Ramazzini Days 2015

LIVING IN A CHEMICAL WORLD, IV EDITION

Ramazzini Institute/ Johns Hopkins University: The Role Of The Ramazzini Institute In The Development Of Systematic Reviews In Environmental Health

Daniele Mandrioli, MD

Cesare Maltoni Cancer Research Center

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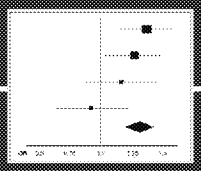


Declaration of Interests

I declare I have no actual or potential competing financial interests, including travel funding, consultancies, board positions, patent and royalty arrangements, stock shares, or bonds.

EVIDENCE BASED TOXICOLOGY: TIMELY OPPORTUNITY

- **Agencies are adopting concepts of systematic reviews and evidence-based methods:** the US National Research Council has recommended adoption of systematic reviews in regulatory decision making and EPA, FDA and the European Food Safety Agency have recently endorsed these evidence-based evaluation.
- **Confusion about "systematic reviews"** in proposals by different stakeholders

NRC (National Research Council). Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press, 2014. 170 p.

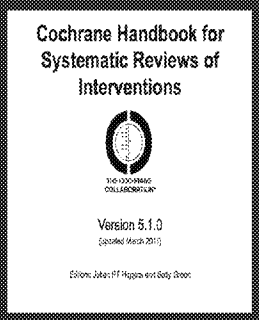
TRANSLATING EVIDENCE BASED METHODS INTO TOXICOLOGY

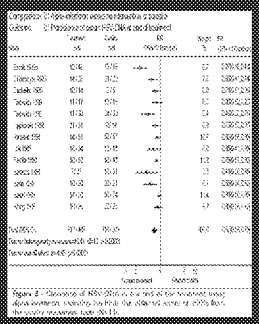
COMMON PRINCIPLES:

- **Clarity in defining the question under analysis** defining populations, exposures, comparators, outcomes, timings, and settings of interest (PECOTS)
- Transparent and replicable **research strategy**
- Transparent **data extraction and presentation**
- Comprehensive **assessment of risk of bias**
- Transparent criteria for determining if **quantitative data integration** is appropriate and conducting data integration, such as **meta-analysis**
- **Appropriate statistical models** for integrating data
- **Discussion of limitations** and cautions in interpretation
- **Disclosure of Conflicts of Interest**

SYSTEMATIC REVIEWS IN TOXICOLOGY

- A Systematic Review is a literature review focused on a research question that tries to identify, appraise, select and synthesize all high quality research evidence relevant to that question.
- All the Cochrane Systematic Reviews are realized according to the Cochrane Handbook for Systematic Reviews of Intervention
- SYSTEMATIC REVIEWS AND META-ANALYSIS ARE NOT SYNONYMS!!!





Advantages of Cochrane Collaboration in leading methods development for Evidence Based Toxicology

➔ Experience with diverse areas of practice

- Demonstrated value of systematic methods for practice and decision making
- Consistency and fairness, even when addressing controversial issues
- Facilitated updating (methods and monographs)
- Over 31.000 people worked with Cochrane Collaboration: experts in every field and every step of Systematic Reviews

➔ International acceptance of Cochrane methods and reviews →enhances acceptance of EBT

TRANSLATING EVIDENCE BASED METHODS INTO TOXICOLOGY

TOXICOLOGY HAS SPECIAL NEEDS:

→Attention to **external validity of nonhuman toxicity** tests for inferring risks to humans (no human RCT in Toxicology!)

→**Validating Methods**

→**Challenges to integrating information:**

- Dealing with the diversity of nonhuman species
- Use of in vitro systems, organotypic cultures, transformed cell lines, and ex vivo preparations
- Validating the validity of "toxicity pathway" studies

→Determining the contribution and value of **mechanistic studies** to overall evaluation of evidence

→Moving beyond harms: generating evidence to support decisions for setting regulatory standards (dose:response)

TOXICOLOGY vs EVIDENCE BASED TOXICOLOGY

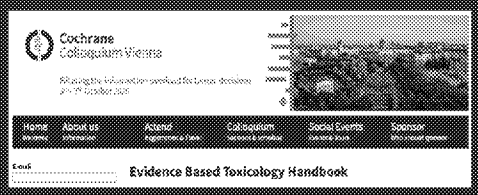
Toxicology	Evidence Based Toxicology
Unclear answers to unclear questions.	Clear formulation of problem (PECOTS)
Non-comprehensive research strategy	Comprehensive research strategy
Non Transparent Methods	Transparent Methods
Unvalidated Methods	Requirement to validate methods prior to use
Inadequate study designs (effect size; expected variability; etc)	Adequate study design
No assessment of risk of bias	Assessment of risk of bias
Inadequate or no statistical modeling	Appropriate statistical modeling based on appropriate study design
Conflict of Interest usually not disclosed	Conflict of Interest Disclosed
Klimisch Scores and Good Laboratory Practices guidelines	Specific evaluation of Risk of Bias and compliance with evidence based practice

Mandrioli D, Silbergeld EK. Evidence from Toxicology: The Most Essential Science for Prevention. Environ Health Perspect. 2015 Jun 19

FIRST STEPS INTO THE WORLD OF COCHRANE

2014: Cochrane Coloquium (India): First consensus and recognition by Cochrane for the need of developing evidence based methods in toxicology

2015: Cochrane Colloquium (Austria): Working groups and aim of the project
expanded (including epidemiology)



2016: Washington, DC

Members of the project include: Ramazzini Institute, Johns Hopkins, Cochrane Collaboration, NTP-OHAT, UCSF, Syrcle, EDF, EFSA, UBA, EPA, WHO

GOALS OF THE RI-JHU PROJECT ON SYSTEMATIC REVIEWS IN ENVIRONMENTAL HEALTH

- ➔ Create a broad community of interest and build a consensus on systematic reviews methods (Cochrane Collaboration, NTP, Ramazzini Institute, Johns Hopkins University, UCSF, EPA, EFSA, FDA, ECHA WHO)
- ➔ To ensure acceptance of Cochrane principles in our future work and endorsement by Cochrane of the methods developed
- ➔ To work effectively with other ongoing efforts in EBT in a consortium and other relevant groups in Cochrane (Public Health, Animal Tests)
- ➔ **To develop work plan for a Cochrane Handbook**

THANK YOU

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