# How evidence-based methodology can contribute to uncertainty assessment

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A CENTURY OF SAVING LIVES
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ebtc
Evidence-based Toxicology Collaboration

# About the EBTC

## What is EBTC?

EBTC is an international collaboration of science, regulatory and industry leaders

## EBTC's Mission

Bring together the international toxicology community to facilitate use of evidence-based toxicology to inform regulatory, environmental and public health decisions

## Funding

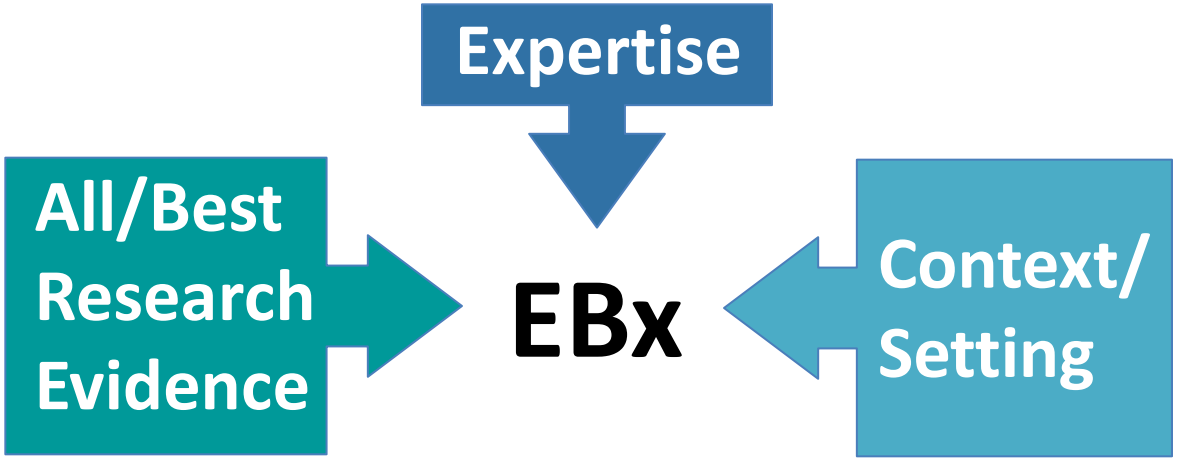
Center for Alternatives to Animal Testing

## Governance

Board of Trustees and Scientific Advisory Committee

# What is 'evidence-based' methodology?

- **Framework** for combining and assessing evidence
- **Origins:** clinical research and healthcare decision-making (e.g., EBM/EBHC/EBP)
- *"… conscientious, explicit and judicious* ***use of current best evidence in making decisions*** *about the care of the individual patient…"* (D. Sackett)



# Why evidence-based approaches?

- **unmanageable amount of information**
- **lack of a critical summary (of evidence)**
- **tradition-based and unjustified decisions**
- **unknown level of uncertainty in decisions**
- **non-transparent, subjective and irreproducible processes**

**reduce uncertainty by using evidence-based methodology**

to retrieve, assess and summarise evidence,
e.g. through systematic reviews, systematic maps

