

# Conducting a Systematic Review for a Global Audience:

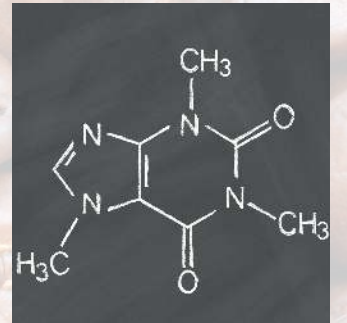
Challenges in Merging Nutrition and Toxicological Evidence for a Safety Assessment of Caffeine

Experimental Biology 2017 | 22 April 2017 | Chicago, IL

TRANSPARENCY



RIGOR



COLLABORATION



In cooperation with the American Society for Nutrition



Supported by the ILSI North America Caffeine Working Group



SCAN ME!





Welcome!

*Welcome to the 2017 ILSI North America Saturday Morning Session at Experimental Biology! For 19 years ILSI North America has been hosting this session in cooperation with the American Society for Nutrition. We are proud of contributing to this conference's program for so long and we are excited to share with you the methodology and findings of a large and rigorous Systematic Review on caffeine. Videos from today's session will be posted on the ILSI North America website in the coming weeks. We hope you find this year's session informative no matter your professional background and we hope to see you again next year.*

### Background for today:

As the field of systematic reviews evolves, there is an increasing number of frameworks and approaches that can be used to conduct such comprehensive research. When conducting systematic reviews, there are questions about how to: develop a protocol and Population, Exposure, Comparator, Outcome (PECO) questions, execute a search strategy, manage data, grade the literature, evaluate and manage biases, and ensure transparency of the process. This session will address these components by using a large multi-endpoint Systematic Review of caffeine which followed the framework of the IOM Report "Finding What Works in Health Care: Standards for Systematic Reviews", as a case study.

There continues to be interest within the scientific community in what is a safe level of caffeine intake and if certain populations should have modified recommendations. Since the 2003 release of the highly cited and valued review by Nawrot et al., "Effects of caffeine on human health", there have been more than 10,000 articles on caffeine published, highlighting the need for an update to this body of work.

The Systematic Review of the effects of caffeine on human health considered the challenges of including nutrition and toxicological evidence. The health endpoints reviewed for caffeine are: acute toxicity, behavior, bone and calcium homeostasis, cardiovascular health, developmental and reproductive toxicity, and pharmacokinetics in four healthy populations. The session will present the lessons learned and will emphasize the efforts taken to ensure transparency and rigor that allow for the achievement of a high level of scientific quality. Specific areas of focus will include challenges with identifying and integrating caffeine intakes by level of adversity (e.g., physiological or clinical endpoints), and difficulties in applying standard risk of bias tools across outcomes and endpoints.

Although this session will focus on the Caffeine Systematic Review as a case study, the process, findings, and lessons are relevant to all nutrition researchers and professionals who utilize systematic reviews.



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## Agenda

- 8:00 – 8:30**    **Breakfast**
- 8:30 – 8:35**    **Welcome**
- *Alison Kretser, MS, RD, ILSI North America*
- 8:35 – 8:45**    **The Caffeine Landscape**
- *Dennis Keefe, PhD, Food and Drug Administration*
- 8:45 – 9:10**    **Striving for the Gold Standard in the Systematic Review Process**
- *Esther Myers, PhD, RDN, FAND, EF Myers Consulting*
- 9:10 – 9:50**    **The Methodology and Challenges of the Caffeine Systematic Review**
- *Daniele Wikoff, PhD, ToxStrategies*
- 9:50 – 10:00**    **Q&A, Moderated by *Dennis Keefe, PhD, FDA***
- 10:00 – 10:15**    **Break**
- 10:15 – 10:25**    **General Results of the Systematic Review**
- *Daniele Wikoff, PhD, ToxStrategies*
- 10:25 – 11:50**    **Results of Specific Health Endpoints**
- **Behavior** – *Harris Lieberman, PhD US Army Research Institute of Environmental Medicine and Charles O'Brien, MD, PhD, University of Pennsylvania*
  - **Reproductive & Developmental Toxicity** – *Jennifer Peck, PhD University of Oklahoma*
  - **Cardiovascular** – *Daniele Wikoff, PhD on behalf of Jeffrey Goldberger, MD, MBA University of Miami*
  - **Bone & Calcium** – *Connie Weaver, PhD, Purdue University*
  - **Acute & Pharmacokinetics** – *Milton Tenenbein, MD, University of Manitoba*
- 11:50 – 12:30**    **Panel Discussion with the Caffeine Systematic Review Project Team Members**
- Moderator: *Dennis Keefe, PhD, FDA*
  - Panel includes: Scientific Advisory Board members, Daniele Wikoff, Alison Kretser
- 12:30**            **Adjourn**



