

“Systematic Review of the potential adverse effects of caffeine consumption in healthy adults, pregnant women, adolescents and children”

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FAQ

1. What does the new paper tell us about the effects of caffeine on public health?

A rigorous new scientific Systematic Review (SR) paper on caffeine safety confirms the benchmark conclusions of Nawrot et al. in 2003 which established the following caffeine intake recommendations:

- ≤ 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.

These findings allow scientists to shift future research to focus on unhealthy populations, sensitive populations and interindividual variability.

2. What are the applications of these findings in the real world?

ILSI North America anticipates the findings of this rigorous, new review will provide value to scientists, regulatory agencies, doctors, dietitians, other health professionals and other stakeholders interested in the topic of caffeine safety and the challenges of merging nutrition and toxicological evidence to assess the safety of a food or ingredient.

This review also provides the research community with data and valuable evidence to support the development and execution of future research on caffeine safety that will impact public health. The complete transparency with which the data has been shared will encourage other researchers to build upon this work.

3. What specific subject areas does this review cover?

The Systematic Review looked at five adverse health effects associated with caffeine consumption and over 2 dozen specific endpoints. The 5 topic areas included general toxicity, cardiovascular effects, bone and calcium, behavior, and reproductive & development.

How our bodies handle caffeine – pharmacokinetics (PK) – and what caffeine does to the body – pharmacodynamics (PD) – were of interest to the researchers but these topic areas were not considered to



be reviewed systematically; rather, the objective was to summarize recent advances in knowledge and to characterize PK as it related to the five health outcomes.

The carcinogenic risks of caffeine were outside the scope of this review, as were any potentially beneficial health outcomes.

4. What are the findings of this review for each of the health outcomes it covers?

The Systematic Review looked at five adverse health effects associated with caffeine consumption and over 2 dozen specific endpoints related to caffeine in the areas of: general toxicity, cardiovascular effects, bone and calcium, behavior, and reproductive & development. Key findings across the topic areas include:

- Acute toxicity: Across 26 studies that provided evidence to evaluate potential acute toxicity due to caffeine intake, 400 mg caffeine/day or 2.5 mg/kg/day was not associated with elevated risks for healthy adults or adolescents, respectively.
- Bone & calcium: Across 14 studies, there was no significant impact associated with intake of ≤ 400 mg/day of caffeine on fracture and fall rates, bone mineral density and osteoporosis or altered calcium homeostasis, particularly under conditions of adequate calcium intake.
- Cardiovascular: Across 191 studies, 400 mg caffeine/day was found to be an acceptable intake which is not associated with adverse cardiovascular effects in healthy adults. The major cardiovascular endpoints evaluated included mortality, morbidity, blood pressure, heart rate, cholesterol and heart rate variability.
- Behavior: Across 81 studies focused on adults, 400 mg caffeine/day was found to be an acceptable intake that is not to be associated with significant concern for adverse behavioral effects. The data were mixed on the endpoints of sleep, anxiety and headache, suggesting significant individual variation in sensitivity to caffeine. There is sparse evidence that caffeine is associated with an increase in risk-taking behavior in adults; however, this is an area that merits further study in adolescents.
- Reproductive & development: Across 58 studies, 300 mg caffeine/day in pregnant women was found to be an acceptable intake which is not associated with negative impacts on fecundability, fertility, male reproductive endpoints, spontaneous abortion, recurrent miscarriage, stillbirth, preterm birth and gestational age, fetal growth, birth defects, childhood cancers or childhood behavior.

5. Why did ILSI North America decide to commission this paper?

Given the amount of research published (over 10,000 papers) since the Nawrot et al. paper (2003) and the NAS IOM Workshop Report on Caffeine in Food and Dietary Supplements: Examining Safety which called for a systematic collection and analysis of research on caffeine safety in 2013, ILSI North America decided to undertake a multi-year research initiative to apply the latest methods and tools and the most current data to determine the state-of-the-science on caffeine safety. ILSI North America wanted to determine if the benchmark levels identified by Nawrot et al were still valid.

