The interpretation of chemical epidemiology studies requires integration with experts on the nature of the reported adverse outcome and toxicologists

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Abstract
Chemical Epidemiology Studies (CES) can be both protective for humans of adverse health effects of chemicals as well as cause alarm leading to unwarranted remedial action and litigation. Inherent problems in conducting CES especially related to the study design goals and assessment of exposure are recognized. Many CES report adverse health outcomes at very low exposure levels implying that humans are uniquely or especially sensitive to the toxicity of these chemicals. Such unique sensitivity to humans would be especially important to scientists in human physiology, medical and toxicology communities. CES are currently appearing in the open literature more frequently and it is expected that they will be appearing even more frequently in the future especially if animal toxicity testing is reduced or eliminated. Experts on the nature of the reported adverse health outcomes should be playing a more critical role in the interpretation of CES because they are best suited to understand the many factors affecting natural and induced variability. Should animal toxicity testing be reduced, the role of toxicologists in the interpretation of CES will need to evolve. This manuscript addresses the need for more uniform standards in conducting, reporting, and review by independent, fully focused experts if CES studies reported in the open literature will be included in the health risk characterization and litigation of chemicals.

Keywords
Chemical epidemiology, human toxicity, risk characterization, alternative toxicity testing

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Introduction
Chemical epidemiology studies (CES) appearing in the open literature have high potential to demonstrate meaningful adverse health outcomes and can preclude continued exposure to susceptible populations and thus can be both economically and socially consequential. Such studies are currently appearing more frequently in the open literature. With the advent and possibility of either greatly reducing or eliminating animal toxicity testing, it is expected that CES will become increasingly more important in assessing public health risk. However, when reports of adverse health outcomes are published in the open literature, the results can also be alarming and initiate unwarranted mitigation procedures. These include the loss of the benefits of useful chemicals, potential replacement with more expensive and perhaps less efficient alternatives and often costly litigation. A fundamental principle is that observations of adverse health outcomes are also implying toxic responses in humans resulting from the chemical affecting specific physiological parameters. Reports of adverse health outcomes at

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very low suspected levels of exposure imply that humans could be uniquely susceptible to the toxicity of the chemical. Therefore, CES need independent critical review by the most appropriate experts to determine if the observations are supported by the conditions of the study and reported data. This communication calls for standardization of conducting and reporting requirements for CES especially for those that appear in the open literature being considered for inclusion in the human risk characterization of the chemical. This standardization will facilitate independent, critical peer-review to render the observations as plausible or otherwise so the appropriate remedial action if needed is supported.

**A novel and evolving plan for the standardization of conducting, reporting and review of CES**

Previous publications describing this proposal called for establishing an independent and fully focused entity that would standardize the conducting and peer-review of CES. This proposal included six separate subcommittees that would have specific functions. There would be an ethics subcommittee that would develop uniform ethical standards especially for access to the supporting data that are critical to an independent evaluation of the study. It would be comprised of epidemiologists, lawyers, ethicists, toxicologists and other representatives deemed necessary or helpful. A second subcommittee would include experts on the nature of the endpoint(s) that may be reported as adverse outcomes. These experts would be medical professionals or other individuals such as anatomists, pathologists, physiologists and human behavior scientists. There would be a subcommittee for assessing exposure by surveys or interviews and another for actual analytical chemistry. There would be a subcommittee for statistics. The toxicology subcommittee would consist of toxicologists knowledgeable of existing animal testing databases and structure-activity relationships (SAR) as well as the various and developing alternative methods for assessing potential toxicity.

