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*"

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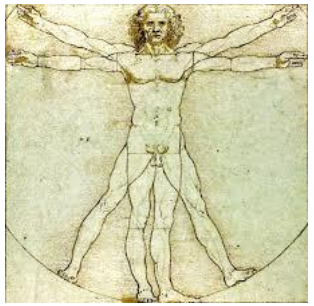
efsa
European Food Safety Authority

Context of the Scientific Opinion

- Pesticides (as regulated chemicals)
  - Regulatory studies
  - Epidemiological evidence



- Specific EU Regulation
- Risk assessment, not research

PLANTS

European Commission

EU Pesticides database

	A	B	C	D	E
1	Pesticides Database - Active Substances (File created on 14/11/2017)				
2					
3	**Substance**	**Active Su**	**Categ**	**List(*)**	**Status under Re**
4	(4Z-9Z)-7,9-Dodecadien-1-ol	817	AT	A4	Not Approved
5	(E)-10-Dodecen-1-yl acetate	824	AT	A4	Not Approved
1367	Zucchini yellow mosaic virus (ZYMV mild strain)	2019	FU	C	Not Approved
1368	Zucchini Yellow Mosaik Virus, weak strain	2020	EL	C	Approved
1369					
1370	**Approved**	**494**			
1371	**Not approved**	**824**			
1372	**Pending**	**27**			
1373	**Banned**	**20**			
1374	**Other**	**0**			
1375	**TOTAL**	**1365**			

Context of the Scientific Opinion

- Complexity of studying associations in the field of pesticide epidemiology:
  - large number of active substances in the market
  - difficulties to measure exposure
  - lack of quantitative (and qualitative) data on exposure to individual pesticides
  - Other confounding factors associated with health effects
- 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 pesticide epi studies in the regulatory process.

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.

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:
  - Study designs
  - Lack of detailed exposure assessment
  - Deficiencies in outcomes assessment
  - Deficiencies in reporting and analysis
  - Selective reporting and bias

1. Thus, firm conclusions cannot be drawn on causal relationships.
2. Outcomes were identified for future investigation
3. A concern was raised about the suitability of regulatory studies to inform on specific and complex human health outcomes.

Scientific Opinion

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

Terms of Reference

1. Review all sources of **gaps** and **limitations** in regard to the quality and relevance **of the available epidemiology studies**.

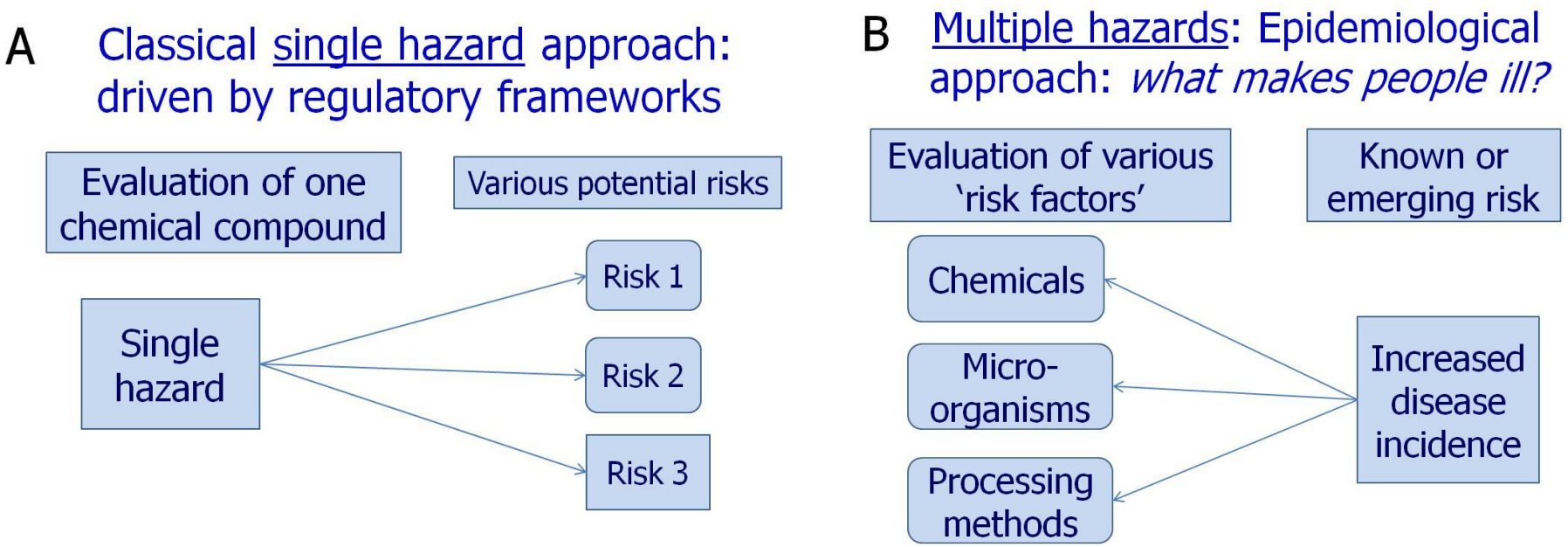
2. Propose **potential refinements** for **future epidemiology studies** to increase the quality, relevance and reliability of the findings and how they may impact pesticide R.A.