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## Who was involved in the Systematic Review?

### **ToxStrategies, Inc.**

*ToxStrategies, Inc. served as the Systematic Review team, providing eight experts to conduct the Systematic Review.*

- Team Leader: Candace Doepker, PhD
- First Author: Daniele Wikoff, PhD

### **Scientific Advisory Board**

- Jeffrey Goldberger, MD, MBA, University of Miami
- Harris R. Lieberman, PhD, U.S. Army Research Institute of Environmental Medicine
- Esther Myers, PhD, RDN, FAND, EF Myers Consulting
- Charles P. O'Brien, MD, PhD, University of Pennsylvania
- Jennifer Peck, PhD, University of Oklahoma
- Milton Tenenbein, MD, University of Manitoba
- Connie Weaver, PhD, Purdue University

### **ILSI North America**

*The Systematic Review was primarily funded by ILSI North America Caffeine Working Group and the remainder of the funding came from unrestricted grants from the American Beverage Association (ABA) and the National Coffee Association (NCA). While the ILSI North America Caffeine Working Group made budgetary decisions, ILSI North America and the grantors had no influence over the researchers' conclusions or professional judgements; rather, the contents of the Systematic Review manuscript reflect solely the views of the authors.*



## Conducting a Systematic Review for a Global Audience: Challenges in Merging Nutrition & Toxicological Evidence for a Safety Assessment of Caffeine

### *Food and Chemical Toxicology*

**Abstract:** To date, one of the most heavily cited assessments of caffeine safety in the peer-reviewed literature is that issued by Health Canada (Nawrot et al., 2003). Since then, >10,000 papers have been published related to caffeine, including hundreds of reviews on specific human health effects; however, to date, none have compared the wide range of topics evaluated by Nawrot et al. (2003). Thus, as an update to this foundational publication, we conducted a systematic review of data on potential adverse effects of caffeine published from 2001 to June 2015. Subject matter experts and research team participants developed five PECO (population, exposure, comparator, and outcome) questions to address five types of outcomes (acute toxicity, cardiovascular toxicity, bone and calcium effects, behavior, and development and reproduction) in four healthy populations (adults, pregnant women, adolescents, and children) relative to caffeine intake doses determined not to be associated with adverse effects by Health Canada (comparators: 400 mg/day for adults [10 g for lethality], 300 mg/day for pregnant women, and 2.5 mg/kg/day for children and adolescents). The a priori search strategy identified >5000 articles that were screened, with 381 meeting inclusion/exclusion criteria for the five outcomes (pharmacokinetics was addressed contextually, adding 46 more studies). Data were extracted by the research team and rated for risk of bias and indirectness (internal and external validity). Selected no- and low-effect intakes were assessed relative to the population-specific comparator. Conclusions were drawn for the body of evidence for each outcome, as well as endpoints within an outcome, using a weight of evidence approach. When the total body of evidence was evaluated and when study quality, consistency, level of adversity, and magnitude of response were considered, the evidence generally supports that consumption of up to 400 mg caffeine/day in healthy adults is not associated with overt, adverse cardiovascular effects, behavioral effects, reproductive and developmental effects, acute effects, or bone status. Evidence also supports consumption of up to 300 mg caffeine/day in healthy pregnant women as an intake that is generally not associated with adverse reproductive and developmental effects. Limited data were identified for child and adolescent populations; the available evidence suggests that 2.5 mg caffeine/kg body weight/day remains an appropriate recommendation. The results of this systematic review support a shift in caffeine research to focus on characterizing effects in sensitive populations and establishing better quantitative characterization of interindividual variability (e.g., epigenetic trends), subpopulations (e.g., unhealthy populations, individuals with preexisting conditions), conditions (e.g., coexposures), and outcomes (e.g., exacerbation of risk-taking behavior) that could render individuals to be at greater risk relative to healthy adults and healthy pregnant women. This review, being one of the first to apply systematic review methodologies to toxicological assessments, also highlights the need for refined guidance and frameworks unique to the conduct of systematic review in this field.



