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Perspective

# Occupational and Environmental Epidemiology Studies Need More Consistent Submission Standards and Independent Critical Review by Fully Focused Experts to Better Serve the International Community

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## Background and Disparities in the Current System

Occupational and environmental epidemiology (OEES) studies currently occur in the open literature at an increased frequency. OEES potentially have serious both social and economic impact. Social factors include that the public in general is impacted and minority groups as well as lesser developed countries may be affected disproportionally. Well conducted OEES demonstrating a factual adverse outcome are obviously important to preclude continued exposure. Well conducted OEES not demonstrating adverse outcomes further assure the safety of chemical usage or lessen concern for hazards for naturally occurring elements. However, when there are unsupported allegations of adverse outcomes there is unnecessary costly remedial cleanup action and replacement chemicals may be more expensive and possibly more toxic to humans. Costly litigation often results either when hazards based on OEES are not recognized or the allegations are not supported by reliable data.

Thus, it is both socially and economically important that OEES be independently critically evaluated to assure that any decision on their significance for regulatory purposes is based on reliable science. Currently, decisions regarding OEES are made by individual countries or in some cases international advisory organizations such as the European Union or the World Health Organization. OEES are often accepted at their face value by these groups. In contrast, animal studies conducted by the chemical industry to satisfy regulatory registration requirements are subjected to much higher levels of review and bars for acceptability. More specifically, animal studies are conducted under current rigid Good Laboratory Practices (GLP), Quality Control (QC), ethics and reporting standards. All their relevant information is available or required to be provided and the studies are subject to onsite audits. They are subjected to multi levels of primary, secondary and often tertiary reviews and then further evaluated by specific (i.e. cancer, developmental, etc.) peer review committees. Thus, many individuals are identified as being responsible for their review and regulatory decisions.

In marked contrast, OEES are conducted under a mixed bag of GLP, QC, ethics and reporting criteria. Currently, supporting data are very difficult to obtain from the conducting institutions and onsite audits are not productive. The individuals and their qualifications responsible for reviewing and verifying that the allegations are supported are not always identified. These disparities in the conduction requirements and the level of review are not serving the public or international community well.

The more involved levels of review and higher bar for acceptance for animal studies is based on the assumption that these studies may be biased and may obscure reactions to treatment. The low bar for accepting OEES assumes that the conducting institutions are not biased. However, institutions conducting OEES can benefit by associating an adverse outcome for a given chemical since it helps in obtaining continued funding. It is unfair to assume that one group is more biased than the other. Therefore, the standards for conducting OEES and

the bar for acceptance for their conclusions should be raised to better assure the public that the institutions' conclusions are reasonably scientifically supported.

## Proposal to consolidate the criteria for what is expected from institutions conducting OEES and establish a means for consistent systematic critical review

In order to address the disparities in the level for acceptability of OEES it was previously proposed in a ToxPoint item [1] and updated [2] that an independent, fully focused entity be established that will consolidate what is expected from institutions conducting OEES as well as provide a means for their independent systematic critical review by well qualified fully focused experts. This original proposal was intended for the entity to be a part of the United States Federal system. Since the ToxPoint item was published it now appears that such a system may well be appropriate for other countries and international regulatory and/or advisory groups. Since there are OEES for naturally occurring, industrial and agricultural chemicals and their wastes as well as drug wastes and other sources of pollution, there should be enough "business" to justify the establishment of this evolving proposed fully focused entity.

OEES as well as pathogen epidemiology studies are inherently difficult to conduct and interpret and each subset within the field of epidemiology requires specific skill sets. For OEES special skills are required to evaluate the many problems including a knowledge of the chemical itself, accurately determining the sources of exposure, eliminating exposure to other agents, correctly assessing for the adverse outcome and knowing the ways this outcome can be affected, and working with diverse populations. Pathogen epidemiology requires skill sets involving knowledge of the pathogen biology, its unpredictable ability to mutate and factors related to its origin and modes of exposure transmission. Prior exposure to pathogens can often be assessed for by antibodies but generally no similar tests are available for exposure to many chemicals which are likely no longer in the body when symptoms develop. Thus, persons conducting and critically reviewing OEES need the same specialized skill sets.

