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Risk Assessment

Current Methods in Risk Assessment of Genotoxic Chemicals

Cartus A, Schrenk D. *Food Chem Toxicol.* 2017 Aug;106(Pt B):574–582. [Article Link](#)

Significance: It is a major challenge for modern toxicology to provide transparent and versatile tools for the risk assessment of compounds with respect to human health. Models such as the Margin of Exposure (MoE) approach or the Threshold of Toxicological Concern (TTC) are discussed.

Chemical contaminants and residues are undesired chemicals occurring in consumer products such as food and drugs, at the workplace and in the environment, i.e. in air, soil and water. These compounds can be detected even at very low concentrations and lead frequently to considerable concerns among consumers and in the media. Thus it is a major challenge for modern toxicology to provide transparent and versatile tools for the risk assessment of such compounds in particular with respect to human health. Well-known examples of toxic contaminants are dioxins or mercury (in the environment), mycotoxins (from infections by molds) or acrylamide (from thermal treatment of food). The process of toxicological risk assessment of such chemicals is based on i) the knowledge of their contents in food, air, water etc., ii) the routes and extent of exposure of humans, iii) the toxicological properties of the compound, and, iv) its mode(s) of action. In this process quantitative dose-response relationships, usually in experimental animals, are of outstanding importance. For a successful risk assessment, in particular of genotoxic chemicals, several conditions and models such as the Margin of Exposure (MoE) approach or the Threshold of Toxicological Concern (TTC) concept exist, which will be discussed.

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

Becker RA, Dreier DA, Manibusan MK, Tony Cox LA, Simon TW, Bus JS. *Regul Toxicol Pharmacol.* 2017 Aug 30. doi: 10.1016/j.yrtph.2017.08.021. [Article Link](#)

Significance: The authors report that there is little scientific confidence in inference models derived from current ToxCast/Tox21 assays for key characteristics to predict cancer.



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 inference models derived from current ToxCast/Tox21 assays 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.

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Threshold and Non-Threshold Chemical Carcinogens: A Survey of the Present Regulatory Landscape

Bevan RJ, Harrison PTC. *Regul Toxicol Pharmacol*. 2017 Aug;88:291–302. [Article Link](#)

Significance: Unless proper differentiation is made between threshold and non-threshold carcinogens, inappropriate risk management measures may be put in place - and lead also to difficulties in translating

For the proper regulation of a carcinogenic material it is necessary to fully understand its mode of action, and in particular whether it demonstrates a threshold of effect. This paper explores our present understanding of carcinogenicity and the mechanisms underlying the carcinogenic response. The concepts of genotoxic and non-genotoxic and threshold and non-threshold carcinogens are fully described. We provide summary tables of the types of cancer considered to be associated with exposure to a number of carcinogens and the available evidence relating to whether carcinogenicity occurs through a threshold or non-threshold mechanism. In light of these observations we consider how different regulatory bodies approach the question of chemical carcinogenesis, looking in particular at the definitions and methodologies used to derive Occupational Exposure Levels (OELs) for carcinogens. We conclude that unless proper differentiation is made between threshold and non-threshold carcinogens, inappropriate risk management measures may be put in place - and lead also to difficulties in translating carcinogenicity research findings into appropriate health policies. We recommend that clear differentiation between threshold and non-threshold carcinogens should be made by all expert groups and regulatory bodies dealing with carcinogen classification and risk assessment.

Gut Health

Food Contact Materials and Gut Health: Implications for Toxicity Assessment and Relevance of High Molecular Weight Migrants

Groh KJ, Geueke B, Muncke J. *Food Chem Toxicol*. 2017 Aug 19;109(Pt 1):1–18. [Article Link](#)

Significance: Studies suggest that some direct food additives, but also some food contaminants, such as pesticide residues and substances migrating from food contact materials (FCMs), may adversely affect the gut barrier or gut microbiota.

Gut health is determined by an intact epithelial barrier and balanced gut microbiota, both involved in the regulation of immune responses in the gut. Disruption of this system contributes to the etiology of various non-communicable diseases, including intestinal, metabolic, and autoimmune disorders. Studies suggest that some direct food additives, but also some food contaminants, such as pesticide residues and substances migrating from food contact materials (FCMs), may adversely affect the gut barrier or gut microbiota. Here, we focus on gut-related effects of FCM-relevant substances (e.g. surfactants, N-ring containing substances, nanoparticles, and antimicrobials) and show that gut health is an underappreciated target in the toxicity assessment of FCMs. Understanding FCMs' impact on gut health requires more attention to ensure safety and prevent gut-related chronic diseases. Our review further points to the existence of large population subgroups with an increased intestinal permeability; this may lead to higher uptake of compounds of not only low (<1000 Da) but also high (>1000 Da) molecular weight. We discuss the potential toxicological relevance of high molecular weight compounds in the gut and suggest that the scientific justification for the application of a molecular weight-based cut-off in risk assessment of FCMs should be reevaluated.

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 Jul;105:194–202. [Article Link](#)

Significance: The aims of this work were to validate a 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.

Caffeine is one of the most consumed stimulants in the world, and is a frequent ingredient of dietary supplements. 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, amphetamine 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.

Food Processing Safety

Postharvest Processes of Edible Insects in Africa: A Review of Processing Methods, and the Implications for Nutrition, Safety and New Products Development

Mutungu C, Irungu FG, Nduko J, Mutua F, Affognon H, Nakimbugwe D, et al. *Crit Rev Food Sci Nutr*. 2017 Aug 30. doi: 10.1080/10408398.2017.1365330. [Article Link](#)

Significance: This review evaluates the available evidence on postharvest processes for edible insects in Africa, with the aim of identifying areas that need research impetus.

