Are Genotoxic and/or Carcinogenic and an Approach for Their Re-Evaluation

Boobis A, Brown P, Cronin MTD, Edwards J, Galli CL, Goodman J, et al. *Crit Rev Toxicol.* 2017 Sep;47(8):705–727. Article Link

Significance: This paper proposes an update of the TTC database, using inclusion and exclusion criteria reflecting current knowledge.

The threshold of toxicological concern (TTC) approach is a resource-effective de minimis method for the safety assessment of chemicals, based on distributional analysis of the results of a large number of toxicological studies. It is being increasingly used to screen and prioritize substances with low exposure for which there is little or no toxicological information. The first step in the approach is the identification of substances that may be DNA-reactive mutagens, to which the lowest TTC value is applied. This TTC value was based on the analysis of the cancer potency database and involved a number of assumptions that no longer reflect the state-of-the-science and some of which were not as transparent as they could have been. Hence, review and updating of the database is proposed, using inclusion and exclusion criteria reflecting current knowledge. A strategy for the selection of appropriate substances for TTC determination, based on consideration of weight of evidence for genotoxicity and carcinogenicity is outlined. Identification of substances that are carcinogenic by a DNA-reactive mutagenic mode of action and those that clearly act by a non-genotoxic mode of action will enable the protectiveness to be determined of both the TTC for DNA-reactive mutagenicity and that applied by default to substances that may be carcinogenic but are unlikely to be DNA-reactive mutagens (i.e. for Cramer class I-III compounds). Critical to the application of the TTC approach to substances that are

likely to be DNA-reactive mutagens is the reliability of the software tools used to identify such compounds. Current methods for this task are reviewed and recommendations made for their application.

Chemical Contaminants

Epigenetic Mechanisms Underlying Toxic Effects Associated With Arsenic Exposure and the Development of Diabetes

Khan F, Momtaz S, Niaz K, Hassan FI, Abdollahi M. *Food Chem Toxicol.* 2017 Sep;107(Pt A):406–417. Article Link

Significance: This research indicates that exposure from low to moderate concentrations of iAs is linked with epigenetic effects.

BACKGROUND: Exposure to inorganic arsenic (iAs) is a major threat to the human health worldwide. The consumption of arsenic in drinking water and other food products is associated with the risk of development of type-2 diabetes mellitus (T2DM). The available experimental evidence indicates that epigenetic alterations may play an important role in the development of diseases that are linked with exposure to environmental toxicants. iAs seems to be associated with the epigenetic modifications such as alterations in DNA methylation, histone modifications, and micro RNA (miRNA) abundance. OBJECTIVE: This article reviewed epigenetic mechanisms underlying the toxic effects associated with arsenic exposure and the development of diabetes. METHOD: Electronic databases such as PubMed, Scopus and Google scholar were searched for published literature from 1980 to 2017. Searched MESH terms were "Arsenic", "Epigenetic mechanism", "DNA methylation", "Histone modifications" and "Diabetes". RESULTS: There are various factors involved in the pathogenesis of T2DM but it is assumed that arsenic consumption causes the epigenetic alterations both at the gene-specific level and generalized genome level. CONCLUSION: The research indicates that exposure from low to moderate concentrations of iAs is linked with the epigenetic effects. In addition, it is evident that, arsenic can change the components of the epigenome and hence induces diabetes through epigenetic mechanisms, such as alterations in glucose transport and/or metabolism and insulin expression/secretion.

Rice Consumption and Squamous Cell Carcinoma of the Skin in a United States Population

Gossai A, Zens MS, Punshon T, Jackson BP, Perry AE, Karagas MR. *Environ Health Perspect.* 2017 Sep 7;125(9):097005. Article Link

Significance: Arsenic exposure through rice consumption may be related to the occurrence of squamous cell carcinoma in the United States, especially among those with relatively low drinking water arsenic exposure.