## Caffeine Systematic Review Quick Facts

- A rigorous new scientific Systematic Review paper on caffeine safety that confirms the conclusions of Nawrot et al. in 2003 which defined appropriate intake levels as:
  - ≤400 mg/day in adults (about 4 cups of coffee per day);
  - ≤300 mg/day in pregnant women; and
  - ≤2.5 mg/kg-day in children and adolescents.
- This study was designed to confirm the longstanding caffeine intake recommendations. 400 mg/day is a higher intake than what is typically consumed, with approximately 90% of Americans consuming less than this amount.<sup>1</sup> Adverse effects cannot be ruled out for consumption above these identified levels, and further detail around specific endpoints can be found in the study.
- The first-of-its-kind in terms of merging nutrition and toxicological evidence, this review analyzed the health endpoints of acute toxicity, behavior, bone and calcium homeostasis, cardiovascular health, developmental and reproductive toxicity, and pharmacokinetics in four healthy populations.

## Resources

### Protocols Outlined on PROSPERO:

- Acute Toxicity: [https://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015026704](https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015026704)
- Behavior: [https://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015027413](https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027413)
- Bone and Calcium: [https://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015026609](https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015026609)
- Cardiovascular: [https://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015026673](https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015026673)
- Reproductive & developmental toxicity: [https://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015026736](https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015026736)

### Open data on AHRQ's Systematic Review Data Repository

- Acute Toxicity: <https://sdr.ahrq.gov/projects/1115/>
- Behavior: <https://sdr.ahrq.gov/projects/1116/>
- Bone and Calcium: <https://sdr.ahrq.gov/projects/1062/>
- Cardiovascular: <https://sdr.ahrq.gov/projects/1114/>
- Reproductive and developmental toxicity: <https://sdr.ahrq.gov/projects/1118/>

The ILSI North America Caffeine Working Group webpage has all materials related to the Systematic Review in one place: <http://ilsina.org/our-work/food-safety/caffeine/>



<sup>1</sup> Diane C. Mitchell, Jon Hockenberry, Robyn Teplansky, Terry J. Hartman, Assessing dietary exposure to caffeine from beverages in the U.S. population using brand-specific versus category-specific caffeine values, Food and Chemical Toxicology, Volume 80, June 2015, Pages 247-252, ISSN 0278-6915, <http://doi.org/10.1016/j.fct.2015.03.024>.



## Speaker Bios

**Dennis Keefe, PhD,**  
US Food & Drug  
Administration

Dennis Keefe, Ph.D., has been the Director of U.S. FDA’s Office of Food Additive Safety (OFAS) since 2011. OFAS is responsible for the premarket review of food additive and color additive petitions, the consideration of independent determinations of GRAS status, and the premarket review of notifications for food contact substances. From 1995- 2011, he was responsible for the international activities of the Office, especially the Codex Alimentarius, and the Codex Committee on Food Additives (CCFA). In this capacity he led the design, development and elaboration of the Codex General Standard for Food Additives. Dr. Keefe received a Bachelor of Science degree from St John’s University in Minnesota; a Master of Science degree in biology and a Doctorate of Philosophy degree (Ph.D.), from The University of Chicago, in the Department of Molecular Genetics and Cell Biology.

