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DRAFT OHAT APPROACH FOR SYSTEMATIC REVIEW AND EVIDENCE INTEGRATION FOR LITERATURE-BASED HEALTH ASSESSMENTS – FEBRUARY 2013

Division of the National Toxicology Program

National Institute of Environmental Health Sciences

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INTRODUCTION

The Office of Health Assessment and Translation (OHAT) conducts literature-based evaluations to assess the evidence that environmental chemicals, physical substances, or mixtures (collectively referred to as "substances") cause adverse health effects and provides opinions on whether these substances may be of concern given what is known about current human exposure levels. The OHAT also organizes workshops or state-of-the-science evaluations to address issues of importance in environmental health sciences. The OHAT is adopting systematic review procedures for these evaluations to enhance transparency for reaching and communicating evidence assessment conclusions. The systematic review format provides increased transparency through a detailed protocol that outlines each step in an evaluation including procedures used to perform a literature search, determine whether studies are relevant for inclusion, extract data from studies, assess study quality, and synthesize data for reaching conclusions. The method for data synthesis includes steps to assess confidence within an evidence stream (i.e., human, animal, and other relevant data[1] separately) and then to integrate across evidence streams to reach hazard identification conclusions (**Figure 1**). These methods are being developed, refined, and implemented according to the procedures established for OHAT literature-based evaluations within the Division of the National Toxicology Program (NTP) at the National Institute of Environmental Health Sciences. [2]

Step 1: Prepare Topic

Prior to conducting an evaluation, the OHAT scopes and focuses the topic to answer the specific question or questions to be addressed in the evaluation. The objective(s) can be to identify a potential health hazard, address a public health issue, or summarize data gaps and identify research needs. In any case, each question is formulated based on PECO principles (**Population** of interest, **Exposure** or Intervention, **Control** or comparator group, and **Outcomes** of interest). For example, do women exposed to chemical X in non-occupational settings have reduced fertility? A draft protocol is then developed to outline the proposed approach to address those questions. The detailed protocol documents the strategy to be used in the evaluation and contains project-specific details for key aspects of the methods including: (1) a comprehensive literature search strategy, (2) criteria for selection of studies relevant to address the question, (3) grouping and hierarchy of outcomes pertinent to the question, (4) data extraction elements, (5) risk of bias assessment, and (6) evaluation of confidence in the body of evidence for answering the question. The protocol contains project-specific details as to how human, animal, and other relevant data will be evaluated and utilized.

The topic for the evaluation and the protocol are developed through an iterative process in which information is obtained by outreach to federal partners, use of technical experts as needed, comment from the public, and consultation from the NTP Board of Scientific Counselors. Project-specific decisions for key aspects of the evaluation are made and documented in the protocol before proceeding with the evaluation. However, it is also recognized that valid reasons for modifying a protocol during the course of an evaluation may be encountered (e.g., see FDA 2010). Revisions to the protocol are permitted in these situations; revisions are documented and justified with notation of when in the process the revisions were made.

Step 2: Search for and Select Studies for Inclusion

Searching for Studies: A comprehensive search of the primary scientific literature is performed. The search covers multiple databases (including, but not limited to, PubMed, TOXNET, Scopus, etc.), with sufficient details of the search strategy documented in the protocol such that it could be reproduced.

[1] See http://oehha.ca.gov/multimedia/green/pdf/GC_Regtext011912.pdf for definition and discussion of "Other relevant data"; in brief it refers to non-endpoint data, including chemical, physical, biochemical, biological or other data that may be important for consideration in an evaluation.

[2] See schematic of the OHAT evaluation process at http://ntp.niehs.nih.gov/go/38138

Specifics of the search also list the dates of the search, frequency of updates, and any limits placed on the search (e.g., language or date of publication). The protocol establishes minimum requirements for inclusion of data from meeting abstracts or other unpublished literature. If a study that may be critical to the evaluation has not been peer reviewed, the NTP will have it peer reviewed.

Selecting Studies for Inclusion: All references identified in the search are screened to select studies relevant to answering the question of the evaluation. The protocol establishes criteria for including or excluding references based on applicable outcomes, relevant exposures, and types of studies. The criteria contain sufficient detail such that use of scientific judgment during the selection process is limited. If major limitations in a specific study type or design for addressing the question are known in advance (e.g., unreliable methods to assess exposure or health outcome), a basis for excluding those studies may be described *a priori* in the protocol. The protocol also outlines the specific plans for: reviewing studies for inclusion, resolving conflicts between reviewers, and documenting the reasons that studies were excluded. Two reviewers screen all references at the title/abstract level and resolve disagreements by reaching consensus through discussion. Any reference possibly meeting the inclusion criteria is retrieved for full text review. Procedures for full text review are tailored to the scope of the review and follow procedures established in the protocol.