# Wider use of evidence-based approaches

## Increasing application of EB-approaches to environmental, public and occupational health

efsa
European Food Safety Authority


efsa EFSA JOURNAL WILEY
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Guidance of EFSA
Application of systematic review methodology to food and feed safety assessments to support decision making
EFSA Guidance for those carrying out systematic reviews European Food Safety Authority
First published: 1 June 2010 Full publication history
DOI: 10.2903/j.efsa.2010.1637 View/save citation
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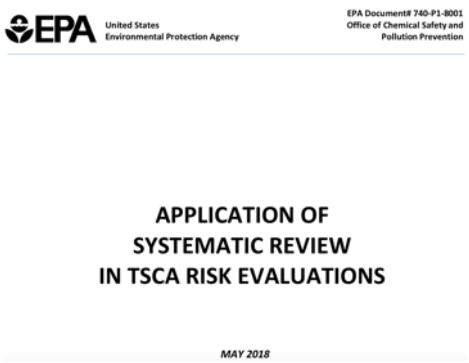
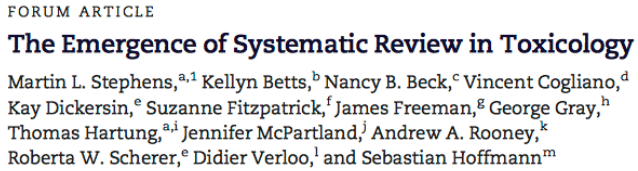
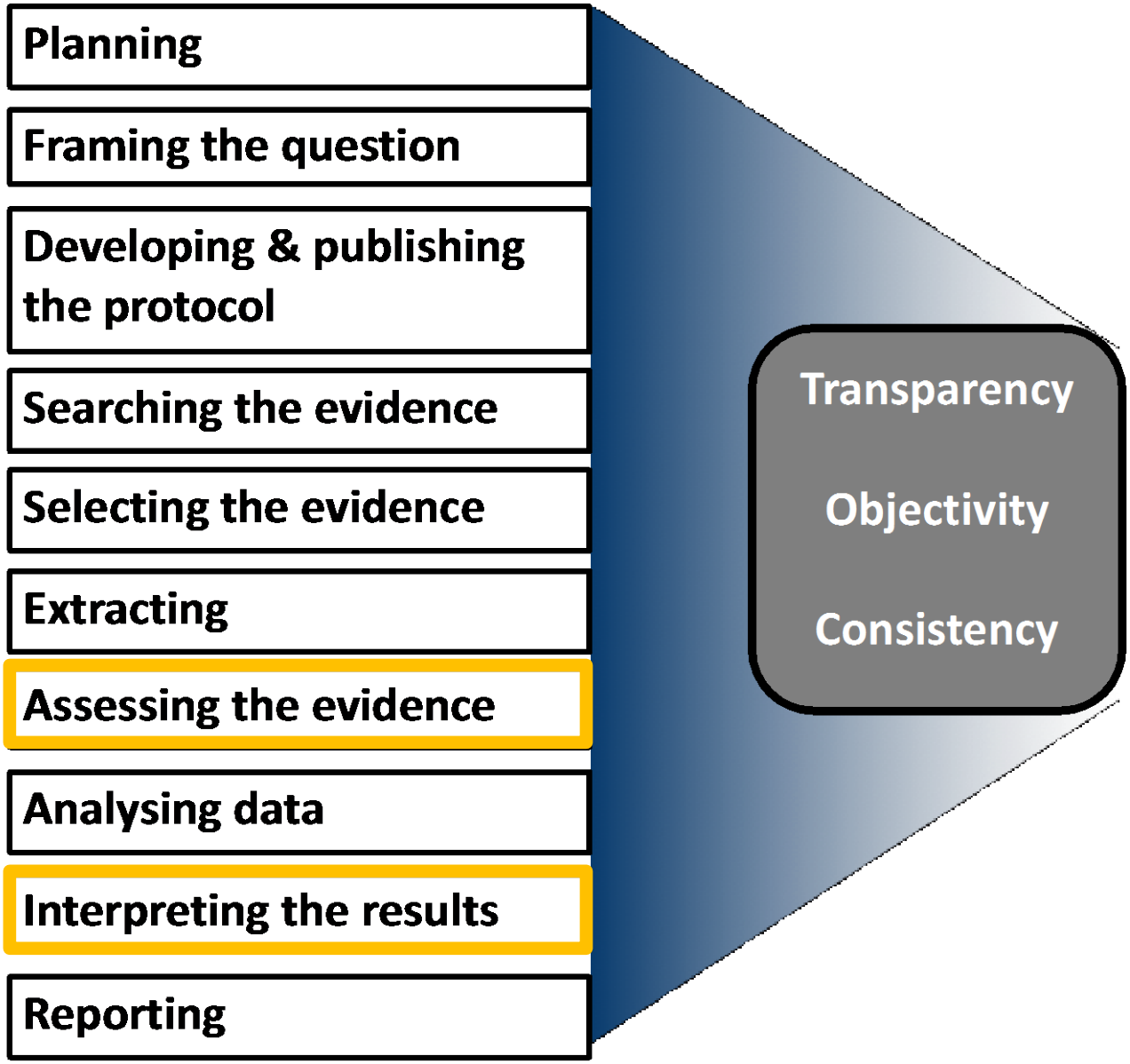
OXFORD SOT Society of Toxicology
www.toxsci.oxfordjournals.org
TOXICOLOGICAL SCIENCES, 152(1), 2016, 10–16
doi: 10.1093/toxsci/kfw059
Advance Access Publication Date: May 5, 2016
Forum Article

