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# Evaluating Safety of Lead in Food

By Rosemary Mattuck, M.S. and Joel Cohen, Sc.D., DABT

*Blood lead modeling is a powerful tool for evaluating potential health effects from lead in food.*

Serious questions about potential risks to human health have continued to center on lead in food, in part driven by the numerous foods that have been the target of California Proposition 65 notices due to the presence of lead (*e.g.*, chocolate, fruit juice, spices, cookies). Naturally occurring metals such as lead may find their way into food products at many points along the journey from farm to fork. Residual lead in food can occur in produce grown in soil with elevated background levels of metals, and drying and storing food products in open-air facilities in close proximity to highways can result in the accumulation of dust containing lead from exhaust emissions. Furthermore, processing operations involved in grinding food ingredients into powder can lead to the accumulation of lead-containing metal particles. Another potential source of metals in food products is migration from inks used in food packaging.

***Naturally occurring metals…may find their way into food products at many points along the journey from farm to fork.***

Chili powder, a common ingredient used in a variety of candies and snack products, is subject to many of the above processes. A U.S. Food and Drug Administration (FDA) analysis of several different candies containing chili-flavored salt reported an average of 313 micrograms of lead per gram of product (µg/g) (U.S. FDA, 2005). By comparison, common background levels for lead in soil range from about 20 to 40 µg/g. Dark chocolate has been alleged to contain lead and cadmium

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I N S I D E



## Letter from the Editors

May 2019

Dear Colleague,

In this issue of *Trends*, we discuss food safety.

The first article is about lead in food, discussing various sources of lead in food and explaining how scientists model lead levels in human blood to characterize exposure when investigating health risks associated with ingesting lead in food products. The second article discusses how growing cannabis and the processing required for its infusion into edibles make these consumer products susceptible to contamination. Nutritional epidemiology is the topic of the third article. It describes how observational epidemiological studies can provide valuable insights on the diet-disease relationship, and highlights the need for careful interpretation of study findings due to possible methodological limitations and biases.

Gradient contributors to this issue include Rosemary Mattuck, M.S.; Dr. Joel Cohen, DABT; Dr. James Rice; Dr. Tom Lewandowski, DABT, ERT, ATS; Dr. A. Dallas Wait; and Dr. Kirsten (Ke) Zu, M.P.H. Joining us with a guest editorial is Dr. Philip Demokritou of the Harvard T.H. Chan School of Public Health, writing about how applications of nanoscale materials can help improve food quality and safety.

We hope that this issue of *Trends* informs you of some hot topics related to food safety.

Yours truly,

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# Evaluating Safety of Lead in Food

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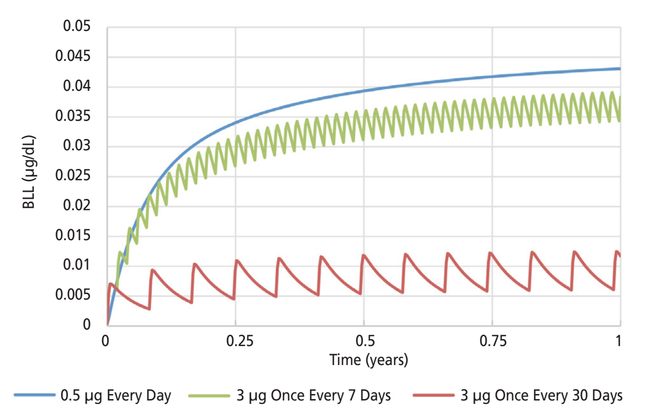
levels above the Proposition 65 safe harbor levels, and a 2018 settlement set thresholds for these metals in chocolate based on its cacao content. The U.S. FDA has also identified imported candy stored in lead-glazed ceramic jars, and lollipops wrapped in paper printed with lead-based ink, as potential sources of concern for lead exposure.

The amount of lead in the blood (blood lead level, or BLL) is the metric used to evaluate potential adverse effects on human health. Therefore, modeling of BLLs is often used to characterize exposure when investigating health risks associated with ingesting lead in food products. The kinetics of lead absorption, distribution, metabolism, storage, and excretion have major implications for the impact of dietary lead exposures on resulting BLLs. Therefore, in addition to the amount of lead in a food, data on the frequency with which people consume particular food products is necessary to fully characterize potential health risks.

### Blood Lead Modeling Results Comparing Adult Lead Intake at the MADL *vs.* Intermittent Exposures to Lead in Food




The Proposition 65 maximum allowable daily level (MADL) for lead is 0.5 µg/day.

