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

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based on joint work (project B10) with

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Project B10: outline and summary

- 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.

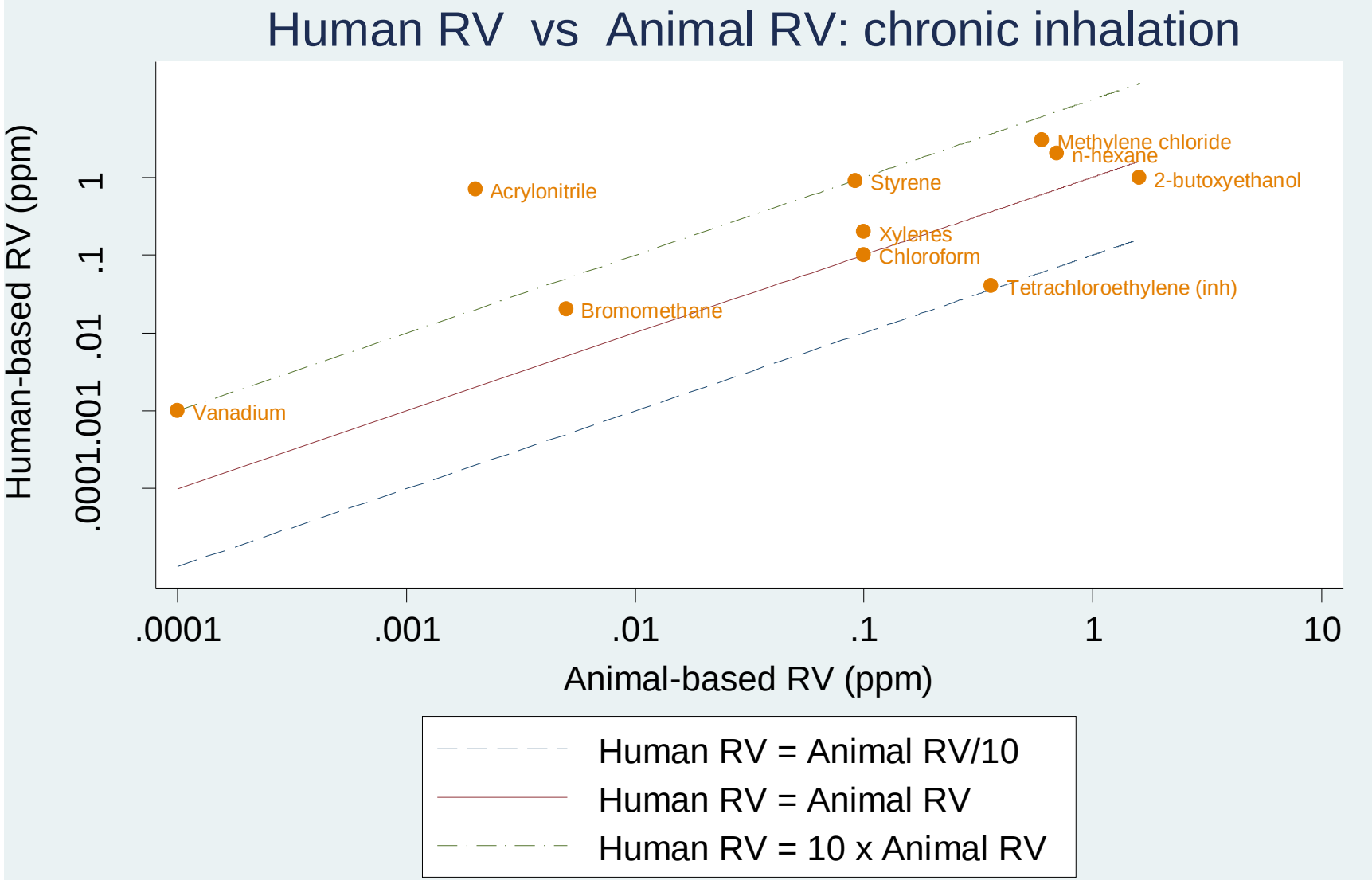
[1] Reference Dose: a daily exposure to the human population ... likely to be without an appreciable risk of deleterious effects during a lifetime [1]

Project B10: outline and summary - ctd.

- 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 notalways 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.

