Bundesinstitut für Risikobewertung

Workshop What does the future hold for harmonised human health risk assessment of plant protection products?

Application of human epidemiological studies to pesticide risk assessment

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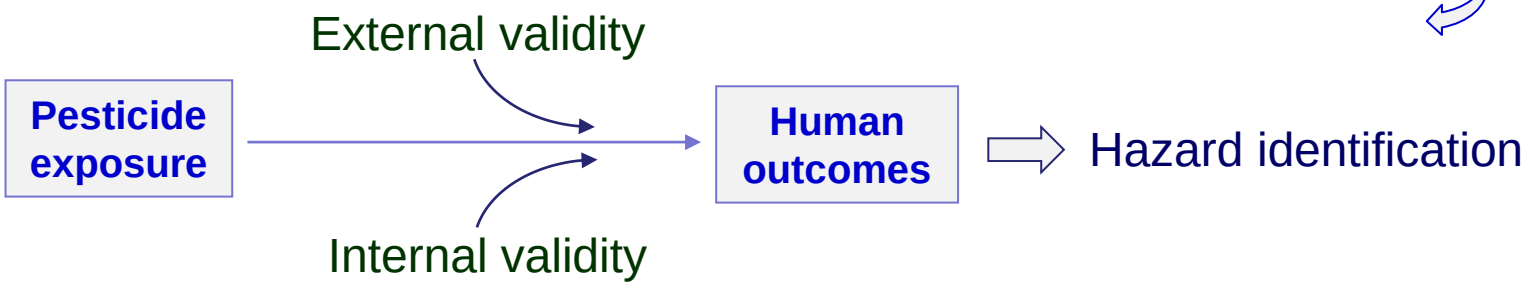
European Food Safety Authority

EU Legislation

- EU Regulation No. 1107/2009 *(placing of plant protection products on the market)*
  - Where available, and supported with data on levels and duration of exposure, and conducted in accordance with recognised standards, epidemiological studies are of particular value and must be submitted.
- EU Regulation No. 283/2013 *(setting out data requirements for active substances)*
  - Relevant epidemiological studies shall be submitted, where available.
- EU Regulation No. 1141/2010 *(renewal of a.s.)*
  - The dossiers submitted for renewal should include new data relevant to the active substance and new risk assessments.

Use of epidemiological studies for pesticide risk assessment

- Human data
  - Case series, PCC, registries, surveillance programs
  - Observational epidemiological studies



- Complexity of studying associations in the field of pesticide epidemiology:
  - large number of active substances in the market
  - difficulties to measure exposure
  - frequent lack of quantitative (and qualitative) data on exposure to individual pesticides

EXTERNAL SCIENTIFIC REPORT

Literature review on epidemiological studies linking exposure to pesticides and health effects[1]

Evangelia E Ntzani, Chondrogiorgi M, Ntritsos G, Evangelou E, Tzoulaki I

Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Grecce

- Relevant significant associations were found.
- A number of limitations were also identified:
  - Weak study designs
  - Lack of detailed exposure assessment
  - Deficiencies in outcomes assessment
  - Deficiencies in reporting and analysis
  - Selective reporting and bias

→ Heterogeneity
Inconsistency

1. The inherent weaknesses of the epidemiological studies assessed do not allow firm conclusions to be drawn on causal relationships.
2. A concern was raised about the suitability of regulatory studies to inform on specific and complex human health outcomes.

EFSA Scientific Opinion 2017

SCIENTIFIC OPINION

EFSA Journal

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Scientific Opinion of the PPR Panel on the follow-up of the findings of the External Scientific Report "Literature review of epidemiological studies linking exposure to pesticides and health effects"

EFSA Panel on Plant Protection Products and their Residues (PPR), Colin Ockleford, Paulien Adriaanse, Philippe Berny, Theodorus Brock, Sabine Duquesne, Sandro Grilli, Susanne Hougaard, Michael Klein, Thomas Kuhl, Ryszard Laskowski, Kyriaki Machera, Olavi Pelkonen, Silvia Pieper, Rob Smith, Michael Stemmer, Ingvar Sundh, Ivana Teodorovic, Aaldrik Tiktak, Chris J. Topping, Gerrit Wolterink, Matteo Bottai, Thohallur Halldorsson, Paul Hamey, Marie-Odile Rambourg, Ioanna Tzoulaki, Daniele Court Marques, Federica Crivellente, Hubert Deluyker and Antonio F. Hernandez-Jerez

