Meta-Analytic Approaches for Multi-Stressor Dose-Response Function Development: Strengths, Limitations, and Case Studies

Jonathan I. Levy* (Boston University), M. Patricia Fabian (Boston University), Junenette L. Peters (Boston University)

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***Corresponding author: jonlevy@bu.edu**

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Abstract

For many policy analyses, including but not limited to cumulative risk assessments, it is important to characterize the individual and joint health effects of multiple stressors. With an increasing focus on psychosocial and other non-chemical stressors, this often involves synthesizing epidemiological evidence using meta-analytic techniques. This approach has limitations if epidemiological studies do not include all of the stressors of interest, making it challenging to pool evidence across studies. In addition, epidemiological studies may include multiple stressors in multivariable models, but these models may not provide outputs in a format necessary for specific risk assessment applications. Given these limitations, novel analytical methods are often needed to synthesize the published literature or to build upon available evidence. In this paper, we discuss three recent case studies that highlight the strengths and limitations of meta-analytic approaches and other research synthesis techniques for human health risk assessment applications. In the first example, a literature-based meta-analysis was used to inform the design of a new epidemiological investigation of the differential toxicity of fine particulate matter constituents, using a risk assessment context to further guide the epidemiological methods. In the second example, a literature synthesis for an effects-based cumulative risk assessment of hypertension risk factors led to a decision to apply structural equation modeling to develop new epidemiological associations rather than relying on the published literature. In the third example, discrete event simulation modeling was used to simulate the impact of changes in the built environment on exposure to environmental pollutants and associated asthma outcomes, linking literature meta-analyses for key associations with a simulation modeling approach to synthesize all of the model components. These case studies emphasize the importance of conducting epidemiology with a risk assessment application in mind, the need for interdisciplinary collaboration, and the value of advanced analytical methods to synthesize epidemiological and other evidence for risk assessment applications.

Keywords: cumulative risk assessment; discrete event simulation; epidemiology; meta-analysis; structural equation modeling

1. Introduction

Health risk assessment increasingly involves evaluating the combined risks to health from multiple stressors, often within the context of cumulative risk assessment [(1)]. Cumulative risk assessment has historically relied on toxicological evidence to determine the effects of multiple stressors, but given interest in psychosocial stress and various socioeconomic factors that cannot be readily evaluated toxicologically [(2)], there has been an increasing focus on methods to incorporate epidemiological evidence into cumulative risk assessment [(3)]. To this point, a recent Federal Register information request from the U.S. Environmental Protection Agency (EPA) sought guidance on "methods for characterizing integrated risks posed by disparate stressors in a [cumulative risk assessment] context. These could include methods and/or study data from epidemiology…" [(4)].

In most situations, risk assessors must gather evidence from published epidemiological studies and synthesize the information. Conventional meta-analytic techniques can be applied (e.g., inverse variance weighting of concentration-response functions across selected studies), but these approaches have limitations, many of which are heightened with interest in simultaneously evaluating multiple stressors. For example, epidemiological studies often focus on individual risk factors of primary interest to the investigators. If only a subset of stressors is included in any individual epidemiological study, it can be challenging to pool evidence across studies. This is both because omitted stressors could be confounders or effect modifiers, and because there may be methodological or other intrinsic features of individual studies that lead to higher or lower estimates. Even when epidemiological studies have incorporated all risk factors of interest into multivariable models, often only selected information is presented or the results omit key information necessary for cumulative risk assessment. As a result, risk assessors must often choose either to combine evidence across a larger number of studies, finding ways to take

account of methodological differences, or to restrict to a smaller number of studies which may not represent the literature as a whole.

In spite of these challenges, the increasingly population-centered framework of cumulative risk assessment requires novel approaches to generate, evaluate, and incorporate epidemiological evidence. In this paper, we discuss three recent case studies in which investigators considered the strengths and limitations of meta-analytic approaches and applied other research synthesis techniques for human health risk assessment applications. In the first case study [5], the differential toxicity of fine particulate matter ($PM_{2.5}$) constituents was evaluated using both a literature meta-analysis and a new epidemiological investigation designed to meet the needs of multi-stressor risk assessments. In the second case study [6], an effects-based cumulative risk assessment focusing on hypertension, researchers similarly evaluated the published literature to determine the effects of multiple stressors but decided to apply structural equation modeling (SEM) to develop new epidemiological associations from a national database rather than relying on the published literature. In the third case study [7], researchers integrated information from epidemiology and exposure monitoring studies to simulate the impact of changes in the built environment on exposure to environmental pollutants, as well as the impact of these changes on lung function and asthma exacerbations. This investigation required both synthesis of the literature on key associations and implementation of a simulation modeling approach to synthesize all of the model components. For each of these case studies, we focus on how the investigators used the published literature in conjunction with alternative strategies for research synthesis. All three of these studies were conducted by authors of this paper, so we focus on research synthesis decisions made by the investigators both within the papers and in the process of planning and scoping the analyses. We then consider the degree to which these analytical approaches generalize to other research applications and conclude by offering a set of criteria that would help in the selection of research synthesis methods.

