Combining Apples and Oranges: Lessons Learned and Advances Made Through International Collaboration

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National Academies
Workshop 2
Evidence integration in chemical assessment
Challenges faced in developing and communicating human health effects conclusions
Acknowledgements

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- Paul Whaley
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- Rob de Vries

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- Elisa Aiassa (EBTC SAC Member)
- Didier Verloo (EBTC Board Member)

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- Ray Wassel (NASEM)

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Outline

• Introduction on evidence-based methods and systematic review
• Key historical milestones in development of the frameworks
• Unique challenges of applying SR to chemicals risk assessment
• Qualitative and quantitative approaches to evidence integration (EFSA WoE, GRADE, OHAT, WHO IARC)
• Summary of key conclusions of the recent international workshops
Challenges in integrating new science in risk assessment

• **Cognitive bias:**
  "I suppose it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail.” Abraham H. Maslow (1966). *The Psychology of Science*. p. 15.

• **Lack of confidence:**
  How does a regulator know if the new information is reliable?

• **Resistance to change:**
Challenges in integrating new science in risk assessment

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• **Lack of confidence:**

  How does a regulator know if the new information is reliable?

• **Resistance to change:**
It’s Hard for Doctors to Unlearn Things. That’s Costly for All of Us.

Procedures live on even after they’ve been proved ineffective. It can lead to harms and wasted resources.

- Cognitive bias: "I suppose it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail." Abraham H. Maslow (1966). The Psychology of Science. p. 15.
- Lack of confidence: How does a regulator know if the new information is reliable?
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• **Lack of confidence:**
  How does a regulator know if the new information is reliable?

• **Resistance to change:**

  Need for a rigorous reproducible framework to validate the new approaches and integrate them appropriately in risk assessment.
Systematic review – some definitions

A systematic review summarises the results of available studies (controlled trials) and provides a high level of evidence on the effectiveness of healthcare interventions. Adapted from Cochrane

A systematic review is a research methodology, which allows testing a hypothesis using pre-existing evidence

Why SR in regulatory assessments?

Regulatory assessments need reproducibility and rigor
SR framework provides transparent traceable records

Adapted from Paul Whaley
What are the differences between *A Review* and the *Systematic Reviews*?

<table>
<thead>
<tr>
<th>Feature</th>
<th>Narrative Review</th>
<th>Systematic Review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Research Question</strong></td>
<td>Often unclear or broad</td>
<td>Specified and specific</td>
</tr>
<tr>
<td><strong>Literature Search</strong></td>
<td>Not usually specified</td>
<td>Explicit search strategy</td>
</tr>
<tr>
<td><strong>Study Selection</strong></td>
<td>Not usually specified</td>
<td>Explicit selection criteria</td>
</tr>
<tr>
<td><strong>Quality Assessment</strong></td>
<td>Not usually present</td>
<td>Appraisal with explicit criteria</td>
</tr>
<tr>
<td><strong>Synthesis</strong></td>
<td>Often qualitative</td>
<td>Often also quantitative</td>
</tr>
</tbody>
</table>

Table adapted from de Vries et al., The ILAR Journal, 2016
History of Evidence-based Methodology in Healthcare

**Origin:**
- Clinical trials in medicine
- Organized and developed by Cochrane: www.cochrane.org

**Field of Application:**
- Compare medical treatments

**Major Principles:**
- Transparency
- Consistency
- Statistical rigor
- Minimization of bias (systematic error) that impacts study quality
- Systematic step-wise approach

**Main Instrument:**
- Systematic review
Evidence-based Methods Steps

1. Identify a problem
2. Formulate question
3. Search for evidence
4. Appraise the evidence
5. Integrate evidence
6. Apply evidence to policy
7. Write protocol
8. Publish!

Steps:

- P – Population
- I (E) – Intervention (Exposure)
- C – Comparator
- O – Outcome(s)

Qualitatively or quantitatively

Engage all stakeholders to implement and change habits

Use validated risk of bias and study quality tools

Broadly!

