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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Context of the Scientific Opinion

- **Pesticides** (as regulated chemicals)
  - Regulatory studies
  - Epidemiological evidence
- **Specific EU Regulation**
- **Risk assessment, not research**

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### EU Pesticides database

<table>
<thead>
<tr>
<th>Substance</th>
<th>Active Sub</th>
<th>Cated</th>
<th>List(*)</th>
<th>Status under Re</th>
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<tbody>
<tr>
<td>(4Z-9Z)-7,9-Dodecadien-1-ol</td>
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<td>FU</td>
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<tr>
<td>Zucchini Yellow Mosaik Virus, weak strain</td>
<td>2020</td>
<td>EL</td>
<td>C</td>
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**Summary**

<table>
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<tbody>
<tr>
<td>Not approved</td>
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<tr>
<td>Pending</td>
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<tr>
<td>Banned</td>
<td>20</td>
</tr>
<tr>
<td>Other</td>
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<tr>
<td>TOTAL</td>
<td>1365</td>
</tr>
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</table>
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.
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.
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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

**A** Classical **single hazard** approach: driven by regulatory frameworks

- Evaluation of one chemical compound
- Various potential risks: Risk 1, Risk 2, Risk 3

**B** **Multiple hazards**: Epidemiological approach: *what makes people ill?*

- Evaluation of various ‘risk factors’:
  - Chemicals
  - Micro-organisms
  - Processing methods
- Increased disease incidence

- 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
Meta-analysis

Quantitative results

- Summary of OR/RR
- Heterogeneity
- Meta-regression
- Presence of bias

Qualitative results

- Hazard identification
- Dose-response assessment
- Identification of critical effects
- Setting reference values

Combined results

Assess risk of bias

- Low reliability
- Medium reliability
- High reliability

Summarize the data

Unacceptable for risk assessment

Assess WoE

Study 1

Study 2

Study 3

... Study n
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
  - 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

- In silico
- In vitro
- In vivo

Precedence

Provided that the same endpoint is covered by the distinct lines of evidence

Reliability (confidence)

Acceptable
Supplementary
Unacceptable

Human

Synthesis of evidence
- Systematic Review
- Meta-analysis

Integration

Concordant data
- Hazard identification
- Hazard characterization

Discordant data
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

Identify areas for further research
Biological plausibility for epi evidence

- Epidemiological studies

- Complementary experimental research needed

- 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?