Owing to the complexity of conducting and reporting data in a manner that assures the privacy of the individual subjects, it is not expected that that conduction of OEES can ever have the same level of reporting criteria as laboratory animal studies. However, owing to the social and economic importance of decisions regarding the use of OEES in defining the hazard characterization, conduction standards and reporting criteria should still be such that any decisions regarding the true hazard of a chemical are based on reliable science as best as possible.

## Suggestions for the structure of the evolving proposed entity

This evolving proposed entity [1,2] could be constructed to consists of several subcommittees each reviewing their subdiscipline independently. These independent subcommittees could be as follows.

**Ethics:** The ethics subcommittee would consist of experts with the special skill sets needed for OEES conduction as well as experts in medical ethics and be primarily responsible for all ethical aspects of OEES. Since this subcommittee would be establishing conduction and submission standards for OEES, it would be working closely with the other subcommittees so that the specific concerns of all subcommittees for what needs to be submitted will be included. An important aspect of this subcommittee would be to devise ways that critical supporting data can be provided that respects the privacy of the individuals involved in the study. It is noted that different OEES may need different ways to discretely provide such data.

**Endpoint evaluation:** The endpoint evaluation subcommittee has a very unique role in the proposed entity and would be responsible for all aspects related to characterization of the adverse outcome. This subcommittee would require specialists that may well have to be recruited for each specific adverse outcome. Since there are so many different types of adverse outcomes, and a particular adverse outcome may be noted in very few OEES, it would not be practical to have full time specialist that know all the intricacies of the many possible adverse outcomes. For example, if the adverse outcome were deficits in neurodevelopment, experts in child development would have to

be recruited. A cancer expert for the particular type of cancer would be recruited. These experts would for the adverse outcomes as best as reasonably possible:

- Describe the basic etiology and character of the adverse outcome in question.
- Describe its natural variation including genetic, race, ethnicity, nutritional and any known environmental factor such as regional differences that affect its variation in the human population.
- Describe how large a group of both exposed, marginally exposed and unexposed persons are needed to make a meaningful statistical difference for the particular adverse outcome. This subcommittee, more so than the statistics subcommittee should know best what the size of the groups should be for each particular adverse outcome because they know about its natural variation parameters.
- Describe the inherent problems in assessing for the adverse outcome in humans such as the need for accurate definition/identification of the outcome by all persons involved in the characterization of the condition among the many individuals in the study. Also, describe related conditions that may be mistaken for the alleged adverse outcome.
- Identify all known chemicals that are established or suspected to affect its occurrence.

The fulltime staff of this subcommittee would initiate and maintain a compendium of chemicals that have been demonstrated to cause adverse outcomes as indicated by OEES. The compendium would include chemical responses that are unique to humans as well as chemicals that elicit similar responses in animals but humans are more sensitive. Anecdotal reports of idiosyncratic incidents could also be included but clearly indicated as such. The compendium would serve as a useful reference for future inquiries.

**Exposure:** This subcommittee will be staffed by experts with occupational and environmental epidemiology training especially related to assessment of exposure when no actual analytical chemistry data are available. Since the adverse outcome may not manifest until long after the exposure, these exposure assessors need skills in interviewing the subjects, their relatives or work associates. Special problems may arise when after the lesion has been reported to be associated with a given chemical persons may try to associate their condition with exaggerated claims of exposure. Therefore, special talents are needed for these exposure assessors to assure that the subjects' claims of exposure are plausible.

**Analytical chemistry:** Similar to the endpoint subcommittee, experts may need to be recruited that are best familiar with the analysis for the chemical in question.

**Statistics:** The statistics subcommittee would be comprised of statisticians specifically trained in statistical tests used to evaluate OEES. The statistics subcommittee would assure that the statistical tests reported in the OEES were appropriate. They could also request that additional tests they deem more appropriate be conducted by the institution. Since OEES do not provide individual subject data, this subcommittee could not do their own analysis unless they request the individual subject data deemed essential for independent review from the conducting institution be provided. In some cases, representatives from the endpoint evaluation and exposure subcommittees would jointly meet to assure that all appropriate data sets are included in the statistical tests conducted by the entity. Requests for individual subject data may prove to be common and would have to be coordinated with the ethics subcommittee.

