Food Safety Briefs

Risk Assessment

Development of a Novel Machine Learning-Based Weighted Modeling Approach to Incorporate *Salmonella enterica* Heterogeneity on a Genetic Scale in a Dose-Response Modeling Framework

Shraddha Karanth, Abani K Pradhan. *Risk Anal.* 2023 Mar;43(3):440-450. doi: 10.1111/risa.13924. **Article link**

Significance: The addition of gene expression data could improve or redefine dose-response relationships for illness related to pathogens.

Estimating microbial dose-response is an important aspect of a food safety risk assessment. In recent years, there has been considerable interest to advance these models with potential incorporation of gene expression data. The aim of this study was to develop a novel machine learning model that considers the weights of expression of *Salmonella* genes that could be associated with illness, given exposure, in hosts. Here, an elastic net-based weighted Poisson regression method was proposed to identify *Salmonella enterica* genes that could be significantly associated with the illness response, irrespective of serovar. The best-fit elastic net model was obtained by 10-fold cross-validation. The best-fit elastic net model identified 33 gene expression-dose interaction terms that added to the predictability of the model. Of these, nine genes associated with *Salmonella* metabolism and virulence were found to be significant by the best-fit Poisson regression model ($p < 0.05$). This method could improve or redefine dose-response relationships for illness from relative proportions of significant genes from a microbial genetic dataset, which would help in refining endpoint and risk estimations.

Foodborne Pathogens

Lipid Oxidation and Volatile Compounds of Almonds as Affected by Gaseous Chlorine Dioxide Treatment to Reduce *Salmonella* Populations

Wenli Wang, David J Smith, Helen Ngo, Zhonglin Tony Jin, Alyson E Mitchell, Xuetong Fan. *Agric Food Chem.* 2023 Mar 22. doi: 10.1021/acs.jafc.3c00267. **Article link**

Significance: Chlorine dioxide gas was used to inactivate pathogens on almonds and promoted lipid oxidation, acid numbers and several chlorine-containing compounds.

The effects of gaseous chlorine dioxide (ClO_2) treatment, applied to inactivate *Salmonella*, on lipid oxidation, volatile compounds, and chlorate levels of dehulled almonds were evaluated during a 3 month accelerated storage at 39 °C. At treatment levels that yielded a 2.91 log reduction of *Salmonella,* ClO_2 promoted lipid oxidation as indicated by increased peroxide values, total acid number, conjugated dienes, and thiobarbituric acid-reactive

substances. Furthermore, several chlorine-containing volatile compounds including trichloromethane, 1-chloro-2-propanol, 1,1,1-trichloro-2-propanol, and 1,3-dichloro-2-propanol were identified in ClO_2-treated samples. However, all the volatile chlorine-containing compounds decreased during the 3 months of storage. Chlorate (26.4 ± 5.1 µg/g) was found on the ClO_2-treated samples. The amounts of non-ethanol alcohols, aldehydes, and carboxylic acids increased following ClO_2 treatments. Some volatiles such as 2,3-butanediol that were present in non-treated samples became non-detectable during post-ClO_2 treatment storage. Overall, our results demonstrated that gaseous ClO_2 treatment promoted lipid oxidation, generation of volatiles of lipid origin, and several chlorine-containing compounds.

Foodborne Illness

Recalls Associated with Food Allergens and Gluten in FDA-Regulated Foods from Fiscal Years 2013 to 2019

Girdhari M Sharma, Yinqing Ma, Stefano Luccioli. *J Food Prot*. 2023 Mar 2;86(4):100069. doi: 10.1016/j.jfp.2023.100069. **Article link**

Significance: Study reviews 1,471 FDA recalls and finds that 1415 were due to presence of major food allergens, 34 recalls were due to gluten-free labeling violation, and 23 recalls involved other allergens.

