

Updating Level of Concern Categories

Mary S. Wolfe, Ph.D.

Division of the NTP, National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors
June 16, 2015



- Background
- Level of concern (LoC) conclusions
- Issues with current LoC framework
- LoC framework project
- Updating LoC categories

**Updating Level
of Concern
Categories**



NTP provides information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public so they can make informed decisions

- NTP's information is not regulatory, although it is authoritative and has been used to inform public health decision-making
- NTP's information types include scientific data and scientific opinions
 - One type of opinion that NTP produces is “level of concern” (LoC) conclusions

There is serious concern that certain intensive medical treatments of male infants may result in di-2-ethylhexyl phthalate (DEHP) levels that adversely affect development of the reproductive tract.





- Background
- Level of concern (LoC) conclusions
- Issues with current LoC framework
- LoC categories project
- Updating LoC categories

**Updating Level
of Concern
Categories**



- LoC conclusion provides an opinion regarding whether an environmental substance might be of concern for causing adverse effects on human health given what is known about its toxicity and current human exposure
- Outcome of in-depth, scientific assessments conducted by NTP Center for Evaluation of Risks to Human Reproduction (1998-2010) and now Office of Health Assessment and Translation (OHAT)
- Qualitative in nature – not a risk assessment – more than a traditional hazard evaluation
- Determined for different population groups – multiple conclusions for a substance
- NTP has derived LoC conclusions for ~20 substances including industrial chemicals, drugs, and chemicals in consumer products



How LoC conclusions are derived and expressed

**Evidence for
toxicity**

+

**Extent of human
exposure and
other factors**

=

Levels of Concern



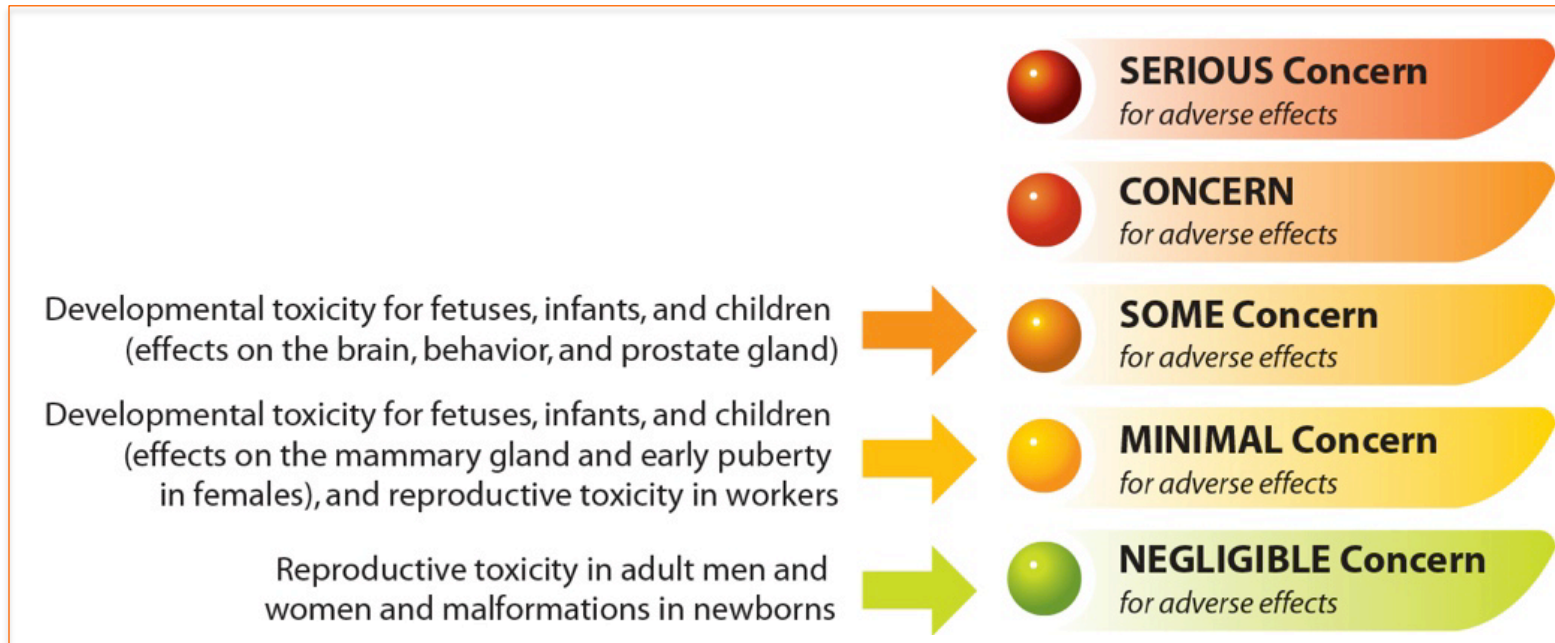
Separately determined for
different population groups

NTP uses a 5-level scale of concern plus 1 category for “insufficient data” and a narrative label for each category



Multiple modalities used to communicate conclusions

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



- Narrative labels for categories, vertical orientation, color gradient
- Arrow and short narrative to describe potential health concern for affected population



- Background
- Level of concern (LoC) conclusions
- **Issues with current LoC framework**
- **LoC framework project**
- **Updating LoC categories**

