Session I. Discussion

What is the overall goal of evidence integration? (I suspect to express the relation between an exposure and the outcomes in terms of an association or effect and the level/degree of certainty we have in it?

Are there any disadvantages to it?

Thinking about Katya's presentation, what can be adopted from structured approaches used for clinical research?

What are the key components of a structured framework for evidence assessment and integration?

Why does the field of Systematic Reviews in toxicology remain fearful of leaving the poorly done research or data out?

Session I Discussion (2)

Is the judgment of something is biological plausible equivalent to saying there is a causal relation, is it the result of evidence integration?

What is biological plausibility?

What are the challenge of addressing biological plausibility in a structured evidence-integration framework?

What are mechanistic data?

Why, do you think, GRADE (following Kris' introduction) does not talk about biological plausibility in the way that Bradford Hill did?

Are there any disadvantages to the use of structured frameworks of evidence integration?

Who develops the questions to be addressed in toxicology?

HEI

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Chair and Professor

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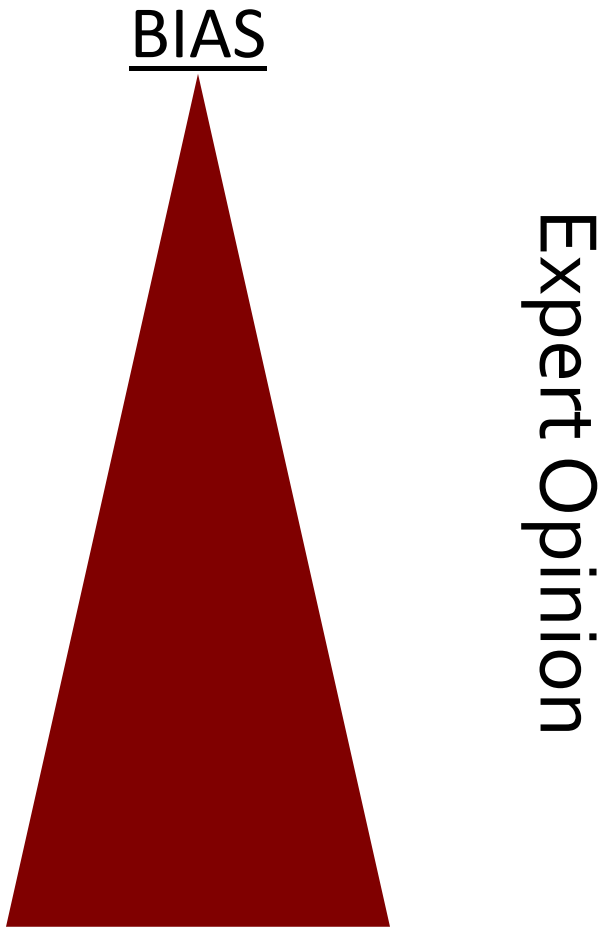
View of a simple clinician and epidemiologist

Quality of evidence

STUDY DESIGN

- Randomized Controlled Trials
- Cohort Studies and Case Control Studies
- Case Reports and Case Series, Non-systematic observations



Schünemann & Bone, Clin Orth Res 2003

Certainty of evidence

How confident in the research?

Are the research studies well done? Risk of bias

Are the results consistent across studies ? Inconsistency

How directly do the results relate to our question? Indirectness

Is the effect size precise - due to random error? Imprecision

Are these all of the studies that have been conducted? Pub. Bias

Is there anything else that makes us particularly certain? Large effects, worst case scenario predictors still strong conclusions, exposure-effect relation

Confidence in causality

100% confident →

0% confident →

← starting point?

<u>Bradford Hill Criteria</u>

Strength
Consistency
Temporality
Biological gradient
Specificity
Biological Plausibility
Coherence
Experiment
Analogy

Good, but insufficient (publication bias?)