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY


EPA United States Environmental Protection Agency
EPA Document# 740-P1-8001
Office of Chemical Safety and Pollution Prevention
APPLICATION OF SYSTEMATIC REVIEW IN TSCA RISK EVALUATIONS
MAY 2018


FORUM ARTICLE
The Emergence of Systematic Review in Toxicology
Martin L. Stephens,[a,1] Kellyn Betts,[b] Nancy B. Beck,[c] Vincent Cogliano,[d] Kay Dickersin,[e] Suzanne Fitzpatrick,[f] James Freeman,[g] George Gray,[h] Thomas Hartung,[a,i] Jennifer McPartland,[j] Andrew A. Rooney,[k] Roberta W. Scherer,[e] Didier Verloo,[l] and Sebastian Hoffmann[m]

# Steps of evidence synthesis




Hoffmann et al. (2017). A primer on systematic reviews in toxicology. Arch Toxicol. 91(7):2551-2575

# Uncertainty

**Sources:** - lack of knowledge
- variability and heterogeneity

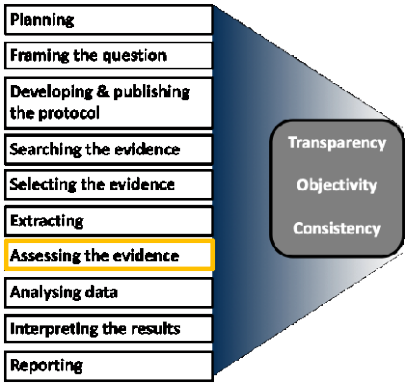
**Extent:** - Quantity, quality and relevance of the data
- Reliability and relevance of model assumptions

| Uncertainties associated with assessment inputs | Uncertainties associated with assessment methodology |
|---|---|
| 1) Ambiguity<br>2) Accuracy and precision of the measures<br>3) Sampling uncertainty<br>4) Missing data within studies<br>5) Missing studies<br>6) Assumptions about inputs<br>7) Statistical estimates<br>8) Extrapolation uncertainty (i.e. limitations in external validity)<br>9) Other uncertainties | 1) Ambiguity<br>2) Excluded factors<br>3) Distributional assumptions<br>4) Use of fixed values<br>5) Relationship between parts of the assessment<br>6) Evidence for the structure of the assessment<br>7) Uncertainties relating to the process for dealing with evidence from the literature<br>8) Expert judgement<br>9) Calibration or validation with independent data<br>10) *Dependency* between sources of uncertainty<br>11) Other uncertainties |

**Table from: EFSA Scientific Committee (2018). Guidance on Uncertainty Analysis in Scientific Assessments. EFSA Journal 16**

# Uncertainty and EB-approaches: Studies

**Uncertainty associated with assessment inputs, i.e. individual studies**




## Study validity

### External validity

the extent to which study results can be generalised and applied (depends on purpose)

### INTERNAL VALIDITY

the extent to which a study minimises systematic errors or biases

### Methodological/study quality

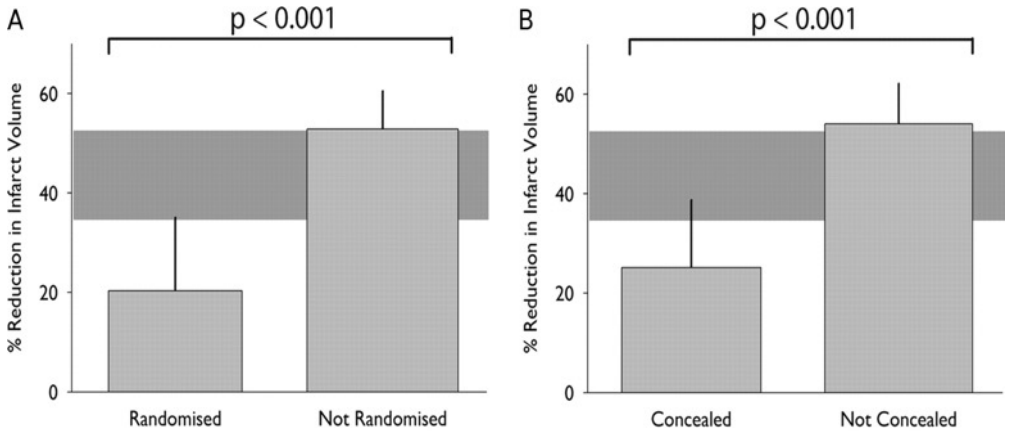
the extent to which the highest standards have been applied