Step 3: Extract Data from Studies

Relevant data are extracted from individual studies selected for inclusion using separate template forms for human, animal, and *in vitro* studies that are customized as needed for specific evaluations. For each study, data extraction is performed by one member of the evaluation team with quality assurance procedures in place and specified in the protocol (e.g., review by another team member). Following completion of an evaluation, data extraction files are made publicly available.

Step 4: Assess the Quality of Individual Studies

"Study quality" or the risk of bias of individual studies is assessed on an outcome-specific basis by using a set of questions to evaluate study design and performance. The risk-of-bias tool considers guidance from the Agency for Healthcare Research and Quality (AHRQ) (Viswanathan *et al.* 2012), which uses specific questions under five domains (selection, performance, attrition, detection, and reporting bias). Individual questions are designated as only applicable to certain general types of study designs (randomized controlled trials, cohorts, case-control studies, cross sectional studies, case series, case reports, and experimental animal studies), with a subset of the questions applying to each study design (see Appendix A for the questions used to assess risk of bias in human and experimental animal studies along with applicability by study design). The protocol details project-specific factors of study design and performance that result in specific risk-of-bias ratings for each question. For each study outcome, all of the applicable questions are answered with one of four options (definitely low, probably low, probably high, or definitely high risk of bias (Guyatt 2012)) following pre-specified criteria detailed in the protocol. All references are assessed on an outcome basis for risk of bias by two reviewers. Discrepancies between the reviewers are resolved by reaching consensus through discussion.

To the extent possible, studies with other relevant data (e.g., exposure data, mechanistic or *in vitro* studies) are subjected to an assessment of study quality or risk of bias, the details of which are included in the protocol.

Step 5: Rate the Confidence in the Body of Evidence

A confidence rating for the body of evidence for a given outcome is developed by considering the strengths and weaknesses of a collection of studies. These ratings reflect confidence that the study findings accurately reflect the true association between exposure to a substance and an effect. The OHAT's method

is based on the GRADE[3] and AHRQ approaches (Balshem *et al.* 2011, Lohr 2012), which are conceptually very similar. The method uses 4 descriptors to indicate the level of confidence in the body of evidence (**Definitions Box 1**). In the context of identifying research needs, a conclusion of "High Confidence" indicates that further research is very unlikely to change OHAT's confidence in the apparent relationship between exposure to the substance and the outcome. Conversely, a conclusion of "Very Low Confidence" suggests that further research is very likely to impact confidence in the apparent relationship. Human and non-human animal data are considered separately, as are other relevant data (e.g., exposure, mechanistic, or *in vitro* data) to the extent possible and/or necessary. When other relevant data are necessary to address the question of the evaluation, the specific methods used to determine confidence for these studies are explained in the protocol. The methods outlined below apply to the bodies of evidence for human studies and experimental animal studies that address a health outcome.

- **High Confidence (++++)** in the association between exposure to the substance and the outcome. The true effect is highly likely to be reflected by the apparent relationship.
- **Moderate Confidence (+++)** in the association between exposure to the substance and the outcome. The true effect may be reflected in the apparent relationship.
- **Low Confidence (++)** in the association between exposure to the substance and the outcome. The true effect is likely to be different than the apparent relationship.
- **Very Low Confidence (+)** in the association between exposure to the substance and the outcome. The true effect is highly likely to be different than the apparent relationship.

Definitions Box 1: Confidence Ratings in the Body of Evidence

Conclusions developed in the subsequent steps of the approach are based on the evidence with the highest confidence. The protocol can be used in Step 2 to exclude studies when major problems in study design or conduct are known in advance and the basis for excluding these studies is described *a priori* in the protocol. The risk-of-bias evaluations that are given to individual studies on an outcome basis in Step 4 are another key means to select the studies for a given outcome with the highest confidence (e.g., see AHRQ 2012a) that will move forward and be used in decision-making at later steps.