**Some basics in the conducting of CES**

The basic principles and problems associated with conducting epidemiology studies and the problems of assessing exposure were cleverly presented at the 25 January 2022 Toxicology Forum (session title: Environmental Epidemiology – What do Toxicologists Need to Know?) by Drs Carol Burns and Judy Lakind, respectively. It was indicated that epidemiology studies are conducted for various reasons with differing goals and there are inherent problems associated with assessing exposure. These goals may include cursory investigations initiated by the conducting institute, attempts to prove an association of an adverse health outcome or to demonstrate that there is no such association between exposure and adverse outcome. A very useful systematic approach designed to promote dialogue across the disciplines involved in integrating CES into risk characterization is a “matrix” program. In essence (briefly), the “matrix” consists of a series of three sets of questions/conditions to be answered/described to address the appropriateness of CES for risk assessment for the three following categories i. hazard identification, ii. dose response and iii. exposure assessment.

Recalling that the title of the winter session of the Toxicology Forum included the question “What do toxicologists need to know?” One of the presenters thoughtfully provided the following response:

“that the toxicologists need to know is precisely why the epidemiology study was conducted. That is, was it designed for exploratory academic reasons, or was it designed to help support risk assessment applications in finding exposures that results in safe or adverse effects? Understanding the level of exposure to humans that results in adverse effects is often difficult and design of the epidemiological study is critical in teasing out confounding elements. Moreover, understanding and hence characterizing exposure is critical in making any estimates of safety. Knowing the purpose of the study and sponsors reflects standards under which the study protocol was designed as well as all factors related to the ethical treatment of the subjects on the study. A specific purpose epidemiology study would also likely have more highly trained individuals to know what to look for and evaluate the exposure symptoms. Studies conducted for academic reasons, although they may be well conducted, would not always have the rigidity in either their protocols, assessment of exposure or quantitation and characterization of the nature of the adverse outcomes.” (Dr Mark Johnson, Email communication, 14 February 2022).

**Who are the most critical and appropriate scientists to determine if CES are demonstrating an adverse outcome in studies less than robust?**

Short answer: The experts on the nature of the observed adverse health outcomes and toxicologists.

If there is high confidence in both the incidence of the observed adverse outcome and exposure data to justify that the study is robust, the association may be considered meaningful. Experts on the nature of the observed adverse health outcome and exposure assessors would both be primarily responsible for the assuring the quality of the study as sufficiently robust.
With the above in mind, probably relatively few CES especially those appearing in the open literature, will meet the criteria as robust. Establishing rigid criteria for the conducting and reporting standards could help in the evaluation of the relevance of less than robust studies. Should uniform standards for conducting and reporting and access to the supporting data not be established as proposed or not followed if proposed, CES will still be appearing in the open literature. In these cases, their quality and interpretation will still need to be ascertained otherwise they may be alarmist to the public with costly litigation resulting or a meaningful association missed. In many of these open literature or other reports, the adverse health outcome is claimed to be associated with very low levels of exposure. In these cases, the burden of determining that the association is meaningful, the experts on the specific nature of the outcomes in humans and toxicologists have a more critical role in determining the plausibility that the adverse outcomes associated with the suspect chemical.

The critical role of the expert on the nature in humans of the reported adverse health outcomes

The experts on the nature of the adverse outcomes are the scientists that are most knowledgeable of the physiology and etiology and the condition in humans as well as factors such as race, gender, culture, geography, diet and any known chemicals or stress factors that can influence the variation of the condition in humans. One critical aspect of their involvement in the review of CES would be to assure that the counts of the outcome(s) are accurate and do not include related conditions or confounding factors that may affect the reported incidence of the adverse outcome. To the extent possible, their assessment should be based on the principles of causation as discussed by Hill.6

The current and evolving role of toxicologists

As mentioned above, a working principle associated with the interpretation of CES is that observations of an adverse health outcome are also implying toxic responses in humans. Therefore, toxicologists should have a critical role in the interpretation of CES. In addition to the above thoughtful response to the question “what do toxicologists need to know?” another answer provided was “do the independent experts on the nature of the adverse outcome concur that the study actually demonstrates the adverse outcome?”. If the experts on the nature of the adverse outcome do concur, the toxicologists can provide support for the decision based on what is already in the existing databases. If the experts on the nature of the adverse outcomes do not concur, the toxicologists can, based on compelling evidence in the toxicity data base, present a case for why it could still be a possible adverse outcome. In the latter case resolution between the experts on the nature of the adverse outcome and the toxicologists would be needed before a plausibility factor is released. As mentioned above, animal toxicity testing may eventually be reduced or even eliminated. Thus, the role of toxicologists is evolving and may eventually change from correlating animal toxicity data to the interpretation of the several evolving means of alternative methods for the evaluation of potential toxicity. This would include developing means to support or challenge the plausibility decision made by the experts on the nature of the adverse health outcomes.