- includes aspects unlikely to impact on internal validity
  - ethical approval
  - sample size calculation
  - reporting

# Uncertainty and EB-approaches: Studies

## Internal validity and quality assessment of individual studies

Studies of low internal validity are more likely biased, possibly resulting in over-/underestimation of the true effect




**Systematically assess all aspects potentially resulting in bias or affecting quality**

# Uncertainty and EB-approaches: Studies

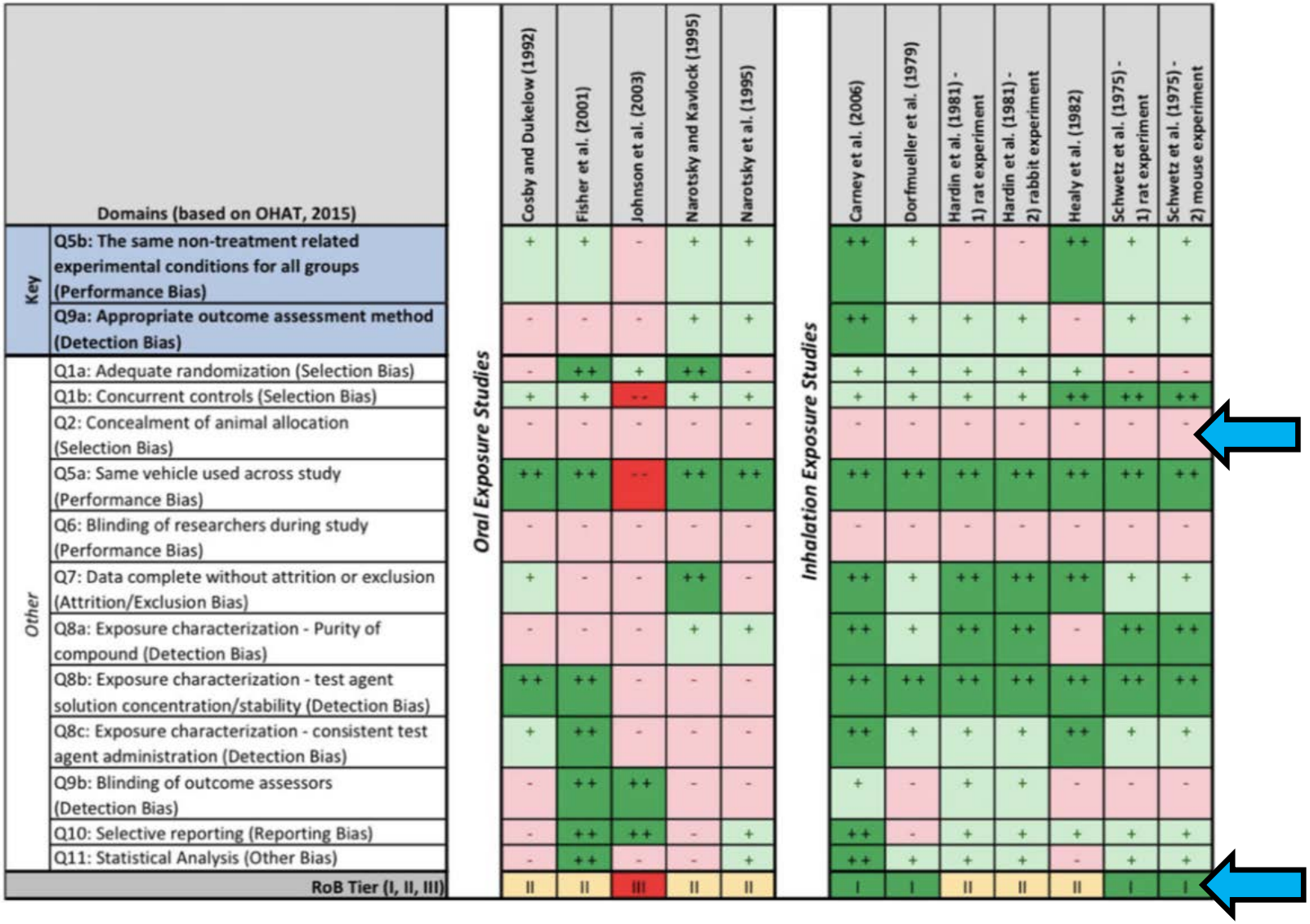
- **biases depend on study type**

| Table 5. OHAT Risk of Bias Tool | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Bias Domains and Questions** | Experimental Animal[1] | Human Controlled Trials[2] | Cohort | Case-control[3] | Cross-sectional | Case Series | in vitro | in silico |
| **Selection Bias** | | | | | | | ? | |
| 1. Was administered dose or exposure level adequately randomized? | X | X | | | | | | |
| 2. Was allocation to study groups adequately concealed? | X | X | | | | | | |
| 3. Did selection of study participants result in appropriate comparison groups? | | | X | X | X | | | |
| **Confounding Bias** | | | | | | | | |