BACKGROUND: Rice contains arsenic, a known skin carcinogen. Rice intake has been associated with arsenic-related skin lesions in South Asia, but its association with skin cancers is as yet unknown. OBJECTIVES: We aimed to investigate whether rice intake contributes to urinary arsenic concentration and risk of squamous cell carcinoma (SCC) of the skin in a U.S. population. METHODS: Rice consumption was assessed using a food frequency questionnaire administered as part of a population-based case-control study of 487 SCC cases and 462 age- and gender-matched controls. Arsenic concentration in household tap water and urine samples were measured using inductively coupled mass spectrometry (ICP-MS) and high-resolution ICP-MS, respectively. Odds ratios (OR) for SCC associated with the frequency of rice consumption were estimated using logistic regression, with adjustment for age, gender, and caloric intake. RESULTS: Those who reported any rice consumption had higher urinary arsenic concentrations than those who did not consume rice, and the association was most pronounced among those with <1μg/L arsenic in their household water (19.2% increase in total urinary arsenic, 95% CI: 5.0, 35.3%). Any rice consumption was associated with a 1.5-fold (95% CI: 1.1, 2.0) higher odds of SCC compared with those who reported no rice consumption, and the relation appeared to be largely among those with <1μg/L water arsenic. CONCLUSION: Rice consumption may be related to the occurrence of SCC in the United States, especially among those with relatively low drinking water arsenic exposure.

Foodborne Illness

Tracking of Listeria monocytogenes in Meat Establishment Using Whole Genome Sequencing as a Food Safety Management Tool: A Proof of Concept

Nastasijevic I, Milanov D, Velebit B, Djordjevic V, Swift C, Painset A, et al. *Int J Food Microbiol.* 2017 Sep 18;257:157–164. Article Link

Significance: Through the use of whole genome sequencing for food safety management, this proof-of-concept study traced L. monocytogenes isolates identified in meat processing units back to the slaughter line.

Repeated Listeria outbreaks particularly associated with Ready-To-Eat (RTE) delicatessen meat products have been reported annually at global level. The most frequent scenario that led to foodborne outbreaks was the post-thermal treatment cross-contamination of deli meat products during slicing and modified atmosphere packaging (MAP). The precondition for such cross contamination is the previous introduction of Listeria into meat processing facilities and subsequent colonization of the production environment, associated with formation of biofilms resilient to common sanitation procedures regularly applied in meat establishments. The use of Whole Genome Sequencing (WGS) can facilitate the understanding of contamination and colonization routes of pathogens within the food production environment and enable efficient pathogen tracking among different departments. This study aimed to: a) provide a proof of concept on practical use of WGS in a meat establishment to define the entry routes and spread pattern of L. monocytogenes, and b) to consider the regular use of WGS in meat processing establishments as a strong support of food safety management system. The results revealed that Listeria spp. was present in slaughter line, chilling chambers, deboning, slicing, MAP, as well as in corridors and dispatch (53 positive samples, out of 240). Eight L. monocytogenes isolates (out of 53) were identified from the slaughterhouse, chilling chambers, deboning, MAP and dispatch. L. monocytogenes isolates were of three different serotypes (1/2a, 1/2c, 4b) and correspondingly of three MLST sequence types. Overall, two pairs of L. monocytogenes isolates were genetically identical, i.e. two serotype 4b isolates (ST1), isolated from water drain at dispatch unit and two isolates obtained from slaughterhouse (floorwall junction at the carcass wash point) and MAP (water drain). These findings indicated that L. monocytogenes isolates identified in meat processing units (MAP, chilling chamber and dispatch) originated from the slaughter line. Further, all eight L. monocytogenes isolates were confirmed to be biofilm producers on glass and stainless steel surfaces. The identification of the main entry routes of L. monocytogenes into meat establishments and tracking the routes for spread of the pathogen are of essential importance to define appropriate risk mitigation strategies for L. monocytogenes in meat production environment. The routine use of WGS for bacterial characterization, as a strong support of food safety management system in meat establishments, will require the cost-effective approach. It may encompass in-house sequencing when sequencing equipment is used for multiple applications (e.g. WGS of pathogens, starter cultures and spoilage organisms).

A Stochastic Model to Assess the Effect of Meat Inspection Practices on the Contamination of the Pig Carcasses

de Freitas Costa E, Corbellini LG, da Silva APSP, Nauta M. *Risk Anal.* 2017 Oct;37(10):1849–1864. Article Link

Significance: A stochastic model applied to Salmonella in pig carcasses can be used to predict changes in the degree of cross-contamination.

