NCASI Foundation is Mobilizing a Comprehensive Research Program in Human Health Risk Assessment

The NCASI Foundation is a 501(c)(3) nonprofit organization that supports the development and application of science to protect public health and was established to carry out the charitable purposes of the National Council for Air and Stream Improvement, Inc. (NCASI). The NCASI Foundation has recently been funding technical activity to improve the Science behind risk and exposure assessments, with initial focus on developing and advancing the use of systematic approaches in reviews of the National Ambient Air Quality Standards (NAAQS). In the coming years, the NCASI Foundation envisions the development of a comprehensive research program around epidemiology and risk assessment science, while advancing the use of alternate approaches to further strengthen and validate the conclusions and facilitate the use of this Science for the benefit of public health.

This research will focus on five topics relevant to the risk assessment of chemicals found and regulated in all media, including air, water, soil and food products. The initial focus will continue to be in developing systematic approaches and review frameworks for use in NAAQS reviews. In the long-term, the research topics identified below can improve the science used in regulatory programs such as the National Ambient Air Quality Standards (NAAQS), Human Health Water Quality Criteria (HHWQC), Integrated Risk Information System (IRIS) toxicity assessments, Toxic Substance Control Act (TSCA) risk assessments, and Proposition 65.

1. **Advancing the Science of Systematic Review in Risk and Exposure Assessments**[1,2,3]

Most public health policies related to chemical emissions, discharges and exposures rely on qualitative reviews of toxicology, epidemiology, and exposure science literature to identify a safe range or level of exposure that protects human health. However, many regulatory agencies have not adopted a systematic approach to literature review that addresses narrow in scope, policy relevant research questions, viz., the selection of studies that address exposures in ranges relevant to policymaking; the evaluation of uncertainty and bias to determine study quality; and the integration of various lines of evidence that are systematically weighted by study quality. The lack of systematic approaches can lead to studies of poor quality or relevance being used for policy decision-making by risk managers. Research pertaining to best practices in systematic reviews helps to build frameworks that can produce more reliable conclusions

[1] Giffe Johnson. Dec 5, 2018. *Comments on the Integrated Science Assessment for Particulate Matter*. Submitted to Clean Air Act Scientific Advisory Committee as Public Comments to the Draft Integrated Science Assessment.
[2] Giffe Johnson. Oct 22, 2019. *Proposed Systematic Review Methodology for the Particulate Matter Integrated Science Assessment*. Submitted to Clean Air Act Scientific Advisory Committee as Public Comments to the Draft Policy Assessment.
[3] Julie E. Goodman, Robyn L. Prueitt, Raymond D. Harbison, Giffe T. Johnson. 2020. *Systematically Evaluating and Integrating Evidence in National Ambient Air Quality Standards Reviews*. Global Epidemiology. Ms. No. GEPI-D-19-00034R1 (Under Review)

regarding the relationship between chemical exposures and potential health effects and provides more realistic guidance to risk managers in setting public health policy.

2. Integrating the Needs of Risk Assessors into Epidemiology[4]

Risk assessors frequently develop recommendations for risk managers and policy decision makers, on the potential human health risks of chemical exposures, based on the integration of toxicology and epidemiological studies. However, epidemiology is often conducted without risk assessment or policy making being a consideration in the study plan or associated methodological approach. This often creates data or information gaps in the results of epidemiological studies that impair the risk assessor's ability to accurately and reliably address the risk management or policy question at hand. Research on best practices to integrate risk assessment needs into epidemiology studies, and the development of effective collaboration and communication forums between academic epidemiologists and practicing risk assessors, has the potential to increase the applicability of primary epidemiological studies for risk management and policy decision making.

3. Advancing the Science of Probabilistic Risk Assessment in Human Health Risk Assessment[5]

Most current regulatory approaches to risk assessment rely on deterministic approaches that use single, upper-bound estimates for various exposure parameters leading to risk estimates that are more conservative than intended and regulatory criteria that are more stringent than needed to meet stated health protection targets. Probabilistic risk assessment (PRA) is an approach to parameterizing exposure values by using a distribution of data for exposure inputs instead of single, upper-bound estimates. By using more exposure data, PRA produces more reliable risk estimates and demonstrates the achievement of health protection targets in a more transparent manner, reducing the unintended conservatism introduced by the deterministic approach. State and Federal regulatory agencies continue to be challenged by limited PRA awareness and the absence of accessible software tools to implement PRA in their respective risk assessment programs. Research that further refines the PRA approach and creates accessible education and implementation tools for PRA increases the potential for State and Federal regulatory agencies to use PRA in regulatory criteria development.