Information on typical food consumption amounts can often be obtained by using the serving size on the nutrition label, or from government databases such as the National Health and Nutrition Examination Survey (NHANES). NHANES includes a two-day dietary recall survey that provides data on typical consumption amounts for a large variety of foods and brands, and is updated every two years. Intake frequency can be obtained from the NHANES Food Frequency Questionnaire (FFQ), which includes data for a more limited set of foods; however, it was last updated in 2005-2006. In addition, market survey firms can provide more recent data on intake frequency for a wider variety of foods.

Physiologically based pharmacokinetic (PBPK) modeling has been used for many years to quantify the impact of lead intake on BLLs. Such modeling approaches have been used by regulators to set permissible levels for lead in environmental media, and by industry to demonstrate compliance with regulatory limits. For example, the Proposition 65 maximum allowable daily level (MADL) for lead is 0.5 µg/day, and is intended to serve as a safe harbor level for the average consumer of a given product (be it food or otherwise). PBPK modeling can be used to demonstrate compliance with Proposition 65 by establishing whether lead exposures from a food product over time would result in BLLs below those associated with lead intakes at the safe harbor level of 0.5 µg/day. The graph presents modeling results for intermittent exposures (consuming 3 µg of lead every 7 days or every 30 days) compared to a daily lead intake at the MADL (0.5 µg/day). This graph demonstrates that intermittent consumption can result in average adult BLLs lower than those resulting from intake at the MADL, even if the lead intake from the food on a given day is greater than 0.5 µg.

Several PBPK models are available for lead, and models need to be carefully chosen based on the specific decision context. For example, the International Commission on Radiological Protection (ICRP) model can estimate impacts of intermittent exposures, while the U.S. EPA's Integrated Exposure Uptake Biokinetic (IEUBK) model does not. Furthermore, consideration of available food frequency data as it relates to the potentially exposed population is necessary to ensure model results appropriately represent potential risks. In summary, while concerns regarding lead in food may not be fading, scientific tools exist to evaluate their potential health implications.

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**Reference:**

U.S. Food and Drug Administration (U.S. FDA). San Francisco District Lab (Alameda, CA). Jacobs, R., C. Castro, G. Peiffer, K. Shippey, J. Wong, S. Yee. San Francisco State University, Dept. of Chemistry & Biochemistry, Palmer, P. 2005. Determination of Lead in Mexican Candy and Flavored Salt Products. FDA/ORA/DFS Laboratory Information Bulletin LIB # 4346. 8p.

# Safety of Cannabis-Infused Edibles Remains Hazy

By James Rice, Ph.D.; Tom Lewandowski, Ph.D., DABT, ERT, ATS; and A. Dallas Wait, Ph.D.

*Cannabis-infused edibles pose a wide range of potential health risks, and further investigation and uniform testing is needed to understand the full extent of any health harms.*

While cannabis remains illegal in the U.S. at the federal level, 33 U.S. states permit medical use and 10 U.S. states, Washington D.C., and several countries have legalized recreational cannabis use. Cannabis-infused edibles are a rapidly growing sector of the cannabis industry. U.S. consumers spent more than $1 billion on edibles in 2017, and combined edibles sales in Canada and the U.S. could top $4 billion by 2022 (Chung, 2018).

***One key challenge...is the lack of consensus on the appropriate analytical testing of cannabis products to ensure their safety.***

Growing cannabis and the processing required for its infusion into edibles makes these consumer products inherently susceptible to contamination by, for example, extraction solvents, growth promoters, and pesticides. Cannabis extracts, which are infused into edibles, are produced by mixing cannabis with a solvent (typically butane, carbon dioxide, or alcohols) to isolate and concentrate chemical components, which not only include Delta-9-THC (the main psychoactive ingredient), but also a large number of other chemicals. These chemicals consist of terpenes (associated with flavor), cannabidiol (CBD, an ingredient with several purported health benefits), other cannabinoids, and possible undesired adulterants.

While attention has focused on the potential safety of residual solvent contamination, toxicologically speaking, this is typically not a particular concern for most commercially produced material because chemicals such as butane have relatively low toxicity. However, the purity of solvents varies (*e.g.,* butane lighter-fluid can contain low levels of benzene). Given the largely unregulated nature of the cannabis market, the risks of adulterated product made with poor quality solvents is a credible concern.