8
Cochrane Principles of Evidence-based Medicine

1. Collaboration
2. Involving, supporting and training people
3. Avoiding duplication of effort
4. Minimizing bias
5. Keeping up-to-date
6. Striving for relevance
7. Promoting access by wide dissemination
8. Ensuring quality
9. Continuity
10. Enabling wide participation in our work
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Impact of Cochrane work on clinical medicine

- The standard of clinical medicine was elevated over the four decades of implementing Cochrane principles
- SR is the main benchmark that physicians and healthcare organizations use to compare treatments
- RCTs are a standard in medicine
- RCTs reporting in the literature was standardized

Result: Cochrane’s work is internationally recognized as the benchmark of the highest-quality information about the effectiveness of health care

Can this be achieved outside of the field of medicine?
International efforts in bringing SR to risk assessment


NAS IRIS Review 2014

EFSA / EBTC Colloquium on Evidence Integration

NAS IRIS Review 2018

NOT a comprehensive list
International efforts in bringing SR to risk assessment


The 1st international forum towards an EBT

NAS IRIS Review 2014

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Timeline:

- 2007
- 2010
- 2014
- 2015
- 2017
- 2018
- 2019

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- 2019: NOT a comprehensive list

The timeline shows key international efforts in bringing Systematic Reviews (SR) to risk assessment, with specific events and publications marked along the timeline.
International efforts in bringing SR to risk assessment

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US EPA SR workshop
NAS Low-Dose Toxicity Report
NAS IRIS Review
Ottawa WoE workshop
NAS IRIS Review 2018
EBTC / GRADE workshop June 12
EBTC / EFSA workshop on epidemiologic evidence October 3

NOT a comprehensive list

A CENTURY OF SAFE MILLIONS AT RISK 1916/2016
SR in risk assessment is driven by the agencies’ needs and international collaborations.
Systematic reviews are the highest level of evidence in healthcare

- **High Confidence**
  - Various but well-defined study designs (mainly RCTs, with some cohort, case-control studies)
  - Single species: human

- **Low Confidence**
  - Case reports
  - Human observational studies
  - Randomized controlled studies
  - Systematic reviews (SR)
Toxicology – a unique challenge or just a new field of SR application?

- Randomized controlled studies
- Epidemiological / observational studies
- Legacy animal, and new \((\text{in vitro, in silico})\)

New

Rarely possible

Various designs

Heterogeneous populations, designs, new science
Toxicology – a unique challenge or just a new field of SR application?

- **SR**
- **Randomized controlled studies**
- **Epidemiological / observational studies**

- New
- Rarely possible
- Various designs

Need tools tailored to these types of evidence and their integration in risk assessments
Evidence integration framework in SR

Evidence integration is evidence into streams of:

- Different populations of patients
  - In clinical medicine: different patient populations
  - In toxicology context: different species
- Different types of studies
  - In clinical medicine: RCTs, observational studies
  - In toxicology: Epidemiological, animal, *in vitro, in silico*

The goal:

Summarize the effect in each stream

The process:

- Certainty of the evidence for the effect is assessed for each stream
- Integration is a function of combined certainty across each stream, generating a judgement of the overall level of confidence in the evidence

*Adapted from Paul Whaley*
Challenges in evidence integration

– **Within an evidence stream:**
  - study design
  - Risk of bias (internal validity)
  - consistency of the outcome measure

– **Across evidence streams:**
  - Study design
  - External validity (aka directness, applicability, generalizability, consistency)
  - Exposure (in vitro to in vivo extrapolation, in silico predictions)
  - Human relevance, species concordance

Photo credit: Telegraph.co.uk
Adapted from Laura Martino, EFSA
Integrating mechanistic information in SRs

Mode-of-action (MoA) or adverse outcome pathways (AOP) knowledge is now available.

