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Food Safety Briefs

Risk Assessment

Opportunities and Challenges Related to Saturation of Toxicokinetic Processes: Implications for Risk Assessment

Yu-Mei Tan, Hugh A Barton, Alan Boobis, Rachel Brunner, Harvey Clewell, Rhian Cope, Jeffrey Dawson, et. al. *Regul Toxicol Pharmacol*. 2021 Dec;127:105070. doi: 10.1016/j.yrtph.2021.105070. **Article link**

Significance: Absorption and metabolism may limit exposure to contaminants as toxicokinetic pathways get saturated, altering the results of risk assessments.

Top dose selection for repeated dose animal studies has generally focused on identification of apical endpoints, use of the limit dose, or determination of a maximum tolerated dose (MTD). The intent is to optimize the ability of toxicity tests performed in a small number of animals to detect effects for hazard identification. An alternative approach, the kinetically derived maximum dose (KMD), has been proposed as a mechanism to integrate toxicokinetic (TK) data into the dose selection process. The approach refers to the dose above which the systemic exposures depart from being proportional to external doses. This non-linear external-internal dose relationship arises from saturation or limitation of TK process(es), such as absorption or metabolism. The importance of TK information is widely acknowledged when assessing human health risks arising from exposures to environmental chemicals, as TK determines the amount of chemical at potential sites of toxicological responses. However, there have been differing opinions and interpretations within the scientific and regulatory communities related to the validity and application of the KMD concept. A multi-stakeholder working group was formed to provide an opportunity for impacted stakeholders to address commonly raised scientific and technical issues related to this topic and, more specifically, a weight of evidence approach is recommended to inform design and dose selection for repeated dose animal studies. Commonly raised challenges related to the use of TK data for dose selection are discussed, recommendations are provided, and illustrative case examples are provided to address these challenges or refute misconceptions.

Foodborne Pathogens

Relationship Between Growth Ability, Virulence, and Resistance to Food-Processing Related Stresses in Non-typhoidal *Salmonellae*.

Silvia Guillén, María Marcén, Ester Fau, Pilar Mañas, Guillermo Cebrián. *Int J Food Microbiol*. 2022 Jan 16;361:109462. doi: 10.1016/j.ijfoodmicro.2021.109462. **Article link**

Significance: 23 *Salmonella* strains belonging to different serovars were examined and compared with their previously determined stress resistance parameters to understand how strains adapt to and resist harsh conditions and food safety interventions.

The ability of *Salmonella* to resist and adapt to harsh conditions is one of the major features that have made this microorganism such a relevant health hazard. However, the impact of these resistance responses on other aspects of *Salmonella* physiology, such as virulence and growth ability, is still not fully understood. The objective of this study was to determine the maximum growth rates (in three different media), virulence (adhesion and invasion of Caco-2 cells), and other phenotypic characteristics (biofilm-forming ability and antimicrobial resistance) of 23 *Salmonella* strains belonging to different serovars, and to compare them with their previously determined stress resistance parameters. Significant differences ($p < 0.05$) in growth rates, virulence, and biofilm-forming ability were found among the 23 strains studied. Nevertheless, whereas less

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than 3-fold change between the lowest and the highest growth rate was observed, the percentage of cells capable of invading Caco-2 cells varied more than 100-fold, that to form biofilms more than 30-fold, and the antibiotic MICs varied up to 512-fold, among the different strains. Results indicate that those strains with the highest cell adhesion ability were not always the most invasive ones and suggest that, in general terms, a higher stress resistance did not imply a reduced growth ability (rate). Similarly, no association between stress resistance and biofilm formation ability (except for acid stress) or antibiotic resistance (with minor exceptions) was found. Our data also suggest that, in *Salmonella*, acid stress resistance would be associated with virulence, since a positive correlation of that trait with adhesion and a negative correlation with invasion was found. This study contributes to a better understanding of the physiology of *Salmonella* and the relationship between bacterial stress resistance, growth ability, and virulence. It also provides new data regarding intra-specific variability of a series of phenotypic characteristics of *Salmonella* that are relevant from the food safety perspective.

Foodborne Illness

A Review of Significant European Foodborne Outbreaks in the Last Decade.