2. Case Study #1: Differential Toxicity of Particle Constituents

For regulatory analyses and other risk assessments addressing $PM_{2.5}$, it is important to know whether different particle constituents have different levels of toxicity, as control strategies

may target some particle constituents but not others. This question has been looked at extensively by the EPA and others [8], with the conclusion that the literature was not yet sufficient to develop constituent-specific concentration-response functions. As discussed in our recent publication [5], the literature could be insufficient because of a lack of relevant studies, or because the studies had methodological limitations or substantial variability in approaches that makes it challenging to synthesize the literature.

Our analysis was conducted in two stages. In the first stage, we formally examined and synthesized the published epidemiological literature to determine if it provided the information necessary for a risk assessment application. Specifically, we searched for studies that provided estimates for four major particle constituents of regulatory interest (sulfate, nitrate, elemental carbon, organic carbon), as derived from multi-constituent models. Concentrations of particle constituents may be correlated with one another and multiple constituents influence health outcomes, so models that only include individual constituents could provide biased concentration-response functions. We also considered it important to calculate the probability that one constituent was more toxic than another, rather than simply giving central estimates or confidence intervals that do not allow for comparisons between constituents. Risk assessments require uncertainty characterization, but assumptions that estimates were uncorrelated with one another could be unfounded.

In the second stage, we conducted a new epidemiological investigation, with the primary objective depending in part on the results of the first stage of our analysis. If the literature synthesis provided robust and interpretable concentration-response functions for all constituents, then the epidemiological investigation would examine the difference between estimates from a literature meta-analysis and a large multi-city investigation. This would help address questions about the importance of methodological choices in the literature or the possibility of publication bias. If the literature synthesis found significant methodological concerns with the published literature, then we would design and implement a new epidemiological investigation with the objective of yielding all of the requisite information for a multi-constituent risk assessment application.

In our literature synthesis, we first reviewed the abstracts of 1,338 articles that addressed $PM_{2.5}$ and health, identifying 65 epidemiological studies evaluating at least one of the four

particle constituents of interest [5]. Focusing on a subset of 42 published studies that provided adequate information to generate concentration-response functions for at least one constituent, we determined that the evidence base did not meet the criteria described above. Specifically, only eight of the 42 studies provided quantitative effect estimates for all four constituents, and most studies reported effect estimates for single-constituent models or implemented multi-constituent models but did not report quantitative findings for all constituents. No study provided information necessary to quantify the probability that a given constituent was more toxic than another constituent or to determine correlations among effect estimates. To be clear, this did not imply that these were fundamentally flawed epidemiological studies, but rather that they were not designed to give inputs to specific types of risk assessment applications. Stated another way, most of these epidemiological studies were trying to determine which particle constituents were most strongly associated with health outcomes of interest, not what the concentration-response functions for all constituents might be.

Our new epidemiological study was therefore intended to provide all of the information that would be needed for risk assessment but was not available from a synthesis of the published literature. Specifically, we applied identical methods to hospital admissions data from 119 counties in the US, yielding county-level estimates that could be readily aggregated at the regional or national level. We incorporated all four constituents into multi-constituent models. We explicitly reported central estimates and confidence intervals for all four constituents, along with the correlations between each pair of beta coefficients, which would allow for uncertainties to be appropriately incorporated into multi-constituent risk assessments. We used the joint posterior distribution of the health effects of the four constituents, coupled with the posterior distribution of their covariance matrix, to estimate the probability that each constituent was more toxic than each other constituent. This provides quantitative insight regarding whether the evidence was sufficient to infer differential toxicity values or whether identical values could be utilized. We were also able to use these outputs to determine probability distributions of ratios of toxicity values, given that risk assessment studies have incorporated such ratios into previous differential toxicity analyses without consideration of the likely degree of uncertainty.