The objective of meat inspection is to promote animal and public health by preventing, detecting, and controlling hazards originating from animals. With the improvements of sanitary level in pig herds, the hazards profile has shifted and the inspection procedures no longer target major foodborne pathogens (i.e., not risk based). Additionally, carcass manipulations performed when searching for macroscopic lesions can lead to cross-contamination. We therefore developed a stochastic model to quantitatively describe cross-contamination when consecutive carcasses are submitted to classic inspection procedures. The microbial hazard used to illustrate the model was Salmonella, the data set was obtained from Brazilian slaughterhouses, and some simplifying assumptions were made. The model predicted that due to cross-contamination during inspection, the prevalence of contaminated carcass surfaces increased from 1.2% to 95.7%, whereas the mean contamination on contaminated surfaces decreased from 1 logCFU/cm² to -0.87 logCFU/cm², and the standard deviations decreased from 0.65 to 0.19. These results are explained by the fact that, due to carcass manipulations with hands, knives, and hooks, including the cutting of contaminated lymph nodes, Salmonella is transferred to previously uncontaminated carcasses, but in small quantities. These small quantities can easily go undetected during sampling. Sensitivity analyses gave insight into the model performance and showed that the touching and cutting of lymph nodes during inspection can be an important source of carcass contamination. The model can serve as a tool to support discussions on the modernization of pig carcass inspection.

Predictive Toxicology

How Well Can Carcinogenicity Be Predicted by High Throughput "Characteristics of Carcinogens" Mechanistic Data?

Becker RA, Dreier DA, Manibusan MK, Cox LAT, Simon TW, Bus JS. *Regul Toxicol Pharmacol.* 2017 Nov;90:185–196. Article Link

Significance: Using the same assignments as IARC of ToxCast/Tox21 assays to the seven key characteristics of carcinogens, the ability to predict cancer hazard for each key characteristic, alone or in combination, was found to be no better than chance.

IARC has begun using ToxCast/Tox21 data in efforts to represent key characteristics of carcinogens to organize and weigh mechanistic evidence in cancer hazard determinations and this implicit inference approach also is being considered by USEPA. To determine how well ToxCast/Tox21 data can explicitly predict cancer hazard, this approach was evaluated with statistical analyses and machine learning prediction algorithms. Substances USEPA previously classified as having cancer hazard potential were designated as positives and substances not posing a carcinogenic hazard were designated as negatives. Then ToxCast/Tox21 data were analyzed both with and without adjusting for the cytotoxicity burst effect commonly observed in such assays.

Using the same assignments as IARC of ToxCast/Tox21 assays to the seven key characteristics of carcinogens, the ability to predict cancer hazard for each key characteristic, alone or in combination, was found to be no better than chance. Hence, we have little scientific confidence in IARC›s inference models derived from current ToxCast/Tox21assays for key characteristics to predict cancer. This finding supports the need for a more rigorous mode-of-action pathway-based framework to organize, evaluate, and integrate mechanistic evidence with animal toxicity, epidemiological investigations, and knowledge of exposure and dosimetry to evaluate potential carcinogenic hazards and risks to humans.

Heavy Metals

Plasma Metal Concentrations and Incident Coronary Heart Disease in Chinese Adults: The Dongfeng-Tongji Cohort

Yuan Y, Xiao Y, Feng W, Liu Y, Yu Y, Zhou L, et al. *Environ Health Perspect.* 2017 Oct 19;125(10):107007. Article Link

Significance: In a cohort of Chinese adults, incidence of coronary heart disease was positively associated with plasma levels of titanium and arsenic and was inversely associated with selenium.

