NTP RESEARCH PROJECT: UPDATING LEVEL OF CONCERN CATEGORIES

PROJECT LEADERS

Kris Thayer, Ph.D., NIEHS/DNTP/OHAT
Mary Wolfe, Ph.D., NIEHS/DNTP/OLPR

Contributors:
Kyla Taylor, M.S. NIEHS/DNTP/OHAT
Shepherd Schurman, M.D. NIEHS/CRU
Grace Kissling, Ph.D. NIEHS/Biostatistics Branch
Mike Shelby, Ph.D, NIEHS retired
David Budescu, Ph.D., (technical advisor) Department of Psychology, Fordham University
Thomas Wallsten, Ph.D., (technical advisor) Department of Psychology, University of Maryland
Barbara Forsyth, Ph.D., (technical advisor) private consultant

BACKGROUND, RATIONALE, AND SPECIFIC AIMS

Background

In 1998, the National Toxicology Program (NTP) initiated literature-based evaluations to provide opinions on whether selected environmental exposures might be of concern for causing adverse effects on human reproduction and development. This involved assessments of the collection of human, experimental animal, and mechanistic scientific evidence for reproductive or developmental toxicity of environmental chemicals, physical agents, or mixtures, and consideration of the levels of current human exposure, and pharmacokinetics (Jahnke et al. 2005; Shelby 2005). These NTP opinions are referred to as "level of concern" (LoC) conclusions. LoC conclusions are qualitative in nature and are currently expressed using a 5-point scale that ranges from "negligible concern" to "serious concern" for adverse effects, with an additional category of "insufficient data" that is used when sufficient information is lacking on hazard and/or exposure to reach a conclusion (Figure 1). NTP used this LoC framework to describe concern for reproductive or developmental effects for 20 substances on the basis of literature-based evaluations conducted by the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR). In 2011, the NTP expanded the scope of CERHR to include all non-cancer health outcomes and renamed it the Office of Health Assessment and Translation (OHAT) (Bucher et al. 2011). OHAT evaluations are also used to develop LoC conclusions.

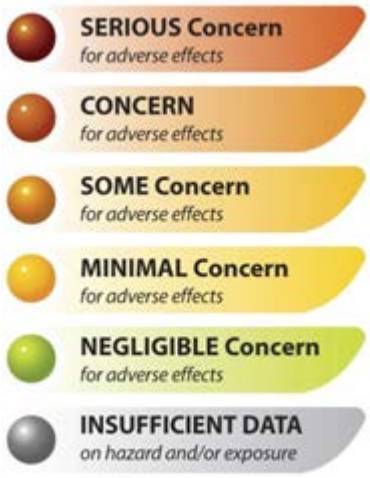
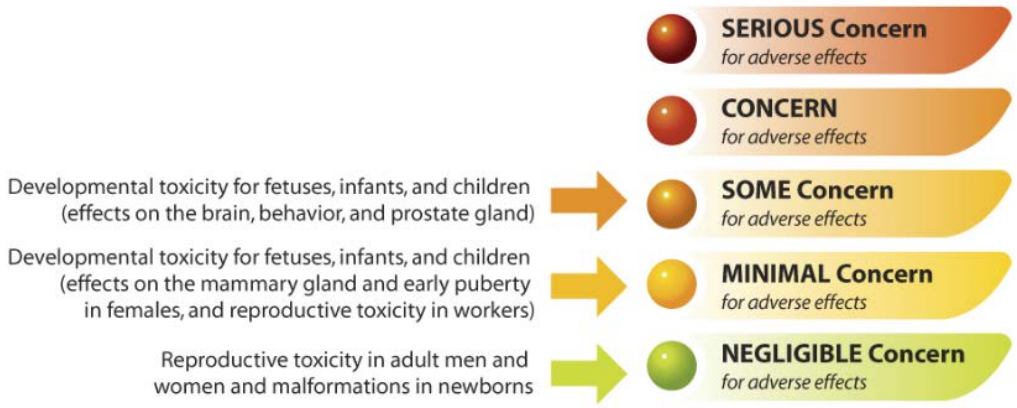


Figure 1. Level of concern categories used from 1998-present

Although LoC categories are not strictly defined, conclusions regarding the appropriate category to choose are based on a number of factors, most typically the hazard identification assessment of the

potential adversity to humans of the health outcomes(s) identified in animal and/or human studies, the extent and nature of exposure, and pharmacokinetic factors. Conclusions regarding LoC for health effect(s) may be determined for specific population groups, e.g., workers, general population, or children (Figure 2). As such, although LoC conclusions have no regulatory authority, they identify specific population groups for which exposure to a chemical should be examined further.