The specific findings from our new epidemiological investigation are reported elsewhere [5], but in general, our analytical approach provided information that would allow for risk

assessments incorporating differential toxicity to be conducted, which would have been challenging from the published literature. For example, we found high probabilities (> 0.99) that elemental carbon had greater toxicity per unit concentrations than other particle constituents for cardiovascular hospital admissions, with weaker evidence of differential toxicity for respiratory hospital admissions. We also found that multiple beta coefficients were significantly correlated with one another (e.g., correlation coefficient of -0.71 between elemental carbon and organic carbon for cardiovascular hospital admissions), information that would not have been available from a literature synthesis. We therefore concluded that if epidemiological investigations were designed with risk assessment applications in mind, synthesis and application of published findings would be less uncertain. The methods we applied would generalize to a variety of multi-stressor epidemiological studies in which exposures may be correlated due to common sources or activity patterns.

3. Case Study #2: Multiple Risk Factors and Hypertension

In our second case, we considered elevated blood pressure (i.e., hypertension), a major contributor to cardiovascular disease. A number of environmental and non-environmental risk factors for hypertension have been identified in the published literature (e.g., sodium consumption, obesity, lack of exercise), although the primary cause of the common type of hypertension is not known. Many of the identified risk factors tend to cluster in a complex network of direct and indirect pathways in their effect on blood pressure. For example, fish consumption may be beneficial for hypertension, but multiple chemicals that contribute to hypertension may be elevated in fish. In this context, standard research synthesis methods may pool evidence in an inappropriate manner, as published epidemiological studies often investigate one pathway controlling for other covariates without appreciating the role of cumulative exposure and the interrelations and influences of mediating factors.

For this case, a component of an effects-based cumulative risk assessment study, we initially conducted a literature review to determine if the epidemiological evidence was sufficient to develop concentration-response functions for the various chemical and non-chemical stressors hypothesized to influence blood pressure in our study population. Given an initial literature

evaluation and the geographic setting for our cumulative risk assessment, we focused on four chemical exposures: lead, cadmium, mercury, and polychlorinated biphenyls (PCBs). Our formal review of the published literature confirmed that the available evidence did not provide insight necessary for cumulative risk assessment. Specifically, the available publications did not typically include investigation of simultaneous exposures or direct and indirect relationships with predictors. We therefore concluded that new epidemiological evidence needed to be derived to inform our cumulative risk assessment.

For complex outcomes involving multiple potential risk factors and pathways, there has been increasing interest in the application of structural equation modeling (SEM) to better understand the joint influence of various risk factors. SEM combines linear regression, path analysis and factor analysis [9] and thus represents a uniform platform for jointly modeling several outcomes simultaneously [10]. Thus, SEM is well suited to assess the relative importance of multiple stressors and how they interact to affect blood pressure in the context of cumulative risk assessment. We applied SEM to data from the National Health and Nutrition Examination Survey (NHANES) 1999-2008 to develop applicable models.

SEM can be thought of as a mathematical representation of the structure of theoretical (i.e., *a priori*-based) relationships among variables rather than a data mining process for model development [11, 12]. When used in a data mining framework, SEM may produce models with good fit but illogical results/pathways [9]. Therefore, we specified the structural models based on previously defined predictive models and logical linkages for each chemical exposure, explicitly considering the influence of factors that could both predict chemical exposures and the blood pressure outcomes. Candidate predictors included demographics (e.g., age, sex, race/ethnicity, country of birth, education); dietary information (e.g., fish and shellfish consumption); and other characteristics (e.g., smoking, access to healthcare, geography).

Given the candidate set of predictors, we selected an optimum subset to eliminate redundancy, reduce noise and address collinearity. This involved manual selection based on univariate and multivariable significance and contribution to the percent variance and automated selection using a stepwise technique and a shrinkage method (i.e., least absolute shrinkage and selection operator (LASSO)).