BACKGROUND: Circulating metals from both the natural environment and pollution have been linked to cardiovascular disease. However, few prospective studies have investigated the associations between exposure to multiple metals and incident coronary heart disease (CHD). OBJECTIVES: We conducted a nested case-control study in the prospective Dongfeng-Tongji cohort, to investigate the prospective association between plasma metal concentrations and incident CHD. METHODS: A total of 1,621 incident CHD cases and 1,621 controls free of major cardiovascular disease at baseline and follow-up visits were matched on age (±5 years) and sex. We measured baseline fasting plasma concentrations of 23 metals and used conditional logistic regression models to estimate odds ratios (ORs) of CHD for metal concentrations categorized according to quartiles in controls. RESULTS: Five metals (titanium, arsenic, selenium, aluminum, and barium) were significantly associated with CHD based on trend tests from single-metal multivariable models adjusted for established cardiovascular risk factors. When all five were included in the same model, adjusted ORs for barium and aluminum were close to the null, whereas associations with titanium, arsenic, and selenium were similar to estimates from single-metal models, and ORs comparing extreme quartiles were 1.32 (95% CI: 1.03, 1.69; p-trend=0.04), 1.78 (95% CI: 1.29, 2.46; p-trend=0.001), and 0.67 (95% CI: 0.52, 0.85; p-trend=0.001), respectively. CONCLUSIONS: Our study suggested that incident CHD was positively associated with plasma levels of titanium and arsenic, and inversely associated with selenium. Additional research is needed to confirm these findings in other populations.

Serum Lipid, Lipoprotein and Apolipoprotein Profiles in Workers Exposed to Low Arsenic Levels: Lipid Profiles and Occupational Arsenic Exposure

Ledda C, Iavicoli I, Bracci M, Avola R, Senia P, Santarelli L, et al. *Toxicol Lett.* 2017 Oct 18;282:49–56. Article Link

Significance: In a study of workers exposed to arsenic, urinary arsenic levels were positively associated with Lp(a), Apo-A1, and Apo-B concentration and Apo-B/Apo-A1 ratio, indicating a potential effect on CVD risk.

Epidemiologic studies have reported that exposure to arsenic (As) is associated with higher risk of cardiovascular disease (i.e., coronary heart disease and peripheral arterial heart disease) and mortality. This cross-sectional study aimed to compare serum lipid, lipoprotein, and apolipoprotein profiles in workers exposed to As. The subjects of this study included 57 workers exposed to As and 57 controls. Demographic characteristics and occupational information were collected through questionnaires. Exposure to As was assessed in indoor air of a workplace and determined using the creatinine values in the urine. Blood samples were collected using immunochemistry and nephelometry to measure the levels of total cholesterol (CHOL), triglycerides (TRIG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), lipoprotein(a) (Lp(a)), apolipoprotein-A1 (Apo-A1), and apolipoprotein-B (Apo-B). No significant difference in the demographic data was detected between the two groups. Urinary As concentration was significantly ($p<0.001$) higher in exposed subjects than in the controls (13.4±6.1 and 4.4±6.1μg/gCreat, respectively). No statistically significant differences were observed in CHOL, TRIG, HDL, and LDL concentrations between the two groups. Lp(a), Apo-B, and Apo-B/Apo-A1 ratio values were significantly higher and the Apo-A1 level was significantly lower in the exposed group than in the control subjects. Regression analysis highlighted a significant ($p<0.001$) association between urinary As and Lp(a), Apo-A1, and Apo-B concentration, and Apo-B/Apo-A1 ratio. This study revealed the influence of As on apolipoproteins, suggesting a potential risk of cardiovascular diseases in subjects exposed to low levels of As.

An In Vitro Cytotoxic Approach to Assess the Toxicity of Heavy Metals and Their Binary Mixtures on Hippocampal HT-22 Cell Line

Karri V, Kumar V, Ramos D, Oliveira E, Schuhmacher M. *Toxicol Lett.* 2017 Oct 5;282:25–36. Article Link

Significance: In an in vitro test of the toxicity of heavy metals, mixtures showed higher toxicity compared to individual metals.

Humans are exposed to a cocktail of heavy metal toxicants in the environment. Though heavy metals are deleterious, there is a paucity of information on the toxicity of mixtures. In this study, four common neurotoxicity heavy metals lead (Pb) cadmium (Cd), arsenic (As), and methylmercury (MeHg) were exposed individually and as mixtures to HT-22 cell line for 8 days. The study established that low dose exposures induced toxicity to the HT-22 cell line during 8days. The results indicates potency dependent response, the toxicity of single metals on the HT-22 cells; MeHg > As > Cd > Pb. The cytotoxicity data of single metals were used to determine the mixtures interaction profile by using the dose additivity and effect additivity method. Metal mixtures showed higher toxicities compared to individual metals. Synergistic, antagonistic or additive effects of the toxicity were observed in different mixtures in low dose exposure. The interactive responses of mixtures depend on the co-exposure metal and their respective concentration. We concluded that the combined effects should be considered in the risk assessment of heavy metal co-exposure and potency. In future, comprehensive mechanistic based investigations needed for understanding the real interactive mixtures effects at molecular level.