For each outcome, collections of studies are given an initial confidence rating by key study design features (see **Figure 1** for Step 5 schematic). The initial rating is downgraded for factors that decrease confidence and upgraded for factors that increase confidence in the results. Then, confidence across all available study designs is assessed. A single, well conducted study may provide evidence of toxicity or a health effect associated with exposure to the substance in question (e.g., see Germolec (2009) and Foster (2009) for explanation of the NTP levels of evidence for determination of "toxicity" for individual studies). If a sufficient body of very similar studies is available, a quantitative meta-analysis may be completed to generate an overall estimate of effect. Finally, confidence conclusions are developed across multiple outcomes for those outcomes that are biologically related. It is recognized that the scientific judgments involved in these confidence ratings are inherently subjective; however, this process provides a transparent framework to document and justify the decisions made to arrive at a final confidence rating.

Initial confidence set by key features of study design for each outcome

An initial confidence rating is determined by the ability of the study design to address causality as reflected in the confidence that exposure preceded and was associated with the outcome (see **Figure 1**, Step 5, column 1). This ability is reflected in the presence or absence of four key study design features that determine initial confidence ratings and studies are differentiated based on whether or not: (1) the exposure to the substance is controlled, (2) the exposure assessment represents exposures occurring prior to the development of the outcome, (3) the outcome is assessed on the individual level (i.e., not population aggregate data), and (4) a comparison group is used within the study. This first key feature, "controlled exposure" reflects the ability of experimental studies in humans and animals to largely eliminate

[3] Grading of Recommendations Assessment, Development and Evaluation Working Group (http://www.gradeworkinggroup.org/). Note, the GRADE guidelines have been adopted by the Cochrane Collaboration (Schünemann *et al.* 2012).

confounding by randomizing allocation of exposure. Therefore, these studies will usually have all four features and receive an initial rating of "High Confidence." Observational studies do not have controlled exposure and are differentiated by presence or absence of the three remaining study design features. For example, prospective cohort studies usually have all three remaining features and receive an initial rating of "Moderate Confidence." See Appendix B for additional examples and discussion.

These study design features are distinct from the risk of bias assessment. Observational animal studies could be considered using these same study design features. The initial ratings are the starting points that reflect the general strengths of study design features, and then studies are evaluated for factors that would downgrade or upgrade confidence in the evidence for a given outcome.

Downgrade confidence rating

Five properties of the body of evidence (risk of bias, unexplained inconsistency, indirectness, imprecision, and publication bias) are considered to determine if the initial confidence rating should be downgraded (see **Figure 1**, Step 5, column 2). For each of the 5 properties, a judgment is made and documented regarding whether or not there are issues that decrease the confidence rating in each aspect of the body of evidence for the outcome. Factors that would downgrade confidence by one versus two levels are specified in the protocol. The reasons for downgrading confidence may not fit neatly into a single property of the body of evidence. If the decision to downgrade is borderline for two properties, the body of evidence is downgraded once to account for both partial concerns. Similarly, the body of evidence is not downgraded twice for what is essentially the same limitation (or upgraded twice for the same asset) that could be considered applicable to more than one property of the body of evidence.

Risk of bias of the body of evidence: Risk-of-bias criteria were described in Step 4 where study quality issues for individual studies are evaluated on an outcome-specific basis. In this step, the previous risk-of-bias assessments for individual studies now serve as the basis for an overall risk of bias conclusion for the entire body of evidence (Guyatt *et al.* 2011e).

Unexplained inconsistency: Inconsistency, or large variability in the magnitude or direction of estimates of effect, that cannot be explained, reduces confidence in the body of evidence. Large inconsistency across studies should be explored, preferably through *a priori* hypotheses that might explain the heterogeneity. If there is less inconsistency within subgroups of the body of evidence (e.g., men versus women), the protocol can also be amended to consider these *post hoc* groupings.

Indirectness: Indirectness can refer to external validity or indirect measures of the health outcome. Indirectness can lower confidence in the body of evidence when the population, exposure, or outcomes measured differ from those that are of most interest. Concerns about directness could apply to the relationship between a measured outcome and a health effect (i.e., upstream biomarker of a health effect), the route of exposure and the typical human exposure, or the study population and the population of interest (Guyatt *et al.* 2011c, Lohr 2012), exposure in the appropriate biological window to affect the outcome, outcome assessed at an adequate amount of time after the exposure for the development of the outcome (Viswanathan *et al.* 2012). Note that administered dose or exposure level is not considered as a factor under indirectness for developing confidence ratings for the purposes of hazard identification. We recognize that exposure level is an important factor when considering the relevance of study findings to human health effects at known human exposure levels. In OHAT's evaluation process ,this consideration occurs after hazard identification as part of reaching a "level of concern" conclusion, where the health effects are interpreted in the context of what is known regarding the extent and nature of human exposure (Twombly 1998, Medlin 2003, Jahnke *et al.* 2005, Shelby 2005).[4]

[4] OHAT is the process of updating the guidance on how hazard identification conclusions will be used to reach level of concern conclusions. Updated draft guidance for reaching level-of-concern conclusions is expected to be released in 2014.

