National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Notes on the use of epidemiological and toxicological data for risk assessment

Working group integration toxicology and epidemiology in risk assessment at RIVM

Epidemiology at RIVM

- Environmental epidemiology
- Cohort studies (Adults: the Doetinchem Cohort Study; Birth cohort: PIAMA Study)
- Survey of infectious disease: PIENTER study
- Health monitor, Youth monitor
- Disease modelling: infectious and chronic disease
- Trend scenarios Public Health Forecast studies

Risk assessment at RIVM

- Includes: environment, food and consumer products (a.o, contaminants, natural toxins, herbs/food supplements, enzyme preparations)

Additives
('E-numbers')

Crop protection

Food contact
materials

Risk Assessment Current practice (deterministic)

Exposure

HBGV

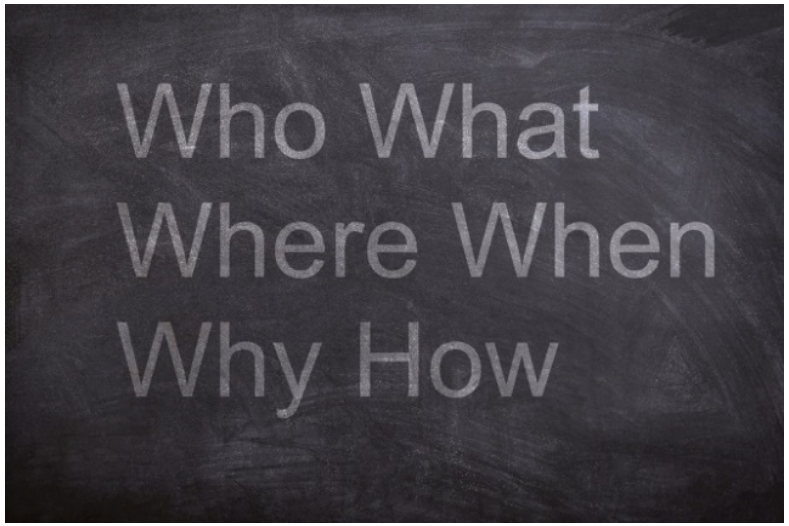
Exposure > HBGV

“Possible risk?”

Use of human data in risk assessment

- There is general agreement that epidemiological data has the potential to improve risk assessment
  - › Effects directly applicable to human health
  - › Cross-species extrapolation factors not needed

- But which epidemiological data is appropriate?



- How and when can it be used?

The RIVM Epitox Workgroup

- Aim of the RIVM Epitox workgroup:
  - Work together on risk assessments using epidemiological data
  - Share experiences performing risk assessments using epidemiological data
  - Brainstorm best practices for epidemiology and toxicology to improve and streamline the use of epidemiological data in risk assessments.

Case study evaluation

The WG evaluated four case-studies using epidemiology data in risk assessments to identify:

1. Challenges
2. Best practices in the use of epi-data (Appraisal and WoE)
3. Tips and tricks
4. Conclusions and next activities

Challenges

- Linking exposure and effect
  - Often not known to which specific chemicals one was exposed
  - (Simultaneous) exposure to multiple chemicals during different life stages
  - Specific exposure levels not known (need to “group” different exposures for modelling)
- No zero exposure in studied population
- Long duration between exposure and clinical manifestation
- Size of the studied population

Challenges

- Mode of action is not known for all substances (also the case for e.g., animal studies for new chemicals)
- Clinical relevance of an endpoint may still be challenging (e.g., translation of endpoints to DALYs)
- Data quality and relevance for (sub)populations
- Dealing with bias (due to co-exposure to other chemicals affecting the same endpoint, loss to follow-up, socio-economic status, background contamination, genetic susceptibility, publication bias)
- No access to raw data

Appraisal and WoE

Weight-of-Evidence for Effect Determination

- Clarification of the question to be answered (purpose and scope)
- Evaluation and weighting of individual data (i.e., individual studies)
- Identification of critical data and endpoints
- Determination/evaluation of effect data
- Quantitative and comparable data whenever possible, e.g., deriving a PoD using Benchmark dose (BMD) modeling approach (EFSA 2017, 2022)
  - › Ideally with individual data
  - › Ideally anonymized individual human health data should be available (e.g., NHANES data)

EFSA 2017. Update: use of the benchmark dose approach in risk assessment
EFSA 2022. Guidance on the use of the benchmark dose approach in risk assessment

Appraisal and WoE

General

- Terminology can differ between disciplines and methods
  - ↳ care should be used when reporting and discussing
- Methods, which may be new or adjusted compared to prior assessments, should be clearly and carefully described.
- A full description of uncertainties and their potential impact (i.e., higher or lower conservativeness) should be provided, along with possible ways to address uncertainties in the future.

Tips and tricks

- Establishing publicly available epidemiological databases and human biomonitoring may improve useability of epidemiological/biomonitoring data in future RA.
  - › Lack of exposure to new substances -> establishing a “baseline” for unexposed populations (reference database of epidemiological/HBM studies needed)
- Provide raw data preferred for BMD
  - › Grouping exposures means individuals with varying exposure are assigned same mean value in the modelling (not ideal)

Conclusions

- Epidemiological studies provide valuable information for risk assessment.
- Changes in methodology and reporting of epidemiological studies will improve usefulness of data for risk assessment.
- *A priori* discussions between epidemiologists and risk assessors about study designs will enhance usefulness for RA.
- More detailed (quantitative) information on exposure, outcome parameters, study population etc., are highly desirable.
- Access to (raw) data for modelling improves reference point estimation.
- Individual data is preferred for BMD modelling.
- Establishing baseline (no) exposure values for new substances (where possible) will also improve modelling of reference points.

Moving forward

- Evaluate a virtual “perfect” epidemiological study
  - Are there still stumbling-blocks?
  - Can they (still) be minimized by protocol adjustments?
  - If not, identify harmonized procedures for addressing remaining issues
- Identify additional possiblities e.g., using human biomonitoring (HBM) data
  - Can effect biomarkers be used (together with NAMs/AOPs/IATAs) to enhance use of epi data in risk assessment?
  - Collection of “negatives” for future use/new substances (“baseline” dataset)?
  - Are there biomarkers of effect(s) that can improve identification of rare effects or effects materializing long after exposure (better link between exposure and effect)?
- Anonymized epidemiological and/or HBM database using NL data?

Acknowledgements