EFSA Scientific Opinion 2017

- Epi studies can assist the peer-review process (renewal of a.s.)
- EFSA PPR Panel Scientific Opinion:
  - Methodology for using epi data for risk assessment
  - Recommendations to improve the quality and reliability of epi studies on pesticides
  - Methodology for the integration of epi data with other lines of evidence
- Enhance the quality and relevance of future epi studies for R.A.:
  - Adequate assessment of exposure
  - Valid and reliable outcome assessment
  - Account for potentially confounding variables
  - Appropriate statistical analysis and reporting of results

Incorporation of epidemiological studies into risk assessment

- Challenge for scientists, risk assessors and risk managers
- Use of evidence synthesis techniques:
  - Summary of data, ↑ statistical power and precision
  - Cannot overcome methodological flaws of individual studies
  - Systematic reviews impact on risk assessment as they strengthen the understanding of pesticide hazards, exposure,…
  - Study evaluation should be performed within a best evidence synthesis framework:
    - Indication on the nature of potential biases
    - Assessment of the overall confidence in the database
  - Assessment of the reliability of individual epidemiological studies (methodological quality and the risk of bias)

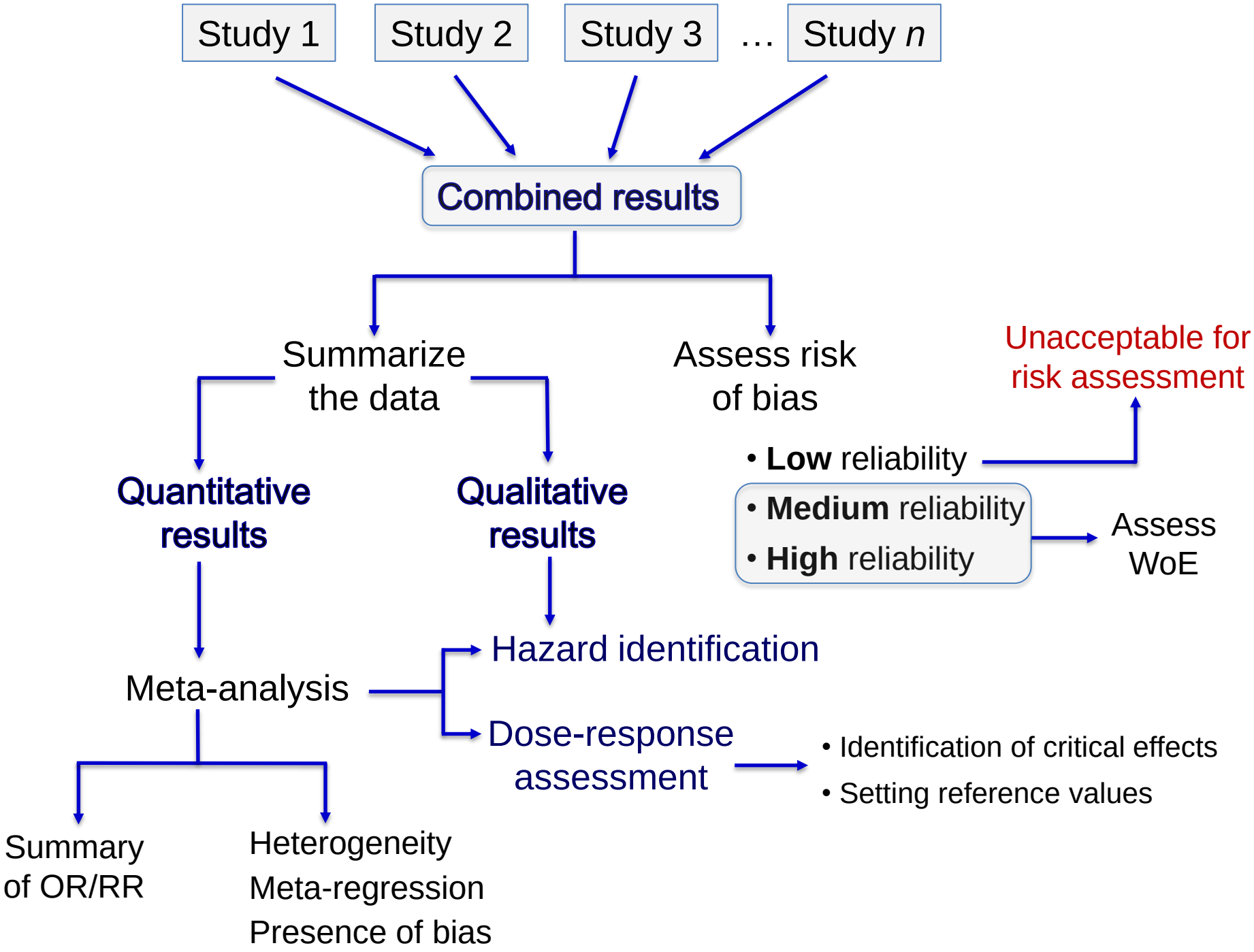
Incorporation of epidemiological studies into risk assessment

