NATIONAL ACADEMIES Sciences Engineering Medicine

Workshops to Support EPA's Development of Human Health Assessments: Triangulation of Evidence in Environmental Epidemiology

May 9th and 11th, 2022

Posters

1. *Triangulation-Based Adjustment Factors for Combined Cancer Risk of Chrysotile Asbestos*

Thomas Bateson, U.S. Environmental Protection Agency

Introduction: The 2020 EPA Risk Evaluation for chrysotile asbestos derived an inhalation unit risk (IUR) based on cancers of the lung, larynx, ovary, and mesothelioma. Ideally, cancer-specific unit risks would be combined to represent the total cancer risk. However, data were insufficient for three cancers. No published asbestos studies reported dose-response results for laryngeal and ovarian cancers. Until 1999, mesothelioma deaths were coded to other causes. The under-ascertainment of mesothelioma cases exerted a downward bias in the dose-response function available for deriving the mesothelioma unit in an absolute risk model. **Methods**: Kopylev et al. (2011) reviewed available literature with quantitative information on mesothelioma under-ascertainment and calculated that multiplying the unit risk from available data by an adjustment factor of 1.39 would address under-ascertainment (on average). An indirect estimate of additional cancer risk from laryngeal and ovarian cancers was determined using adjustment factors based on a comparison of the excess deaths from lung cancer with the number of excess deaths from the ovarian and laryngeal cancers based on published asbestos studies. **Results**: The lung cancer unit risk was derived directly from available dose-response data. Multiplying this value by triangulation-based individual adjustment factors for laryngeal cancer (1.02) and ovarian cancer (1.04) and then combining this lung, larynx, and ovarian unit risk with the adjusted mesothelioma unit risk yielded the combined cancer IUR of 0.16 per f/cc. **Conclusion**: Triangulation-based methods allowed for estimation of cancer-specific adjustment factors to support derivation of a chrysotile asbestos IUR for all four cancers.

2. *Meta-Analytic Methods for Evidence Triangulation in Environmental Epidemiology*

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A Pubmed search with meta-analysis and environmental as terms in the title or abstract gave 3,094 articles. A subsequent search limiting terms to title identified 190 articles published since 1991. Of these, 90 assessed associations between environmental factors or interventions and one or more health outcomes. Twenty-nine articles (32%) are amenable to triangulation. A review of Environmental Health meta-analysis published by Sheehan and Lam supplemented this search. In this review 48 meta-analyses were examined for consistency with publication guidelines. Of these 40% were amenable to triangulation. Most synthesized evidence use the combination of cohort and case-control studies, few include randomized designs.
Three basic statistical methods have been developed to synthesize evidence obtained via different study designs. These are: (1) a naive approach, where pooling of information occurs without concerns of the study design; (2) a Bayesian approach in which information from non-randomized designs is estimated and used as prior information in the model containing the randomized information; and (3) a hierarchical model in which study design has its own level in the hierarchy. This level allows to model specifics of the study design, including sources of bias. These methods have been developed for clinical applications by far, and their translation to environmental epidemiology needs additional considerations. The hierarchical approach seems the most promising, given its intrinsic flexibility. This work will review the articles amenable to triangulation, as well as the proposed synthesis methods, their advantages, and limitations, and how they would apply in the specific context of environmental epidemiology.

3. *Meaningfully Incorporating Indigenous Health Definitions, Priorities, and Impacts into Assessments of Environmental Stressors*
Jamie Donatuto, Swinomish Indian Tribal Community

This poster will provide a framework for how to equitably center human health risk assessments conducted in/with Indigenous communities on the community's health definitions and priorities. Current HHRAs are not founded on the concepts and priorities of health that many Indigenous communities hold as central to their world views: that humans and the environment are in reciprocal, symbiotic relationships. Many Indigenous communities define health beyond the individualistic, physiological outcomes on which current HHRAs are based. This poster provides both triangulation to acknowledging and incorporating multiple worldviews, and to related evidence integration methods, specifically how to incorporate what is often considered as "intangible" health outcomes in HHRA. The poster will depict the 6 Indigenous Health Indicators developed and implemented by the Swinomish Indian Tribal Community and

how they are assessed: community connection, resources security, cultural use and practices, education, resilience, and self-determination. Without centering assessments on what the people in question prioritize, the assessments will not be successful.