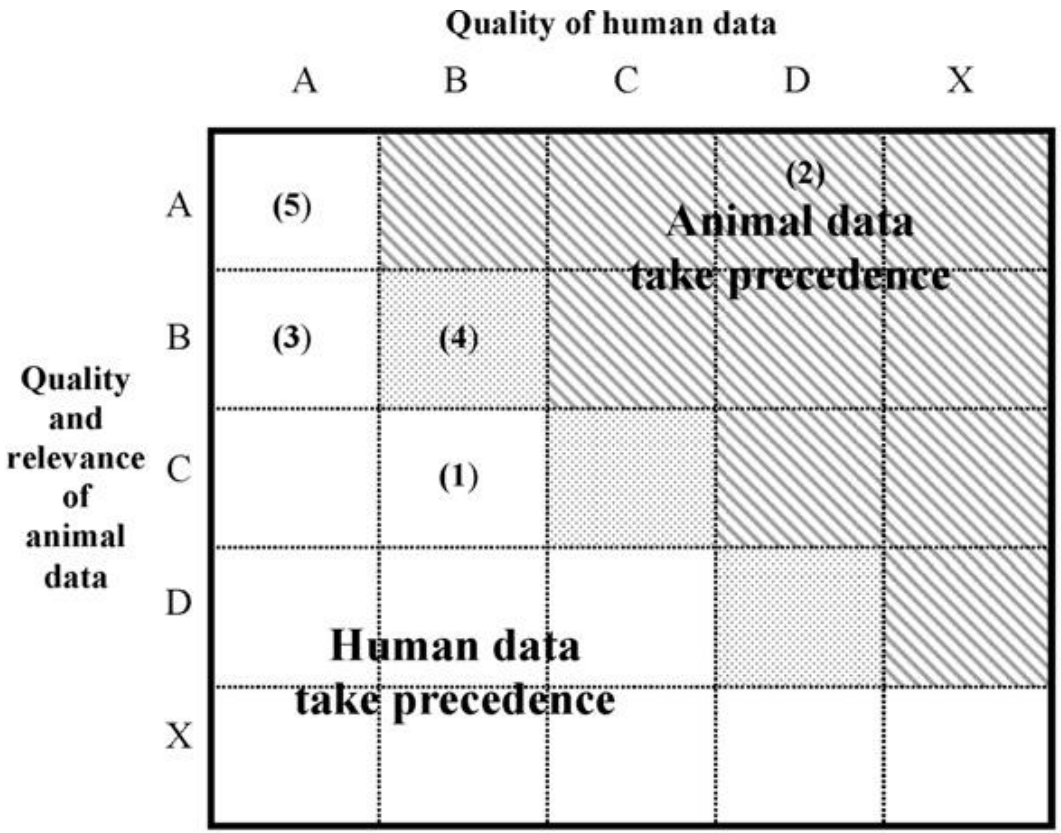
Reference values (RVs) from human and animal data

(*from* Vassaux et al, 2013) [2]



Obtaining reference doses from human and animal data

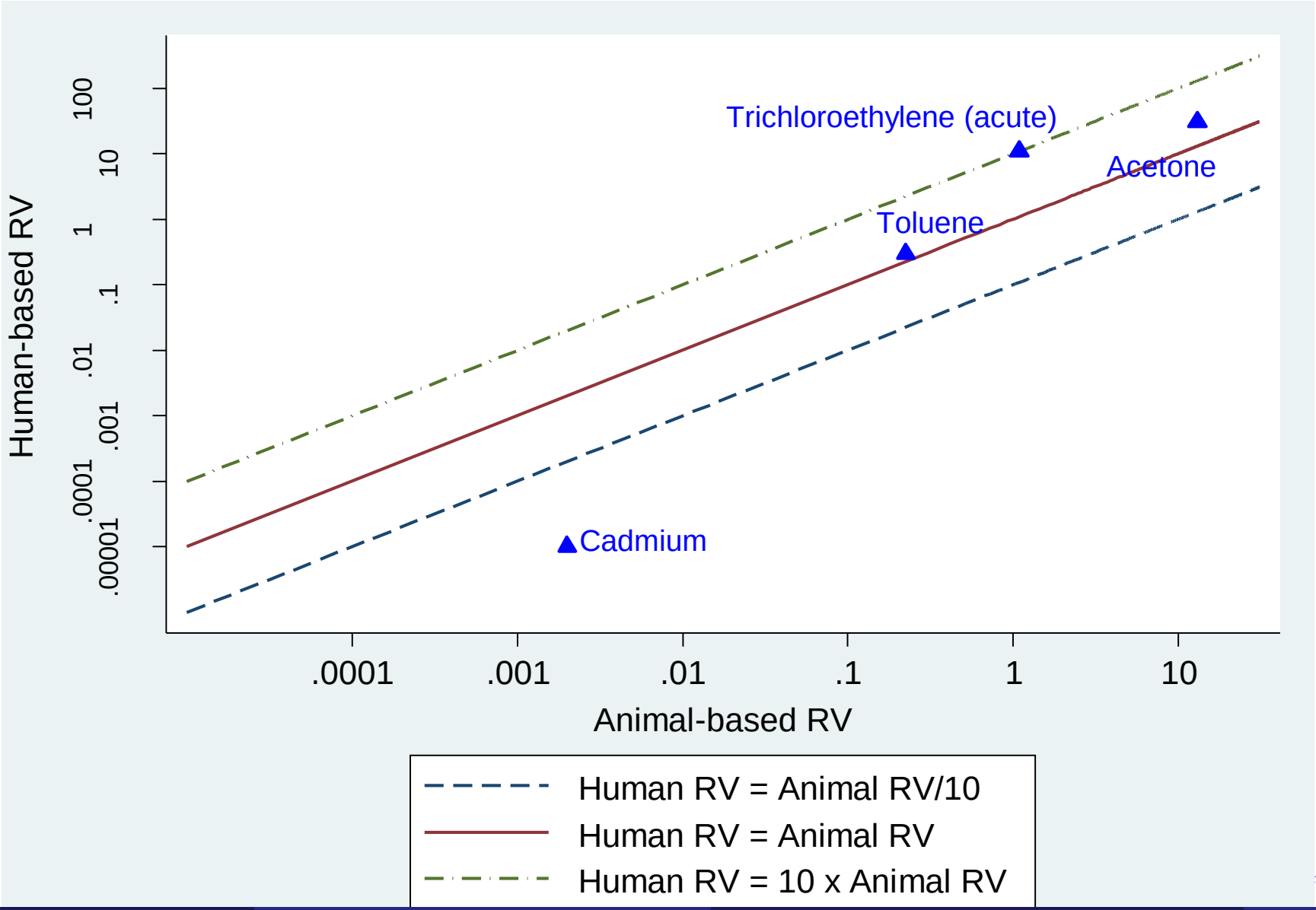
(*from* Lavelle et al, 2012) [3]