Eleonora Sarno, Denise Pezzutto, Mirko Rossi, Ernesto Liebana, Valentina Rizzi. *J Food Prot*. 2021 Dec 1;84(12):2059-2070. doi: 10.4315/JFP-21-096. **Article link**

Significance: A series of pathogen outbreaks in the EU highlighted the need to harmonize bioinformatics outputs and computational approaches to facilitate detection and investigation of foodborne illnesses.

Foodborne diseases remain a global public health challenge worldwide. The European surveillance system of multistate foodborne outbreaks integrates elements from public and animal health and the food chain for early detection, assessment and control. This review includes descriptions of the significant outbreaks that occurred in Europe in the last decade. Their significance and relevance to public health is derived from the changes, improvements, and novelties that pushed toward building a safer food system in the European Union, certainly driven by the One Health approach. In 2011, a point source monoclonal outbreak of infections caused by *Escherichia coli* serotype O104:H4 in sprouted seeds resulted in hundreds of cases of hemolytic uremic syndrome and several fatalities. In 2015, a prolonged outbreak of *Listeria monocytogenes* infections caused by contamination of frozen corn in Europe resulted in 47 cases and nine deaths. In 2016, a persistent polyclonal outbreak of *Salmonella Enteritidis* was linked to the consumption of eggs and was associated with hundreds of cases. The outbreak evaluations highlight the importance of rapid sharing of data (e.g., sequencing and tracing data) and the need for harmonizing bioinformatics outputs and computational approaches to facilitate detection and investigation of foodborne illnesses. These outbreaks led to development of a legal framework for a European collaboration platform for sharing whole genome sequence data and enabled the enforcement of existing hygiene and food safety provisions and the development of new hygiene guidelines and best practices. This review also briefly touches on the new trends in information technologies that are being explored for food traceability and safety. These technologies could enhance the traceability of food throughout the supply chain and redirect the conventional tracing system toward a digitized supply chain.

Mycotoxins

Current and Emerging Tools of Computational Biology to Improve the Detoxification of Mycotoxins

Natalie Sandlin, Darius Russell Kish, John Kim, Marco Zaccaria, Babak Momeni. *Appl Environ Microbiol*. 2021 Dec 8;AEM0210221. doi: 10.1128/AEM.02102-21. **Article link**

Significance: The use of computational tools can help discover strains and enzymes that detoxify harmful mycotoxins-fungi-produced toxins that contaminate food and feed. The tools also help develop biological enzymes that are capable of rendering them less harmful.

Biological organisms carry a rich potential for removing toxins from our environment, but identifying suitable candidates and improving them remain challenging. We explore the use of computational tools to discover strains and enzymes that detoxify harmful compounds. In particular, we will focus on mycotoxins-fungi-produced toxins that contaminate food and feed-and biological enzymes that are capable of rendering them less harmful. We discuss the use of established and novel computational tools to complement existing empirical data in three directions: discovering the prospect of detoxification among underexplored organisms, finding important cellular processes that contribute to detoxification, and improving the performance of detoxifying enzymes. We hope to create a synergistic conversation between researchers in computational biology and those in the bioremediation field. We showcase open bioremediation questions where computational researchers can contribute and highlight relevant existing and emerging computational tools that could benefit bioremediation researchers.

Food Packaging

Recent Advances in Intelligent Food Packaging Materials: Principles, Preparation and Applications

Hao Cheng, Hao Xu, David Julian McClements, Long Chen, Aiquan Jiao, Yaoqi Tian, Ming Miao, Zhengyu Jin. *Food Chem*. 2021 Dec 2;375:131738. doi: 10.1016/j.foodchem.2021.131738. **Article link**

Significance: Smart packaging materials are being developed to continuously monitor the properties of packaged foods and provide real-time information about their maturity, quality and safety. Different sensing methods can be used to detect alterations in food properties, such as those based on changes in time, temperature, humidity, oxygen levels, pH, chemical composition, or microbial contamination.