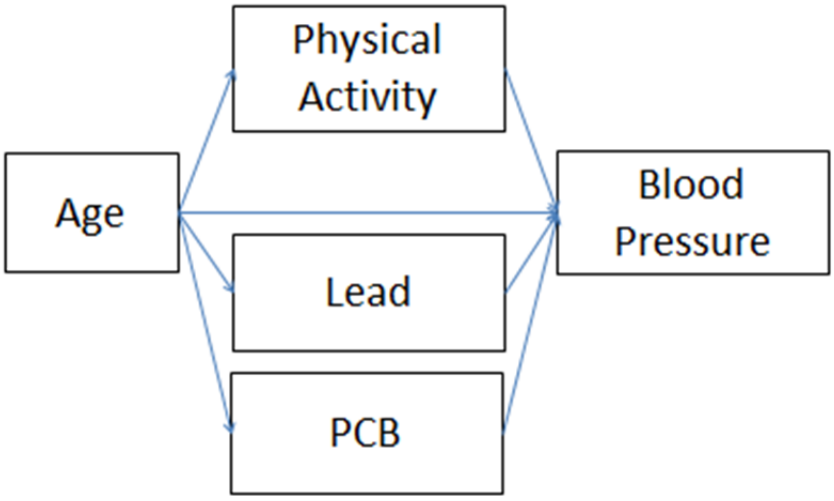
Traditionally, SEM functions best modeling normally distributed continuous data, but many predictors of exposures (e.g., smoking status, physical activity) are either categorical in nature or only available as categorical variables within surveys. One way categorical variables can be addressed is by using latent variable models; however, in the case of risk assessment, we are interested in knowing the contribution of the specific covariate. Alternatively, recent enhancements that allow a generalized linear model framework have facilitated the modeling of categorical data in SEM [9, 11, 12]. The assumption of normal distribution must also be considered as environmental exposures are often log-normally distributed. Several approaches have been proposed for dealing with non-normal data; however, each approach has its drawbacks [9]. For example, less restrictive estimators require substantial sample size such that the application of two of these estimators - weighted least squares for arbitrary distributions and diagonally least squares - were unsuccessful with our final sample size of approximately 1,000. Our final approach was to log-transform data as traditionally done in the environmental literature, mindful that this strategy affects our ability to interpret results.

Another consideration in determining the appropriateness of SEM as a research synthesis tool is that risk assessment applications often rely on large public data resources to generate distributions and associations in the absence of site-specific data. Many of these data resources involve complex surveys such as the NHANES, where sampling design could violate traditional SEM assumptions. The effect of not accounting for sample design can vary from minimal effect to substantial bias [13-16]. In our application, we found similar results for the SEM predicting blood pressure whether or not we used recommended methods that account for cluster, strata and weights. It is worth noting that models generated in SEM do not by themselves represent casual inference due to issues of potential misspecification. In addition to fitting our models based on thoughtfully specified models, we also tested the goodness of fit using several fit indices, which vary in sensitivity to model misspecification [17].

Despite limitations, SEM provided quantitative relationships of the relative importance of chemical exposures on blood pressure accounting for their relationship with non-chemical predictors, information that was not available from standard literature synthesis methods. The ability to use a joint model approach in SEM made it possible to estimate the interrelations between both independent and intermediate variables. For example, age was associated with

elevated blood pressure, but was also associated with lead and PCB concentrations owing to accumulation in body stores. Age was also predictive of level of physical activity, also related to blood pressure (Figure 1). Thus, we were able to mutually adjust for the effect of a primary variable not mediated by intermediary variables and the effect of intermediates conditioned on the primary variable [10]. This capability allowed us to not only model cumulative risk factors in a way that more realistically represents human exposures but to also gain insight into underlying pathways.

Figure 1. Simplified example diagramming direct and indirect relationships of age, chemical and nonchemical factors and blood pressure.



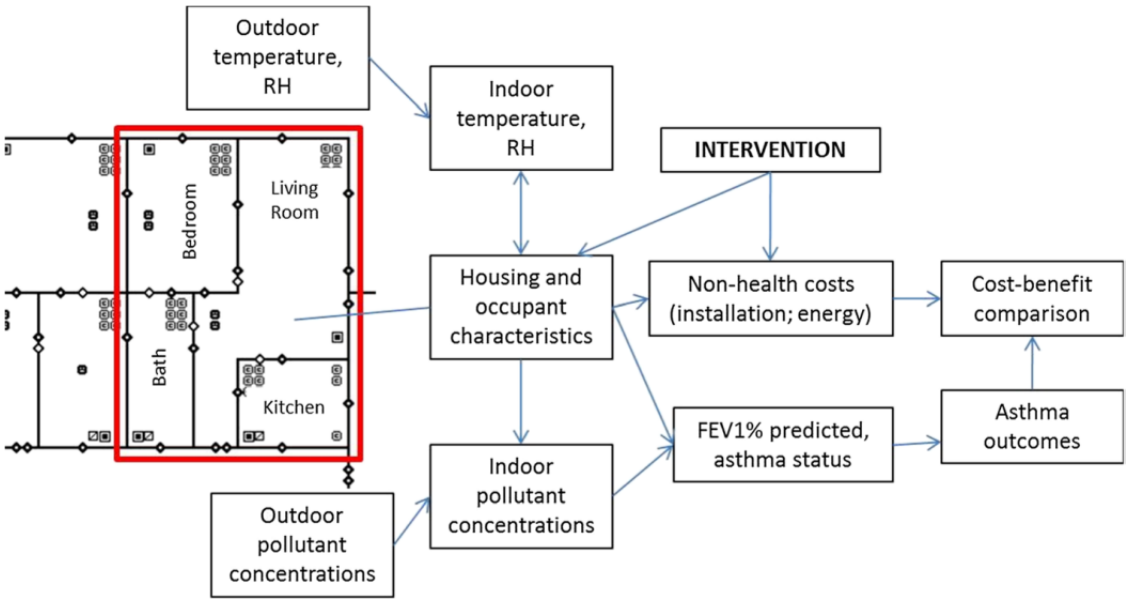
4. Case Study #3: Asthma Exacerbations and the Indoor Environment

