ILSI North America Request for Proposals

Development of a Framework for Evidence-Based Risk Assessment of Potential Carcinogens in Human Diets

About ILSI North America:

The International Life Sciences Institute (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. The Institute carries out its mission by sponsoring relevant research, education programs and workshops, seminars, and publications, as well as providing a neutral forum for government, academic and industry scientists to address scientific issues for the well-being of the public. ILSI North America’s programs are supported primarily by its industry membership.

The ILSI North America Food and Chemical Safety committee promotes science-based assessment of the chemical safety of foods to support the advancement of public health. To learn more about the Committee, please visit: https://ilsina.org/our-work/food-safety/food-and-chemical-safety/ and to learn more about ILSI North America’s research, please visit: https://ilsina.org/funded-projects/

ILSI North America adheres to strict procedures to maintain scientific integrity in all of our work. These requirements are described in the attached TOP Guidelines and Guiding Principles for Scientific Integrity addendums.

Project Background:

The process of risk assessment of chemicals that are potentially carcinogenic in humans often relies on extrapolation from carcinogenicity bioassays in test animals or other systems. There is a growing belief in the scientific community that evidence-based risk assessment can replace or supplement historical, over-protective guidance-based approaches since these approaches may not provide an accurate understanding of the real risk presented by potential carcinogens, and in some cases may be misleading. However, there is no consensus within the scientific community on an approach or framework for the application of an evidence-based risk assessment.

This project proposes the development of a framework to facilitate the risk assessment of potential human dietary carcinogens. Such a framework will consider the relevance and interspecies extrapolation of exposure, toxicokinetics, as well as the toxicological mechanisms of action underlying observed tumors. In the case of compounds that exert carcinogenicity via a genotoxic mode of action, the framework should include decision criteria that elucidate
circumstances when it is appropriate to assume the default approach of non-threshold, and when it is not appropriate.

This project aims to improve risk assessment of potential human dietary carcinogens by categorizing potential exposure and mode of action scenarios leading to a carcinogenic response, followed by development of an evidence-based framework based on specific examples. A framework that encompasses all types of exposure and modes of action would be too broad in scope. Therefore, it is proposed that first, the categorization of potential exposure and mode of action scenarios leading to a carcinogenic response is conducted. This would then be followed by the development of a framework based on sectoral examples such as hepatically activated electrophiles that are potential genotoxic carcinogens.

Objective 1: Development of a framework/decision tree

Review pertinent literature to categorize exposure-mode of action scenarios of potential relevance to an evidence-based framework approach, and for each scenario identify factors that indicate whether an evidence-based approach may be appropriate. Develop an evidence-based framework for specific categories (e.g., metabolically activated electrophiles).

Objective 2: Case studies

Using the framework/decision tree developed during Phase 1, evaluate several compounds relevant to food or food ingredients. Examples could include process-formed compounds (e.g., acrylamide, furfuryl alcohol) and/or flavors (e.g., beta-myrcene)

Deliverables:

- One publication each from Objectives 1 and 2 in an appropriate peer-reviewed journal
- Periodic project updates to the Committee via webinar
- Formal presentation of results to the Committee in-person or by webinar

Proposal Content:

Research Approach:

- Please provide your approach to achieving the objectives described above. Identify key research questions, anticipated primary and secondary outcomes, methodology, and analytic plan.
- Please describe your approach to validate the proposed framework.

Investigator Credentials:

- Please describe your credentials and experiences as they pertain to the successful completion of this project including previous experience within the scope of the proposal.
- Please attach your peer-reviewed publications in this area.
- Please attach the CVs of the principal and co-investigators.
**Anticipated Challenges**: please identify challenges likely to be experienced in the conduct of the project and elaborate on your approach to address them.

**Publication Plan**: please provide your proposed publication plan per the Deliverables section above.

**Resources**: Please describe the resources available to you to complete the project.

- **Budget**: Please provide a budget summary and indicate if any additional funding sources will be used for this project. Please note that ILSI North America limits overhead to 10% of project costs. Also, ILSI North America will pay publication fees for the required open access to articles in journals.

- **Timeline**: please provide a proposed timeline for project completion including milestones.

- **Potential Conflicts of Interest**: List any potential conflicts of interests for all investigators, co-investigators, collaborators. We suggest using the Conflict of Interest Guidelines as set forth by the American Society for Nutrition: [https://nutrition.org/publications/guidelines-and-policies/conflict-of-interest/](https://nutrition.org/publications/guidelines-and-policies/conflict-of-interest/)

**Page Limit**: no more than five pages.

**Deadline**: Complete proposals must be received by March 31, 2020. Please submit them by email to Neal Saab at isaab@ils.org

**References**:

4. Non-neoplastic lesions found only in the two-year bioassays but not in shorter toxicity studies of rats. Mizuho Nonaka, Kouhei Amakasu, Yukie Saegusa, Misaki Naota, Takuya Nishimura, Kumiko Ogawa, Akiyoshi Nishikawa. Regulatory Toxicology and Pharmacology 86 (2017) 199e204
5. What is the meaning of ‘A compound is carcinogenic’? Dieter Schrenk. Toxicology Reports 5 (2018) 504–511