Imprecision: Imprecision is the lack of certainty for an estimate of effect for a specific outcome. A precise estimate enables the evaluator to determine whether or not there is an effect (i.e., it is different from the comparison group). Confidence intervals of the estimates of effect provide the primary evidence used in considering the imprecision of the body of evidence (Guyatt *et al.* 2011b).

Publication bias: Publication bias specifically pertains to the body of evidence, as selective reporting within a study is covered in risk-of-bias criteria addressing these limitations (Guyatt *et al.* 2011d). There is empirical evidence that studies with negative results (no association) are less likely to be in the published literature. Negative studies may also be affected by "lag bias" or longer time to publication. While some publication bias is inevitable, downgrading is reserved for when serious concern for publication bias significantly decreases confidence in the body of evidence.

Upgrade confidence rating

Four properties of the body of evidence (large magnitude of effect, dose-response, all plausible confounding, and cross-species/population/study consistency) are considered to determine if the confidence rating should be upgraded (see **Figure 1**, Step 5, column 3). For each of the 4 properties, a judgment is made and documented regarding whether or not there are factors that increase the confidence rating in each aspect of the body of evidence for the outcome. Factors that would upgrade confidence by one versus two levels are specified in the protocol.

Large magnitude of effect: A large magnitude of effect is defined as an observed effect that is sufficiently large such that it is unlikely to have occurred as a result of bias from potential confounding factors.

Dose-response: A plausible dose-response relationship between level of exposure and the outcome increases confidence in the result because it reduces concern that the result could be due to chance. Multiple observational human studies with varied exposure levels can contribute to an overall picture of the dose-response. It is important to recognize that the dose-response relationship may not be monotonic and that biological plausibility should be considered in evaluating the dose-response relationship.

All plausible confounding: This element refers to consideration of confounding, healthy worker effect, or effect modification that would bias the effect estimate towards the null. When a body of evidence is potentially biased by one of these factors in a direction that strengthens the findings (i.e., counter to the observed effect), confidence in the results is increased.

Cross-species/population/study consistency: Three types of consistency in the body of evidence can increase confidence in the results: across animal studies - consistent results reported in multiple experimental animal models or species; across dissimilar populations - consistent results reported across populations that differ in factors such as time, location, and/or exposure; and across study types - consistent results reported from studies with different design features.

Other: Additional factors specific to the topic being evaluated (for example, particularly rare outcomes) may result in increasing a confidence rating. These other factors would be specified and defined in the protocol.

Combine confidence conclusions for all study types and multiple outcomes

Conclusions are based on the evidence with the highest confidence when considering evidence across study types and multiple outcomes. Confidence ratings are initially set based on key design features of the available studies for a given outcome (e.g., for experimental studies separately from observational studies). The studies with the highest confidence rating form the basis for the confidence conclusion. As outlined previously, consistent results across studies with different design features increase confidence in the combined body of evidence and can result in an upgraded confidence rating moving forward to Step 6. If the only available body of evidence receives a "Very Low Confidence" rating, then conclusions for those outcomes will not move on to Step 6.

After confidence conclusions are developed for a given outcome, conclusions for multiple outcomes and the entire evaluation are developed. The project-specific definition of an outcome and the grouping of biologically related outcomes used in this step follow the definitions developed *a priori* in the protocol; deviations are taken with care, justified, and documented. When outcomes are sufficiently biologically related that they may inform confidence on the overall health outcome, confidence conclusions may be developed in two steps. Each outcome would first be considered separately. Then, the related outcomes would be considered together and re-evaluated for properties that relate to downgrading and upgrading the body of evidence. The project-specific explanation of the strategy used to combine confidence ratings across multiple outcomes is documented in the protocol.[5]