Asthma exacerbations are complex phenomena associated with exposure to multiple environmental stressors, including allergens (e.g., dust mites, cockroach allergens) and air pollutants (e.g., ozone (O_3), nitrogen dioxide (NO_2), fine particulate matter ($PM_{2.5}$), and environmental tobacco smoke (ETS)) [18, 19]. Non-pollutant related factors associated with exacerbations include exacerbation history, respiratory infections, asthma medication compliance, and access to health care [20-22]. In this case study, our goal was to build a model of

pediatric asthma which would allow us to evaluate the impact of multiple building interventions in low-income multi-family housing on asthma exacerbations.

We used discrete event simulation modeling (DEM) as a tool to synthesize the relationships among pollutants, lung function and asthma exacerbations [7]. DEM is a systems science approach used to model complex systems which evolve over time [23]. These models have been used in health policy analyses of multiple diseases such as schizophrenia [24], malaria [25], diabetes [26], and breast cancer [27, 28]. Some of the strengths of DEM are flexibility in incorporating multiple types of data (e.g., raw data distributions, equations, regression models, data matrices), ability to incorporate multiple exposures and model interactions, flexibility to vary factors over time, and the ability to develop programs in multiple computer languages. One limitation of DEM is the intensive computational demand, which depends greatly on the number of subjects and length of time simulated, as well as the simulated discrete time steps. Figure 2 presents a schematic of the DEM model.

Figure 2. Schematic of the discrete event simulation model for pediatric asthma in the indoor environment (reproduced from Fabian et al. 2012 [7])



Our asthma exacerbation model required: 1) finding or constructing links between building characteristics and exposure to multiple pollutants, 2) associating each pollutant exposure with an intermediate physiological predictor of asthma outcomes (in this case lung function), and 3) associating lung function directly with asthma outcomes of interest. Pollutants (NO_2, $PM_{2.5}$, cockroach allergen and mold), lung function (percent predicted forced expiratory volume in 1 second (FEV1%)), and outcomes (asthma symptom-days, clinic visits, emergency room visits, and hospitalizations) were selected based on their ability to meet all three requirements above. This meant that some pollutants that were associated with health outcomes in epidemiological studies were not included, as they could not be modeled following the logical flow of the simulation model (i.e., they could not be modeled in the indoor environment or could not be associated with our intermediate lung function metric).

We parameterized the model and included pollutants and outcomes using a combination of methods, including: synthesizing information from the epidemiological literature, incorporating raw data from previous public housing studies, developing new equations to model non-linear relationships among the multiple factors, and using multizone airflow and contaminant transport software (CONTAM) to predict pollutant concentrations from indoor and outdoor combustion sources based on building characteristics [7]. Each component was built with an eye toward the other components, knowing that an interpretable model would need to be internally consistent. For example, we built predictive regression models explaining variability in outputs from CONTAM, rather than using CONTAM outputs directly, so that the indoor air predictions could be used within the daily flow of the DEM. Similarly, the averaging times for pollutant concentration estimates needed to be aligned with epidemiological evidence – for example we used the 5-day average outdoor NO_2 and $PM_{2.5}$ concentrations to estimate the effect of NO_2 and $PM_{2.5}$ on lung function as indicated in our reference study [29]. More details about the model components and how they were synthesized have been published elsewhere [7, 30]. The resulting DEM was used to evaluate the impact of multiple interventions on asthma exacerbations (and costs) in a simulated low-income housing pediatric population [31]. The interventions included energy saving building changes (e.g., weatherization) and other building policies (e.g., non-smoking policy, increased ventilation, pollution source replacement).

Ultimately, our model involved research synthesis at multiple levels – many components required a systematic literature review, considering both the strength of the epidemiology and field study literature and the degree to which outputs could be aligned with other model components. Some epidemiological evidence was relevant for understanding the overall strength of the literature but could not be directly applied within our model. The DEM was itself a research synthesis tool, as it linked evidence across multiple domains to inform policy choices. This modeling approach is valuable for complex health outcomes, with the flexibility to incorporate other pollutants, outcomes and relationships as more information becomes available.