Traditionally, food packaging is used for improving food quality and providing consumers with descriptions of products. A new generation of intelligent ("smart") packaging materials is being developed to continuously monitor the properties of packaged foods and provide real-time information about their maturity, quality, and safety. In this paper, recent research in the development, properties, and applications of intelligent food packaging materials is summarized. Initially, we review the different sensing methods that can be used to detect alterations in food properties, such as those based on changes in time, temperature, humidity, oxygen levels, pH, chemical composition, or microbial contamination. The different approaches that can be used to design intelligent packaging materials are then highlighted, including films, bar codes, and labels. A number of applications of these packaging materials are then discussed to demonstrate their potential in the food industry. Finally, the challenges and future directions of food packaging are discussed.

Heavy Metals

Threshold Effects of Total Copper Intake on Cognitive Function in US Older Adults and the Moderating Effect of Fat and Saturated Fatty Acid Intake

Xiaoxu Wang, Xuelian Li, Yufang Xing, Weijing Wang, Suyun Li, Dongfeng Zhang, Wei Zheng, Xiaoli Shen. *J Acad Nutr Diet*. 2021 Dec;121(12):2429-2442. doi: 10.1016/j.jand.2021.06.002. **Article link**

Significance: This study identifies threshold effects of copper intake on cognitive function. Copper intake below the inflection point was positively associated with cognitive function. High fat and high SFA intake may protect older adults against a decline in cognitive test scores related to high copper intake.

Background: Evidence for a relationship between total copper intake and cognition is lacking, and few studies have assessed the moderating effect of dietary fat and saturated fatty acid (SFA) intake on this relationship. **Objective**: Our aim was to explore the curvilinear association between total copper intake and cognitive function in older adults, and to clarify the moderating effect of dietary fat and SFA intake on the association. **Design**: This was a cross-sectional analysis of data from National Health and Nutrition Examination Surveys 2011-2014. **Participants**: The analysis included 2,483 participants aged 60 years and older. **Main outcome measures**: Cognitive function was evaluated by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word Learning subtest, the Animal Fluency Test, and the Digit Symbol Substitution Test (DSST). S**tatistical analyses performed:** Smooth curve fitting and two-piecewise linear regression models were performed to address the nonlinear association between total copper intake and cognitive function. Multivariable quadratic regression models and analyses stratified by total fat or SFA intake were used to assess the effects of the interaction between copper and fat intake and between copper and SFA intake on cognitive function. **Results**: There was a nonlinear association between total copper intake and cognitive test scores. The inflection point of copper was 0.8 mg/d for the Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest and 1.4 mg/d for both the Animal Fluency test and the DSST. When copper intake was below the inflection point, positive associations were apparent for copper intake and Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest scores (β = 3.9; 95% CI 1.2 to 6.5), Animal Fluency test scores (β = 1.7, 95% CI .9 to 2.6), and DSST scores (β = 6.0, 95% CI 3.8 to 8.3). When copper intake was above the inflection point, a nonsignificant downward trend was found. Interactive effects between total copper and total fat intake (P interaction = .000) and between total copper and SFA intake (P interaction = .011) on the DSST scores were observed. In the low-fat intake and low SFA intake groups, DSST scores first increased and then decreased with increasing copper. However, in the high fat intake and high SFA intake groups, DSST scores first increased and

then flattened with increasing copper. **Conclusions**: The present study suggests a nonlinear association between copper intake and cognitive function and identifies threshold effects of copper intake on cognitive function. Copper intake below the inflection point was positively and independently associated with cognitive function. High fat and high SFA intake may protect older adults against a decline in DSST scores related to high copper intake.

Chemical Contaminants

Occurrence of Ethyl Carbamate in Foods and Beverages: Review of the Formation Mechanisms, Advances in Analytical Methods, and Mitigation Strategies.

Eileen Abt, Victoria Incorvati, Lauren Posnick, Robin Benjamin W Redan. *J Food Prot*. 2021 Dec 1;84(12):2195-2212. doi: 10.4315/JFP-21-219. **Article link**

Significance: The by-product ethyl carbamate can be found in beverages, breads, soy sauce and wines. Various mitigation methods are described as being used to maintain EC concentrations below allowable limits, including distillation, enzymatic treatments and genetic engineering of yeast.