- Study quality parameters and their associated weight:

Parameter	High	Moderate	Low
Study design and conduct			
Population			
Exposure assessment			
Outcome Assessment			
Confounder control			
Statistical Analysis			
Reporting of results			

Risk of bias

- Data from epi studies are not currently used for pesticide risk assessment in a systematic and consistent manner
- No harmonised framework on how to assess epi studies

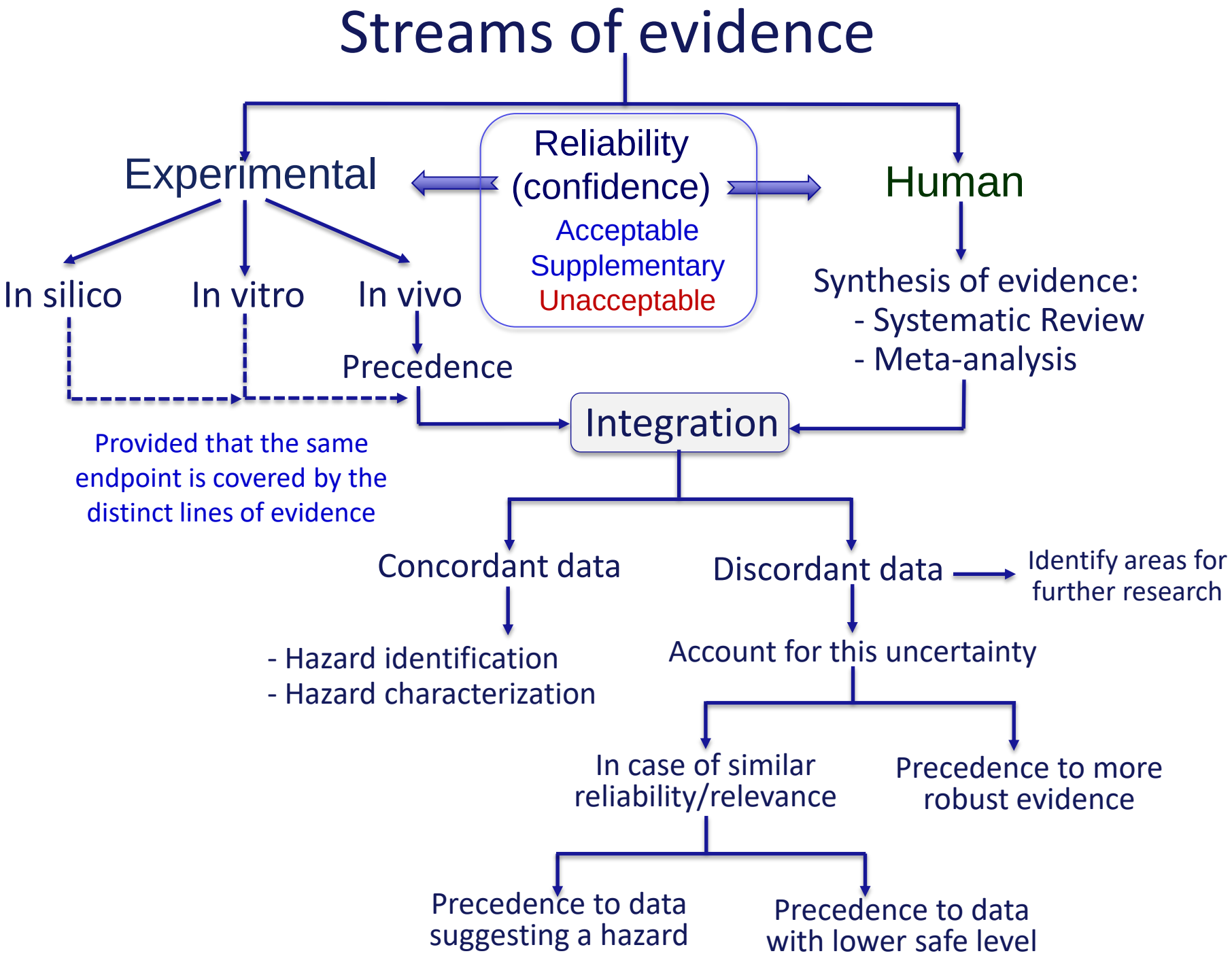

Study 1
Study 2
Study 3
…
Study *n*
Combined results
Summarize the data
Assess risk of bias
Unacceptable for risk assessment
• **Low** reliability
• **Medium** reliability
• **High** reliability
Assess WoE
Quantitative results
Qualitative results
Meta-analysis
Hazard identification
Dose-response assessment
• Identification of critical effects
• Setting reference values
Summary of OR/RR
Heterogeneity
Meta-regression
Presence of bias

Integrating epidemiological evidence with experimental toxicology data

- An integrated approach is needed to integrate data from epidemiology and toxicology
- Weight the different sources of evidence:
  - Epidemiological studies
  - *In vivo* studies
  - *In vitro* / *in silico* studies

  → Bradford-Hill Criteria → Causative relationships

  - Identification of **biological plausibility** (mechanistic approach)
- For each standalone line of evidence:
  - Quality assessment of single studies – **Reliability**
  - Assess strength of (pooled) evidence – **Relevance**
  - Integrate the standalone LoE - **Consistency**