**Animal toxicity and structure activity relationships (SAR) subcommittee:** When available animal toxicity and SAR data may indicate that the chemical in question can cause the alleged adverse outcome and would thus support the allegations. Although the dose levels associated with the induction of the condition in animals may be much higher than the exposures occurring in the OEES, this could indicate that humans are especially sensitive to the chemical. In cases where there are no suggestions in the animal toxicity or SAR data for the

adverse outcome, this alone would not remove a concern that the OEES are demonstrating a relationship between exposure and outcome in humans.

## The entities report

Once the individual subcommittees complete their reviews, the Chairperson would convene a meeting so that each subcommittee can review the reports of all other subcommittees. After a consensus is reached, a report would be prepared for signature by all participants. Minority essays can be appended. The report would delineate clearly whether the available data as presented are robust enough to support the allegations for an adverse outcome and recommend mitigation as needed.

A more likely outcome is that the entity's report may determine that additional data are needed and delineate the justification for requiring the supporting data. In this case the ethics subcommittee would provide guidance for means to procure the data in an ethical manner that assures the privacy of the participating individuals.

Lastly, the entity may identify serious deficiencies and advise that the OEES do not support adverse outcomes.

The reports would be incorporated into the entity's website and specifically made available to the institution conducting the study and when appropriate the industries concerned with the production of the chemicals. Concerned stakeholders can appeal the decisions. However, objections must be based on detailed science. Pandering passionate appeals would not be accepted. The entity Chairperson would consider the detailed objections and depending on the nature of the objections, reconvene the subcommittees for possible revisions. If deemed appropriate an open meeting can be held where the entity would defend its decisions and the objections made public.

## Current examples

The current situations with glyphosate and chlorpyrifos are examples as to how a well-organized independent and fully focused proposed entity would benefit the public. Glyphosate is currently recognized as being associated with increased incidence of non-Hodgkin's Lymphoma (NHL) and "billion" dollar awards have been made to the plaintiffs. A law firm currently advertises in the American media soliciting persons with NHL to join the continuing litigation. Recently, the United States Supreme Court denied a petition to appeal the lower courts awards. However, the relationship between NHL and glyphosate is contentious [3]. In this case, early review of some epidemiological studies could have precluded continued exposure to glyphosate. Or early review may have lessened the justification for the court awards to the plaintiffs.

Chlorpyrifos is now rather commonly accepted as resulting in neurodevelopmental deficits in children following maternal exposure and based on this allegation has been banned or restricted. However, after multiple Science Advisory Panel meetings in the USA, problems with the original epidemiology publications have been recognized. Further, the conducting institution would not provide requested data critical to making an independent evaluation [4]. Early critical review by the proposed entity could well have detected these problems with the original epidemiology studies.

## Benefits

This evolving proposal is first and foremost a means to benefit the public by being protective against meaningful hazards and identifying unsupported allegations. The public and all stakeholders or otherwise interested parties should appreciate that OEES will be based on better and consistent standards for their conduction and decisions on their relevance made following appropriate critical evaluation by fully focused experts. Comments on benefits relating to some of the stakeholders are as follows:

Underdeveloped countries would be assured that decisions on OEES were made independent of the political pressures from the individual countries. This could preclude the "dumping" of pesticides and other chemicals on underdeveloped nations or depriving them of

useful chemicals that may result in requiring more expensive alternatives. Also, recommendations would be made on the need for cleanup of contaminated areas but for some cases unnecessary remedial cleanup would be avoided.

Regulatory Agencies in Individual Countries. If the proposed entity were to be established, the burden and expense of the individual countries reviewing OEES would be lessened and the system eventually could prove to be overall more cost effective.

Institutions conducting OEES following the uniform standards for what needs to be included in OEES, would stand a better chance of having their OEES accepted by the entity as well as the individual countries. These institutions should appreciate that their OEES would be reviewed by fully focused and well qualified peers with the same specific skill sets they have and would be required in conducting OEES. Over time, their works would be better respected by the public.

Industry and public interest groups would have the opportunity to challenge the decisions of the entity but must do so with supporting data. Lawsuits based on passion rather than reliable science would be rendered moot. Public interest groups could not say that OEES were ignored.

### Bottom line

The substance is that this evolving proposal for the conduction and systematic review of OEES can be designed to benefit the public and all stakeholders. The processes as above are suggestions and certainly subject to refinement. This perspective is presented here to stimulate discussion and comments, either favorable for a path forward or otherwise, will be most welcome.

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