Step 6: Translate Confidence Ratings into Level of Evidence for Health Effect

The level of evidence is assessed separately within the human, experimental animal, and to the extent possible and necessary, other relevant data sets. The level of evidence for health effects conclusions reflect both the overall confidence in the association between exposure to the substance and the outcome (effect or no effect) and the direction of the effect (toxicity or no toxicity; see **Figure 1** for Step 6 schematic). The strategy uses 4 terms to describe the level of evidence for health effects. These descriptors reflect both the confidence in the body of evidence for a given outcome and the direction of effect. There are 3 descriptors that will be considered in Step 6 ("High Level of Evidence," "Moderate Level of Evidence," and "Low Level of Evidence") that directly translate from the confidence ratings that exposure to the substance is associated with a heath effect and a fourth designation ("Evidence of No Health Effect") to indicate confidence that the substance is not associated with a health effect (**Definitions Box 2**). Because of the inherent difficulty in proving a negative, a conclusion of evidence of no health effect is only reached when there is high confidence in the body of evidence. A low or moderate level of evidence results in a conclusion of inadequate evidence to reach a conclusion.

- **High Level of Evidence:** There is high confidence in the body of evidence for an association between exposure to the substance and the health outcome(s).
- **Moderate Level of Evidence:** There is moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome(s).
- **Low Level of Evidence:** There is low confidence in the body of evidence for an association between exposure to the substance and the health outcome(s), or no data are available.
- **Evidence of No Health Effect:** There is high confidence in the body of evidence that exposure to the substance is not associated with the health outcome(s).

Definitions Box 2: Level of Evidence for Health Effects Descriptors

Although the conclusions describe associations, a causal relationship is implied and the ratings describe the level of evidence for health effects in terms of confidence in the association or the estimate of effect determined from the body of evidence. **Table 1** outlines how the Bradford Hill considerations on causality (Hill 1965) are related to the process of evaluating the confidence in the body of evidence and then integrating the evidence (based on the GRADE approach as described in Schünemann *et al.* 2011).

[5] The product of an OHAT evaluation may vary (e.g., NTP monograph or peer-reviewed publication). For example, in state of the science evaluations, it may be appropriate to end the process after rating the confidence in the available evidence in Step 5 and developing a summary of data gaps and research needs.

Table 1: Aspects of the Hill considerations on causality within the OHAT Approach

Hill Consideration	Relationship to the OHAT Approach
Strength	Considered in upgrading the confidence in the body of evidence for ***large magnitude of effect*** and downgrading confidence for ***Imprecision***
Consistency	Considered in upgrading confidence in the body of evidence for ***consistency across study types***, ***across dissimilar populations***, or ***across animal species****; and in integrating the body of evidence among human, animal, and other relevant data*; also in downgrading confidence in the body of evidence for ***unexplained inconsistency***
Temporality	Considered in ***initial confidence ratings*** by key features of study design, for example experimental studies have an initial rating of "High Confidence" because of the increased confidence that the controlled exposure preceded outcome
Biological gradient	Considered in upgrading the confidence in the body of evidence for evidence of a ***dose-response*** relationship
Biological plausibility	Considered in examining non monotonic ***dose-response*** relationships and developing confidence conclusions across biologically related outcomes, particularly outcomes along a pathway to disease. Other relevant data that inform plausibility such as physiologically based pharmacokinetic and mechanistic studies are considered in *integrating the body of evidence*. Also considered in downgrading the confidence in the body of evidence for ***indirectness***
Experimental evidence	Considered in setting ***initial confidence ratings*** by key features of study design and downgrading for ***risk of bias***

Step 7: Integrate Evidence to Develop Hazard Identification Conclusions

To determine the hazard identification conclusion, the highest level of evidence for a health effect from each of the evidence streams is combined in the final step of the evidence assessment process. Hazard identification conclusions may be reached on individual outcomes (health effects) or groups of biologically related outcomes, as appropriate, based on the evaluation's objectives and the available data. The rationale for such conclusions is documented as the evidence is combined within and across evidence streams, and the conclusions are clearly stated as to which outcomes are incorporated into each conclusion. The four hazard identification conclusion categories are:

- Known to be a hazard to humans
- Presumed to be a hazard to humans
- Suspected to be a hazard to humans
- Not classifiable or not identified to be a hazard to humans

In Step 7, the evidence streams for human studies and non-human animal studies, which have remained separate through the previous steps, are integrated along with other relevant data and, if necessary, with consideration of special situations related to exposure information that may apply across evidence streams. Hazard identification conclusions are developed by integrating the highest level of evidence for health effects conclusions from the human and the animal evidence streams. First, the level of evidence for health effects conclusion for human data from Step 6 ("High," "Moderate," or "Low") is considered together with the level of evidence for health effects conclusion for non-human animal data to reach one of four hazard identification conclusions (see Step 7 in **Figure 1**).