4. *Per- and polyfluoroalkyl substances (PFAS) exposure and untargeted human metabolomics: a scoping review*

Pengfei Guo, Tristan Furnary, Vasilis Vasiliou, Qi Yan, Kate Nyhan, Dean P. Jones, Caroline H. Johnson, and Zeyan Liew, Department of Environmental Health Sciences, Yale School of Public Health

Objective: To summarize the application of untargeted human metabolomics that assessed metabolite and metabolic pathway alterations associated with per- and polyfluoroalkyl substances (PFAS) exposure. **Recent Findings:** Eleven human studies published before April 1st, 2021 were identified through database searches and citation chaining. The sample sizes ranged from 40-965, involving children and adolescents (n=3), non-pregnant adults (n=5), or pregnant women (n=3). High-resolution liquid chromatography–mass spectrometry was the primary analytical platform to measure both PFAS and metabolome. PFAS were measured in either plasma (n=6) or serum (n=5), while metabolomics were conducted using plasma (n=6), serum (n=4), or urine (n=1). Four types of PFAS (perfluorooctane sulfonate (n=11), perfluorooctanoic acid (n=10), perfluorohexane sulfonate (n=9), perfluorononanoic acid (n=5)) and PFAS mixtures (n=7) were the most studied. Alterations to tryptophan metabolism and the urea cycle were most reported PFAS-associated metabolomic signatures. Numerous lipid metabolites were also associated with PFAS exposure, especially key metabolites in glycerophospholipid metabolism which is critical for biological membrane functions, and fatty acids and carnitines which are relevant to the energy supply pathway of fatty acid oxidation. Other important metabolome changes reported included the tricarboxylic acid (TCA) cycle and purine and pyrimidine metabolism. **Conclusions:** Untargeted human metabolomics has been used to study the physiological changes associated with PFAS exposure. Multiple PFAS were associated with alterations in amino acid and lipid metabolism, but these results are driven by one type of pathway analysis. Standardizing methodology and reporting is recommended for result comparison. Future studies should consider prospective design, confounding bias, and measurement errors.

5. *Developing Adjustment Factors for Combined Cancer Risk of Trichloroethylene*

Martha Powers, U.S. Environmental Protection Agency

Introduction: The Integrated Risk Information System (IRIS) assessment for trichloroethylene (TCE) found that human data were sufficient to support dose-response modeling and to develop an inhalation unit risk (IUR) for renal cell carcinoma (RCC). However, human and rodent data suggest that TCE exposure also increases the risk of non-Hodgkin's lymphoma (NHL) and liver cancer. A combination of two different approaches was used to adjust the IUR to account for potential increased risk of these additional cancer types. **Methods**: A factor was developed and applied to the IUR to obtain a combined unit risk estimate (i.e., lifetime extra risk for developing any of the three types of cancer). The adjustment factor to account for the relative contributions to extra risk was calculated from two different data sets: meta-analyses of human epidemiologic data for the three cancer types, and a large cohort study with relative risk (RR) estimates for all three cancer types. **Results:** The factor developed accounted for the relative contributions of the three cancer types combined in contrast to the extra risk for RCC alone. The calculations based on two different data sets yielded comparable values for the adjustment factor (both within 25% of the selected factor of 4). **Conclusion:** Relative contributions to extra risk were estimated in the absence of dose-response data by calculating an adjustment factor for the additional risk of NHL and liver cancer, in addition to RCC alone. The use of two data sets analyzed by different methods provided more robust support for the use of the factor of 4, based on high-quality epidemiological data.

6. *Assessing Confounding by Co-Exposure Across Per- and Polyflouroalkyl Substances (PFAS) Using Triangulation*

Elizabeth Radke-Farabaugh, U.S. Environmental Protection Agency

Introduction: Evaluation of health effects of highly correlated chemicals like per- and polyfluoroalkyl substances (PFAS) is complicated by the potential for confounding. **Methods:** As part of a systematic review of the hepatic effects of perfluorooctanoic acid (PFOA), we used a triangulation approach to assess the potential for confounding across PFAS. This included consideration of studies with varying exposure scenarios and subsequent different sources of bias, as well as examination of reported correlations and multipollutant modeling results within and across studies. **Results:** Twenty-five studies reported on the association between PFOA exposure and hepatic effects. Fourteen were in the general population using biomarkers in blood, in which individuals are exposed to a mixture of PFAS and it can be challenging to disentangle individual effects. Eight studies were in workers exposed to PFOA via inhalation and two were in communities with significant PFOA drinking water contamination. In these studies, PFOA

exposure is predominant so there is less confounding by other PFAS but there may be potential for selection bias (e.g., healthy worker effect in occupational studies and heightened awareness of PFAS exposure and toxicity in contamination communities) and other confounding (occupational). For all exposure scenarios, the majority of studies reported associations between PFOA exposure and increased alanine aminotransferase in blood. **Conclusion:** Consistency in the direction of association combined with differences in the sources of bias across studies with different exposure sources reduces the likelihood that the observed effects can be fully explained by confounding across PFAS.