6. What are the strengths and limitations of this review?



Strengths:

- This was a first-of-its kind effort in terms of the merging of nutrition and toxicological evidence; the rigor that went into the Systematic Review process; and the complete transparency with which we are sharing the data.
- The paper is highly transparent and robust.
- The researchers remained independent from the funding organizations; in other words, the role of the funders was limited to providing resources.

Limitations

- It's difficult to accurately track daily caffeine intake, which is true of all dietary intake data.
- We studied the effects of caffeine intake without accounting for any possible distinctions among food sources of caffeine.

7. What are the major outstanding questions about caffeine safety?

This Systematic Review did not consider the effects of caffeine intake in conjunction with other substances such as alcohol, nor did it explore the impact of caffeine consumption on children under the age of three, unhealthy populations or sensitive populations. In addition, research is sparse on the effects of very high levels of intake among healthy adults.

The results of this Systematic Review support a shift in caffeine research to focus on characterizing caffeine's 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., co-exposures), and outcomes (e.g., exacerbation of risk-taking behavior) that could render individuals to be at greater risk. We encourage the research community to continue to explore these topics.

8. How was this review conducted to ensure it meets high scientific standards?

At every point in the evolution of this study, the research team followed the most rigorous scientific protocols and used the most advanced tools to evaluate the literature to assure a valid and objective outcome.

The Systematic Review was structured using the NAS IOM publication, "Finding What Works in Health Care—Standards for Systematic Reviews" as guidance (Eden et al., 2011). This resource outlines the gold standards associated with each aspect of conducting a Systematic Review. Consistent with these standards, the first step involved establishing a team with the appropriate expertise and experience.

In addition to eight scientists from ToxStrategies, a private consulting firm providing services on toxicology and risk assessment issues to private and public organizations, the team included seven Scientific Advisory Board (SAB) members with expertise in the following areas: systematic reviews, caffeine, epidemiology, bone and calcium, reproduction, behavior, pharmacokinetics, acute toxicity and clinical medicine.

The SAB members on the project team are affiliated with top universities and research institutions including University of Pennsylvania, University of Miami, Purdue University, University of Oklahoma, University of Manitoba and the U.S. Army Research Institute of Environmental Medicine. ToxStrategies and some of the



members of the SAB received funds or an honorarium from ILSI North America for conducting the study. Each study team member and each SAB member completed a comprehensive conflict of interest (COI) questionnaire that documented both financial and nonfinancial COIs before they were brought onto the research team. They also completed a second COI questionnaire as required by the journal Food and Chemical Toxicology.

Individual protocols for the review of each of the outcomes were published on the PROSPERO registration, a global registry for Systematic Reviews.

At no point in the process were the researchers' scientific conclusion or professional judgements subject to the funders' control; rather, the contents of the Systematic Review manuscript reflect solely the view of the authors.

9. Who funded this research?

The Systematic Review was primarily funded by ILSI North America. In this capacity, ILSI North America was only included in decisions that impacted the budget. The organization had no influence over the researchers' conclusions or professional judgements; rather, the contents of the Systematic Review manuscript reflect solely the view of the authors. While the study was primarily funded by ILSI North America, the remainder of the funding came from unrestricted grants from the American Beverage Association (ABA) and the National Coffee Association (NCA).

10. Who is ILSI North America and what is its mission?

ILSI North America is a public, nonprofit foundation that provides a forum for government, academia and industry to advance understanding of scientific issues related to the nutritional quality and safety of the food supply by sponsoring research programs, educational seminars and workshops and publications. ILSI North America receives financial support primarily from industry members.

ILSI has been working in food safety and nutrition for nearly 40 years. The organization is built upon the premise that collaboration with government, academia and industry is the best way to solve public health issues. The organization has been successful in leading large collaborations and does not shy away from expert scientists from any sector.

Learn more about the Systematic Review on the [ILSI North America website](#).