ILSI North America

Food Safety Briefs

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Caffeine

Determination of Caffeine and Identification of Undeclared Substances in Dietary Supplements and Caffeine Dietary Exposure Assessment

Neves DBDJ, Caldas ED. *Food Chem Toxicol.* 2017 Mar 30 [Epub ahead of print]. doi: 10.1016/j.fct.2017.03.06. Article Link

Significance: The aims of this work were to validate a GC-MS method for the quantitation of caffeine and identification of other substances in supplements, mainly weight loss products, and to estimate the caffeine intake by consumers.

Sample preparation included extraction with chloroform: water in ultrasonic bath, centrifugation and analysis of the organic layer for caffeine quantitation, and extraction with methanol for identification of other substances. A total of 213 samples of 52 supplement products not registered in Brazil and seized by the Brazilian Federal Police were analyzed. From the 109 samples that declared the amount of caffeine present, 26.6% contained more than 120% of the specified content. Considering the maximum recommended dose stated on the product labels, the consumption of 47.9% of the samples would lead to a daily intake of caffeine above the safe limit of 400 mg. Undeclared drugs, including sibutramine, phenolphthalein, amphepramone and femproporex were found in 28 samples. These results show that consumers of dietary supplements should be aware that these products might contain caffeine at levels that could represent potential health risks, in addition to undeclared pharmaceutical drugs.

The Impact of Coffee Consumption on Blood Pressure, Cardiovascular Disease and Diabetes Mellitus

Chrysant SG. *Expert Rev Cardiovasc Ther.* 2017 Mar;15(3):151–156. Article Link

Significance: Based on the evidence from these studies, coffee consumption in moderation, is safe and is beneficial in both healthy persons as well as patients with high BP, CVD, HF, cardiac arrhythmias or DM

Coffee is the most widely consumed beverage, next to water. However, there has been a long-standing controversy regarding its safety on blood pressure (BP) and cardiovascular disease (CVD) and intuitively, physicians dissuaded their patients from coffee drinking. Areas covered: This controversy was, primarily, based on older prospective studies or case reports, which showed a positive association of coffee drinking with the incidence of hypertension and CVD. In contrast to these reports, recent, well controlled, studies have demonstrated either a neutral or beneficial effect of moderate coffee consumption (3-4 cups/day), on BP, CVD, heart failure (HF), cardiac arrhythmias, or diabetes mellitus (DM). For the preparation of this special report, an English language focused search of the Medline database was conducted between 2010 and 2016 on studies with data on effect on the coffee consumption in patients with high BP, CVD, HF, cardiac arrhythmias or DM. Of the 94 abstracts reviewed, 34 pertinent papers were selected, and the findings from these papers together with collateral literature will be discussed in this special report. Expert commentary: Based on the evidence from these studies, coffee consumption in moderation, is safe and is beneficial in both healthy persons as well as patients with high BP, CVD, HF, cardiac arrhythmias or DM. Therefore, coffee restriction is not warranted for these patients, although some caution should be exercised.

Risk Assessment

International Consensus Guidelines for the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome: Executive Summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology

Nowak-Węgrzyn A, Chehade M, Groetch ME, Spergel JM, Wood RA, Allen K, et al. *J Allergy Clin Immunol.* 2017 Feb 4 [Epub ahead of print]. doi: 10.1016/j.jaci.2016.12.966. Article Link

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Significance: These are the first international evidence-based guidelines to improve the diagnosis and management of patients with FPIES (Food protein-induces enterocolitis).

Food protein-induced enterocolitis (FPIES) is a non-IgE cell- mediated food allergy that can be severe and lead to shock. Despite the potential seriousness of reactions, awareness of FPIES is low; high-quality studies providing insight into the pathophysiology, diagnosis, and management are lacking; and clinical outcomes are poorly established. This consensus document is the result of work done by an international workgroup convened through the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma & Immunology and the International FPIES Association advocacy group. These are the first international evidence-based guidelines to improve the diagnosis and management of patients with FPIES. Research on prevalence, pathophysiology, diagnostic markers, and future treatments is necessary to improve the care of patients with FPIES. These guidelines will be updated periodically as more evidence becomes available.