Allergens are one of the leading causes of food recalls in the US. The Food and Drug Administration (FDA) enforces requirements relating to major food allergens (MFAs) and gluten-free labeling to ensure food safety for allergic and celiac patients, respectively. Violative foods are subject to recalls. In this study, recall data for FDA-regulated foods were analyzed for fiscal years (FYs) 2013-2019 to identify trends and root causes associated with 1471 food allergen and gluten recalls. Of the 1471 recalls, 1415 recalls were due to MFAs, 34 recalls were due to gluten-free labeling violation and 23 recalls involved other allergens. Recalls due to MFAs overall increased during the study period with a peak incidence in FY 2017. MFA recall health hazard classifications were assessed as Class I (51.2%), Class II (45.5%), and Class III (3.3%). A majority of MFA recalls involved one allergen (78.8%). Milk was the most common MFA involved in MFA recalls (37.5%), followed by soy (22.5%) and tree nuts (21.6%). Almond, anchovy, and shrimp were the most common allergens recalled within the MFA groups of tree nuts, fish, and Crustacean shellfish, respectively. About 97% of MFA recalls involved one product category and among them, the category of 'bakery products, dough, bakery mixes and icings' ranked first (367 recalls), followed by the category of 'chocolate and cocoa products' (120 recalls). Labeling-associated errors accounted for 71.1% of MFA recalls with known root causes (914 out of 1286). It is important for the industry to develop and implement appropriate allergen controls to reduce the number of MFA recalls.

Mycotoxins

Stilbenoids as Promising Natural Product-Based Solutions in a Race against Mycotoxigenic Fungi: A Comprehensive Review

Trang Minh Tran, Vessela Atanasova, Charles Tardif, Florence Richard-Forget. *J Agric Food Chem*. 2023 Mar 23. doi: 10.1021/acs.jafc.3c00407. **Article link**

Significance: Stilbenoids extracted from renewable agricultural wastes like grape canes and forestry byproducts can serve as antimycotoxin agents.

Exposure to mycotoxins can pose a variety of adverse health effects to mammals. Despite dozens of mycotoxin decontamination strategies applied from pre- to postharvest stages, it is always challenging to guarantee a safe level of these natural toxic compounds in food and feedstuffs. In the context of the increased occurrence of drug-resistance strains of mycotoxin-producing fungi driven by the overuse of fungicides, the search for new natural-product-based solutions is a top priority. This review aims to shed a light on the promising potential of stilbenoids extracted from renewable agricultural wastes (e.g., grape canes and forestry byproducts) as antimycotoxin agents. Deeper insights into the mode of actions underlying the bioactivity of stilbenoid molecules against fungal pathogens, together with their roles in plant defense responses, are provided. Safety aspects of these natural compounds on humans and ecology are discussed. Perspectives on the development of stilbenoid-based formulations using encapsulation technology, which allows the bypassing of the limitations related to stilbenoids, particularly low aqueous solubility, are addressed. Optimistically, the knowledge gathered in the present review supports the use of currently underrated agricultural byproducts to produce stilbenoid-abundant extracts with a high efficiency in the mitigation of mycotoxins in food and feedstuffs.

Heavy Metals

Transcriptional Control of *hgcAB* by an ArsR-Like Regulator in *Pseudodesulfovibrio mercurii* ND132

Significance: Arsenic significantly impacted rates of mercury methylation but responses vary with culture conditions.