- If the human level of evidence conclusion is high, the hazard identification conclusion is "known" based on the human data alone.
- If the human level of evidence conclusion is moderate, the hazard identification conclusion depends on the strength of the non-human animal evidence. The hazard identification conclusion is "presumed" if the non-human evidence conclusion is high or moderate. The conclusion is "suspected" if the non-human evidence conclusion is low.
- If the human level of evidence conclusion is low, the hazard identification conclusion depends on the strength of the non-human animal evidence. The hazard identification conclusion is "presumed" if the non-human level of evidence conclusion is high. The hazard identification conclusion is "suspected" if the non-human level of evidence conclusion is moderate, and the conclusion is "not classifiable" if the non-human evidence conclusion is low.

Any impact of other relevant data on the hazard identification conclusion derived by integrating the human and non-human animal streams is considered next (see Step 7 in **Figure 1**). Other relevant data could include, but are not limited to, mechanistic data, *in vitro* data, or data based on upstream indicators of a health effect. Note that mechanistic data or another type of other relevant data is not required to reach a final hazard identification conclusion. A detailed rationale accompanies the conclusion along with an explanation as to how the other relevant data contributed to the final hazard identification conclusion.

- If other relevant data provide strong support for biological plausibility of the relationship between exposure and the health effect, the hazard identification conclusion may be upgraded (indicated by black "up" arrows in Step 7 graphic in **Figure 1**) from that initially derived by considering the human and non-human animal evidence together. The initial hazard identification conclusion of "presumed" is upgraded to "known." The initial hazard identification conclusion of "suspected" is upgraded to "presumed." It is envisioned that strong evidence for a relevant biological process from mechanistic or *in vitro* data could result in a conclusion of "suspected" in the absence of human epidemiology or experimental animal data.
- If other relevant data provide strong opposition for biological plausibility of the relationship between exposure and the health effect, the hazard identification conclusion may be downgraded (indicated by gray "down" arrows in Step 7 graphic in **Figure 1**) from that initially derived by considering the human and non-human animal evidence together. The initial hazard identification conclusion of "presumed" is downgraded to "suspected." The initial hazard identification conclusion of "suspected" is downgraded to "not classifiable."

In communicating the outcome of the evaluation, the NTP compiles a draft document that presents the hazard identification conclusions. A summary of key scientific judgments made during development of the conclusions is outlined and justified. As appropriate, the NTP also discusses information about outcomes from evidence streams not used in reaching a final hazard identification conclusion placing them into the proper context of whether or not they are supportive. Although the seven steps in the OHAT Approach result in a hazard identification conclusion, in some cases the health effects are then interpreted in the context of what is known regarding the extent and nature of human exposure as part of reaching a "level of concern" conclusion (Twombly 1998, Medlin 2003, Jahnke *et al.* 2005, Shelby 2005).[4] The draft monograph undergoes peer review and public comment as part of the overall process for it preparation and publication.[6]