**Alison Kretser, MS,  
RD,**  
ILSI North America

Alison Kretser, MS, RD, Director, Science Programs, International Life Sciences Institute North America. Ms. Kretser has over 25 years of experience working in the field of nutrition and health. At ILSI North America, Ms. Kretser has responsibility for the organization’s work on scientific integrity and staff management of the food safety programs. She serves as the project director for the public-private partnership “A Partnership for Public Health: USDA Branded Food Products Database.” The goal of this Partnership is to improve public health and the sharing of open data by expanding and enhancing the USDA National Nutrient Database with nutrient composition and ingredient information on branded foods and store brand data provided by the food industry. ILSI North America is a public, non-profit, scientific, foundation that advance the understanding and application of science related to the nutritional quality and safety of the food supply. ILSI North America is primarily funded by the food industry. Ms. Kretser received a Bachelor of Science degree from the University of Delaware and a Master of Science degree in nutrition from Syracuse University.

**Harris R.  
Lieberman, PhD,**  
U.S. Army Research  
Institute of  
Environmental  
Medicine

*Behavior Outcomes*

Harris R. Lieberman, Ph.D., is a Research Psychologist in the Military Nutrition Division of the U.S. Army Research Institute of Environmental Medicine (USARIEM), a laboratory located in Natick, Massachusetts. He is an internationally recognized expert in cognitive function, nutrition, performance and stress and has published over 200 original, full-length papers in scientific journals and edited books. Dr. Lieberman received his Ph.D. in Physiological Psychology in 1977 from the University of Florida and then conducted research at the Department of Psychology and Brain Science at MIT where he established a laboratory that studied the effects of food constituents and drugs on human behavior and brain function. In 1990, he joined the civilian research staff of USARIEM where he continued his work in nutrition, behavior and stress. His recent research has addressed the effects of various nutritional factors including caffeine, dietary supplements, diets and environmental stress on cognitive performance, physiology and brain function in Service Members and civilians. Dr. Lieberman has conducted a number of laboratory and field studies examining the behavioral effects of caffeine and studied patterns of caffeine use in a





number of military and civilian populations including the Army, Navy, Marines and the general U.S. population using NHANES data. He is an internationally recognized expert on the behavioral effects of caffeine and currently serves as Government Advisor to the Caffeine Working Group of ILSI North America.

**Esther Myers, PhD,  
RDN, FAND,  
EF Myers Consulting**

*Systematic Review  
Expert*

Esther Myers, Ph.D., RDN, FAND is currently the CEO, EF Myers Consulting, Inc. She is an internationally recognized speaker, author, and researcher on systematic reviews, evidence based guideline development, nutrition care process and dietetic outcomes. She is a contributing author to Nutrition Today on evidence based topics. Before her retirement in 2013, she served as Chief Science Officer of the Academy of Nutrition and Dietetics for over 12 years. In that role, she was instrumental in developing the Academy’s Evidence Analysis Library that currently has over 40 systematic review projects. The Academy also provided consultant support to the USDA CNPP in the development of their Nutrition Evidence Library that conducts systematic review to support the US Dietary Guidelines Advisory Committee. Prior joining the Academy staff in October 2000, she was the Chief Consultant to the USAF Surgeon General. Dr. Myers received her undergraduate degree from North Dakota State University, Master’s Degree from the Ohio State University and Doctorate from Kansas State University.

**Charles P. O’Brien,  
MD, PhD, University  
of Pennsylvania**

*Behavior Outcomes*

Charles P. O'Brien, M.D., Ph.D., is Kenneth Appel Professor and Founding Director of the Center for Studies of Addiction at the University of Pennsylvania. In addition, Dr. O'Brien served as Chief of Psychiatry at the Philadelphia VA Medical Center from 1980 to 2008. He earned his MD and PhD from Tulane University School of Medicine in New Orleans, LA, and received his residency training in internal medicine, neurology, and psychiatry at Harvard Medical School in Boston, MA, Tulane University, the University of London in the United Kingdom, and the University of Pennsylvania. Dr. O'Brien was elected to the Institute of Medicine of the National Academy of Sciences in 1991 and has received numerous research and teaching awards, as well as an honorary doctorate from the University of Bordeaux in 1994, the Nathan B. Eddy Award for Research on Addiction from the College on Problems of Drug Dependence in 2003, the American Psychiatric Association Research Award in 2000, and the 2010 Gold Medal for Research from the Society on Biological Psychiatry. In 2010, he received the Sarnat International Prize for Mental Health from the Institute of Medicine, and in 2012, the Jellinek International Award for Alcoholism Research and the Isaacson Award for Alcoholism Research. In 2013 he received the Chevalier (Knight) of the French Legion of Honor for his contributions to French addiction science, In 2015, he received the Lifetime Science Award from NIDA/NIH for research contributions. Dr. O'Brien has been an adviser on drug policy to local and national governments since the 1970s, has chaired or served as a member of numerous Institute of Medicine committees dealing with the science and policy matters of abused drugs, and has recently served as Chair of the Substance Use Disorders Committee for revision of DSM-5. Despite a large clinical responsibility, Dr. O'Brien has