| 4. Did the study design or analysis account for important confounding and modifying variables? | | | X | X | X | X | | |
| **Performance Bias** | | | | | | | | |
| 5. Were experimental conditions identical across study groups? | X | | | | | | | |
| 6. Were the research personnel and human subjects blinded to the study group during the study? | X | X | | | | | | |
| **Attrition/Exclusion Bias** | | | | | | | | |
| 7. Were outcome data complete without attrition or exclusion from analysis? | X | X | X | X | X | | | |
| **Detection Bias** | | | | | | | | |
| 8. Can we be confident in the exposure characterization? | X | X | X | X | X | X | | |
| 9. Can we be confident in the outcome assessment? | X | X | X | X | X | X | | |
| **Selective Reporting Bias** | | | | | | | | |
| 10. Were all measured outcomes reported? | X | X | X | X | X | X | | |
| **Other Sources of Bias** | | | | | | | | |
| 11. Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)? | X | X | X | X | X | X | | |

- **quality criteria**

(see e.g. Lynch et al. (2016). Systematic comparison of study quality criteria. RTP 76)

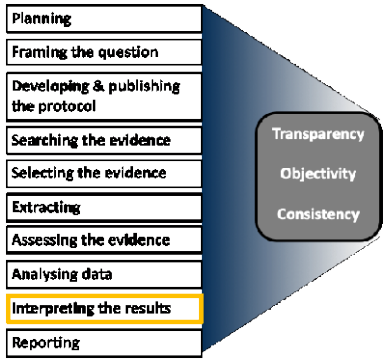
# Uncertainty and EB-approaches: Studies