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).

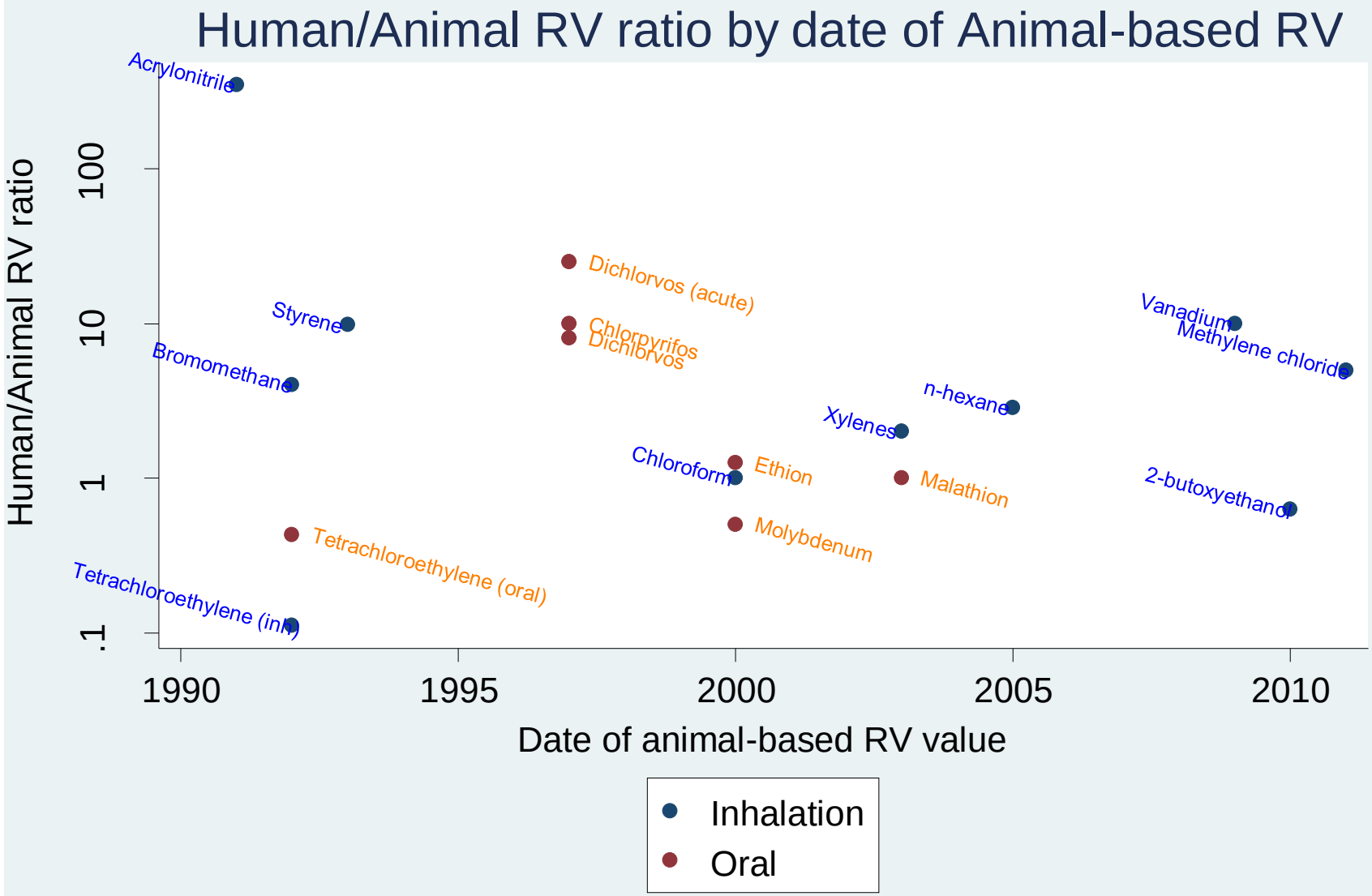
(1) sulphanilic acid; (2) glycidol; (3) mectins; (4) methylene chloride; (5) hydrogen fluoride