Figure 2. NTP conclusions regarding the possibilities that human development or reproduction might be adversely affected by exposure to bisphenol A



The LoC framework has been useful as an approach for integrating conclusions on hazard identification with what is known about human exposure without conducting a quantitative risk assessment, which falls outside the scope of NTP activities. However, as part of implementing systematic review for its literature-based health assessments, NTP is updating its LoC framework. The intent is to enhance understanding of what the categories mean, improve transparency in how LoC conclusions are reached, and identify strategies for improving the framework as a risk communication tool (Birnbaum et al. 2013; NTP 2013; Rooney et al. 2014).

The NTP's decision to update the LoC framework is driven by several factors. First, the selection of five LoC categories for the current LoC framework was arbitrary. To our knowledge, there is very limited research to draw from when establishing the number of categories. Hence, there is value in determining whether a 5-point LoC scale is optimal or the most intuitive. Second, it appears that the public and some of NTP's scientific advisors have experienced confusion regarding the meaning of LoC categories, in particular the meaning of "some concern" and "minimal concern" (NTP 2008). This confusion indicates a need to establish more appropriate labels for LoC categories and clarify what the various LoC categories mean. Third, as part of implementation of systematic review methodologies in literature-based evaluations, NTP has changed the approach and categories it uses to describe hazard conclusions for non-cancer endpoints (Rooney et al. 2014). In particular, the previous approach for developing LoC conclusions was based on separate hazard identification assessments of animal and human studies. The new approach integrates across animal and human evidence and then considers the degree of support from *in vitro* or *in vivo* cellular and molecular based studies (mechanistic studies/other relevant data) to reach a single category for hazard identification (Figure 3). Thus, the new hazard identification assessment approach and hazard categories need to be incorporated into the LoC framework.

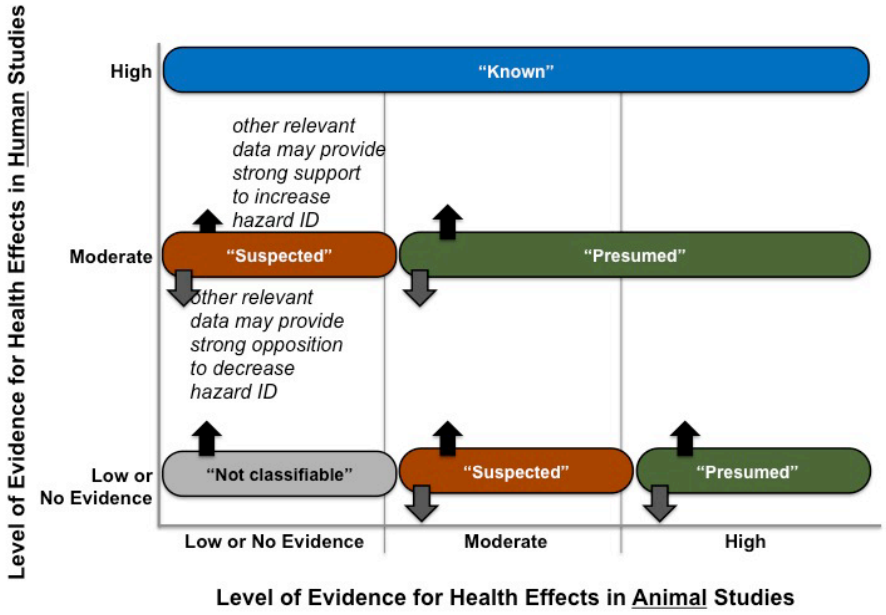


Figure 3. OHAT approach for evidence integration to develop hazard identification conclusions