The *hgcAB* gene pair encodes mercury (Hg) methylation capability in a diverse group of microorganisms, but its evolution and transcriptional regulation remain unknown. Working from the possibility that the evolutionary function of *HgcAB* may not be Hg methylation, we test a possible link to arsenic resistance. Using model Hg methylator *Pseudodesulfovibrio mercurii* ND132, we evaluated transcriptional control of *hgcAB* by a putative ArsR encoded upstream and cotranscribed with *hgcAB*. This regulator shares homology with ArsR repressors of arsenic resistance and S-adenosylhomocysteine (SAH)-responsive regulators of methionine biosynthesis but is distinct from other ArsR/SahR proteins in *P. mercurii*. Using quantitative PCR (qPCR) and RNA sequencing (RNA-seq) transcriptome analyses, we confirmed this ArsR regulates *hgcAB* transcription and is responsive to arsenic and SAH. Additionally, RNA-seq indicated a possible link between *hgcAB* activity and arsenic transformations, with significant upregulation of other ArsR-regulated arsenic resistance operons alongside *hgcAB*. Interestingly, wild-type ND132 was less sensitive to As(V) (but not As(III)) than an hgcAB knockout strain, supporting the idea that *hgcAB* may be linked to arsenic resistance. Arsenic significantly impacted rates of Hg methylation by ND132; however, responses varied with culture conditions. Differences in growth and metabolic activity did not account for arsenic impacts on methylation. While arsenic significantly increased *hgcAB* expression, *hgcAB* gene and transcript abundance was not a good predictor of Hg methylation rates. Taken together, these results support the idea that Hg and As cycling are linked in *P. mercurii* ND132. Our results may hold clues to the evolution of *hgcAB* and the controls on Hg methylation in nature. IMPORTANCE: This work reveals a link between microbial mercury methylation and arsenic resistance and may hold clues to the evolution of mercury methylation genes (*hgcAB*). Microbes with *hgcAB* produce methylmercury, a strong neurotoxin that readily accumulates in the food web. This study addresses a critical gap in our understanding about the environmental factors that control *hgcAB* expression. We show that *hgcAB* expression is controlled by an ArsR-like regulator responsive to both arsenic and S-adenosylhomocysteine in our model organism, *Pseudodesulfovibrio mercurii* ND132. Exposure to arsenic also significantly impacted *Pseudodesulfovibrio mercurii* ND132 mercury methylation rates. However, expression of *hgcAB* was not always a good predictor of Hg methylation rates, highlighting the roles of Hg bioavailability and other biochemical mechanisms in methylmercury production. This study improves our understanding of the controls on *hgcAB* expression, which is needed to better predict environmental methylmercury production.

Food Packaging

Characterization of a New Polymeric Food Contact Coating with Emphasis on the Chemical Analysis and Safety Assessment of Non-Intentionally Added Substances (NIAS)

Significance: A new process helps to identify, characterize and prioritize for safety assessment low molecular weight Non-Intentionally Added Substances.

Regulators have established safety requirements for food packaging raw materials and finished products, including by-products of polymer synthesis known as non-intentionally added substances (NIAS). However, there are no official guidance or regulations for best practices to evaluate the safety of NIAS. Here we described the process we followed to identify, characterize, and prioritize for safety assessment low molecular weight NIAS from an epoxy coating (V70) made with tetramethyl bisphenol F-based diglycidyl ether resin (TMBPF-DGE). We assembled a database of 15000 potential oligomers with masses up to 1000 Da and conducted extraction and migration testing of V70 coating. Acetonitrile extract contained higher number and concentration of substances compared to ethanolic-based food simulants. The extract contained 16 substances with matches in the database with estimated concentration of 18.27 μg/6 dm2; seven of these substances have potentially genotoxic oxirane functionality. TMBPF-DGE + hydroquinone (TMBPF-DGE + HQ) was most abundant (55% of total concentration) and was synthesized and prioritized for safety assessment. TMBPF-DGE + HQ exposure from can beverage was estimated at 5.2 μg/person/day, and it was not mutagenic or genotoxic in in vitro assays. The overall mixture of substances that migrated into ethanolic simulant was also negative in the mutagenicity bioassay. Our findings suggest that exposure to TMBPF-DGE + HQ from the V70 coating is exceedingly small and that the coating migrates are not genotoxic.