**Updating Level
of Concern
Categories**



Issues with Current LoC Framework

- Selection of a 5-level scale of concern was arbitrary
 - Is there a number of categories that is optimal or most intuitive?
- Confusion over meaning of different LoC category labels (“some concern” vs “minimal concern” vs. “negligible concern”)
 - What are suitable labels? Words? Numbers?
- Multiple modalities for communicating LoC conclusions (e.g., colors, vertical orientation, labels, arrow, narrative description)
 - Are these modalities effective? Use same or different ones?
 - Are there other modalities or technologies (e.g., interactive, web-based technologies) we should consider?
- OHAT approach for systematic review and evidence integration has a new process for reaching hazard conclusions and new categories
 - Categories: “known”, “presumed”, or “suspected” to be a hazard, and “not classifiable”
 - Need to incorporate into framework for deriving LoC conclusions





- Background
- Level of concern (LoC) conclusions
- Issues with current LoC framework
- LoC framework project
- Updating LoC categories

**Updating Level
of Concern
Categories**



Objective

Develop an improved LoC framework for communicating NTP's opinion about whether a substance might be of concern for causing adverse effects in humans, given what is known about its toxicity and level of exposure

Specific aims

1. Determine 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 other technologies (e.g., interactive web-based strategies) to enhance the communicability of LoC conclusions
4. Obtain stakeholder feedback on revised LoC framework as a transparent communication tool, and refine, if needed



Objective

Develop an improved LoC framework for communicating NTP's opinion about whether a substance might be of concern for causing adverse effects in humans, given what is known about its toxicity and level of exposure

Specific aims

Focus 1st on updating LoC categories

1. Determine 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 stakeholder feedback on revised LoC framework as a transparent communication tool, and refine, if needed.



- Background
- Level of concern (LoC) conclusions
- Issues with current LoC framework
- LoC framework project
- **Updating LoC categories**

**Updating Level
of Concern
Categories**



General approach to study

- Engage ~160 experts in toxicology, epidemiology, and risk assessment to sort “LoC cards” into LoC categories
 - Five stakeholder groups: academia, industry, non-government organizations, federal government, and state agencies
- Create LoC cards
 - Hypothetical LoC scenarios with information about hazard, toxicity, exposure, and population of concern
- Mimic process for deriving LoC conclusions with “LoC card sorting” exercises
 - Experts work independently
- Use a web-based tool for LoC card sorting exercises
 - Train experts to use the tool



LoC card

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

Hazard: “Known, Presumed, Suspected, or Not Classifiable” 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 and level of evidence for human and experimental animal studies are from the OHAT Approach.



Specific Aim 1: Determine optimal number of LoC categories

| | |
|----------|--|
| Trial A | 100 experts sort LoC cards into undefined number (≤ 10) of LoC categories Use web-based tool |
| Trial B | Same as Trial A; ~2-4 weeks apart |
| Analyses | Identify number of LoC categories (X levels) |



Specific Aim 2: Test updated LoC category scale and determine suitable labels for categories

| | |
|----------|---|
| Trial C | 100 experts sort LoC cards into X-level LoC categories: <ul style="list-style-type: none">• Propose labels for categories• Identify and rank order which LoC scenario factors influenced category selection• Rate confidence in category selection using 7-point scale Use web-based tool |
| Trial D | Use labels from Trial C Other steps as Trial C; ~2-4 weeks apart |
| Analyses | <ul style="list-style-type: none">• Reliability of card assignments to LoC categories• Which scenario factors most influenced category selection• Experts' confidence in category selection• Repeat analyses of results from Trial D by sector |



Updating LoC Categories

LoC card sorting

Open and read
LoC cards

Place cards
in category

Trial C: name
categories

Trials A & B: edit
of categories
option

Category 1 = lowest LoC

Number of categories: X [Edit](#)

The interface displays a card sorting process. On the left, an 'Uncategorized' list contains four cards:

- Card 1: [K] 1: What is your level of concern for [health effect] for [population group]? [H H]
- Card 2: [P] 2: What is your level of concern for [health effect] for [population group]? [M M]
- Card 3: [NH] 3: What is your level of concern for [health effect] for [population group]? [L L]
- Card 4: [NC] 4: What is your level of concern for [health effect] for [population group]? [IE H]

On the right, five category columns are shown:

- Category 1: Edit
- Category 2: Edit (Contains Card 2)
- Category 3: Edit
- Category 4: Edit
- Category X: Edit (Contains Card 1)

Yellow arrows indicate the movement of cards from the 'Uncategorized' list to the category columns: Card 1 moves to Category X, Card 2 moves to Category 2, and Card 3 moves to Category 1.



Status and Next Steps

- Reviewed by Institutional Review Board – exempt status
- Complete set of LoC cards
- Preparing submission to OMB for review/approval
- Conduct a pilot
- Begin project following OMB approval



Updating LoC Categories

- Project leads
 - Kristina Thayer, Office of Health Assessment and Translation (OHAT)
 - Mary Wolfe, Office of Liaison, Policy, and Review
- Contributors
 - Kyla Taylor, OHAT
 - Grace Kissling, Biostatistics Branch
 - Shepherd Schurman and NIEHS Clinical Research Unit
 - David Budescu, Fordham University
 - Thomas Wallsten, University of Maryland
 - Barbara Forsyth, private consultant
- DNTP advisory group
 - Chad Blystone
 - Mike DeVito
 - Dori Germolec
 - Ruth Lunn
 - Scott Masten
 - Mike Shelby, retired NIEHS
 - Ray Tice, retired NIEHS
 - Nigel Walker
- Technical assistance
 - Andy Shapiro, Program Operations Branch

Questions?