In many African cultures, insects are part of the diet of humans and domesticated animals. Compared to conventional food and feed sources, insects have been associated with a low ecological footprint because fewer natural resources are required for their production. To this end, the Food and Agriculture Organization of the United Nations recognized the role that edible insects can play in improving global food and nutrition security; processing technologies, as well as packaging and storage techniques that improve shelf-life were identified as being crucial. However, knowledge of these aspects in light of nutritional value, safety, and functionality is fragmentary and needs to be consolidated. This review attempts to contribute to this effort by evaluating the available evidence on postharvest processes for edible insects in Africa, with the aim of identifying areas that need research impetus. It further draws attention to potential postharvest technology options for overcoming hurdles associated with utilization of insects for food and feed. A greater research thrust is needed in processing and this can build on traditional knowledge. The focus should be to establish optimal techniques that improve presentation, quality and safety of products, and open possibilities to diversify use of edible insects for other benefits.

Listeria monocytogenes

Occurrence and Growth of *Listeria monocytogenes* in Packaged Raw Milk

Castro H, Ruusunen M, Lindström M. *Int J Food Microbiol*. 2017 Aug 23;261:1–10. [Article Link](#)

Significance: The increased availability of packaged raw drinking milk necessitates the investigation of the occurrence and growth of *Listeria monocytogenes* in raw milk during distribution and storage.

The occurrence of *L. monocytogenes* in 105 retailed raw milk bottles, 115 bulk tank milk samples, 23 in-line milk filter socks and in 50 environmental samples collected from an on-farm dairy establishment were investigated. Growth of inoculated low-level *L. monocytogenes* contamination was also investigated in two types of raw milk packaging, namely in 1-litre plastic bottles and 3-litre bag-in-boxes, both stored at three different storage temperatures of 6, 8 and 10°C. The occurrence of *L. monocytogenes* was higher (4.8%) in bottled raw milk stored until the use-by-date of the package compared to fresh bulk tank milk (1.7%). *L. monocytogenes* counts were ≤ 13 CFU/ml in bottled raw milk and ≤ 1 CFU/ml in bulk tank milk. *L. monocytogenes* was not detected in the packaging facility, but occurred very frequently (39%) in the milk filter socks. Subtyping of *L. monocytogenes* isolates using pulsed-field gel-electrophoresis revealed seven pulsotypes, of which two occurred in multiple samples. Targeted inoculum levels of 1-2CFU/ml yielded *L. monocytogenes* counts ≥ 100 CFU/ml within seven days of storage in 22% of the raw milk packages stored at 6°C, and in all of the raw milk packages stored at 8°C. The frequent occurrence of *L. monocytogenes* in raw milk and the ability of a low-level *L. monocytogenes* contamination to grow at refrigeration temperatures highlight the importance of consumer education regarding the appropriate raw milk storage and handling.



Scientific Integrity

The Influence of the Team in Conducting a Systematic Review

Uttley L and Montgomery P. *Syst Rev*. 2017 Aug 1;6(1):149. [Article Link](#)

There is an increasing body of research documenting flaws in many published systematic reviews' methodological and reporting conduct. When good systematic review practice is questioned, attention is rarely turned to the composition of the team that conducted the systematic review. This commentary highlights a number of relevant articles indicating how the composition

of the review team could jeopardize the integrity of the systematic review study and its conclusions. Key biases require closer attention such as sponsorship bias and researcher allegiance, but there may also be less obvious affiliations in teams conducting secondary evidence-syntheses. The importance of transparency and disclosure are now firmly on the agenda for clinical trials and primary research, but the meta-biases that systematic reviews may be at risk from now require further scrutiny.

Relationship Between Research Outcomes and Risk of Bias, Study Sponsorship, and Author Financial Conflicts of Interest in Reviews of the Effects of Artificially Sweetened Beverages on Weight Outcomes: A Systematic Review of Reviews

Mandrioli D, Kearns CE, Bero LA. *PLoS One*. 2016 Sep 8;11(9):e0162198. [Article Link](#)

Background: Artificially sweetened beverage consumption has steadily increased in the last 40 years. Several reviews examining the effects of artificially sweetened beverages on weight outcomes have discrepancies in their results and conclusions.

Objectives: To determine whether risk of bias, results, and conclusions of reviews of effects of artificially sweetened beverage consumption on weight outcomes differ depending on review sponsorship and authors' financial conflicts of interest. **Methods:** We performed a systematic review of reviews of the effects of artificially sweetened beverages on weight. Two assessors independently screened articles for inclusion, extracted data, and assessed risks of bias. We compared risk of bias, results and conclusions of reviews by different industry sponsors, authors' financial conflict of interest and journal sponsor. We also report the concordance between review results and conclusions. **Results:** Artificial sweetener industry sponsored reviews were more likely to have favorable results (3/4) than non-industry sponsored reviews (1/23), RR: 17.25 (95% CI: 2.34 to 127.29), as well as favorable conclusions (4/4 vs. 15/23), RR: 1.52 (95% CI: 1.14 to 2.06). All reviews funded by competitor industries reported unfavorable conclusions (4/4). In 42% of the reviews (13/31), authors' financial conflicts of interest were not disclosed. Reviews performed by authors that had a financial conflict of interest with the food industry (disclosed in the article or not) were more likely to have favorable conclusions (18/22) than reviews performed by authors without conflicts of interest (4/9), RR: 7.36 (95% CI: 1.15 to 47.22). Risk of bias was similar and high in most of the reviews. **Conclusions:** Review sponsorship and authors' financial conflicts of interest introduced bias affecting the outcomes of reviews of artificially sweetened beverage effects on weight that could not be explained by other sources of bias.