7. Chemical carcinogenicity revisited 2: Current knowledge of carcinogenesis shows that categorization as a carcinogen or non-carcinogen is not scientifically credible. John E. Doe, Alan R. Boobis, Vicki Dellarco, Penelope A. Fenner-Crisp, Angelo Moretto, Timothy P. Pastoor, Rita S. Schoeny, Jennifer G. Seed, Douglas C. Wolf. Regulatory Toxicology and Pharmacology Volume 103, April 2019, Pages 124-129

Addendum I

Adoption of the Center of Open Science’s Transparency and Openness Promotion Guidelines by ILSI North America

Background:
The Center for Open Science’s Transparency and Openness Promotion (TOP) Guidelines provide actionable steps for institutions to practice and promote transparent, reproducible, and rigorous research. ILSI North America is a TOP Guidelines signatory. By becoming a signatory, ILSI North America is supporting the principles expressed in the guidelines through their implementation by its funded researchers. The TOP Guidelines include eight modular standards for promoting transparent, reproducible and rigorous research, each with three levels of increasing stringency. Beginning July 1, 2018, all new research studies moving forward will strive to adhere to the levels of the TOP Guidelines specified below, recognizing that this process will take time and effort to achieve.

TOP Guidelines:

1. **Data Citation Standards (Level 3):** Cite shared data. Don’t publish until it is appropriately cited.
2. **Data Transparency (Level 2):** Data must be shared to the maximal extent allowed by ethical and legal constraints.
3. **Analytic Methods (Code) Transparency (Level 2):** Analytic methods (code) must be shared to the maximal extent allowed by ethical and legal constraints.
4. **Research Materials Transparency Level 2):** Materials must be shared to the maximal extent allowed by ethical and legal constraints.
5. **Design and Analysis Transparency (Level 2):** The researcher must use reporting guidelines when writing up publications. Equator-network website provides a huge choice of standards for research designs. [http://www.equator-network.org/](http://www.equator-network.org/) The researcher is asked to select one and register the standard you have selected.
6. **Study Preregistration (Level 2):** When the researcher preregisters his/her study in an independent, institutional registry (e.g., [http://osf.io/](http://osf.io/), [https://www.crd.york.ac.uk/prospero/](https://www.crd.york.ac.uk/prospero/), [http://clinicaltrials.gov/](http://clinicaltrials.gov/)), which is encouraged but not required, ILSI North America will request a third party (e.g., Center for Open Science) verify that preregistration adheres to the specifications for preregistration before data collection.
7. **Analysis Plan Preregistration (Level 2):** When the researcher preregisters his/her study analysis plan in an independent, institutional registry (e.g., [http://osf.io/](http://osf.io/), [https://www.crd.york.ac.uk/prospero/](https://www.crd.york.ac.uk/prospero/), [http://clinicaltrials.gov/](http://clinicaltrials.gov/)), which is encouraged but not required, ILSI North America will request a third party (e.g., Center for Open Science) verify that the Analysis Plan adheres to the preregistered plan (deviations must be transparently reported) before data collection.
8. **Replication (Level 1):** ILSI North America will occasionally put out a call for replication studies as part of our RFP process.

Learn more about ILSI North America’s implementation of the TOP Guidelines [here](#).
Addendum II

ILSI North America’s Guiding Principles for Funding Food Science and Nutrition Research

Background:
The scientific process requires open, transparent examination and honest interpretation of data, regardless of a researcher’s affiliation or source of funding. To address the potential influence of funding source on scientific research, ILSI North America developed 8 Guiding Principles for Funding of Food Science and Nutrition Research.¹ These guidelines were specifically designed to protect the integrity and credibility of the scientific record. All projects supported by ILSI North America must adhere to these principles.

Guiding Principles for Funding Food Science and Nutrition Research:

In the conduct of public/private research relations, all relevant parties shall:

1. Conduct or sponsor research that is factual, transparent, and designed objectively, and, according to accepted principles of scientific inquiry, the research design will generate an appropriately phrased hypothesis and the research will answer the appropriate questions, rather than favor a particular outcome;

2. Require control of both study design and research itself to remain with scientific investigators;

3. Not offer or accept remuneration geared to the outcome of a research project;

4. Ensure, before the commencement of studies, that there is a written agreement that the investigative team has the freedom and obligation to attempt to publish the findings within some specified time frame;

5. Require, in publications and conference presentations, full signed disclosure of all financial interests;

6. Not participate in undisclosed paid authorship arrangements in industry-sponsored publications or presentations;

7. Guarantee accessibility to all data and control of statistical analysis by investigators and appropriate auditors/reviewers;

8. Require that academic researchers, when they work in contract research organizations (CROs) or act as contract researchers, make clear statements of their affiliation; and require that such researchers publish only under the auspices of the CRO.

Learn more about ILSI North America’s 8 Guiding Principles for Funding Food Science and Nutrition Research here.