Human-data-based RVs compared with RVs derived from available animal data (*from* Vassaux et al, 2013) [2]

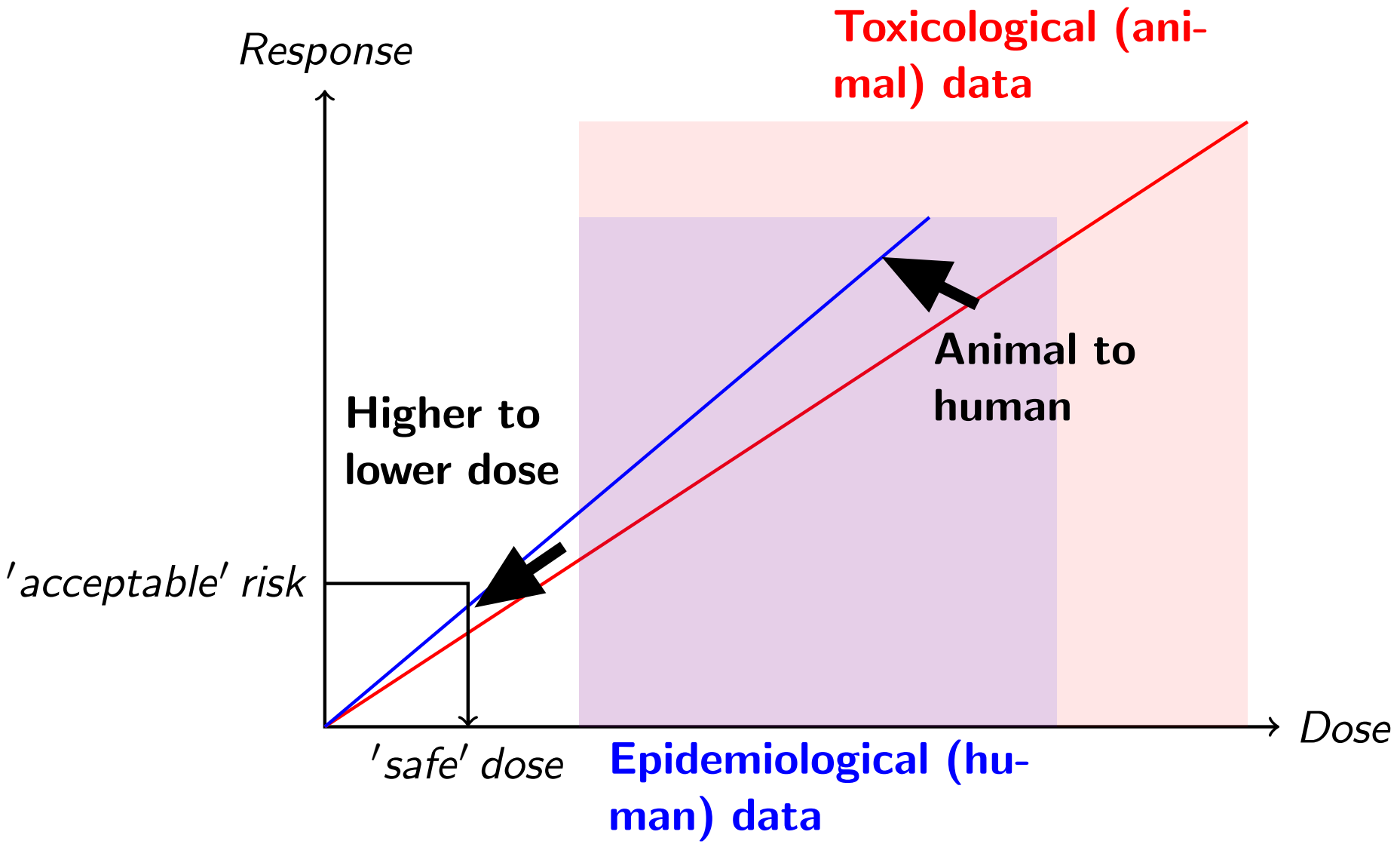


Explaining variations in ratio of human and animal RVs

(*from* Vassaux et al, 2013) [2]



Dose and interspecies extrapolations



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.

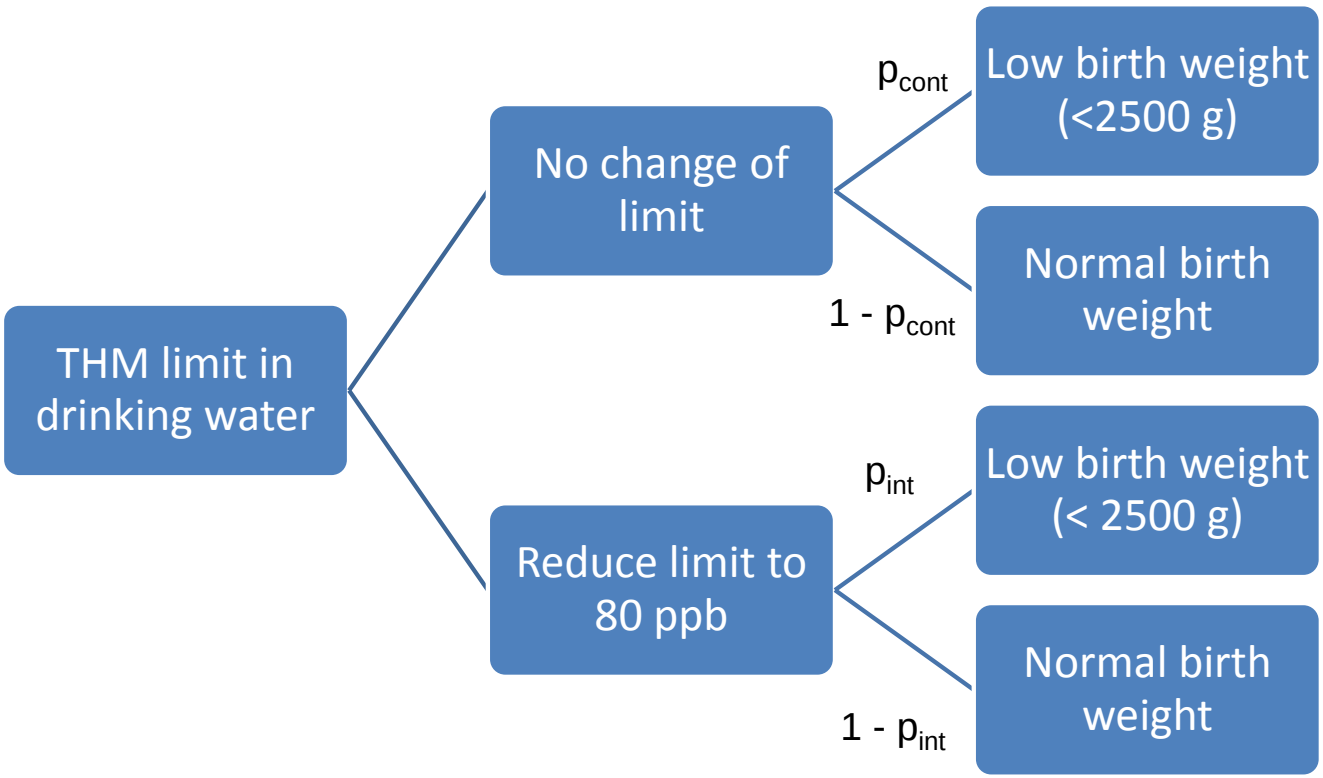
'Optimising' available data: a hierarchy of approaches to designing the next study

- Joint model for epidemiological and toxicological data provides basis for integrated approaches to research priority and design decisions, whichever approach adopted: [6],[7]

'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



EVSI for new epidemiological or toxicological studies

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

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

where the sample yields information on a subset Y of X

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- 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

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