3. Identify areas in which information and/or criteria are insufficient or lacking and propose **recommendations** for how to conduct pesticide epidemiological studies in order to improve and optimize the **application in risk assessment**.

4. Discuss **how to make appropriate use of epidemiological findings** in risk assessment of pesticides during the peer review process of DARs, and their **integration** with data from experimental toxicology.

Epi data for pesticide risk assessment

- Several types of human data
- Acute vs. chronic effects:
  - Hazardous doses are more readily detectable
  - Many diseases are associated with multiple risk factors

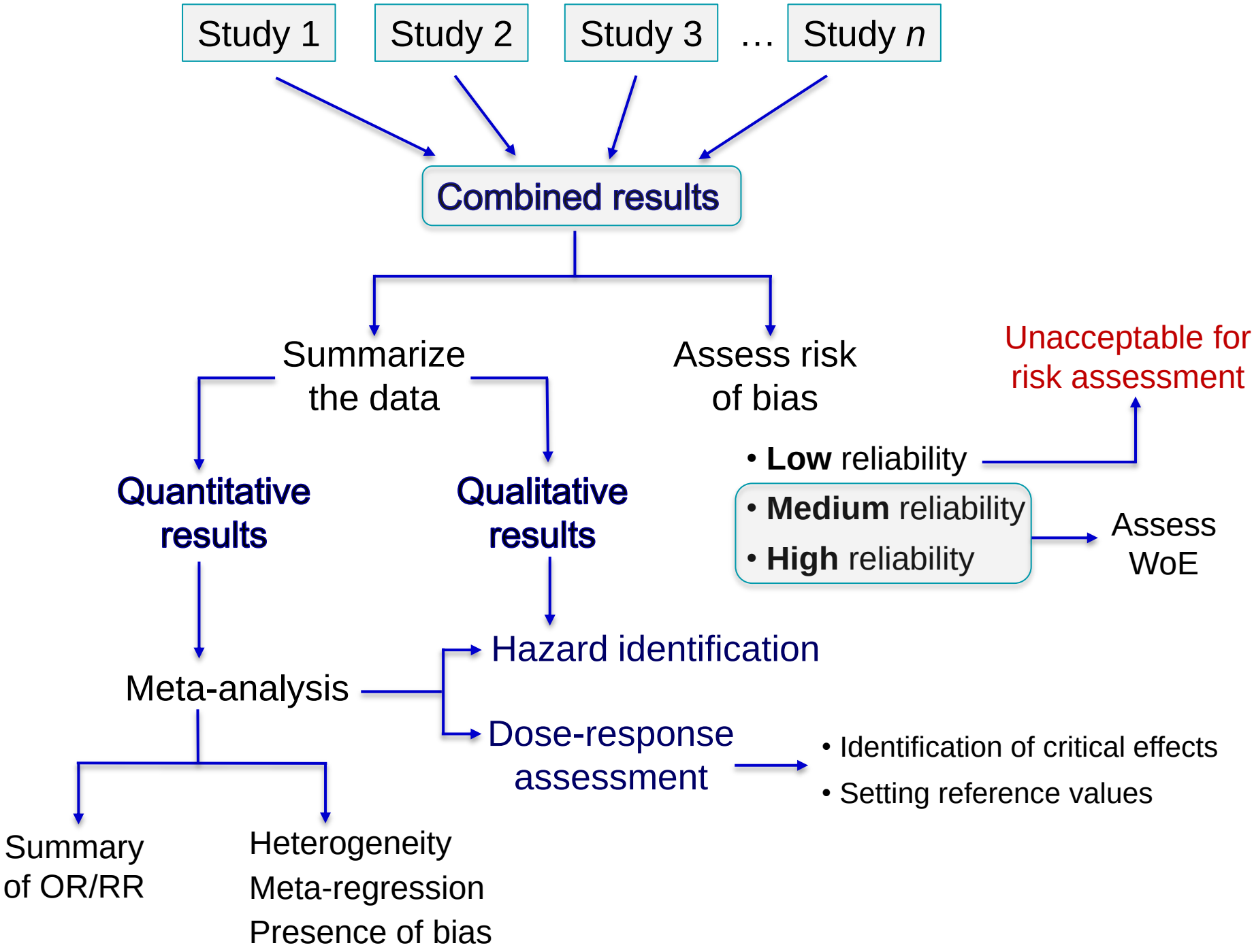


- Need of well designed and conducted studies for C → E

Epi data for pesticide risk assessment

- Enhance the quality and relevance of epidemiological research on pesticides for risk assessment:
  - Adequate assessment of exposure at individual level
  - Valid and reliable outcome assessment
  - Accounting for potentially confounding variables
  - Adequate statistical analysis and reporting of results

- Growing use of systematic reviews:
  - ↑ understanding potential hazards of pesticides
  - Evidence synthesis is challenging (for pesticides)
  - Assessment of methodological quality (including risk of bias) of individual epidemiology studies
  - Can identify associations with robust and credible evidence
  - Highlight uncertainties and data gaps