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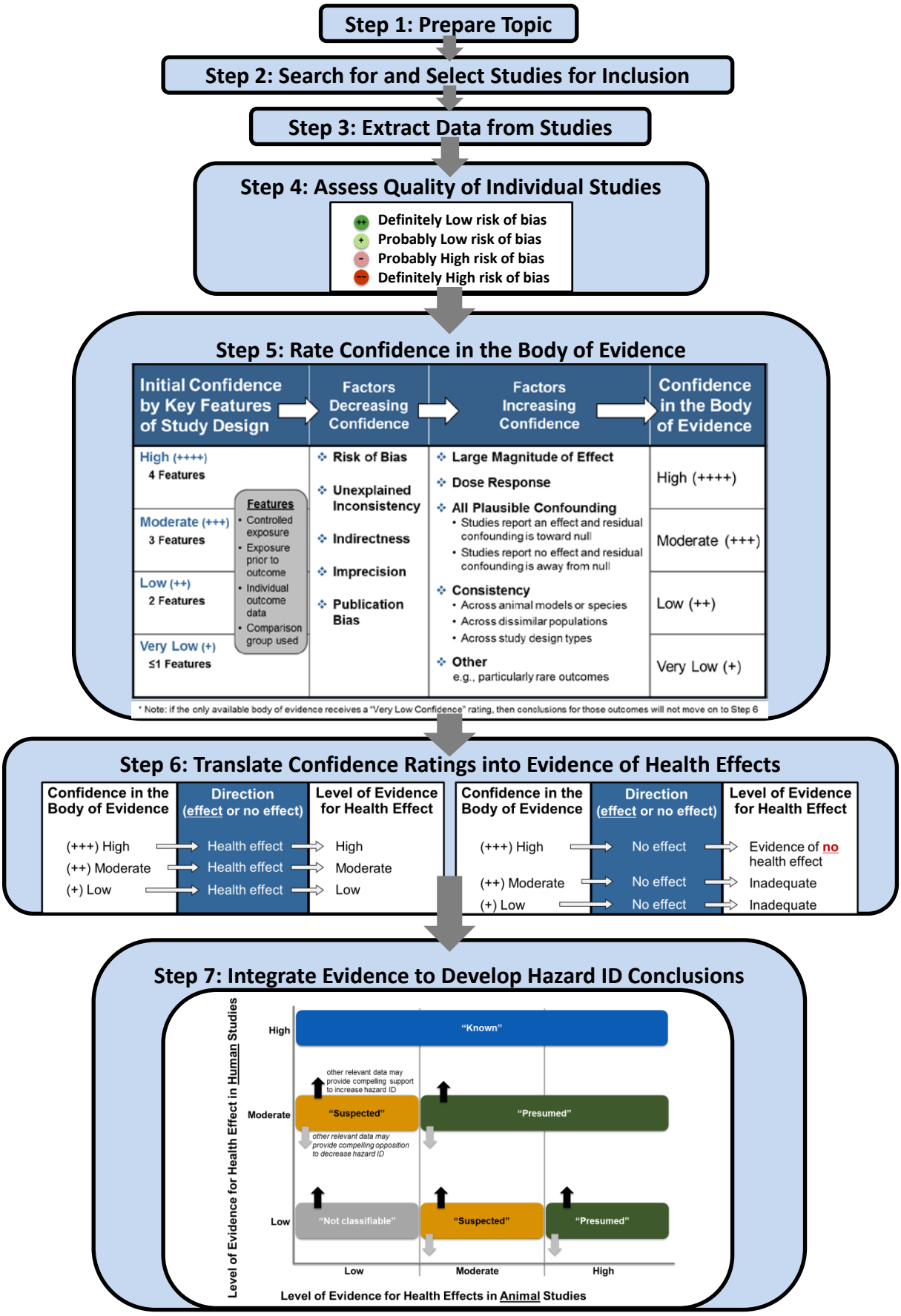
[6] For hazard identification evaluations conducted by the OHAT, the draft monograph undergoes peer review and public comment as part of its overall process for preparation and publication (http://ntp.niehs.nih.gov/go/38138).

The NTP sought consultation on specific topics in an initial draft approach (then called the Draft NTP Approach) by a working group of the BSC on August 28 – 29, 2012. The working group provided a report with recommendations to the BSC at its meeting on December 11, 2012; the report was unanimously accepted by the BSC. Information, presentations, and minutes (when available) from the June and December meetings are at http://ntp.niehs.nih.gov/go/9741. The NTP prepared this "Draft OHAT Approach for Systematic Review and Evidence Integration for Literature-based Health Assessments – February 2013," (Draft OHAT Approach – February 2013) taking into consideration input from the BSC working group, BSC, and the public.

Figure 1: The Draft OHAT Approach for Conducting Literature-Based Evidence Assessments



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Appendix A: Draft Risk of Bias Questions

	Experimental Animal	Human Controlled Trials[1]	Cohort	Case-control	Cross-sectional	Case Series
SELECTION BIAS						
Was administered dose or exposure level adequately randomized? Randomization requires that each human subject or animal had an equal chance of being assigned to any study group including controls (e.g., use of random number table or computer generated randomization).	X	X				
Was allocation to study groups adequately concealed? Allocation concealment requires that research personnel do not know which administered dose or exposure level is assigned at the start of a study. Human studies also require that allocation be concealed from human subjects prior to entering the study. *Note: 1) a question under performance bias addresses blinding of personnel and human subjects to treatment during the study; 2) a question under detection bias addresses blinding of outcome assessors.*	X	X				
Were the comparison groups appropriate? Comparison group appropriateness refers to having similar baseline characteristics between the groups aside from the exposures and outcomes under study.			X	X	X	
Did the study design or analysis account for important confounding and modifying variables? *Note: a parallel question under detection bias addresses reliability of the measurement of confounding or modifying variables.*	X	X	X	X	X	X
PERFORMANCE BIAS						
Did researchers adjust or control for other exposures that are anticipated to bias results?	X	X	X	X	X	X
Were experimental conditions identical across study groups?	X					
Did deviations from the study protocol impact the results?	X	X	X	X	X	X
Were the research personnel and human subjects blinded to the study group during the study? Blinding requires that study scientists do not know which administered dose or exposure level the human subject or animal is being given (i.e., study group). Human studies also require blinding of the human subjects when possible.	X	X				