The U.S. EPA tightly regulates the use of pesticides, specifying the crops on which they can be used, the pests that can be controlled, the timing of application, and allowable concentrations in crops at the time of harvest. No equivalent federal regulatory structure exists for cannabis, so states typically allow use of only very low potency, broad-use pesticides on cannabis. However, research published by the Cannabis Safety Institute (Voelker *et al.*, 2015) revealed the measurable presence of a large number of pesticides in cannabis extracts, several of which are not allowed under state regulatory programs, and several of which were above concentrations allowed in food crops by the U.S. EPA (see figure). Similarly, the presence of pesticides in edibles raises concerns regarding California's Proposition 65, which lists many of the pesticides that have been detected in cannabis products. Proposition 65 lawsuits based on pesticide concentrations in edibles seem likely.

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**Levels of Pesticides Commonly Found in Cannabis and Cannabis Products[a]**

| Pesticide | Mean Conc. (mg/kg)[b] | Max Conc. (mg/kg)[b] | CA limits for non-inhaled products (mg/kg)[c] | CA Prop 65 Safe Harbor (mg/day) | Prohibited for use with cannabis in CA |
|---|---|---|---|---|---|
| Azadirachtin | 1.8 | 3.5 | NA | NA | NO |
| Bifenthrin | 0.60 | 32 | 0.5 | NA | YES |
| Diazinon | 0.030 | 0.10 | 0.2 | NA | YES |
| Malathion | 0.080 | 10.5 | 5 | 0.18 | YES |
| Myclobutanil | 1.5 | 65 | 9 | Listed – no value | YES |
| Piperonyl butoxide | 0.33 | 410 | 8 | NA | NO |

Notes:

(a) Pesticides most frequently detected in cannabis products by CSI (2015).

(b) Mean concentrations represent samples of both cannabis flowers and cannabis extracts, while max concentrations are for cannabis extracts only.

(c) Available at https://www.bcc.ca.gov/law_regs/readopt_text_final.pdf.

# Nutritional Epidemiology & Food Safety

By Kirsten (Ke) Zu, Ph.D., Sc.D., M.P.H.

*Nutritional epidemiology, which can suggest connections between diet and disease, can help guide food safety regulations.*

Nutritional epidemiology, a subdiscipline of epidemiology, involves research to investigate the diet-disease relationship. In recent years, nutritional epidemiology has increasingly informed and impacted regulations and guidelines regarding food safety.

The human diet is complex and highly variable. What a person eats can change by the day of the week and season. Changes in lifestyle or health can also lead to changes in diet. In nutritional epidemiology studies, most of which are observational in nature, the habitual diet may be best assessed by surveying the typical consumption frequency and amount of various foods and beverages. Evidence from nutritional epidemiology can be particularly informative regarding the safety of substances in foods or beverages because the information is generated directly from human populations with real-world consumption levels and patterns.

***...causal conclusions regarding exposure-disease relationships can never be drawn from a single epidemiology study.***

However, these observational studies can be vulnerable to a variety of biases and errors in the study design, implementation, and analyses. A lack of thorough evaluation of biases and errors and their impact on the results can lead to erroneous interpretations and conclusions.

This is often the case when findings from nutritional epidemiology studies are taken at face value and sensationalized in the media. For example, earlier this year, a variety of print and broadcast media outlets reported findings from a recent large-scale human study linking consumption of drinking diet beverages with a three-fold increased risk of stroke and dementia. However, the media stories generally failed to mention that the observed link between diet beverages and stroke and dementia could be due to a phenomenon known as reverse causation, *i.e.,* that people who had higher risk of developing stroke or dementia (*e.g.,* diabetics) had switched from regular beverages to diet ones.

Moreover, epidemiology is a discipline built on statistics. Observational epidemiology studies report statistical associations in samples of the general population; therefore, causal conclusions regarding exposure-disease relationships can never be drawn from a single epidemiology study. When high-quality epidemiology studies report consistent findings across multiple populations, however, the likelihood that a causal relationship exists markedly increases.

Many hazard-based chemical-specific regulations impact food and beverage products. For example, the California Proposition 65 law regulates hundreds of chemicals that could cause cancer or reproductive/developmental effects and requires labeling on consumer products that may contain any of these chemicals. Among many other foods, coffee has been implicated in litigation under Proposition 65 because it contains acrylamide that is generated in the roasting process. However, coffee, one of the most consumed beverages worldwide, is a complex mixture of many substances in addition to acrylamide. Numerous nutritional epidemiology studies have evaluated coffee consumption and cancer outcomes, and collectively support a health-protective effect. Given such overwhelming evidence, in June 2018, the California Office of Environmental Health Hazard Assessment (OEHHA) initiated a proposed rulemaking clarifying that exposures to Proposition 65 listed chemicals in coffee created by and inherent in the roasting of coffee beans and brewing of coffee do not pose a significant cancer risk (California OEHHA, 2018).