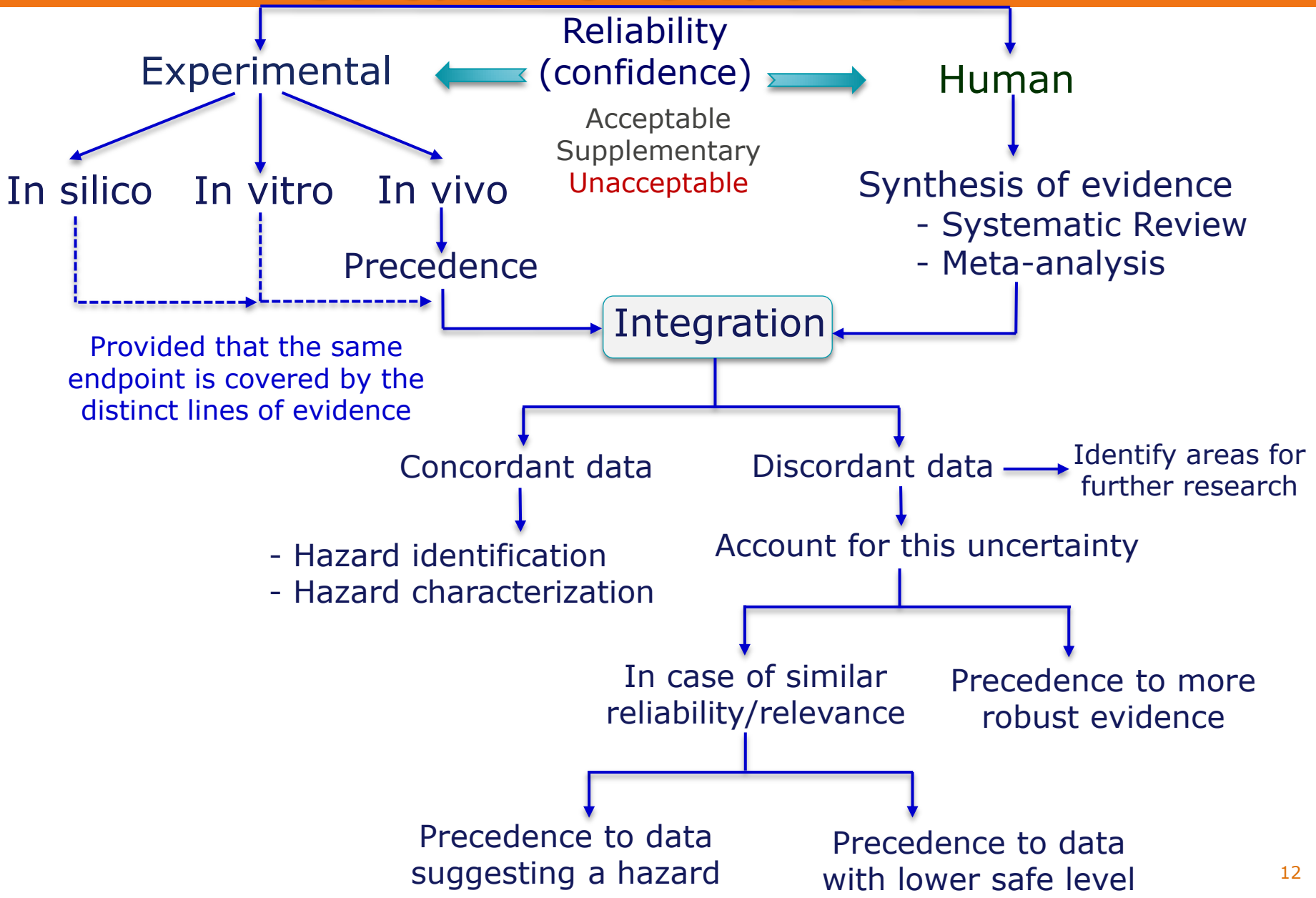

Study 1
Study 2
Study 3
…
Study *n*
Combined results
Summarize the data
Assess risk of bias
Unacceptable for risk assessment
• **Low** reliability
• **Medium** reliability
• **High** reliability
Assess WoE
Quantitative results
Qualitative results
Meta-analysis
Hazard identification
Dose-response assessment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

Integration of epi and toxicology