been able to establish and direct a clinical research program that has had a major impact on the treatment of addictive disorders. His research group has been responsible for numerous discoveries such as opioid antagonists for alcoholism and the Addiction Severity Index described in more than 550 publications. Many of these discoveries are used throughout the world for the treatment of addictive disorders.

**Jennifer Peck, PhD,**  
University of  
Oklahoma

*Reproductive and  
Developmental  
Outcomes*

Jennifer David Peck, Ph.D., is an Associate Professor of Epidemiology in the Department of Biostatistics and Epidemiology at the University of Oklahoma Health Sciences Center, College of Public Health and Adjunct Associate Professor in the Department of Obstetrics and Gynecology within the College of Medicine. Her research addresses reproductive and perinatal health outcomes associated with clinical, lifestyle, and environmental factors. She served as a Scientific Advisory Board member for the systematic review of the effects of caffeine on human health, sponsored by the ILSI North America Caffeine Working Group, contributing expertise in epidemiologic research methods and reproductive and perinatal endpoints. She is the co-author of a comprehensive review of the reproductive effects of caffeine, published in Food and Chemical Toxicology in 2010, and has served as a scientific advisor for the ILSI North America Caffeine Working Group since 2013. Dr. Peck’s current research includes studies of clinical and patient characteristics impacting infertility treatment outcomes, environmental exposures associated with development of gestational diabetes, and postpartum factors influencing lactation outcomes.

**Milton Tenenbein,**  
MD,  
University of  
Manitoba

*Acute Toxicity  
Outcomes*

*Pharmacokinetics  
Expert*

Dr. Tenenbein is a practicing pediatrician and toxicologist at the Children’s Hospital in Winnipeg Manitoba. He is currently a Professor of Pediatrics, Pharmacology, Internal Medicine and of Community Health Sciences at the University of Manitoba. In the past he served as the Director of Emergency Services at Children’s Hospital and as the Director of the Manitoba Poison Control Centre for over three decades. Dr. Tenenbein graduated from the University of Manitoba, Faculty of Medicine in 1973. He did his pediatric residency at Children’s Hospital in Winnipeg and at the Isaack Walton Killam Hospital in Halifax, Nova Scotia. He obtained certification in Pediatrics from the Royal College of Physicians and Surgeons of Canada and in Toxicology from the American Board of Medical Toxicology. He began his practice of Pediatric Emergency Medicine in 1977 and is one of the founders of that sub-specialty in Canada. In addition to an active Clinical Toxicology practice involving both children and adults, Dr. Tenenbein’s other constituencies include Pediatric Emergency Medicine, Injury Prevention and Native Canadian Health. He has served in leadership positions in the Canadian Pediatric Society and in the American Academy of Pediatrics. He has served as a consultant to ad hoc committees of Health Canada and of the US FDA. Dr. Tenenbein has served as President of both the Canadian Association of Poison Control Centres and of the American Academy of Clinical Toxicology. Dr. Tenenbein has contributed over 200 publications, over 30 book chapters and is a senior editor of a Pediatric Emergency Medicine textbook. He is a reviewer for many journals and has been or currently is the member of several editorial boards.



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Dr. Tenenbein has received career achievement awards from five medical societies including the Victor Marchessault Award from the Canadian Pediatric Society, the Jim Seidel Award from the American Academy of Pediatrics, the Louis Roche Award from the European Association of Poisons Centres and Clinical Toxicologists, the Career Achievement Award from the American Academy of Clinical Toxicology and the Matthew Ellenhorn from the American College of Medical Toxicology.

