Comments of the Evidence-Based Toxicology Collaboration on

Th Draft OHAT Approach for Systematic Review and Evidence Integration for Literature-based Health Assessments – February 2013

June 11, 2013

The Evidence-Based Toxicology Collaboration (EBTC) appreciates the opportunity to provide comments on the Office of Health Assessment and Translation's draft approach for systematic review and evidence integration for literature-based health assessments, dated February 2013 (see http://ntp.niehs.nih.gov/?objectid=960B6F03-A712-90CB-8856221E90EDA46E). The EBTC is group of scientists in academia, industry, and government who are interested in translating evidence-based approaches from medicine and health care (EBM/HC) to toxicology (EBT). Our primary focus is on using systematic reviews and related evidence-based tools to assess test method performance and other applications of these approaches, including the assessment of the associations between chemicals and health effects – the subject of the OHAT draft approach.

The EBTC website (www.ebtox.com) provides background information on the Collaboration, including the members of our Steering Committees in North America and Europe, our mission and vision, historical background, and current work groups. The affiliations of Steering Committee members are provided o the website for identification purposes only and are not meant to imply endorsement by the affiliations of EBTC work products, including these comments.

The primary perspectives informing our comments o the draft OHAT approach are: (1) the fidelity of what is being proposed to EBM as developed by the Cochrane Collaboration, and (2) our sense of how best to translate the systematic review process from EBM to EBT. Thus, we have striven to produce comments that are true to the Cochrane legacy and the needs of toxicology.

We have relied heavily on the OHAT approach document itself and less on the draft protocols intended to illustrate its implementation (see http://ntp.niehs.nih.gov/?objectid=960B6F03-A712-90CB-8856221E90EDA46E). We have focused primarily on OHAT Steps 1-5, which closely track the elements of conventional EBM/HC systematic review. We have only a few comments on OHAT's Steps 6-7, which go beyond the elements of a typical systematic review in an effort to meet OHAT's particular needs. The absence of comment on any particular issue is not meant to imply endorsement.

The EBTC looks forward to OHAT's responses to our and others' comments o the draft OHAT approach.

I. Systematic Review Elements (OHAT approach Steps 1-5)

A. General Comments

1. The EBTC endorses the OHAT's effort to apply systematic reviews in toxicology, for reasons mentioned in comment #2, immediately below.

2. In its draft document, OHAT singles out its desire to enhance transparency through the use of systematic reviews. Such evidence-based approaches also enhance objectivity, consistency, and – through feedback - the conduct and reporting of studies. These added benefits could also be mentioned, even if they are not OHAT's primary reasons for adopting systematic reviews. Transparency, objectivity, and consistency are especially welcome in a field such as toxicology, where stakeholders in industry, non-governmental organizations, and regulatory agencies may have different assessments of the state of the science.

3. The OHAT approach document is succinct and to the point – lean roadmap of how OHAT plans to use systematic reviews for its purposes. However, its brevity necessarily limits acknowledgement of the historical roots of systematic reviews in EBM/HC. Can this legacy be more appropriately acknowledged? Also, one could more extensively address the benefits of systematic reviews versus narrative reviews (enhancing transparency, objectivity, consistency, for example). Moreover, one could map the OHAT approach "steps" to the Cochrane Collaboration's guidance steps for systematic reviews. For example, OHAT's "preparing the topic" (Step #1) corresponds to the Cochrane Collaboration's framing the question and preparing a protocol. Similarly, meta-analysis is signature feature of many EBM/HC systematic reviews, yet is mentioned only in passing in OHAT's Step 5. Such a mapping would also serve to delineate standard practice of systematic reviews from OHAT's approach, which stresses certain steps of systematic reviews and then applies the results to an OHAT-specific process of data integration, which is unrelated to standard practice in systematic reviews.

4. Similarly, perhaps the draft document's emphasis on brevity could also be relaxed in order to:
    a. Clarify the OHAT approach with one or more examples that illustrate the essence of the various steps in the approach document itself, in addition to the examples provided in the draft protocols.
    b. Justify why certain tools were selected over other ones, rather than simply presenting the selected tools.
    c. Define and clarify terms that are used with specific meaning, such as 'outcome', 'evidence stream', and 'body of evidence'.

5. The OHAT approach seems especially appropriate for substances with substantial yet conflicting literature; hence the need for a systematic review to sort out a somewhat confusing situation. If all the literature pointed in the same direction, there would hardly be the need for a labor- and time-intensive review. Is this the case, and if so, could OHAT elaborate on this in the introduction? Would the OHAT approach also be applied to data-poor substances, so that, for example, data gaps could be identified?

6. Dose and exposure are alluded to here and there throughout the framework document, such as in the PECO principles of OHAT Step (Prepare the Topic). However, it is not clear how dose and exposure fit into the OHAT framework. Will there be specific doses/exposure ranges associated with each identified health outcome?

B. Specific Comments o Individual Steps and Components of the OHAT Approach

1. Step 1 (Prepare topic)

We agree that the application of the PECO principles is appropriate to frame the question of systematic review. Given the inevitable iterative nature of a draft systematic review protocol, will successive iterations of the topic and protocol be made publicly available?

2. Step 2 (Search for and select studies for inclusion)

Searching for studies: 'Grey literature' sources present special challenges for systematic reviews. Federal regulatory agencies that receive studies from industry are source of grey literature, yet they present special challenges to reviewers seeking to gain access to such literature. However, some of these agencies are members of the NTP, and thus OHAT might have ready access to such literature, perhaps with certain safeguards stipulated. We think that reasonable attempts should be made to include these databases in searches.

