Key questions for the regulators

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Ultimate goal of the regulatory risk assessment:

> **Define if an estimated exposure is exceeding a health based toxicological threshold**

How?

> **Definition of the hazard**
>
> **Definition of a dose response relationship**
>
> **Definition of doses of no (adverse) effects**
>
> **Consideration of intra and interspecies differences**

Establish «legal» ref values

Perform risk assessment

> Epidemiology studies could inform on hazard identification and characterization (i.e. dose-response assessment).
>
> However, exposure information is usually limited and less controlled than in the experimental conditions.

EPI STUDIES & HAZARD IDENTIFICATION

Can epidemiology identify specific health effects?

- **Effects not observed in the experimental tests**
  (e.g. subjective effects such as nausea or headache).
- **End points not explored in the experimental tests**
  (e.g. end points of interest for Parkinson's disease are unlikely to be evaluated).
- **Confirm the human relevance of effects identified in the experimental tests**
  (e.g. neurodevelopmental effects seen with chlorpyrifos).
- **Inclusion in study(ies) of sensitive population subgroups ("yopi") may reveal particular effect.**

Overall, epi studies would directly assess health effects on the population of concern, at relevant exposure levels, complemented by the *in vitro* and *in vivo* experimental outcomes.

EPI STUDIES & HAZARD CHARACTERIZATION

Can epidemiology help/be substantial deriving NOAELs (or PoD)?

- **Are data good enough to conclude on dose-response relationship?**

  (limited exposure information, difficulty in isolating dose-response relationships for one chemical in case of multiple exposure).

- **Which PoD to be used?**

  NOAEL approach traditionally used in pesticides RA in EU.

  Exposure data in EPI often do not fall into a small number of well defined dosage groups.

  BMD approach more suitable for EPI data ?

  Should RA of pesticides be implemented by BMD approach?

EPI STUDIES & UNCERTAINTIES

How to account for uncertainties? Need of UF?

- **Default UF :** 10 (interspecies differences) and 10 (intraspecies differences) used in pesticides RA (when based of animal data).
- **With human data:**

    No need of interspecies factor.

    Intraspecies factor very much depends on the study (homogenous sample vs sample covering intraspecies variation).

- **Relevance of different population groups.**

    Is the studied population representative? Inclusion of different groups (e.g. the young, old and susceptible)?

- **The random error in the risk estimate is represented by the confidence interval (size of the study/ies).**

    In case of wide confidence interval, do we need a UF larger than one?

QUALITY OF EPI STUDIES & UNCERTAINTIES

Quality of the human data/uncertainties

- **Uncertainties vs exposure: accurate exposure estimates is the greatest limitation in epi data**

    ➔**additional UF ?**

    Use only data with biomarkers of exposure?

- **UF vs confounders.** Confounding factors can be controlled in the design and in the analysis of the studies, providing that the confounding factors have been identified and measured. Regarding pesticides, it may be difficult to control for potentially confounding co-exposures .

    ➔**additional UF ?**

- **Need of agreed criteria.**

EPI STUDIES IN PESTICIDES RISK ASSESSMENT 1/2

Integration of epidemiological studies in pesticides RA.

- **Are epi studies suitable for (premarketing) risk assessment?**

    Should it fit better to renewals?

- **Epi studies are not available by definition for new AS.**

    Use of data on class analogs for whom epi study(ies) are available with the support of mechanistic studies?

- **In case of renewals, is the length of the follow up sufficient to define the outcome of the studies ?**
  Should we use validated biomakers of effects?

- **Epi data could be used in a quantitative RA when they meet the requisite criteria, particularly for exposure assessment.**

EPI STUDIES IN PESTICIDES RISK ASSESSMENT 2/2

Integration of epidemiological data in pesticides RA.

- **Should epidemiology be seen in the frame of a stepwise approach** (i.e. the epi study identifies a concern and this triggers the execution of further considerations)?

- **If so, how to make the best use of them in the regulatory field?**

    Epi studies are focused on a relatively narrow spectrum of effects vs broader spectrum of effects evaluated in guidelined toxicity studies.

    Epidemiological studies often limited by the amount of available data on dose and tend to address exposure–response relationships (based on whether exposure occurred or not).

    → **Establish «legal» ref values is therefore challenging.**

- **Weight of evidence approach:** need of WoE analysis for epi studies since not contributing to risk characterization.

EPI STUDIES VS EXPERIMENTAL DATA

How can the concern highlighted in epi studies be solved by experimental studies? Case by case?

- When both epidemiological and experimental data are available,

  →occurrence of similarity of effects between humans and animals should be considered.

- Biological explanation often not established when the epidemiologic evidence becomes available →need for additional *in vitro* or *in vivo* studies to explore pathogenesis, hypothesized modes of action and to build adverse outcome pathways.

- The adverse outcome pathways could potentially identify critical data gaps and needs for additional research (earlier biomarkers of a key event precursor to clinical disease).

EPI STUDIES IN PESTICIDES RISK ASSESSMENT

Thank you for your attention