- 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

  WoE → 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



Biological plausibility for epi evidence

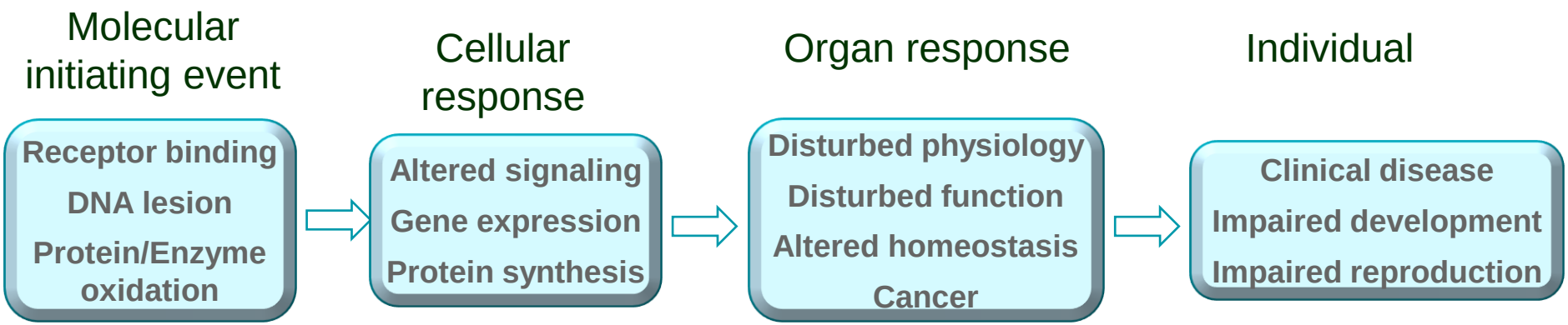
- Epidemiological studies

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.
- 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 weigh their conclusions.
- Integration of all lines of scientific evidence would benefit from moving to a mechanistic-based risk assessment.

Questions?