In summary, it is critical to consider the study quality and the consistency of results within and across studies when interpreting evidence from nutritional epidemiology. Consistent findings from multiple high-quality studies can provide important information regarding the safety or risk of substances in food and beverages.

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**Reference:**

California Office of Environmental Health Hazard Assessment (OEHHA). 2018. Proposed Adoption of New Section Under Article 7 No Significant Risk Levels Section 25704 Exposures to Listed Chemicals in Coffee Posing No Significant Risk.

## Safety of Cannabis-Infused Edibles Remains Hazy

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The lack of dose consistency and delayed intoxication associated with edibles can result in unintentional overconsumption. The risks of highly elevated cannabinoid doses are not well understood. Studies have reported that the ingestion of extracts themselves (which can contain much higher THC concentrations than smoked cannabis) produces increased physiological dependence and withdrawal symptoms versus smoked cannabis (Loflin *et al.*, 2014; Meier, 2017). Data also show some developmental effects in children of women who have high cannabis consumption during pregnancy (Colorado DPHE, 2018). However, the few available health effects studies lack

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# What's New at Gradient

## Awards and Announcements

**Barbara D. Beck** has been appointed to the Environmental Protection Agency's panel of science advisers.

## Publications

**Goodman, J.E.,** H.N. Lynch, **L.R. Rhomberg.** 2018. Letter to the Editor re: Guyton *et al.* 2018. Application of the Key Characteristics of Carcinogens in Cancer Hazard Identification. *Carcinogenesis.* 39(8):1089-1090. DOI:10.1093/carcin/bgy066.

**Long, C.M., N.L. Briggs, I.A. Bamgbose**. 2019. Synthesis and health-based evaluation of ambient air monitoring data for the Marcellus Shale region. *J. Air Waste Manag. Assoc.* DOI:10.1080/10962247.2019.1572551. January 30. [Epub ahead of print].

Mebane, C.A., ..., **D.B. Mayfield,** ..., **T.A. Verslycke.** 2019. Scientific integrity issues in environmental toxicology and chemistry: Improving research reproducibility, credibility, and transparency. *Integrated Environmental Assessment and Management.* DOI:10.1002/ieam.4119.

**Rhomberg, L.R., D.B. Mayfield, R.L. Prueitt, J.W. Rice.** 2018. A bounding quantitative cancer risk assessment for occupational exposures to asphalt emissions during road paving operations. *Critical Reviews in Toxicology.* pp.1-25.

## Upcoming Presentations

**St. Louis, MO. May 13-16, 2019.** American Coal Ash Association World of Coal Ash Conference.

- **"CCP Beneficial Use Risk Assessment: Case Studies for Three Different Applications."** A. Bittner, A. Lewis.
- **"Evaluating Climate Change Impacts on Coal Combustion Residual Surface Impoundments and Landfills."** N. Briggs, K. Herman, A. Lewis, A. Bittner.
- **"Evaluating Ecological Damages Associated with Coal Ash."** T. Verslycke.
- **"Regional Screening Levels for the Appendix IV Constituents without MCLs: Looking Under the Hood."** A. Lewis.
- **"Risk-based Considerations for Establishing Alternative Groundwater Standards at Coal Combustion Product Sites."** A. Lewis, A. Bittner.

**Québec City, Québec. June 25-28, 2019.** Air & Waste Management Association's (A&WMA's) 112th Annual Conference & Exhibition.

- **"Validation Assessment of a Recently Developed Spatiotemporal Exposure Metric for Use in Epidemiological Studies of Populations Living Near Unconventional Oil & Gas Well Pads."** C. Long, S. Zhao, N. Briggs.

# Safety of Cannabis-Infused Edibles Remains Hazy

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comprehensiveness, largely due to a lack of funding and federal restrictions on cannabis research. This appears to be changing as agency policies shift towards making cannabis research somewhat less difficult.

One key challenge in this marketplace is the lack of consensus on the appropriate analytical testing of cannabis products to ensure their safety. States have conflicting laws in terms of what is allowed and what must be tested. Moreover, there is a lack of consistent guidance on analytical methods, detection limits, and the sets of chemicals of interest.

As with many products, human ingenuity in devising new ways to expose ourselves to chemicals can far exceed our understanding of the potential health risks of those exposures. The ingestion of cannabis-infused edibles will continue to grow. Therefore, there is a need to establish more rigorous and consistent testing standards and to research the potential health effects of increased THC exposures and potential contaminants in edibles.

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**References:**


Chung, H. October 2018. Cannabis edibles will soon be a $4 billion business.