Abstract: Ethyl carbamate (EC) is a process contaminant that can be formed as a by-product during fermentation and processing of foods and beverages. Elevated EC concentrations are primarily associated with distilled spirits, but this compound has also been found at lower concentrations in foods and beverages, including breads, soy sauce, and wine. Evidence from animal studies suggests that EC is a probable human carcinogen. Consequently, several governmental institutions have established allowable limits for EC in the food supply. This review includes EC formation mechanisms, occurrence of EC in the food supply, and EC dietary exposure assessments. Current analytical methods used to detect EC will be covered, in addition to emerging technologies, such as nanosensors and surface-enhanced Raman spectroscopy. Various mitigation methods have been used to maintain EC concentrations below allowable limits, including distillation, enzymatic treatments, and genetic engineering of yeast. More research in this field is needed to refine mitigation strategies and develop methods to rapidly detect EC in the food supply.

Caffeine

Pharmacokinetic, Pharmacological, and Genotoxic Evaluation of Deuterated Caffeine

Ryan M Parente, Paul M Tarantino, Bradford C Sippy, George A Burdock. *Food Chem Toxicol*. 2021 Dec 30;112774. doi: 10.1016/j.fct.2021.112774. **Article link**

Significance: Deuterated d9-Caffeine may prove to be an alternative to caffeine that may be consumed with less frequency, at lower doses, and with less exposure to downstream active caffeine metabolites. Characterization of d9-caffeine's genotoxic potential, pharmacodynamic and pharmacokinetic behavior is critical in establishing how it may differ from caffeine.

Altering caffeine's negative physiological effects and extending its duration of activity is an active area of research; however, deuteration as a means of achieving these goals is unexplored. Deuteration substitutes one or more of the hydrogen atoms of a substance with deuterium, a stable isotope of hydrogen that contains an extra neutron. Deuteration can potentially alter the metabolic profile of a substance, while maintaining its pharmacodynamic properties. d9-Caffeine is a deuterated isotopologue of caffeine with the nine hydrogens contained in the 1, 3, and 7 methyl groups of caffeine substituted with deuterium. d9-Caffeine may prove to be an alternative to caffeine that may be consumed with less frequency, at lower doses, and with less exposure to downstream active metabolites of caffeine. Characterization of d9-caffeine's genotoxic potential, pharmacodynamic, and pharmacokinetic behavior is critical in establishing how it may differ from caffeine. d9-Caffeine was non-genotoxic with and without metabolic activation in both a bacterial reverse mutation assay and a human mammalian cell micronucleus assay at concentrations up to the ICH concentration limits. d9-Caffeine exhibited a prolonged systemic and brain exposure time in rats as compared to caffeine following oral administration. The adenosine receptor antagonist potency of d9-caffeine was similar to caffeine.

Food Allergens

Food Allergy Across the Globe

Vanitha Sampath, Elissa M Abrams, Bahman Adlou, Cezmi Akdis, Mübeccel Akdis, Helen A Brough, Susan Chan, et. al. *J Allergy Clin Immunol*. 2021 Dec;148(6):1347-1364. doi: 10.1016/j.jaci.2021.10.018. **Article link**

Significance: Reviews the global prevalence of food allergy, current understandings of the causes of FA, and the latest guidelines for preventing, diagnosing, and treating FA.

The prevalence of food allergy (FA) is increasing in some areas of the globe, highlighting the need for better strategies for prevention, diagnosis, and therapy. In the last few decades, we have made great strides in understanding the causes and mechanisms underlying FAs, prompting guideline updates. Earlier guidelines recommended avoidance of common food allergens during pregnancy and lactation and delaying the introduction of allergenic foods in children aged between 1 and 3 years. Recent guidelines for allergy prevention recommend consumption of a healthy and diverse diet without eliminating or increasing the consumption of allergenic foods during pregnancy or breast-feeding. Early introduction of allergenic foods is recommended by most guidelines for allergy prevention after a period of exclusive breast-feedng (6 months [World Health Organization] or 4 months [European Academy of Allergy and Clinical Immunology]). New diagnostics for FA have been developed with varied availability of these tests in different countries. Finally, the first oral immunotherapy drug for FA was approved by the US Food and Drug Administration and European Medicines Agency in 2020. In this review, we will address the global prevalence of FA, our current understanding of the causes of FA, and the latest guidelines for preventing, diagnosing, and treating FA. We will also discuss similarities and differences between FA guidelines.