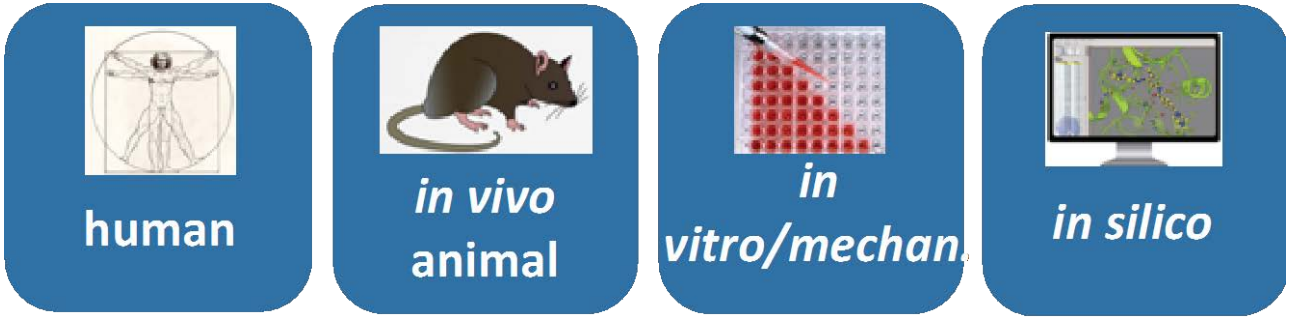
| | Domains (based on OHAT, 2015) | Oral Exposure Studies | | | | | Inhalation Exposure Studies | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cosby and Dukelow (1992) | Fisher et al. (2001) | Johnson et al. (2003) | Narotsky and Kavlock (1995) | Narotsky et al. (1995) | Carney et al. (2006) | Dorfmueller et al. (1979) | Hardin et al. (1981) - 1) rat experiment | Hardin et al. (1981) - 2) rabbit experiment | Healy et al. (1982) | Schwetz et al. (1975) - 1) rat experiment | Schwetz et al. (1975) - 2) mouse experiment |
| Key | Q5b: The same non-treatment related experimental conditions for all groups (Performance Bias) | + | + | - | + | + | ++ | + | - | - | ++ | + | + |
| Key | Q9a: Appropriate outcome assessment method (Detection Bias) | - | - | - | + | + | ++ | + | + | + | - | + | + |
| Other | Q1a: Adequate randomization (Selection Bias) | - | ++ | + | ++ | - | + | + | + | + | + | - | - |
| Other | Q1b: Concurrent controls (Selection Bias) | + | + | -- | + | + | + | + | + | + | ++ | ++ | ++ |
| Other | Q2: Concealment of animal allocation (Selection Bias) | - | - | - | - | - | - | - | - | - | - | - | - |
| Other | Q5a: Same vehicle used across study (Performance Bias) | ++ | ++ | -- | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| Other | Q6: Blinding of researchers during study (Performance Bias) | - | - | - | - | - | - | - | - | - | - | - | - |
| Other | Q7: Data complete without attrition or exclusion (Attrition/Exclusion Bias) | + | - | - | ++ | - | ++ | + | ++ | ++ | ++ | + | + |
| Other | Q8a: Exposure characterization - Purity of compound (Detection Bias) | - | - | - | + | + | ++ | + | ++ | ++ | - | ++ | ++ |
| Other | Q8b: Exposure characterization - test agent solution concentration/stability (Detection Bias) | ++ | ++ | - | - | - | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| Other | Q8c: Exposure characterization - consistent test agent administration (Detection Bias) | + | ++ | - | - | - | ++ | + | + | + | ++ | + | + |
| Other | Q9b: Blinding of outcome assessors (Detection Bias) | - | ++ | ++ | - | - | + | - | + | + | - | - | - |
| Other | Q10: Selective reporting (Reporting Bias) | - | ++ | ++ | - | + | ++ | - | + | + | + | + | + |
| Other | Q11: Statistical Analysis (Other Bias) | - | ++ | - | - | + | ++ | + | + | + | - | + | + |
| | RoB Tier (I, II, III) | II | II | III | II | II | I | I | II | II | II | I | I |

Wikoff et al. (2018). Role of Risk of Bias in Systematic Review for Chemical Risk Assessment: A Case Study in Understanding the Relationship Between Congenital Heart Defects and Exposures to Trichloroethylene. Int J Toxicol 37.

# Uncertainty and EB-approaches: Body of evidence




## Uncertainty related to the populations/evidence streams




## Integrate evidence within and across streams

- (in-)consistency of findings, incl. heterogeneity
- external validity, e.g. human relevance
- effect sizes
- (in-)directness

# Uncertainty and EB-approaches: Confidence in the body of evidence

**G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation working group: common, sensible and transparent approach to grading quality (or certainty) of evidence and strength of recommendations

**GRADE Environmental Health Project Group explores application to environmental and occupational health**


# Uncertainty and EB-approaches: Confidence in the body of evidence

GRADE-inspired approaches

National Toxicology Program
U.S. Department of Health and Human Services

**Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration**

| Initial Confidence by Key Features of Study Design | Factors Decreasing Confidence | Factors Increasing Confidence | Confidence in the Body of Evidence |
|---|---|---|---|
| High (++++) 4 Features | • Risk of Bias<br>• Unexplained Inconsistency<br>• Indirectness<br>• Imprecision<br>• Publication Bias | • Large Magnitude of Effect<br>• Dose Response<br>• Residual Confounding<br>– Studies report an effect and residual confounding is toward null<br>– Studies report no effect and residual confounding is away from null<br>• Consistency<br>– Across animal models or species<br>– Across dissimilar populations<br>– Across study design types<br>• Other<br>– e.g., particularly rare outcomes | High (++++) |
| Moderate (+++) 3 Features | | | Moderate (+++) |
| Low (++) 2 Features | | | Low (++) |
| Very Low (+) ≤1 Features | | | Very Low (+) |