Overall, the justifications for the conclusions of the experts on the nature of the adverse outcome and the toxicologists would be clearly delineated so that interested parties would need to provide detailed responses to address or challenge the plausibility conclusions.

Correlation of reports of adverse health outcomes with animal toxicity data

In the assessment of the significance of reported adverse health outcomes, assuming that the animal toxicity or other available data must correlate with the reports in the CES is a non-starter. An authoritative summary of concordance for the predictive value between human and animal toxicity7 for pharmaceuticals determined that for rodent and non-rodent species to be 71%, for non-rodents alone 63%, and for rodents alone only 43%. Another useful source for comparing animal and human toxicity is Experimental and Clinical Neurotoxicology8 where the animal toxicity databases are compared with the toxicity reports in humans for about 400 neurotoxic chemicals. A very common simpler example is the dermal toxicity of urushiol, the active chemical in the production of the dermal reactions to poison ivy. Most humans react to urushiol at very low exposure levels but many animals are not affected. For example, goats are used to clear areas of this plant.

When CES report adverse outcomes at very low levels of suspected exposure, this would be of high concern to both the human physiology, medical and toxicology communities. This is especially true when the report concerns a commonly occurring disease such as a type of cancer or Parkinson’s disease. Thus, declaring that humans are uniquely sensitive to a chemical should require very critical review by the appropriate experts with the proper knowledge of the nature of the adverse health outcomes and their variability as well as principles of toxicology. In this regard, sets of standard criteria need to be established for determining that humans are uniquely sensitive to a particular chemical especially at very low exposure levels.
Bias in conducting and review of CES

The potential for bias in conducting and review of CES was recently included in the discussion of the National Academy of Science workshop on the triangulation of environmental epidemiological studies as a confounder in their interpretation. Examples include that bias in the form of interpreting an adverse health outcome by the conducting institution exists because they have the incentive to continue funding for their institutions. The regulatory agencies also have their inherent biases that work both ways because promoting an adverse outcome gives career advancement for some individuals. On the other hand, there are accusations that the agencies are delaying action because of external influence.

The current system of the way studies submitted by pesticide registrants to meet standard toxicity data requirements includes that the submitted study reports be transcribed by a resource consuming practice into Data Evaluation Records at taxpayers’ expense. This practice is based on the assumption that the reports provided by the company are biased in favor of including their own selection of data and interpretation. For animal studies especially with pesticides, there are strict standards for Good Laboratory Practices (GLP) and Quality Assurance (QA) and complete data submission and the reviewers can request additional data as well as conduct on-site audits. In contrast, CES appearing in the open literature are essentially accepted at their face value and GLP and QA are variable. Access to the supporting data is very limited and onsite audits are not usually allowed or productive. This discrepancy in the level of review is not fair to the public.

Standardization of conducting and reporting criteria that institutions conducting CES should follow if their publications will be incorporated into the risk characterization of the chemical

Some regulatory agencies within the US federal government already have set criteria for the review of and incorporation of CES into human health risk characterization. These were described at the winter session of the Toxicology Forum together with references. For example, the USEPA (A. Neman Forum presentation and Ref. 10), the US Army Public Health Center (M. Johnson Forum presentation and Ref. 11) and the National Institutes of Occupational Safety and Health (F. Hearl Forum presentation and NIOSH Current Intelligence Bulletins.12,13) The epidemiology societies also have standards for conducting of CES to assure the ethical treatment of the subjects as well as other factors. However, all of these standards are not uniformly applicable to academic institutions conducting CES to address their cursory interests or to investigate the safety of chemicals. In this regard, there should be at least some minimum standards for the conducting and reporting and access to the supporting data that will apply to institutions conducting CES for academic or cursory investigations if the regulatory agencies are going to incorporate their observations into the risk characterization. Such standards would help in making litigation judgements.