[1] Human Controlled Trials (HCTs): studies in humans with a controlled exposure, including Randomized Controlled Trials (RCTs) and non-randomized experimental studies

Appendix A: Draft Risk of Bias Questions

	Experimental Animal	Human Controlled Trials[1]	Cohort	Case-control	Cross-sectional	Case Series
ATTRITION/EXCLUSION BIAS						
Were outcome data incomplete due to attrition or exclusion from analysis? Attrition rates are required to be similar and uniformly low across groups with respect to withdrawal or exclusion from analysis	X	X	X	X	X	
DETECTION BIAS						
Were the outcome assessors blinded to study group or exposure level? Blinding requires that outcome assessors do not know the study group or exposure level of the human subject or animal when the outcome was assessed.	X	X	X	X	X	X
Were confounding variables assessed consistently across groups using valid and reliable measures? Consistent application of valid, reliable, and sensitive methods of assessing important confounding or modifying variables is required across study groups. *Note, a parallel question under selection bias addresses whether design or analysis account for confounding.*	X	X	X	X	X	X
Can we be confident in the exposure characterization? Confidence requires valid, reliable, and sensitive methods to measure exposure applied consistently across groups.	X	X	X	X	X	X
Can we be confident in the outcome assessment? Confidence requires valid, reliable, and sensitive methods to assess the outcome and the methods should be applied consistently across groups.	X	X	X	X	X	X
SELECTIVE REPORTING BIAS						
Were all measured outcomes reported?	X	X	X	X	X	X
OTHER						
Were there any other potential treats to internal validity (e.g., inappropriate statistical methods)? On a project specific basis, additional questions for other potential threats to internal validity can be added and applied to study designs as appropriate.						

Appendix B: Study Design Features for Initial Confidence Rating in Body of Evidence Schematic

Study Design	Controlled exposure	Exposure prior to outcome	Individual outcome data	Comparison group used
Human controlled trial*	+	+	+	+
Experimental animal	+	+	+	+
Cohort	-	+/-	+	+
Case-Control	-	+/-	+	+
Cross-sectional†	-	-	+	+
Ecologic	-	+/-	+/-	+
Case series/report	-	+/-	+	-

Symbols indicate if the study design generally includes each of the three key study design features:
(+) usually include; (+/-) may or may not include; (-) unlikely to include.

* Human controlled trial study design used here refers to studies in humans with a controlled exposure including randomized controlled trials and non-randomized experimental studies

† Cross-sectional study design used here refers to population surveys with individual data (e.g., NHANES) distinct from population surveys with aggregate data (i.e., ecologic studies).

Study design labels can distinguish between the relative strengths of study designs, but they are imprecise and often include a mix of design features that impact the ability of a study to address causality. Instead, four key study design features can be used to differentiate the ability of the study to address causality as reflected in the confidence that exposure preceded and was associated with the outcome. The presence or absence of these four features will need to be assessed on an outcome-specific basis. "Controlled exposure" of subjects to the substance is the factor that distinguishes experimental studies from observational studies, and the experimental study design will also typically include the other three key features in both human and animal studies. The key feature that distinguishes between the relative strengths of observational epidemiologic study designs is "Exposure prior to outcome," (i.e., the exposure assessment represents exposures that occurred prior to the development of the outcome). In these cases it is unlikely that an association could be the result of reverse causation - where the outcome contributes to the exposure. Prospective cohort studies usually have all three key study design features; however, when the exposures and outcomes are assessed at the start of a prospective study, these results will only have 2 key features and more closely resemble a cross-sectional study.

Studies without individual-level information on outcomes and other covariates cannot control for additional confounding variables and may lead to inappropriate inferences or an "ecologic fallacy". This limitation is captured with the second key feature "Individual outcome data." An ecologic study can refer to exposures assessed via aggregate data (air pollution by zip code of residence) with individual subject outcome information (which would receive a "+" for the second feature); or it could refer to exposures and outcomes assessed on aggregate data (trends in a city's air pollution and hospitalizations for asthma) and receive a "-".

Without a comparison group there is limited ability to evaluate the association of an exposure and outcome. The third key feature "Comparison group used," distinguishes case series and case reports from the other study designs because they typically lack a comparison group.