4. Application of Bayesian and Other Novel Approaches to Causal Inference

Traditional epidemiological methods for demonstrating cause and effect between exposure and disease suffer from substantial limitations in terms of the over-reliance on measured data, the exclusion of preexisting knowledge on results, and the inability to evaluate complex, multi-factorial systems. Most epidemiological literature currently used in policy assessment relies on traditional epidemiological approaches as alternative methods have not been widely applied in environmental epidemiology. Bayesian approaches and other novel methods (e.g. counterfactuals, natural experiments, quasi-experimental design, etc.) that can potentially improve the analytical performance of epidemiological studies and provide more realistic estimates of cause and effect relationships, either exist or are currently under development. Advancing the science and application of Bayesian approaches to causal inference

---

[4] Judy S. LaKind, Carol J. Burns, Heidi Erickson, Stephen E. Graham, Scott Jenkins, Giffe T. Johnson. 2020. *Bridging the Epidemiology Risk Assessment Gap:* An NO2 Case Study of the Matrix. (In press) https://doi.org/10.1016/j.gloepi.2020.100017

[5] NCASI & Arcadis. 2018. *Derivation of Human Health Water Quality Criteria: Review of Key Scientific and Technical Assumptions and Approaches*, Second Edition.

may provide a more realistic characterization of cause and effect relationships between chemical exposure and disease relationships. Recent foundational work[6,7,8] funded through the PM Research Consortium[9] demonstrates the potential for applying novel approaches to causal inference. Extending the science and application of Bayesian and other approaches to casual inference will ensure the further validation of cause & effect relationships and will provide additional certainty when considering policies to protect public health.

5. Best Approaches for Identifying, Categorizing, and Applying Confounder Data in Epidemiological Studies[10]

The inclusion and assessment of confounders, variables that are also relevant to the exposure and disease of interest and alter the estimated impact of exposure on disease, is another important area of potential improvement. While confounders are typically discussed in epidemiological studies, their impact on the reliability of conclusions drawn regarding exposure/disease relationships cannot always be reliably quantified. Several issues regarding confounding remain in current epidemiology practice, viz., identification of applicable confounders, selection of sources for reliable confounder data, treatment of individual level confounding data versus regional level confounding data, and estimation of the magnitude of unmeasured confounding present in studies, to name a few. Recent work funded through the PM Research Consortium[11], demonstrated an approach to adjust measures of association to account for unmeasured confounding and additional work is ongoing[12]. Research that produces novel methods and approaches to facilitate better inclusion of confounders, or that otherwise mitigates the presence of confounding in studies, has the potential to greatly enhance the reliability of the conclusions drawn in epidemiological studies and the potential to reduce the occurrence of false positive outcomes in both the ascertainment of risk and the magnitude of estimated risks resultant from an epidemiological investigation.

---

[6] Sanders, Nicholas J; Barreca, Alan; Neidell, Matthew J. 2020. *Estimating Causal Effects of Particulate Matter Regulation on Mortalit*y. Epidemiology. 31:2 160-167

[7] Zhulin He, Zhengyuan Zhu, and Hengfang Wang. 2019. *Quantify the Short-term Causal Effect of Fine Particulate Matter on Mortality*. Draft Report to PM Research Funding Consortium.

[8] Fan, M; Wang, Yi. 2019. The Impact of PM2.5 on Mortality in Older Adults: *Evidence from a Natural Experiment in the United States*. Draft Report to PM Research Funding Consortium.

[9] Multi-industry (utility, petrochemical and forest products) consortium with AF&PA, API, and EPRI.

[10] Greven S, Dominici F, Zeger S. *An Approach to the Estimation of Chronic Air Pollution Effects Using Spatio-Temporal Information*. J Am Stat Assoc. 2011;106(494):396-406.

[11] Pun VC, Kazemiparkouhi F, Manjourides J, Suh HH. *Long-Term PM2.5 Exposure and Respiratory, Cancer, and Cardiovascular Mortality in Older US Adults*. Am J Epidemiol. 2017 Oct 15;186(8):961-969.

[12] Zhang X, Faries DE, Li H, Stamey JD, Imbens GW. *Addressing unmeasured confounding in comparative observational research*. Pharmacoepidemiol. Drug Saf. 2018 Apr;27(4):373-382.