Examples:

- OHAT framework: mechanistic data can inform changes to the level of evidence
- 2019 update to the IARC preamble: mechanistic evidence is a distinct stream in its own right

What can be done to systematically incorporate mechanistic evidence into systematic reviews of chemicals’ exposures?

Adapted from Paul Whaley
Qualitative Approach:
NTP Office of Health Assessment and Translation (OHAT)

7-step framework for SR and evidence integration

Applications:
- PFOA/PFOS immunotoxicity
- Air pollution and children’s health
- Mountaintop removal mining

Software tools available

DistillerSR
Sciome
sysrev
EPI-Reviewer 4

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Lisbon - October 2017
EFSA-EBTC Colloquium on
Evidence integration in risk assessment: the science of combining apples and oranges

EFSA / EBTC Colloquium Goals

• Build on EFSA’s pioneering experience in SR
• Bring together international stakeholders to discuss the state-of-the-art and challenges in evidence integration in risk assessment in:
  • Healthcare
  • Food safety
  • Environmental health
  • Occupational health
• Learn from each other
Lisbon Colloquium Structure

HI: hazard identification
HC: hazard characterisation
DG: discussion group

Welcome & objectives

Intro to HI
Lecture 1: Introduction to evidence integration for HI: overview of qualitative and quantitative methods and challenges

Intro to HC
Lecture 5: Introduction to dose-response modelling to derive health-based guidance values: current practice and challenges

Lecture 2: Integrating evidence within and across evidence streams using qualitative methods
Lecture 3: Recent developments for combining evidence within evidence streams: bias-adjusted meta-analysis
Lecture 4: Quantitative approaches to combining evidence across evidence streams
Lecture 2: Combining evidence on multiple endpoints in dose-response assessments: multivariate models
Lecture 7: Lecture Other quantitative methods for combining multiple studies and endpoints

Author: Laura Martino, EFSA
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DG1 Qualitative methods for integrating evidence within- and across evidence streams for HI

DG2 Bias-adjusted meta-analysis

DG3 Quantitative approaches to combining evidence across evidence streams for HI

DG4 Using multiple endpoints and multiple studies for dose-response modelling: quantitative approaches

Author: Laura Martino, EFSA
Qualitative methods currently used or being actively adapted:

- GRADE (more guidance is needed, e.g., GRADE workshop on *in silico* computational models)
- OHAT NTP framework

Quantitative methods (i.e., bias-adjusted meta-analysis) promise:

- Reduce subjectivity
- Identify sources of uncertainty and variability
  - Purported drawbacks: complexity, lengthy explanation may be necessary

Comment: all new approaches go through this period of adaptation
Lisbon Colloquium Identified Barriers

- **Published literature limitations:**
  - More data (*in vivo, in vitro*, computational, regulatory, individual animal / experiment data) is needed
  - Structured abstracts in published literature

- **Experimental design improvements:**
  - Appropriate design (e.g., power calculations) to address research questions
  - Need for a distinct separation of assessment of study quality and reporting of study quality
  - Need for operationalizing the concept of biological plausibility
  - Need for a sustainable common open data depository
Lisbon Colloquium Identified Barriers

- More data (in vivo, in vitro, computational, regulatory, individual animal/experiment data) is needed
- Published literature

Objectives:

- Appropriate design (e.g., power calculations) to address the need for a sustainable common open data depository

Clinical literature standard

- Need for a sustainable common open data depository

A CENTURY OF SAVING LIVES—MILLIONS AT A TIME 1916/2016
Lisbon Colloquium Identified Barriers

Abstract

Objective To determine the effectiveness of lessons in the Alexander technique, massage therapy, and advice from a doctor to take exercise (exercise prescription) along with nurse delivered behavioural counselling for patients with chronic or recurrent back pain.

Design Factorial randomised trial.

Setting 64 general practices in England.