Features: • Controlled exposure • Exposure prior to outcome • Individual outcome data • Comparison group used

## Navigation guide

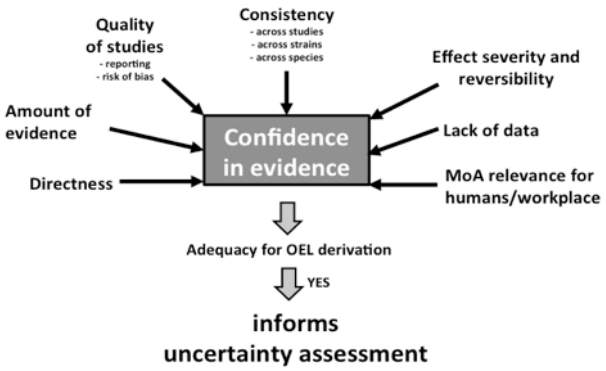
| Risk of Bias | Quality of Evidence | Strength of Evidence |
|---|---|---|
| Risk of bias is determined for ***each individual study***. | Quality is rated ***across all studies***. Human evidence begins as 'moderate quality' and may be downgraded (-1 or -2) or upgraded (+1 or +2) according to criteria. | Strength is rated ***across all studies***. The final ratings represent the level of certainty of toxicity. |
| **Domains**<br>• Recruitment strategy<br>• Blinding<br>• Exposure assessment<br>• Confounding<br>• Incomplete outcome data<br>• Selective reporting<br>• Conflict of interest<br>• Other bias | **Downgrade Criteria**<br>• **Risk of bias across studies**<br>• Indirectness<br>• Inconsistency<br>• Imprecision<br>• Publication bias<br>**Upgrade Criteria**<br>• Large magnitude of effect<br>• Dose response<br>• All possible confounding would confirm negative result | **Considerations**<br>• **Quality of body of evidence**<br>• Direction of effect<br>• Confidence in effect<br>• Other compelling attributes of the data that may influence certainty |
| **Determinations**<br>*(for each risk of bias domain)*<br>• Low risk<br>• Probably low risk<br>• Probably high risk<br>• High risk | **Rating**<br>*(based on all quality criteria)*<br>• High quality<br>• Moderate quality<br>• Low quality | **Rating**<br>*(based on all strength considerations)*<br>• Sufficient evidence<br>• Limited evidence<br>• Inadequate evidence<br>• Evidence of lack of toxicity |

European Commission

**Methodology for derivation of occupational exposure limits of chemical agents**

The General Decision-Making Framework of the Scientific Committee on Occupational Exposure Limits (SCOEL)

2017



# Confidence in the body of evidence: Example from the navigation guide

**Table 2** Summary of the quality ratings given to each body of evidence.

| Rating factor | Human | Nonhuman mammalian | Nonmammalian |
|---|---|---|---|
| Initial rating | Moderate | High | High |
| Downgrade factors | | | |
| Risk of bias across studies | 0 | –1 | –1 |
| Indirectness | 0 | 0 | –1 |
| Inconsistency | 0 | 0 | 0 |
| Imprecision | 0 | 0 | 0 |
| Publication bias | 0 | 0 | 0 |
| Upgrade factors | | | |
| Large magnitude of effect | 0 | NA | NA |
| Dose response | 0 | NA | NA |
| Confounding minimizes effect | 0 | NA | NA |
| Overall grade | 0 | –1 | –2 |
| Resulting rating | Moderate | Moderate | Low |

based on study design

confidence rating

Lam J et al. (2014). The Navigation Guide - evidence-based medicine meets environmental health: integration of animal and human evidence for PFOA effects on fetal growth. Environ Health Perspect. 122(10):1040-51.

# Conclusions

- evidence-based methodology offers approaches to uncertainty assessment

- ‘quality’ assessment and confidence assessment when integrating evidence are directly linked to uncertainties
and fields of active research


- the application of EB methods to uncertainty assessment are (yet) to be explored, identifying opportunities, but also limitations

# (Time for) Questions

**www.ebtox.org**