Chemical Contaminants

Probabilistic Points of Departure and Reference Doses for Characterizing Human Noncancer and Developmental/Reproductive Effects for 10,145 Chemicals

Nicolò Aurisano, Olivier Jolliet, Weihsueh A Chiu, Richard Judson, Suji Jang, Aswani Unnikrishnan, Marissa B Kosnik, Peter Fantke. *Environ Health Perspect*. 2023 Mar;131(3):37016. doi: 10.1289/EHP11524. **Article link**

Significance: A new risk review expands the coverage of chemicals from 744 to 8,023 for general noncancer effects, and from 41 to 6,697 for reproductive/developmental effects.

Background: Regulatory toxicity values used to assess and manage chemical risks rely on the determination of the point of departure (POD) for a critical effect, which results from a comprehensive and systematic assessment of available toxicity studies. However, regulatory assessments are only available for a small fraction of chemicals. **Objectives:** Using in vivo experimental animal data from the U.S. Environmental Protection Agency's Toxicity Value Database, we developed a semiautomated approach to determine surrogate oral route PODs, and corresponding toxicity values where regulatory assessments are unavailable. **Methods**: We developed a curated data set restricted to effect levels, exposure routes, study designs, and species relevant for deriving toxicity values. Effect levels were adjusted to chronic human equivalent benchmark doses (BMDh). We hypothesized that a quantile of the BMDh distribution could serve as a surrogate POD and determined the appropriate quantile by calibration to regulatory PODs. Finally, we characterized uncertainties around the surrogate PODs from intra- and interstudy variability and derived probabilistic toxicity values using a standardized workflow. **Results:** The BMDh distribution for each chemical was adequately fit by a lognormal distribution, and the 25th percentile best predicted the available regulatory PODs [$R2 \geq 0.78$, residual standard error (RSE)≤ 0.53log10 units]. We derived surrogate PODs for 10,145 chemicals from the curated data set, differentiating between general noncancer and reproductive/developmental effects, with typical uncertainties (at 95% confidence) of a factor of 10 and 12, respectively. From these PODs, probabilistic reference doses (1% incidence at 95% confidence), as well as human population effect doses (10% incidence), were derived. **Discussion:** In providing surrogate PODs calibrated to regulatory values and deriving corresponding toxicity values, we have substantially expanded the coverage of chemicals from 744 to 8,023 for general noncancer effects, and from 41 to 6,697 for reproductive/developmental effects. These results can be used across various risk assessment and risk management contexts, from hazardous site and life cycle impact assessments to chemical prioritization and substitution.

Caffeine

Acute Effects of Coffee Consumption on Health among Ambulatory Adults

Gregory M Marcus, David G Rosenthal, Gregory Nah, Eric Vittinghoff, Christina Fang, Kelsey Ogomori, Sean Joyce, et. al. *N Engl J Med*. 2023 Mar 23;388(12):1092-1100. doi: 10.1056/NEJMoa2204737. **Article link**

Significance: Consumption of caffeinated coffee did not result in significantly more daily premature atrial events than avoiding caffeine.

Background: Coffee is one of the most commonly consumed beverages in the world, but the acute health effects of coffee consumption remain uncertain. **Methods:** We conducted a prospective, randomized, case-crossover trial to examine the effects of caffeinated coffee on cardiac ectopy and arrhythmias, daily step counts, sleep minutes, and serum glucose levels. A total of 100 adults were fitted with a continuously recording electrocardiogram device, a wrist-worn accelerometer, and a continuous glucose monitor. Participants downloaded a smartphone application to collect geolocation data. We used daily text messages, sent over a period of 14 days, to randomly instruct participants to consume caffeinated coffee or avoid caffeine. The primary outcome was the mean number of daily premature atrial contractions. Adherence to the randomization assignment was assessed with the use of real-time indicators recorded by the participants, daily surveys, reimbursements for date-stamped receipts for coffee purchases, and virtual monitoring (geofencing) of coffee-shop visits. **Results**: The mean (±SD) age of the participants was 39±13 years; 51% were women, and 51% were non-Hispanic White. Adherence to the random assignments was assessed to be high. The consumption of caffeinated coffee was associated with 58 daily premature atrial contractions as compared with 53 daily events on days when caffeine was avoided (rate ratio, 1.09; 95% confidence interval [CI], 0.98 to 1.20; P = 0.10). The consumption of caffeinated coffee as compared with no caffeine consumption was associated with 154 and 102 daily premature ventricular contractions, respectively (rate ratio, 1.51; 95% CI, 1.18 to 1.94); 10,646 and 9665 daily steps (mean difference, 1058; 95% CI, 441 to 1675); 397 and 432 minutes of nightly sleep (mean difference, 36; 95% CI, 25 to 47); and serum glucose levels of 95 mg per deciliter and 96 mg per deciliter (mean difference, -0.41; 95% CI, -5.42 to 4.60). **Conclusions**: In this randomized trial, the consumption of caffeinated coffee did not result in significantly more daily premature atrial contractions than the avoidance of caffeine.