Advantages of an independent, fully focused entity to facilitate the design and review of CES

It was not a conclusion of the winter session of the Toxicology Forum that an independent, fully focused entity to set standards for the conducting of CES and retrieval of data for independent review is feasible at this time. A centralized advisory entity could still be incorporated into an existing non-regulatory department. Such an entity might also be established by an international organization such as the WHO. There are several advantages to centralizing at least some of the aspects associated with the conducting and review of CES as follows.

–Standardization of the conducting, reporting and retrieval of supporting data for CES that will be incorporated into the risk characterization of a chemical. It is far better to have these basic standards uniform across the regulatory agencies. The best practices currently employed by the several regulatory agencies could be incorporated into these standards. Having such standardization is for the benefit of all stakeholders especially including the institutions conducting CES since they will have a better chance of their work and interpretation being accepted. As for data access, having an independent fully focused entity with specifically well-trained staff sworn to the protection of the privacy of individuals who visit the conducting institution in the presence of the institutional staff to review the supporting data in a coded format (not actually identifying the subjects) could satisfy the ethics concerns for securing the privacy of the subjects. This visiting staff would consist of experts on the nature of the reported adverse outcome, lawyers, ethicists, toxicologists, epidemiologists and exposure assessors. The conducting institutions could eventually be more willing to be receptive to representatives of a fully focused entity rather than the representatives of the individual agencies. Such independent review of the supporting data would be critical to establishing the plausibility or non-plausibility of the relationship of the chemical to the adverse outcome.

–Availability of the appropriate experts. Regulatory agencies focus on the regulations associated with
possible adverse health effects of chemicals. Since there are so many different types of possible adverse outcomes, no single agency would have the right experts with the appropriate expertise on the nature of all of the possible adverse outcomes in humans. An independent fully focused entity could be a “brokerage” for recruiting the appropriate nature of the adverse outcome experts. Over time, the entity would be building better working relationships with these recruited experts and the experts would become more willing to work with the entity rather than the individual agencies.

–Integration of the developing alternative methods for assessing toxicity into the interpretation of CES. As mentioned above, the role of toxicologists could gradually change from the interpretation of animal toxicity data relative to the reported adverse outcome to interpreting the alternative approaches for assessing the safety of chemicals. It would be better overall for all agencies and the epidemiology and toxicology communities to have the same set of standards for the applicability of these future alternative methods for integration into risk characterization.

–Establishing criteria for unique human sensitivity and maintaining a compendium of chemicals established to be uniquely sensitive to humans. Standardization of criteria for establishing that humans are uniquely or especially more sensitive would best be accomplished by an entity fully focused on the interpretation of CES. The proposal for an independent entity includes maintaining a compendium of chemicals determined and how they were determined to be especially so or uniquely sensitive to humans. Organizing and maintaining such a compendium would best be done by the independent entity rather than the individual agencies that would probably focus on their own chemicals. The compendium would serve as a useful precedent reference for all agencies.

–Less bias in the review of the studies. The staff of the entity would not have an interest in decisions concerned with regulating the chemical and should be less partial to public pressure and concerns. They would then be more focused on the accuracy and interpretation of the supporting data. In contrast, representatives from the individual agencies may possibly have their own agendas that can bias the interpretation of the CES.