Schünemann et al. JECH 2010

Why did GRADE not use Bradford Hill Characteristics

- Not complete
- Not operationalized
  - Random error
  - Experimental design
  - Consistency
  - Biological plausibility, etc
- Not completely thought through
  - Association
  - Intervention
  - Prognosis
  - Tests, etc
- Not fit for what follows from an exposure assessment – policy & interventions

Rating of the certainty

Consider lowering or raising level of certainty during evidence synthesis (e.g. systematic review)		Level of certainty rating by systematic review author	Reconsideration of certainty of evidence domains for decisions (e.g. guideline developer)	Level of certainty rating by those suggesting a decision (e.g. guideline developer)
Reasons for considering lowering or raising certainty (bias and precision and accuracy assessment for PICO posed by systematic review author using OIS based on realistic rather than patient important effect)		*Certainty in evidence across those grading criteria by systematic review author (e.g. for Summary of Findings Table or Evidence Profile)*	*Certainty of evidence altered in the context of decision-making, e.g. for judgments on the GRADE Evidence to Decision Criteria*	*Certainty in evidence across those grading criteria by outcome and considering evidence across outcomes for decision-making[&]*
↓ Lower if	↑ Higher if*			
Risk of Bias Inconsistency Indirectness Imprecision Publication bias	Large effect Dose response All plausible confounding & bias □ would reduce a demonstrated effect or □ would suggest a spurious effect if no effect was observed	High ⊕⊕⊕⊕ Moderate ⊕⊕⊕□ Low ⊕⊕□ □ Very low ⊕□ □ □	May alter certainty related to judgments about the GRADE domains, primarily indirectness (application of evidence to specific PICO question) or imprecision (balancing of health benefit and harms in the context of considering the importance of outcomes and baseline risks).	High ⊕⊕⊕⊕ Moderate ⊕⊕⊕□ Low ⊕⊕□ □ Very low ⊕□ □ □

Schünemann, JCE 2016

Certainty in the evidence

Interventions

- In vitro/In silico
- In vivo (animals)
- Human non-randomized studies/RCTs in animals
- RCTs in humans

Exposures

- In vitro/In silico
- In vivo (animals)
- Human non-randomized studies/RCTs in animals
- RCTs in humans

Certainty in the evidence

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Certainty in the evidence

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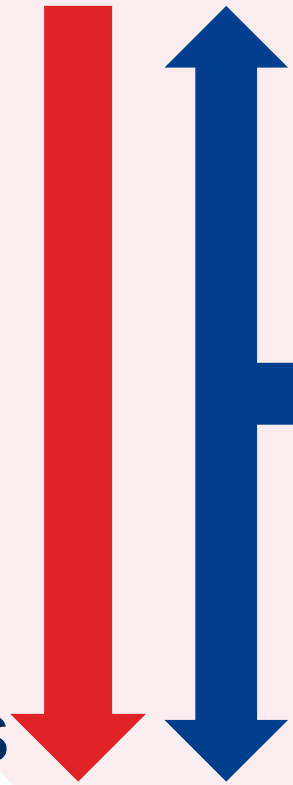

Exposures

- In vitro/In silico
- In vivo (animals)
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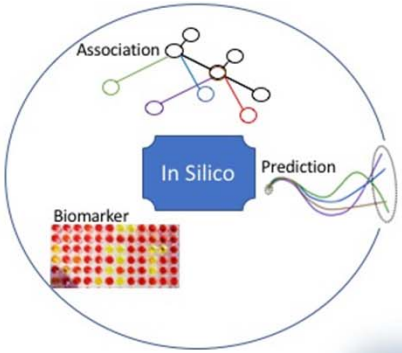
- RCTs in humans

Whatever the question

The population of interest is in humans



What is biological plausibility?

- “one component of a method of reasoning that can establish a cause-and-effect relationship between a biological factor and a particular disease or adverse event (Wikipedia)”
- refers to “to consistency between data and biological theory or mechanism” (EFSA Weight of Evidence).

Workshop conclusion

Biological plausibility refers to "adherence between individual pieces and the body of evidence and biological theory and mechanism as evaluated/expressed by:

Directness/relevance of the data/applicability to humans

Consistency

Strong association

Risk of bias/reliability"

Workshop conclusion

Biological plausibility is the “result of an evaluation of existing certainty domains.”

When the assessors are certain in the estimate of the effect or association, they conclude that biological plausibility is likely.

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Bradford Hill criteria

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WHAT IS

BIOLOGICAL PLAUSIBILITY?

Bradford Hill criteria

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WHAT IS

BIOLOGICAL PLAUSIBILITY?

WHAT IF AN ASSOCIATION IS PLAUSIBLE BUT THERE'S NO EVIDENCE OR EVIDENCE BUT NO PLAUSIBILITY?


GRADE

TELL US IN A FEW WORDS

WHAT

„READ ACROSS IS"

YOUR ELEVATOR SPEECH!