5. Discussion and Conclusions

These three case studies help to reinforce a few overarching themes regarding research synthesis methods as applied to epidemiological evidence for multi-stressor risk assessment, including literature-based meta-analyses and other analytical approaches. For risk assessment applications in which the effects of multiple stressors are of interest, it can be challenging to extract all necessary information from the published epidemiological literature in an unbiased manner. In each case study, the published epidemiological literature was reasonably robust with good supporting evidence for causality, but there were few or no publications that could be directly applied to the risk assessment or policy analysis applications. This led to either new epidemiology being developed (in the first and second cases) or a narrowly focused strategy for synthesizing the published literature (in the third case). Ideally, epidemiologists who might be aware of the end use of their publications could apply methods that would facilitate that end use, but rarely are these applications either known in advance or under consideration by epidemiologists. Related to this point, each of the case examples involved an interdisciplinary collaboration including epidemiologists working alongside risk assessors, simulation modelers, clinicians, or others involved in the end use of the epidemiology. This increased the likelihood that epidemiological evidence, either collected from the literature or developed through new analyses, would be suitable for the application.

In addition, each of the case studies illustrated how an advanced analytical method can be used to synthesize epidemiological and other evidence for risk assessment applications. Multi-

site epidemiological analyses, using Bayesian approaches to pool evidence across a large number of geographic locations, can synthesize evidence that might have otherwise been reported as numerous individual estimates. This addresses concerns regarding methodological variability and potential publication bias, while increasing statistical power. It would be relatively rare to have risk assessment applications where the opportunity existed to conduct new epidemiology across many locations, but the value of this approach reinforces the importance of explicitly examining methodological consistency across studies and whether geographic heterogeneity exists prior to conducting literature-based meta-analyses. A crucial question in synthesizing epidemiological evidence across studies is whether differences in effect estimates reflect uncertainty or variability, and the statistical approaches that we used addressed this question. More broadly, even in situations where multi-site epidemiology is not viable, Bayesian concepts and calculation approaches can be useful ways to formally consider how additional epidemiological evidence could modify an existing prior distribution.

Structural equation models offer an alternative analytical strategy for new epidemiological investigations. SEMs are reputed to offer the broadest statistical application representing an integration of analytic tools rather than a singular approach [(12)]. They can provide a comprehensive evaluation of complex models involving direct and indirect relationships expressed in multiple linear equations compared to traditional techniques involving separate evaluations of components of complex relationships based on individually-modeled equations [(9)]. When multiple stressors potentially operate at multiple levels, standard epidemiological approaches can potentially yield misleading or uninterpretable findings, and pooled estimates from literature-based synthesis approaches could have significant errors. SEM can help determine pathways of influence and can provide appropriate estimates for individual stressors given the complexity of the multi-stressor and multi-level environment. Implementing SEM involves specific expertise, so this would need to be reserved for applications in which standard approaches are clearly not yielding the requisite information. There are also assumptions and precautions regarding the use of SEM including distribution structure and sample size. However, our case study illustrates that publicly available data can provide the foundation for some SEM applications, so that conducting a new epidemiological analysis does not require significant data collection. More generally, SEM can be used to strengthen insights about

dominant associations and potential causal pathways, which can allow for more targeted literature synthesis.

In contrast, discrete event simulation models do not generate new epidemiological evidence, relying on the published literature and available raw data with all of its strengths and weaknesses. However, the fact that multiple information sources can be synthesized with DEMs allows us to study research questions that may not be possible to answer with individual epidemiological or toxicological studies. In the case of our asthma exacerbation study, hospitalizations are events which, although influenced by environmental factors, occur rarely (an average of 0.03 hospitalizations per year per asthmatic). An epidemiological study of the impact of smoking policy changes or structural building changes on environmental pollutants and asthma hospitalizations would be logistically challenging, so one might think that risk assessments including asthma hospitalizations as an outcome would be impractical. However, the linked structure of the DEM coupled with the ability to simulate millions of children allowed us to easily study this outcome. Thus, DEMs can be useful tools for policy analysis, and for the study of rare events. In addition, the simulation framework and explicit linkage across model elements allows for iterative model refinement. Any module can be updated as new information becomes available, and the subset of exposures that most influence the choice among risk management policies can be investigated in more detail.