Streams of evidence
Experimental
Reliability (confidence)
Acceptable
Supplementary
Unacceptable
Human
In silico
In vitro
In vivo
Precedence
Synthesis of evidence:
- Systematic Review
- Meta-analysis
Integration
Provided that the same endpoint is covered by the distinct lines of evidence
Concordant data
Discordant data
Identify areas for further research
- Hazard identification
- Hazard characterization
Account for this uncertainty
In case of similar reliability/relevance
Precedence to more robust evidence
Precedence to data suggesting a hazard
Precedence to data with lower safe level

Biological plausibility for the interpretation of epi evidence

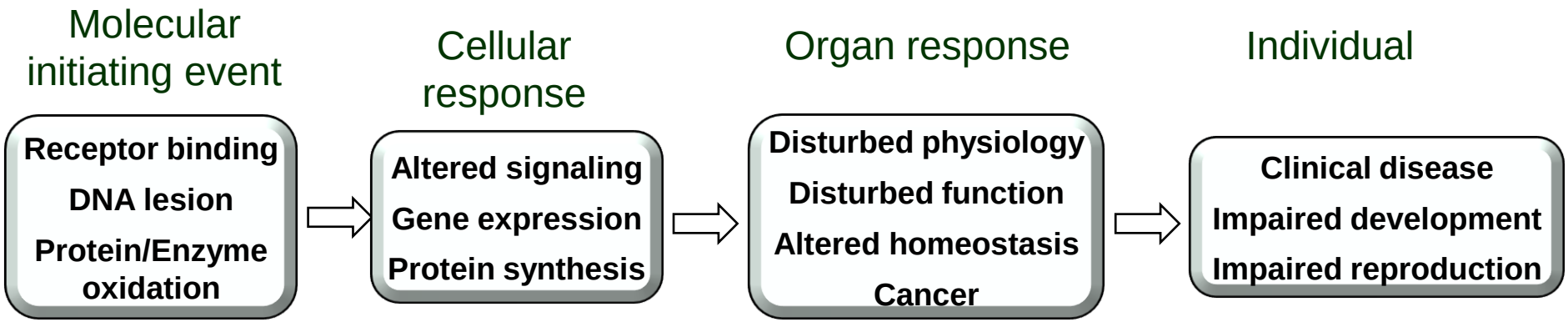
- Epidemiological studies

External exposure → Clinical disease

- Complementary experimental research needed

External exposure → Absorbed dose → Target organ dose → Early biologic effect → Altered function or structure → Clinical disease

- AOP framework may be an appropriate tool



Conclusions

- Current epidemiological studies can be useful for hazard identification of pesticides (evidence synthesis)
- Better designed epi studies may improve quantitative risk assessment of pesticides
- Biological plausibility can lend support to the associations between pesticide exposure and complex diseases
- AOP and MoA data can be used to assess the findings of epi studies in order to weight their conclusions
- Integration of all lines of scientific evidence would benefit from moving to a mechanistic-based risk assessment

Questions?