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**Connie Weaver,**  
PhD, Purdue  
University

*Bone & Calcium  
Outcomes*

Connie M. Weaver, Ph.D., is a Distinguished Professor at Purdue University in the Department of Nutrition Science in West Lafayette, Indiana. She is an elected member of The National Academies of Science, Engineering, and Medicine since 2010 and a member of the Food and Nutrition Board. She is a member of the FDA Science Advisory Board and the NIH Advisory Committee on Research on Women's Health. She is founder and director of the Women's Global Health Institute (WGHI) at Purdue University. The mission of the WGHI is to improve the health of women globally through research and training by proactively identifying the causes and prevention of diseases related to women. She is Deputy Director of the National Institutes of Health funded Indiana Clinical and Translational Science Institute since 2008. Her research interests include mineral bioavailability, calcium metabolism, and bone and cardiovascular health.

Dr. Weaver is past-president of American Society for Nutritional Sciences (ASN). She is on the Board of Trustees of the International Life Sciences Institute, Showalter Biomedical Research Committee, and the Science Advisory Board of Pharmavite. For her contributions in teaching, Dr. Weaver was awarded Purdue University's Outstanding Teaching Award. Her honors include the Purdue University Health Promotion Award for Women (1993), the Institute of Food Technologists' Babcock Hart Award (1997), the USDA A.O. Atwater Lecture Award (2003), the NAMS/Glaxo Smith Kline Consumer Healthcare Calcium Research Award (2006), the Purdue University Sigma Xi Faculty Research Award (2006), the ASN Robert H Herman Award (2009), the Natural Products Association's Burton Kallman Scientific Award (2010), the Linus Pauling Research Prize Award (2011), the Spirit of the Land Grant Award (2013), the Herbert Newby McCoy recipient (2012), this award is the most prestigious research honor given by Purdue University), the Trailblazer Award (2016) by the Institute of Food Technology (IFT) and the Academy of Nutrition and Dietetics (AND), an award to recognize "exceptional leaders" who have advanced the science at the interface of dietetics and food science, and the David Kritchevsky Career Achievement Award, American Society for Nutrition/ASN Foundation (2017). Dr. Weaver was appointed to the 2005 Dietary Guidelines Advisory Committee for Americans. She has published over 390 research articles to date. Dr. Weaver received a Bachelor of Science and Master of Science in food science and human nutrition from Oregon State University. She received a Ph.D. in food science and human nutrition from Florida State University and holds minors in chemistry and plant physiology.

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**Daniele Wikoff,**  
**PhD,**  
ToxStrategies, Inc.

Daniele Wikoff, Ph.D., is the Health Sciences Practice Leader for ToxStrategies based in Asheville, North Carolina. With more than ten years of experience in the fields of toxicology and risk assessment, she specializes in evaluating human health risks associated with exposures to a wide variety of consumer products, food ingredients and additives, pharmaceuticals, and industrial chemicals. Her primary areas of interest include systematic reviews and incorporation of weight of evidence information in applied risk assessments, as well as the development of health-based toxicity values. Her work often involves scientific and technical oversight, analysis, interpretation and critiques of data, as well as preparation of reports and peer-reviewed scientific manuscripts. Dr. Wikoff is active in the scientific community, highlighted by her role on the Science Advisory Council of the Evidence-Based Toxicology Collaboration.

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## About ILSI North America

ILSI North America is a public, non-profit, scientific foundation that advances the understanding and application of science related to the nutritional quality and safety of the food supply.

### Our Values



#### Collaboration

We work with industry, government, and academic scientists to conduct research to benefit the health of the public.



#### Scientific Integrity

We commit to publishing our results no matter what the outcome.



#### Transparency

We are committed to making our research methods and data available to the scientific community.



#### Public Benefit

Our projects must address issues of broad public health interest and offer benefit to the health of the public.

Learn more at [www.ilsina.org](http://www.ilsina.org)



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## Notes





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