Colorado Department of Public Health & Environment Monitoring. 2018. Health Concerns Related to Marijuana in Colorado.

Loflin, M., M. Earleywine. 2014. A new method of cannabis ingestion: the dangers of dabs? *Addict. Behav.* 39(10):1430-1433.

Meier, M.H. 2017. Associations between butane hash oil use and cannabis-related problems. *Drug Alcohol Depend.* 179:25-31.

Voelker, R., M. Holmes. June 2015. Pesticide Use on Cannabis. Cannabis Safety Institute. 19p.

# Guest Editorial: Nanoscale Solutions for Food

By Philip Demokritou, Ph.D.

*Nanotechnology innovations have the potential to transform food quality, safety, and nutrition.*

Engineered nanoscale particles, or substances smaller than 100 nanometers in at least one dimension, are used in a wide variety of agri-food-related applications to enhance quality, taste, and safety. Some prominent examples include the use of silver nanoparticles as antimicrobial agents in foods and food packaging materials, titanium dioxide nanoparticles as whitening agents in foods, and nanocellulose as a low-calorie substitute for carbohydrate additives or as an anticaking agent. Ongoing research at the Harvard T.H. Chan School of Public Health's Center for Nanotechnology and Nanotoxicology is investigating potential risks to human health posed by food-related applications of nanoscale materials, as well as how emerging nanotechnology innovations can help improve food quality, safety, and nutrition.

***...nanoenabled technologies may offer a safe, cost-effective, and versatile approach for reducing food-borne pathogens and extending shelf-life.***

For example, recent studies by Harvard researchers are demonstrating the potential of engineered water nanostructures (EWNS) as a safe, chemical-free, cost-effective tool for eliminating foodborne pathogens. EWNSs are generated by using a combined electrospraying and ionization process. The resulting nanodroplets pose unique physical and chemical properties, and are highly mobile due to their size and surface charge. Furthermore, they contain massive payloads of reactive oxygen species (ROS), can be used as carriers of other nature inspired antimicrobials such as lysozyme and citric acid, and can be targeted to surfaces of interest (*e.g.,* a kitchen countertop or the surface of a tomato) using an electric field. Direct contact between an EWNS and a foodborne pathogen can release the ROS or antimicrobial load, doing serious damage and effectively killing the pathogen. Food related pathogens such as *E. coli* can be inactivated from surfaces in less than a minute of exposure by delivering miniscule amounts (pico to nanogram amounts) of active ingredients due to the targeted surface delivery and synergistic effects of active ingredients and ROS. More importantly, there are no toxic byproducts and sensory changes for fruits, such as berries and tomatoes. In light of these results, such nanoenabled technologies may offer a safe, cost-effective, and versatile approach for reducing foodborne pathogens and extending shelf-life.

Another nanoscale material is currently being investigated for its unique nutritional properties. Nanocellulose has typically been used for food applications including stabilizing whipped toppings and salad dressings, improving the texture and appearance of breads, and reducing moisture loss of ground meats as they cook. New research, however, suggests that adding nanocellulose to a high-fat food could lead to significant reductions in the amount of fat absorbed in the body. Several different types of tests conducted to date, including acellular simulated gastrointestinal tract models, *in vitro* cellular models, and rodent bioassays for oral exposures to a high fat food supplemented with nanocellulose particles, all support reductions in fat absorption of up to almost 50%. Proposed mechanisms attribute the observed effects to the ability of nanocellulose particles to bridge together multiple fat droplets into larger clusters, reducing the total surface area available for the action of fat-digesting enzymes (lipases), and the ability of nanocellulose to sequester bile salts required for efficient fat digestion (DeLoid *et al.,* 2018). These findings could provide a new tool for blocking unwanted substances (*e.g.*, fat, carbohydrates, toxins) from being absorbed in the gut, promoting weight loss, and managing obesity using naturally occurring nanoscale biopolymers. As research such as this progresses, it is expected that nanotechnology will continue to contribute to significant advancements related to food quality, safety, and nutrition.

*Dr. Philip Demokritou is the Director of the Center for Nanotechnology and Nanotoxicology, and Director of the Laboratory for Environmental Health Nanoscience, at the Harvard T.H.Chan School of Public Health. He can be reached at pdemokri@hsph.harvard.edu.*

**Reference:**

DeLoid, G.M. … P. Demokritou. Reducing Intestinal Digestion and Absorption of Fat Using a Nature-Derived Biopolymer: Interference of Triglyceride Hydrolysis by Nanocellulose. *ACS Nano.* 2018. 12(7):6469-6479. DOI:10.1021/acsnano.8b03074.

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