Benchmark Dose Modeling Estimates of the Concentrations of Inorganic Arsenic That Induce Changes to the Neonatal Transcriptome, Proteome, and Epigenome in a Pregnancy Cohort

Rager JE, Auerbach SS, Chappell GA, Martin E, Thompson CM, Fry RC. *Chem Res Toxicol.* 2017 Oct 16;30(10): 1911–1920. Article Link

Significance: Identified benchmark does measures useful in estimating doses at which prenatal inorganic arsenic exposure may influence prenatal outcomes.

Prenatal inorganic arsenic (iAs) exposure influences the expression of critical genes and proteins associated with adverse outcomes in newborns, in part through epigenetic mediators. The doses at which these genomic and epigenomic changes occur have yet to be evaluated in the context of dose-response modeling. The goal of the present study was to estimate iAs doses that correspond to changes in transcriptomic, proteomic, epigenomic, and integrated multi-omic signatures in human cord blood through benchmark dose (BMD) modeling. Genome-wide DNA methylation, microRNA expression, mRNA expression, and protein expression levels in cord blood were modeled against total urinary arsenic (U-tAs) levels from pregnant women exposed to varying levels of iAs. Dose-response relationships were modeled in BMDExpress, and BMDs representing 10% response levels were estimated. Overall, DNA methylation changes were estimated to occur at lower exposure concentrations in comparison to other molecular endpoints. Multi-omic module eigengenes were derived through weighted gene co-expression network analysis, representing co-modulated signatures across transcriptomic, proteomic, and epigenomic profiles. One module eigengene was associated with decreased gestational age occurring alongside increased iAs exposure. Genes/proteins within this module eigengene showed enrichment for organismal development, including potassium voltage-gated channel subfamily Q member 1 (KCNQ1), an imprinted gene showing differential methylation and expression in response to iAs. Modeling of this prioritized multi-omic module eigengene resulted in a BMD(BMDL) of 58(45) μg/L U-tAs, which was estimated to correspond to drinking water arsenic concentrations of 51(40) μg/L. Results are in line with epidemiological evidence supporting effects of prenatal iAs occurring at levels <100 μg As/L urine. Together, findings present a variety of BMD measures to estimate doses at which prenatal iAs exposure influences neonatal outcome-relevant transcriptomic, proteomic, and epigenomic profiles.

Levels of Plasma Selenium and Urinary Total Arsenic Interact to Affect the Risk for Prostate Cancer

Hsueh YM1, Su CT2, Shiue HS3, Chen WJ4, Pu YS5, Lin YC6, et al. *Food Chem Toxicol.* 2017 Sep;107(Pt A):167–175. Article Link

Significance: This is the first epidemiological study to examine the combined effects of plasma selenium and urinary total arsenic levels on the odds ratio for prostate cancer (PC). Data suggest that a low plasma selenium level coupled with a high urinary total arsenic concentration creates a significant risk for aggressive PC.

This study investigated whether plasma selenium levels modified the risk for prostate cancer (PC) related to arsenic exposure. We conducted a case-control study that included 318 PC patients and 318 age-matched, healthy control subjects. Urinary arsenic profiles were examined using HPLC-HG-AAS and plasma selenium levels were measured by ICP-MS. We found that plasma selenium levels displayed a significant dose-dependent inverse association with PC. The odds ratio (OR) and 95% confidence interval (CI) for PC was 0.07 (0.04-0.13) among participants with a plasma selenium level >28.06 μg/dL vs. ≤19.13 μg/dL. A multivariate analysis showed that participants with a urinary total arsenic concentration >29.28 μg/L had a significantly higher OR (1.75, 1.06-2.89) for PC than participants with ≤29.89 μg/L. The combined presence of a low plasma selenium level and a high urinary total arsenic concentration exponentially increased the OR for PC, and additively interacted with PSA at levels ≥20 ng/mL. This is the first epidemiological study to examine the combined effects of plasma selenium and urinary total arsenic levels on the OR for PC. Our data suggest a low plasma selenium level coupled with a high urinary total arsenic concentration creates a significant risk for aggressive PC.