Participants 579 patients with chronic or recurrent low back pain, 144 to six Alexander technique lessons, 144 to six massage therapy lessons, 144 to six exercise prescription lessons and 144 to six control sessions. In each group, 88 subjects were randomised to exercise prescription, 86 to massage and 86 to Alexander technique.

Interventions Normal care (control), six sessions of either Alexander technique, massage or exercise prescription. All sessions took place in the patient’s home.

Main outcome measures Roland Morris Disability Questionnaire (number of days in pain).

Results Exercise and massage were more effective than no treatment (compared with control B) with effect size 1.40, 95% confidence interval (95% CI) –2.77 to 0.00,eacher CI –1.77 to 0.00, and p = 0.076; and p = 0.076, respectively). No significant differences were found between the two intervention groups. The effect of 24 lessons alone (Roland Morris Disability score 18) was better than control measures. All patients who completed the study were satisfied with the results.

Conclusions Further research is needed to determine the effectiveness of lessons in the Alexander technique from patients with chronic back pain. Six lessons followed by exercise prescription were more effective than control measures.

Trial registration National Research Register N0028108728.
Lisbon Colloquium Conclusions – future directions

• Continue adaptation and validation of GRADE and NTP OHAT methodologies to hazard identification and risk assessment
• Continue developing quantitative methods such as bias-adjusted meta-analysis and build more use cases
• Consider developing a (GRADE-based) framework for ascertaining biological plausibility
Lisbon Colloquium Conclusions – future directions 2

- Work is best progressed led by a **community of knowledge** of toxicologists, epidemiologists, regulators and statisticians.
- This community is collaboratively developing, testing & harmonizing new tools.
- This community should also promote training opportunities on the various methods and regular exchange through scientific conferences and workshops.

**Future: AI-powered living SR:**
Lisbon Colloquium Conclusions – future directions 2

• Work is best progressed led by a community of knowledge of toxicologists, epidemiologists and statisticians
• This community is collaboratively developing, testing & harmonizing new tools
• This community should also promote training opportunities on the various methods available through scientific conferences and journals.

Future: AI-powered living SR:

PECO question
Literature search
Review by Machine learning
Continuous Updates
Living SR
Ottawa Expert Workshop

Agenda:

Session 1: Recent Advances in Risk Science Including New Approach Methodologies in Weight of Evidence Evaluation (Chair: T. Hartung)

Session 2: Summarizing the Evidence (Chair: Jeff Lewis, ExxonMobil)

Session 3: Qualitative Data Synthesis (Chair: Kris Thayer, US EPA)

Session 4: Quantitative Data Synthesis (Chair: Greg Paoli, Risk Sciences International)

Steering Committee:
Tara Barton-Maclaren, Health Canada;
Thomas Hartung, Johns Hopkins;
Daniel Krewski, University of Ottawa;
Kristina Thayer, US EPA;
Jeff Lewis, Exxon Mobil Biomedical Research.

Output: Workshop report to be published in ALTEX

Follow-up: Another meeting is planned for Fall 2019 TBD
Building the momentum and the community of knowledge

Closing remarks:

- The foundation of SR in healthcare is laid down by Cochrane
- Fit-for-purpose adaptation of tools is led by international government agencies (EFSA, NTP OHAT, US EPA)
- Interdisciplinary community of knowledge is already active, building momentum following Cochrane example
- Immediate tasks of the community are to harmonize the terminology and validate new tools
- The community could convene a regular yearly (?) science forum with series of webinars / projects during the year
- This community should also develop methodology and practical training opportunities for all stakeholders
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Martin Stephens, Associate Director
Sebastian Hoffmann, SEH Consulting
Paul Whaley, University of Lancaster
Rob de Vries, SYRCLE

**CAAT**
Thomas Hartung (EBTC Founder)

**US EPA:**
Kris Thayer
Michelle Angrish

**Tox Strategies:**
Daniele Wikoff
Questions?

Thank You!

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