A Framework for Cumulative Risk Assessment in the 21st Century

Moretto A, Bachman A, Boobis A, Solomon KR, Pastoor TP, Wilks MF, et al. *Crit Rev Toxicol.* 2017 Feb;47(2):85–97. doi: 10.1080/10408444.2016.1211618. Article Link

Significance: The ILSI Health and Environmental Sciences Institute (HESI) has developed a framework to support a transition in the way in which information for chemical risk assessment is obtained and used (RISK21).

The approach is based on detailed problem formulation, where exposure drives the data acquisition process in order to enable informed decision-making on human health safety as soon as sufficient evidence is available. Information is evaluated in a transparent and consistent way with the aim of optimizing available resources. In the context of risk assessment, cumulative risk assessment (CRA) poses additional problems and questions that can be addressed using the RISK21 approach. The focus in CRA to date has generally been on chemicals that have common mechanisms of action. Recently, concern has also been expressed about chemicals acting on multiple pathways that lead to a common health outcome, and non-chemical other conditions (non-chemical stressors) that can lead to or modify a common outcome. Acknowledging that CRAs, as described above, are more conceptually, methodologically and computationally complex than traditional single-stressor risk assessments, RISK21 further developed the framework for implementation of workable processes and procedures for conducting assessments of combined effects from exposure to multiple chemicals and non-chemical stressors. As part of the problem formulation process, this evidence-based framework allows the identification of the circumstances in which it is appropriate to conduct a CRA for a group of compounds. A tiered approach is then proposed, where additional chemical stressors and/or non-chemical modulating factors (ModFs) are considered sequentially. Criteria are provided to facilitate the decision on whether or not to include ModFs in the formal quantitative assessment, with the intention to help focus the use of available resources to have the greatest potential to protect public health.

Low-Dose Mixture Hypothesis of Carcinogenesis Workshop: Scientific Underpinnings and Research Recommendations

Miller MF, Goodson WH, Manjili MH, Kleinstreuer N, Bisson WH, Lowe L. *Environ Health Perspect.* 2017 Feb;125(2):163–169. doi: 10.1289/EHP411. Article Link

The current single-chemical-as-carcinogen risk assessment paradigm might underestimate or miss the cumulative effects of exposure to chemical mixtures, as highlighted in recent work from the Halifax Project. This is particularly important for chemical exposures in the low-dose range that may be affecting crucial cancer hallmark mechanisms that serve to enable carcinogenesis. Could ongoing low-dose exposures to a mixture of commonly encountered environmental chemicals produce effects in concert that lead to carcinogenesis? A workshop held at the NIEHS in August 2015 evaluated the scientific support for the low-dose mixture hypothesis of carcinogenesis and developed a research agenda. Here we describe the science that supports this novel theory, identify knowledge gaps, recommend future methodologies, and explore preventative risk assessment and policy decision-making that incorporates cancer biology, environmental health science, translational toxicology, and clinical epidemiology. The theoretical merits of the low-dose carcinogenesis hypothesis are well founded with clear biological relevance, and therefore, the premise warrants further investigation. Expert recommendations include the need for better insights into the ways in which noncarcinogenic constituents might combine to uniquely affect the process of cellular transformation (in vitro) and environmental carcinogenesis (in vivo), including investigations of the role of key defense mechanisms in maintaining transformed cells in a dormant state. The scientific community will need to acknowledge limitations of animal-based models in predicting human responses; evaluate biological events leading to carcinogenesis both spatially and temporally; examine the overlap between measurable cancer hallmarks and characteristics of carcinogens; incorporate epigenetic biomarkers, in silico modelling, high-performance computing and high-resolution imaging, microbiome, metabolomics, and transcriptomics into future research efforts; and build molecular annotations of network perturbations. The restructuring of many existing regulatory frameworks will require adequate testing of relevant environmental mixtures to build a critical mass of evidence on which to base policy decisions.

Toxicology

Evaluating the Impact of the U.S. National Toxicology Program: A Case Study on Hexavalent Chromium

Xie Y, Holmgren S, Andrews DMK, Wolfe MS. *Environ Health Perspect*. 2017 Feb;125(2):181–188. doi: 10.1289/EHP21. Article Link

Significance: This study identified a broad and objective approach for assessing NTP's effectiveness, including methodological needs for more thorough and efficient impact assessments in the future.