Selecting studies for inclusion: Unreliable methods are given as an example of major limitations that could lead to *priori* exclusion. How is the reliability of methods assessed? Guidance should be provided in order to reduce subjectivity of such *priori* exclusions, which might impact the result of the review. We think that other major limitations not related to study design or type might justify *priori* exclusion. Therefore, we propose to include in general the option of exclusion criteria, if well justified and documented.

3. Step 3 (Extract data from studies)

It should be noted that standard systematic review procedures are applied in this step.

4. Step 4 (Assess the quality of individual studies)

It should be acknowledged that the quality and completeness of reporting might have an impact on 'study quality'. Therefore, this aspect should be considered, for example, as a preparatory step or part of study quality assessment.

It remains to be seen how risk of bias approach designed for human studies performs for other data streams.

General study parameters, such as test substance identity, purity, and stability; animal housing; and dose administration, might impact quality and thus should be accounted for.

Further details or some examples on confounding variables would be helpful.

It should be noted that standard systematic review procedures are applied in this step (two assessors and consensus-building discussion of discrepancies).

5. **Step 5 (Rate the confidence in the body of evidence)**

We think that the size of the body of evidence might qualify as another property to be used for down-grading or up-grading. Imagine a situation in which the evidence with the highest confidence level consists of very few studies, and the evidence of lower confidence, potentially leading to different conclusions, comprises many more studies.

The structure of the assessment could be better explained. We understand that the assessment is done within each data stream grouped by outcome.

As key study design features are used to group studies, these should be defined and/or illustrated with examples.

The assignment of confidence levels is central to the OHAT approach, given that they are later translated into evidence levels. Yet assignments of confidence ratings are admittedly subjective. This is certainly contrary to the spirit of EBM/HC, which is the legacy on which OHAT draws. Critics could charge that the subjectivity of the narrative review is being replaced by a new form of subjectivity. This element of the framework should be better justified.

It is stated that 'Conclusions developed in the subsequent steps of the approach are based on the evidence with the highest confidence.' It is not clear what 'evidence' this refers to (evidence of an entire data stream or of an outcome within a data stream). Is the other evidence (with lower levels of confidence) disregarded? This would be contrary to the spirit of EBM/HC.

6. **Peer review** (see, for example, PFOS/PFOA draft protocol, p. 58)

OHAT will send out its draft systematic reviews for peer review. Will OHAT also send out its draft protocols for peer review and/or public comment prior to implementation? This would be in line with standard practice in EBM/HC.

II. Evidence integration (Steps 6-7)

A. General Comments

1. Evidence integration or synthesis is a critical step in a systematic review, typically allowing the reviewers to derive an unbiased, quantitative estimate of the overall impact of a health care intervention on an outcome. This is relatively straightforward in the context of EBM/HC, which relies heavily on randomized controlled trials as its signature study type. Systematic reviews in toxicology have the challenge of integrating evidence across diverse data streams (studies on humans, animals, cells and tissues, etc.). There is no evidence-based mechanism

for quantitatively integrating such diverse study types. Instead, OHAT uses the term "evidence integration" to refer to its objective of transparently and qualitatively integrating data streams to assign the association between chemical and health outcome to one of several categories of strength of evidence. This distinction between standard practice in EBM/HC and the OHAT framework for toxicology could perhaps be better clarified, in keeping with our general comment I.A.3 above.

2. Similarly, the OHAT focus is not on deriving a measure of the overall quantitative relationship between a chemical and a health outcome. Indeed, OHAT descriptors "reflect the confidence in the body of evidence for a given outcome and the direction of effect" but not its magnitude. In fact, the framework provides little guidance on how to derive an overall quantitative estimate of effect, even within an evidence stream. (Meta-analysis is mentioned only briefly in Step 5, for example.) The magnitude of an effect figures into Steps 6-7 only as confidence upgrader.

3. The studies typically assessed in systematic reviews in EBM/HC are randomized, controlled trials in humans, whereas studies reviewed in EBT are typically heterogeneous (see Comment II.A.1). The latter can could include studies in humans that seek to directly assess the association in question (epidemiological evidence) but could also include studies in various model systems (*in vivo* or *in vitro*) that seek to model the human situation. Because of this heterogeneity, study relevance (to the human situation) emerges as critical new issue in EBT. Assessing only the internal validity or risk of bias of these model systems would be inadequate. One should also assess their relevance or bearing on the human phenomenon of interest. Some *in vivo* or *in vitro* models may be more relevant to the human situation than are other models. The OHAT approach addresses this complex issue through an *priori* qualitative weighting system. Human evidence is a given primary role, and animal (*in vivo*) evidence is given secondary role. Other evidence, such as from mechanistic or *in vitro* studies, is assigned an adjunctive role. The EBTC suggests that that the OHAT consider giving all types of data due consideration, and, at least initially, studies of the highest quality should have the primary role, with lower quality studies having less weight, regardless of the data stream. These qualitative weightings themselves should be supported by evidence where possible. Over time, the biological relevance (and evidence thereof) of *in vivo* and *in vitro* models for humans should be taken into consideration in order to strengthen the evidence-base of the approach.

4. Relatedly, we note that *in vitro* studies (and the evidence they provide) are considered by default less relevant than animal and human evidence (see, for example, the first bullet point o page 8 of the approach document). The approach thus seems poorly positioned to incorporate current trends in toxicology towards *in vitro* models (possibly human-based), such as envisioned by the National Academy of Sciences' 2007 report on *Toxicity Testing in the 21st Century* Given that such studies will, by necessity, involve incorporation of an understanding of mechanism- or mode- of action, we expect that greater consideration will be extended to *in vitro* and other non-animal methods in the future, as their mechanistic relevance to human biology is assessed.

III. Appendix A

Please clarify what an “X“ in the columns signifies.

IV. Appendix B

Please clarify what are the three design features mentioned in the bottom of the table in this Appendix.