Conclusion

Due to inherent problems in conducting and assessment of exposure in CES, experts on the nature of reported adverse health outcomes as well as toxicologists should be playing more critical key roles in reviewing CES to determine if the associations between outcomes and exposure are plausible. This is especially true if a report of an adverse outcome is made when the exposure is well below toxicity that would be predicted or there are no supporting indications in the animal toxicity or other databases. CES are already appearing more frequently in the open scientific literature. Since alternatives are currently developing that may eventually replace animal toxicity testing, CES are expected to appear even more frequently. This means that consistent conducting and reporting standards and mechanisms for accessing the supporting data need to be developed to better support the inclusions of reported of adverse health outcomes into risk characterization. The advent of alternatives to animal testing also means that the role of toxicologists will need to evolve to both integrate data from these alternative methods into the interpretation of the study as well as to design alternative studies that will reinforce a conclusion that the adverse outcome is plausibly related to exposure.

Author’s note

This communication is partly based on the Winter Meeting of the Toxicology Forum entitled “Environmental Epidemiology – What do Toxicologists Need to Know” – virtual held 25 January 2022. Since this communication reflects the perspective of the author, it is not meant to be a summary of this meeting. The List of Speakers and presentation titles are C.J. Burns, “Things (some) Toxicologists Don’t Know that Drive (me) Epidemiologists Crazy”. J. S. LaKind, “Epidemiology and Exposure Assessment: What Toxicologists Need to Know (or remember)” A. Neman, “Putting the Pieces Together. The Role of Epidemiology and Evidence Integration in Regulatory Review.” M.S. Johnson, “Using Epidemiological Data within Evidence Integration Techniques to Derive Toxicity Reference Values.” F. J. Hearl, “Occupational Epidemiology & Criteria Development: Quality Assurance and Control.” J.D. Doherty, “Chemical Epidemiology at the Crossroads of Toxicology. An Evolving Proposal to Consolidate the Requirements for Conducting and Reporting and Their Review by Fully Focused Experts.”

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References

1. Doherty JD. Bridging the gap between alleged toxicity and forcing chemical regulation: science transparency demands a specialized interagency peer review panel for chemical epidemiology. *Toxicol Sci* 2020; 177(1): 156–157.

2. Doherty JD. Occupational and environmental epidemiology studies need more consistent submission standards and independent critical review by fully focused experts to better serve the International Community. *EC Pharmacol Toxicol* 2021; 9(8): 92–96.

3. Burns CJ, LaKind JS, Mattison DR, et al. A matrix for bridging the epidemiology and risk assessment gap. *Glob Epidemiol* 2019; 1: 100005.

4. LaKind JS, Burns CJ, Erickson H, et al. Bridging the epidemiology risk assessment gap: an NO2 case study in Matrix. *Glob Epidemiol* 2020; 2: 100017.

5. Burns CJ and Lakind JS. Using the matrix to bridge the epidemiology/risk assessment gap: a case study. *Crit Rev Toxicol* 2021; 51(7): 297–311.

6. Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965; 58: 295–300.

7. Olsen H, Betton G, Robinson D, et al. Concordance of the toxicity of pharmaceuticals in humans and in animals. *Regul Toxicol Pharmacol* 2000; 32: 56–67.

8. Spencer PS and Schaumberg HH (eds) *Experimental and clinical neurotoxicology.* 2nd ed. Oxford University Press, 2000.

9. Whelan C, Beins K and Guyton KZ (2022) Triangulation of evidence in environmental epidemiology. In: Proceedings of a Workshop, 9–11 May 2022. National Academy of Sciences.

10. USEPA/OPP Framework (2016) *US Environmental Protection Agency* – December 28, 2016. Office of Pesticide Programs’ Framework for incorporating human epidemiological & incident data in risk assessments for pesticides.

11. Lent EM, Sussan TE, Leach GJ, et al. Using evidence integration techniques in the development of health-based occupational exposure levels. *Int J Toxicol* 2021; 40(2): 178–195.

12. Whittaker C, Rice F, McKerman L, et al. *Current intelligence bulletin 68: NIOSH chemical carcinogen policy.* Washington, DC: NIOSH, 2016.

13. Daniels RD, Gilbert SJ, Kuppusamy SP, et al. Current intelligence bulletin 69: practices in occupational risk assessment. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2020-106, (Revised 03/2020), 2020. DOI: 10.26616/NIOSHPUB2020106revised032020externalicon.