Broadly, the choice among these (or other) methods for research synthesis of epidemiological evidence ultimately relates to the specific application. Any research synthesis approach should be designed for purpose – a strategy that is successful for one application may either be inapplicable or unwieldy for another application. Just as the proper scope of a risk assessment can only be determined by knowing the risk management context [(32)], so should the research synthesis approach be driven by the risk assessment content, structure, and timing. The key insight that our case examples provide is that multi-stressor risk assessment will often require information that goes beyond standard linkage of literature-based epidemiology with exposure estimates, either in how the epidemiological evidence is generated or in how it is applied.

As shown in Table 1, each of the four general strategies we discussed for epidemiological literature synthesis (literature-based meta-analysis, multi-site epidemiology with Bayesian

methods to pool evidence, structural equation modeling, and discrete event simulation modeling) has advantages and disadvantages, and investigators should ask a series of diagnostic questions to determine which research synthesis method would be most appropriate. For example, if the published epidemiological literature adequately provides concentration-response functions for multiple individual stressors and the objective is to prioritize among stressors, DEMs or related approaches could be used to synthesize the evidence in a manner that informs policy choices and research priorities. If the health outcome of interest can be impacted by multiple exposures and occurs rarely, then DEMs are a good approach to leverage insight from related associations in the literature. If methodological inconsistency or between-site heterogeneity makes a literature-based meta-analysis challenging, multi-site epidemiology using Bayesian methods to pool evidence may be warranted. If the literature is challenging to synthesize because the stressors of interest operate at multiple levels, SEM could be informative. We encourage future researchers to explicitly consider these and other research synthesis techniques to provide relevant outputs for cumulative risk assessments and other multi-stressor investigations.

Table 1: Comparison of alternative research synthesis methods for including epidemiological evidence in multi-stressor risk assessments (RA).

Approach	Most likely application	Strengths	Weaknesses
Literature meta-analysis	• RAs of limited number of related chemicals, where causality has been well established	• Analytically less complex • Integrates current state of knowledge	• Non-uniform methods • General lack of insight regarding multi-stressor associations
Multi-site epidemiology with Bayesian methods to pool evidence	• RA of mixtures of correlated pollutants (e.g., air pollution) • RA of chemical exposures monitored regularly, where associations may vary spatially	• Standardized methods across locations • Ability to "borrow strength" across site-specific analyses	• Statistically complex • Only applicable to limited number of exposures that can be characterized over many locations
Structural equation modeling	• Cumulative RA of chemical and non-chemical stressors • RAs in which non-chemical stressors could influence exposures and outcomes	• Clarifies pathways among multi-level stressors • Flexible modeling approach	• Statistically complex • Works best with continuous and normally-distributed covariates
Discrete event simulation modeling	• RA applications with time-varying associations and feedback loops • RAs in which multiple policy options are under consideration • RA of rare outcomes which would be logistically challenging to study with only epidemiology	• Integrates multiple types of data (epidemiology studies, raw data, equations, data matrices) to answer complex health outcome questions • Allows for evaluation of intervention scenarios modifying individual or clusters of factors • Generates evidence for policy analysis • Allows for inclusion of rare events and dynamic systems	• Statistically complex and computationally demanding • Model parameterization limited by published literature

References

1. US Environmental Protection Agency. Framework for Cumulative Risk Assessment. Washington, DC: Risk Assessment Forum, 2003. Report No.: EPA/630/P-02/001F.
2. Sexton K, Linder SH. Cumulative risk assessment for combined health effects from chemical and nonchemical stressors. Am J Pub Health, 2011;101:S81-S88.
3. Levy JI. Is epidemiology the key to cumulative risk assessment ? Risk Anal, 2008;28:1507-1513.
4. US Environmental Protection Agency. Request for Information and Citations on Methods for Cumulative Risk Assessment. Washington, DC: Federal Register, 2013. Docket ID No. EPA-HQ-ORD-2013-0292.
5. Levy JI, Diez D, Dou Y, Barr CD, Dominici F. A meta-analysis and multisite time-series analysis of the differential toxicity of major fine particulate matter constituents. Am J Epidemiol, 2012;175:1091-1099.
6. Peters JL, Fabian MP, Levy JI. Multiple chemical and non-chemical exposures related to blood pressure within the National Health and Nutrition Examination Survey. Presented at Environmental Health 2013, Boston, MA, Mar 3-6 2013.
7. Fabian MP, Stout NK, Adamkiewicz G, Geggel A, Ren C, Sandel M, Levy JI. The effects of indoor environmental exposures on pediatric asthma: a discrete event simulation model. Environ Health, 2012;11:66.
8. Industrial Economics. Uncertainty Analyses to Support the Second Section 812 Benefit-Cost Analysis of the Clean Air Act. Cambridge, MA: Prepared for Office of Air and Radiation, US Environmental Protection Agency, 2010.
9. Tomarken AJ, Waller NG. Structural equation modeling: Strengths, limitations, and misconceptions. Ann Rev Clin Psychol, 2005;1:31-65.
10. De Stavola BL, Nitsch D, Silva ID, McCormack V, Hardy R, Mann V, Cole TJ, Morton S, Leon DA. Statistical issues in life course epidemiology. Am J Epidemiol, 2006;163:84-96.
11. Kline RB. Principles and Practice of Structural Equation Modeling, Third Edition. New York: The Guilford Press, 2011.
12. Valluzzi JL, Larson SL, Miller GE. Indications and limitations of structural equation modeling in complex surveys: Implications for an application in the Medical Expenditure Panel

