Reference doses: animal or human data .. or both?

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based on joint work (project B10) with

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Human exposure standards to environmental chemicals are often based partly on animal data.

Here, Reference Values (RVs)\(^1\) identified from animal studies are compared with those from human studies for a systematic sample of chemicals.

Systematic literature review approaches identified c.170 substances for which substantial human and animal data available.

A purposive sample of 20 was chosen from them to include substances in several categories (metals, solvents, pesticides, other) and to cover a range of adverse health effects.

In this subsample of 20, where data were of sufficient quality, RVs identified from human data were compared with those from animal data.

\(^1\)Reference Dose: a daily exposure to the human population ... likely to be without an appreciable risk of deleterious effects during a lifetime.\(^{[1]}\)
Main finding: For some substances the human-based and animal-based RVs were very similar, but some differ by factors of order 10 (and in isolated cases, more than this).

Exploratory analyses do not revealed clear patterns of variation of the ratios of the human- and animal-based RVs.

Additional finding: uncertainty in risk assessment is not always adequately considered or reported.

**Combining** human and animal data in derivation of RVs is explored in a proof-of-principle example.

This demonstrates how design of additional studies could be improved.
Reference values (RVs) from human and animal data 
(from Vassaux et al, 2013) [2]

Human RV vs Animal RV: chronic inhalation

Human RV = Animal RV/10
Human RV = Animal RV
Human RV = 10 x Animal RV
Obtaining reference doses from human and animal data
(from Lavelle et al, 2012) [3]

Positive data take precedence (be it animal or human). If data are not concordant, the data with a steeper slope or lower safe level should be used, but should be moderated by the upper risk level of the “less positive” data (see text).

(1) sulphanilic acid; (2) glycidol; (3) mectins; (4) methylene chloride; (5) hydrogen fluoride
Human-data-based RVs compared with RVs derived from available animal data (from Vassaux et al, 2013) [2]

![Graph showing comparison between human and animal-based RVs for different chemicals. The graph plots the human-based RV on the y-axis against the animal-based RV on the x-axis. The chemicals compared include Toluene, Acetone, Trichloroethylene (acute), and Cadmium. The graph includes lines indicating different human-based RV calculations: Human RV = Animal RV/10, Human RV = Animal RV, Human RV = 10 x Animal RV.]

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Explaining variations in ratio of human and animal RVs
(from Vassaux et al, 2013) [2]
Dose and interspecies extrapolations

Toxicological (animal) data

Epidemiological (human) data

Response

Dose

'acceptable' risk

Higher to lower dose

'safe' dose

Animal to human
Synthesis and uncertainty

- Need to assess robustness to alternative data synthesis and risk assessment models.
- Model uncertainty may have a critical impact on extrapolations [4].
- Many other sources of uncertainty in risk assessment not adequately dealt with (see WHO report) [5], including uncertainty due to:
  - between-species extrapolation,
  - population heterogeneity,
  - confounding, and
  - measurement errors.

- Systematic approaches to synthesis of evidence contributes to assessment and minimisation of uncertainty through using all relevant, good quality data available.
Joint model for epidemiological and toxicological data provides basis for integrated approaches to research priority and design decisions, whichever approach adopted: [6],[7]
'Optimising’ available data: a hierarchy of approaches to designing the next study

- Joint model for epidemiological and toxicological data provides basis for integrated approaches to research priority and design decisions, whichever approach adopted: [6],[7]
  - 'Gedanken experiment’ comprising addition of a study
  - Simulation of an additional study, re-estimating synthesis results after it is included
  - ...and hence exploration of several alternative next studies through sensitivity analyses
  - ...for example, in respect of the relative value of animal and human evidence
  - Stochastic versions of simulations above [8]
  - More formal decision methods - value of information approaches [9]
Proof-of-principle example: decision model for lowering trihalomethane (THM) exposures in drinking water

- **THM limit in drinking water**
  - No change of limit
    - \( p_{\text{cont}} \)
      - Low birth weight (<2500 g)
    - \( 1 - p_{\text{cont}} \)
      - Normal birth weight
  - Reduce limit to 80 ppb
    - \( p_{\text{int}} \)
      - Low birth weight (<2500 g)
    - \( 1 - p_{\text{int}} \)
      - Normal birth weight

Need estimates of benefits and costs for each outcome

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Expected value of *sample* information (EVSI) measures the value of a *new study* providing specific information on the uncertain $X$:

$$EVSI = E_Y \left( \max_t E_{X|Y}(NB(t, X)) \right) - \max_t E_X(NB(t, X))$$

where the sample yields information on a subset $Y$ of $X$
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where the sample yields information on a subset $Y$ of $X$.

Calculating EVSI for an additional toxicological study and, separately, for an additional epidemiological study should help decide which is better choice:

- e.g. EVSI for study of births in 2 UK Regions for 3 years ($n=150K$ vs. $n=150K$) may be estimated as £19434
- e.g. EVSI for toxicological study of 25 S-D rats exposed to chloroform and 25 controls estimated as £16793
Summary and recommendations

- The case for substituting human-based evidence for animal-based evidence is limited.
- Increasing use and reporting of systematic review approaches in compiling human and animal data for RV calculations should become universal practice.
- Similarly, reasons for final preference being given to use of human or animal data, particular endpoints, and particular studies data sets should be explicitly stated.
- Approaches (beyond use of uncertainty factors) to acknowledging and quantitative reporting of uncertainty in estimated RVs and other critical values should be adopted.
- Strategy for collection of further data should be explicit and optimised as far as possible.
- Further comparisons of human- and animal-based and combined RVs should be explored in a larger sample.
References