Evaluating the impact of federally funded research with a broad, methodical, and objective approach is important to ensure that public funds advance the mission of federal agencies. Researchers aimed to develop a methodical approach that would yield a broad assessment of National Toxicology Program's (NTP's) effectiveness across multiple sectors and demonstrate the utility of the approach through a case study. A conceptual model was developed with defined activities, outputs (products), and outcomes (proximal, intermediate, distal) and applied retrospectively to NTP's research on hexavalent chromium (CrVI). Proximal outcomes were measured by counting views of and requests for NTP's products by external stakeholders. Intermediate outcomes were measured by bibliometric analysis. Distal outcomes were assessed through Web and LexisNexis searches for documents related to legislation or regulation changes. The approach identified awareness of NTP's work on CrVI by external stakeholders (proximal outcome) and citations of NTP's research in scientific publications, reports, congressional testimonies, and legal and policy documents (intermediate outcome). NTP's research was key to the nation's first-ever drinking water standard for CrVI adopted by California in 2014 (distal outcome). By applying this approach to a case study, the utility and limitations of the approach were identified, including challenges to evaluating the outcomes of a research program. This study identified a broad and objective approach for assessing NTP's effectiveness, including methodological needs for more thorough and efficient impact assessments in the future.

Modeling Exposure in the Tox21 *In Vitro* Bioassays

Fischer FC, Henneberger L, König M, Bittermann K, Linden L, Goss K, et al. *Chem Res Toxicol*. 2017 Mar 19 [Epub ahead of print]. doi: 10.1021/acs.chemrestox.7b00023. Article Link

Significance: High-throughput *in vitro* bioassays are becoming increasingly important in the risk characterization of anthropogenic chemicals. Large databases gather nominal effect concentrations (C_{nom}) for diverse modes of action.

However, the biologically effective concentration can substantially deviate due to differences in chemical partitioning. In this study, we modeled freely dissolved (C_{free}), cellular (C_{cell}), and membrane concentrations (C_{mem}) in the Tox21 GeneBLAzer bioassays for a set of neutral and ionogenic organic chemicals covering a large physicochemical space. Cells and medium constituents were experimentally characterized for their lipid and protein content and partition constants were collected from the literature or predicted by mechanistic models. The chemicals exhibited multifaceted partitioning to proteins and lipids with distribution ratios spanning over eight orders of magnitude. Modeled C_{free} deviated over five orders of magnitude from C_{nom}, and can be compared to *in vivo* effect data, environmental concentrations and the unbound fraction in plasma, which is needed for the *in vitro* to *in vivo* extrapolation. C_{cell} was relatively constant for chemicals with membrane lipid-water distribution ratios of 1000 or higher and proportional to C_{nom}. Representing a sum parameter for exposure that integrates the entire dose from intracellular partitioning, C_{cell} is particularly suitable for the effect characterization of chemicals with multiple target sites and the calculation of their relative effect potencies. Effective membrane concentrations indicated that the specific effects of very hydrophobic chemicals in multiple bioassays are occurring at concentrations close to cytotoxicity. The equilibrium partitioning model including all relevant system parameters and a generic set-up is attached as an excel workbook to this paper and can readily be applied by everyone to diverse *in vitro* bioassays.

Scientific Integrity

Ensuring Scientific Integrity in the Age of Trump

Goldman GT, Berman E, Halpern M, Johnson C, Kothari Y, Reed G, et al. *Science*. 2017 Feb 17;355(6326):696–698. doi: 10.1126/science.aam5733. Article Link

With the new Donald J. Trump Administration comes uncertainty in the role that science will play in the U.S. federal government. Early indications that the Administration plans to distort or disregard science and evidence, coupled with the chaos and confusion occurring within federal agencies, now imperil the effectiveness of our government. Evidence from the past 20 years demonstrates that, when faced with such threats, supporters of science can take steps to protect the integrity of science in the federal policy-making process. The scientific community will need to connect science-informed policy to positive outcomes and staunchly defend scientific freedom. It must also spotlight political interference in science-based policy development and be prepared to protect scientists—both within and outside the government—against executive or legislative overreach. A range of scientific integrity and transparency policies across federal agencies provides critical tools but must be enforced and protected.