Survey (MEPS). 2003 Joint Statistical Meetings - Section on Survey Research Methods, 2003:4345-4352.

13. Stapleton LM. An assessment of practical solutions for structural equation modeling with complex sample data. Struct Equ Modeling, 2006;13:28-58.

14. Hahs-Vaugn DL. A primer for using and understanding weights with national datasets. J Exp Educ, 2005;73:221-248.

15. Asparouhov T. Sampling weights in latent variable modeling. Struct Equ Modeling, 2005;12:411-434.

16. Kaplan D, Ferguson AJ. On the utilization of sample weights in latent variable models. Struct Equ Modeling, 1999;6:305-321.

17. Hooper D, Coughlan J, Mullen M. Evaluating model fit: A synthesis of the structural equation modelling literature. 7th European Conference on Research Methodology for Business and Management Studies, 2008:195-200.

18. Sharma HP, Hansel NN, Matsui E, Diette GB, Eggleston P, Breysse P. Indoor environmental influences on children's asthma. Pediatr Clin North Am, 2007;54):103-120.

19. Committee on the Assessment of Asthma and Indoor Air. Clearing the Air: Asthma and Indoor Exposures. Washington DC: National Academy Press, 2000.

20. NHLBI. National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart Lung and Blood Institute, National Institutes of Health, 2007.

21. Johnston NW, Sears MR. Asthma exacerbations. 1: epidemiology. Thorax, 2006; 61:722-728.

22. Spahn JD, Cherniack R, Paull K, Gelfand EW. Is forced expiratory volume in one second the best measure of severity in childhood asthma? Am J Respir Crit Care Med, 2004;169:784-786.

23. Law AM, Kelton WD. Simulation Modeling and Analysis. Boston, MA: McGraw-Hill Higher Education, 2000.

24. Heeg BM, Damen J, Buskens E, Caleo S, de Charro F, van Hout BA. Modelling approaches: the case of schizophrenia. Pharmacoeconomics, 2008;26:633-648.

25. McKenzie FE, Wong RC, Bossert WH. Discrete-event simulation models of plasmodium falciparum malaria. Simulation, 1998;71:250-261.

26. Chen J, Alemao E, Yin D, Cook J. Development of a diabetes treatment simulation model: with application to assessing alternative treatment intensification strategies on survival and diabetes-related complications. Diabetes Obes Metab, 2008;10 Suppl 1:33-42.
27. Tosteson AN, Stout NK, Fryback DG, Acharyya S, Herman BA, Hannah LG, Pisano ED. Cost-effectiveness of digital mammography breast cancer screening. Ann Intern Med, 2008;148:1-10.
28. Fryback DG, Stout NK, Rosenberg MA, Trentham-Dietz A, Kuruchittham V, Remington PL. The Wisconsin breast cancer epidemiology simulation model. J Natl Cancer Inst Monogr, 2006;36:37-47.
29. O'Connor GT, Neas L, Vaughn B, Kattan M, Mitchell H, Crain EF, Evans R, 3rd, Gruchalla R, Morgan W, Stout J, Adams GK, Lippmann M. Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol, 2008;121:1133-1139.
30. Fabian P, Adamkiewicz G, Levy JI. Simulating indoor concentrations of NO_2 and $PM_{2.5}$ in multifamily housing for use in health-based intervention modeling. Indoor Air, 2012;22:12-23.
31. Fabian MP, Adamkiewicz G, Stout NK, Sandel M, Levy JI. A simulation model of building intervention impacts on indoor environmental quality, pediatric asthma, and costs. J Allergy Clin Immun, 2013;in press. http://dx.doi.org/10.1016/j.jaci.2013.06.003.
32. Committee on Improving Risk Analysis Approaches Used by the U.S. EPA. Science and Decisions: Advancing Risk Assessment. Washington, DC: National Academy Press, 2008.