Once OHAT has a revised LoC framework, the intent is to retain the use of multiple modalities for visual communication of LoC categories. Many authors encourage the use of multiple modalities in risk communication (Budescu et al. 2009; Budescu et al. 2012; Galesic and Garcia-Retamero 2013; Garcia-Retamero et al. 2012; Trevena et al. 2013; Zipkin et al. 2014), and the current LoC framework uses several: (1) narrative descriptions (e.g., "minimal concern," or "concern"), (2) an arrow and short narrative to describe the potential health concern (e.g., "effects on the brain", example in Figure 2), (3) a color gradient with "negligible concern" as green and "serious concern" as red, and (4) vertical orientation with "negligible concern" placed at the bottom of the scale and "serious concern" at the top (Figure 1). OHAT will re-assess the various modalities currently used for visual communication of LoC categories. We will consider how they might apply to the revised LoC framework and what changes might be needed. Finally we will explore other technologies such as interactive web-based formats with "click to see more" functions that would allow the reader to access through web links more technical descriptions of the evidence used to reach the LoC conclusion.

OBJECTIVE

The objective of this project is to develop an improved LoC framework for communicating NTP's opinion about whether a selected substance might be of concern for causing adverse effects in humans, given what is known about its toxicity and level of human exposure.

The specific aims for development of the revised LoC framework are to:

(1) Determine the optimal number of LoC categories.
(2) Test the revised X-level LoC categories and determine suitable labels for the categories.
(3) Identify visual and/or web-based strategies to enhance the communicability of LoC conclusions.
(4) Obtain additional stakeholder feedback, including from the general public and clinicians, on the revised LoC framework as a transparent communication tool and refine, if needed.

Information is provided about the approach for carrying out Specific Aims 1 and 2. Addressing these specific aims should provide empirical evidence to support any changes made to the number of categories and labels in the revised LoC framework. Following completion of Specific Aims 1 and 2, the approaches for Specific Aims 3 and 4 will be developed and carried out.

General information for Specific Aims 1 and 2

- Engage ~160 experts in toxicology, epidemiology, and risk assessment from five NTP stakeholder sectors (academia, industry, non-government organizations, and federal and state agencies) to sort hypothetical LoC scenarios ("LoC cards") into categories.
- LoC cards are hypothetical scenarios that present information about toxicity and level of human exposure and ask a question regarding the perceived LoC for a specific population group (Figure 4). Experts use information in the scenarios to select their LoC category for the population group.
- LoC card sorting is done using a web-based tool. Experts are trained to use the tool and sort the LoC cards into categories independently.

Figure 4. Sample LoC Card Scenario*

What is your level of concern for [health effect] for [population group]?

Hazard: "Known, Presumed, Suspected, or No Evidence of Hazard" hazard identification category

Human evidence: "*High, Moderate, Low, or "Inadequate"* level of evidence for health effects in human studies

Brief description of the evidence supporting the level of evidence category.

Animal evidence: "*High, Moderate, Low, or "Inadequate"* level of evidence for health effects in animal studies

Brief description of the evidence supporting the level of evidence category.

Mechanistic/other evidence:

Brief description of any evidence and whether it affects the hazard identification conclusion.

Exposure description:

- Information on exposure level(s) and population group(s).
- Information on margin of exposure and its basis.

***** The categories for hazard identification conclusions and level of evidence for human and experimental animal studies are from the OHAT approach (Figure 3).

Specific Aim 1: Determine the optimal number of LoC categories.

a. Trial A. 100 experts (~20 per sector) sort LoC cards into LoC categories with no guidance on number of categories (except a number ≤10) using the web-based tool. This exercise is repeated in Trial B to assess rater reliability.
b. Results from Trials A and B are used to identify the number of LoC categories (X levels) used in Specific Aim 2.

Specific Aim 2: Test the revised X-level LoC category scale and determine suitable labels for the categories.

a. Trial C. 100 experts (60 new with ~20 per sector and 40 from Trials A and B) sort LoC cards into the X-level LoC categories and propose a label for each X-level category.
b. Experts (1) identify and rank order the factors (hazard category, human evidence, animal evidence, mechanistic/other evidence, exposure description, and population group for concern)

that influenced their selection of the LoC category and (2) rate their confidence in that category selection using a 7-point scale ranging from 1 = "not confident" to 7 = "highly confident."

c. Results from Trial C are used to identify suitable labels for the X-level LoC categories used in subsequent specific aims.
d. Results from Trial C are used to determine the consistency of categorization of LoC scenarios in the revised LoC framework and evaluate rating-of-confidence opinions with its use.
e. Results from Trial C are used to identify which factors most contribute to experts placing individual scenarios into the LoC categories.

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