NTP BSC Working Group Report on the Draft NTP Report

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Outline

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- Description of the NTP BSC WG Report
- WG recommendations
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  - Step 2: Search for and select studies for inclusion
  - Step 3: Extract data from studies
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  - Step 5: Rate the confidence in the body of evidence
  - Step 6: Translating confidence rating into evidence of health effects
  - Step 7: Integrate evidence to develop hazard ID conclusions
- Conclusions

The NTP BSC WG Report

Content

- The report summarizes discussion during the face-to-face meeting of the NTP BSC WG on August 28 and 29, 2012
- The report covers the discussions of the WG on each of the seven steps in the NTP Approach

Format for each step

- Brief overview capturing the NTP's Approach
- Recommendations for which the WG achieved consensus
- Specific comments for consideration by NTP
  - The *comments for consideration* **do not** represent a recommendation or a consensus opinion of the WG
  - These *comments for consideration* provide the BSC and the NTP a complete picture of the WG discussions that led to the WG recommendations
  - Some comments may represent a minority or divergent opinion

Step 1: Prepare Topic

WG recommendations:

1) For each substance being evaluated, the NTP should establish a draft protocol including risk of bias (RoB) questions *a priori*.
2) Development of the draft protocol for evaluation a substance should follow an iterative process and be refined upon subsequent steps (up to Step 4) and become immutable (except in rate document circumstances) prior to reaching conclusions on hazard assessment.
3) Consideration of relevant human exposure levels including specific and susceptible populations should inform the scope of the topic
4) The NTP should consider a broad spectrum of scientific information to clearly reach decisions regarding study design or preparing the topic for a hazard assessment.

Step 2: Search for and Select Studies for Inclusion

WG recommendations:

1) NTP should conduct a thorough literature search for all studies relevant to human health for a given topic or hazard assessment. The literature search strategy should be transparently described in NTP's hazard assessment documents.

2) Studies utilized for subsequent steps of systematic review should be independently peer reviewed. If they have not yet been peer reviewed, the NTP should arrange for peer review, utilizing existing NTP processes to conduce independent peer reviews.

3) Specific data types (*e.g.,* pharmacokinetic (PK), *in vitro*) data should be identified with respect to informing the hazard assessment.

Step 3: Extract Data from Studies

WG recommendations:

1) The NTP should utilize separate data extraction frameworks for animal and human datasets and not be overly concerned with a homogeneous approach for different types of datasets.
2) Data entry should be quality controlled, for example, via conduct by two independent data extractors.
3) Initially, the NTP should incorporate more weight to non-apical studies.

Step 4: Assess the Quality or Risk of Bias of Individual Studies

WG recommendations:

1) The approach outlined by the NTP to evaluate study quality or RoB of individual studies is reasonable and supported by the WG.
2) The WG suggested rewording the 18 RoB questions to more plainly address study quality with language that aids in the interpretation of the question for animal studies.
3) The WG suggested dropping the designation of a subset of questions as *major* risk of bias questions.
    - The WG recognized NTP was attempting to use the *major* questions as a means of excluding lower quality studies as the basis for conclusions.
    - The WG was split on the question of excluding studies. However, the WG did not support a pre-defined subset of RoB questions as being more definitive compared to other questions or to use these pre-defined subset of *major* RoB to exclude studies for every systematic review that might be undertaken by the NTP.

Step 5: Rate the Confidence in the Body of Evidence

WG recommendations:

1) The WG suggested several changes to initial confidence ratings:

   a) That the term *ecological studies* be removed from consideration as a study type for initial confidence rating (*ecological* refers to exposure classification, not a study type).

   b) The WG suggested that caution should be used when evaluating the initial confidence for case-reports as they could be used as the basis for important public health decisions, depending on the study question.

   c) The WG suggested that case-control and nested case-control studies could be given the same initial confidence rating as cohort studies because there are high quality case-control and nested case-control studies that are comparable to cohort studies.

Step 5: Rate the Confidence in the Body of Evidence

WG recommendations (continued):

1) The WG suggested several changes to initial confidence rating.
2) The WG suggested that some of the reasons for downgrading confidence in the body of evidence should be explained in greater detail. In comparison to RoB, the issues were not thoroughly described.
3) The WG supported the NTP's list of factors that could decrease confidence in a body of evidence and the factors that could increase confidence in a body of evidence. Specifically, the WG agreed that consistency across study designs, populations, and species should be part of the NTP's list of factors that could increase confidence in a body of evidence. In addition, the WG suggested adding consideration of *rare outcomes*, *harm*, and *specificity* as factors that could increase confidence in a body of evidence.

Step 6: Translating Confidence Rating into Evidence of Health Effects

WG recommendations:

1) The WG suggested changing the terms used to describe evidence of a health effect or the descriptors. While *sufficient* was an acceptable term, *limited*, and *inadequate* had connotations that make the terms problematic for describing a set of studies that could then move forward as the basis for conclusions.

Step 7: Integrate Evidence to Develop Hazard Identification Conclusions

WG recommendations:

1) The WG suggests that the figures explaining the NTP approach (7A and 7B) should indicate that other relevant data could either increase or decrease the hazard ID conclusion (as presented they suggest it could only increase).
2) The WG suggests that evidence of no effect should be added to Figure 7A and B.
3) Upgrading (or downgrading) of conclusions should be done only with strong scientific evidence.

Working Group Conclusions

- The WG commended the NTP for taking proactive steps to increase the transparency of hazard assessments
- The WG enthusiastically supported the development of the Approach
- The WG encourages the NTP to advance and evolve methodologies for hazard assessment
- NTP's methodology is consistently moving forward the state-of-the science for hazard assessment and is responsive to recent recommendations from authoritative scientific organizations (e.g., National Academies of Science, NAS)

Acknowledgements

NTP BSC Working Group

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- Mary Wolfe – Director
- Lori White – Designated Federal Official

Review Question

Please comment on the working group's draft report and recommendations to the NTP.

ACTION:

The BSC will be asked to vote on acceptance of the draft working group report.