Food Allergens

Cofactors in Food Anaphylaxis in Adults

Significance: In adults, cofactors such as exercise, alcohol and sleep deprivation are reportedly involved in approximately 30% of anaphylaxis reactions.

Around 25%-50% of food-induced allergic reactions in adults causes anaphylaxis, and epidemiological evidence suggests that food is the most common cause of anaphylaxis. Reaction severity is unpredictable, and patients will often experience reactions of variable severity, even to an identical exposure (both dose and allergen). A common explanation for this phenomenon has been the impact of "cofactors" - factors which might contribute to reaction severity independent of the allergen exposure. Cofactors can influence reaction severity in two ways: either by reducing the reaction threshold (i.e. the dose needed to trigger any symptoms) so that patients have no symptoms in the absence of the cofactor and only react with the cofactor present, or by increasing reaction severity - such that individuals have only mild symptoms in the absence of the cofactor, but a more severe reaction when the cofactor is present. Indeed, the same patient may have reactions with different cofactors or even need more than one cofactor to develop a severe reaction. Cofactors reportedly play a role in approximately 30% of anaphylaxis reactions in adults. Exercise, NSAIDs, alcohol and sleep deprivation are the most frequent cofactors reported. Routine evaluation of the possible involvement of cofactors is essential in managing patients with food anaphylaxis: in patients with a suggestive history but a negative oral food challenge, cofactors should be taken into account in order to provide appropriate advice to reduce risk of future anaphylaxis.

Emerging Science Areas

Emerging Area: Phage Research

An Overview of the Use of Bacteriophages in the Poultry Industry: Successes, Challenges and Possibilities for Overcoming Breakdowns

Significance: A cocktail of different bacteriophages could broaden their antibacterial activity in typical situations with multiple clinical strains and show promise with poultry.

The primary contaminants in poultry are Salmonella enterica, Campylobacter jejuni, Escherichia coli, and Staphylococcus aureus. Their pathogenicity together with the widespread of these bacteria, contributes to many economic losses and poses a threat to public health. With the increasing prevalence of bacterial pathogens being resistant to most conventional antibiotics, scientists have rekindled interest in using bacteriophages as antimicrobial agents. Bacteriophage treatments have also been investigated as an alternative to antibiotics in the poultry industry. Bacteriophages' high specificity may allow them only to target a specific bacterial pathogen in the infected animal. However, a tailor-made sophisticated cocktail of different bacteriophages could broaden their antibacterial activity in typical situations with multiple clinical strains infections. Bacteriophages may not only be used in terms of reducing bacterial contamination in animals but also, under industrial conditions, they can be used as safe disinfectants to reduce contamination on food-contact surfaces or poultry carcasses. Nevertheless, bacteriophage therapies have not been developed sufficiently for widespread use. Problems with resistance, safety, specificity and long-term stability must be addressed in particular. This review highlights the benefits, challenges and current limitations of bacteriophage applications in the poultry industry.

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