7. *Triangulation of evidence based on a formal causal model: An example using a directed acyclic graph (DAG) in assessing benzene as a potential cause of chronic lymphocytic leukemia (CLL)*

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Rationale: Benzene causes acute myeloid leukemia and myelodysplastic syndrome (MDS), however, conflicting results from observational epidemiological studies and evaluation of various potential biases present challenges in determining whether benzene causes other malignancies such as chronic lymphocytic leukemia (CLL). A formal structural causal model such as a directed acyclic graphic (DAG) visually presents a framework in which multiple potentially causal relationships (i.e., "confounding") simultaneously may be considered– and whether the epidemiological evidence aligns with the causal model. **Approach:** A quality-based systematic review of benzene and CLL was informed by a formal causal DAG developed based on epidemiological, toxicological, and mechanistic evidence. Specifically, these evidence streams were used in an iterative process which generated the formal causal DAG or "I-DAG". Arcs in DAGs are assumed to represent true causal relationships (the "faithfulness assumption") but are challenged when associations are not biologically plausible or contradicted by toxicological and epidemiological evidence, allowing the causal model to be refined. **Results/Discussion:** Benzene appears not to be a clear cause of CLL, a disease of elusive environmental causes. A causal DAG provided a framework for evaluating the possible roles environmental stressors including benzene within the context of all possible causes. Beginning with and refining a causal model may help prevent erroneously labeling observed associations "causal" that arise due to chance, bias and confounding. The DAG allows evaluation of the epidemiological evidence based on a biologically grounded causal model rather than attempting to guess at a causal model solely from observational data and their statistical manipulation.

8. *Application of Risk of Bias for Environmental Epidemiology Evidence Characterization and Integration in Support of Risk Assessment: A case study evaluating the relationship between exposure to dioxin-like compounds (DLCs) and sperm count*

Jon Urban, Daniele Wikoff, and Laurie Haws, ToxStrategies, Inc.

The development of toxicity values based on human data is often preferred when sufficient evidence is available since it avoids uncertainties associated with animal data relevance. Epidemiological study designs vary in uncertainties and risk of bias (RoB) potential, however, and present challenges when synthesizing such datasets for identifying causal and exposure-response relationships. As a case study, we utilized the NTP-OHAT RoB Tool to evaluate the reliability of the environmental epidemiological evidence base relevant to characterizing exposure-response relationships between early life exposures to dioxin-like compounds (DLCs) and reduced sperm count. The evidence base was defined a priori following a systematic review protocol. The relevant epidemiological evidence base was limited to only three studies, from which study design information and dose-response data were extracted. All three studies were critically appraised for internal validity per the NTP-OHAT RoB tool. Key RoB domains included: Inclusion of appropriate confounders, exposure characterization, and outcome reporting. All three studies met the criteria for "high risk of bias" for one or more key RoB domains, as well as attrition/exclusion bias. Applying NTP-OHAT data synthesis guidance, confidence in environmental epidemiological evidence stream for characterizing dose-response was categorized as low to very low. While the human studies were not suitable for quantitative dose-response assessment, they were considered for qualitative or contextual use in hazard assessment. This case study demonstrates the utility of the NTP-OHAT tool in characterizing what are common limitations often encountered in environmental epidemiology studies, and the challenges they can pose for characterizing exposure response relationships.

9. *Strengthening the Reliability of Information to be Combined*

S. Stanley Young and Warren B. Kindzierski

Combining information from multiple sources (studies) in environmental epidemiology is a common task for decision makers in inferring causality. There is an important step before combining information; the reliability of each information source should be evaluated. Reliability should not be assumed as claimed risk factor−disease relationships may fail to replicate. Also, because many hypotheses can be tested in a study,

researchers may be more inclined to publish positive relationships with many negative relationships remaining unpublished. The reliability of information to be combined should not be taken at face value. Environmental epidemiology methods require a strong statistical component to develop useful and interpretable causal relationships. Our idea is to use two techniques, one ancient (simple counting) and one relatively new (p-value plots) to evaluate statistical reliability. A source can be examined to determine the analysis search space (number of hypotheses tested). How many hypotheses were open to the researcher to search for a positive relationship. The larger the search space the greater the opportunity that a claimed relationship (or its size) could have been influenced by chance. A p-value plot is simple. The p-value linked to each source is determined, and the ranked p-values are plotted against the integers. If the p-values fall on a roughly 45-degree line (they roughly are uniformly distributed), then there is evidence that chance is at play. The benefit of examining the reliability of the information to be combined is that the decision maker can be more confident chance is not driving the decision process.