# UNCERTAINTY IN TOXICOLOGY

Inaugural SoBRA meeting

"Uncertainty in Contaminated Land Risk Assessment"

RSC Chemistry Centre, Royal Society of Chemistry

Burlington House, LONDON, 17th December 2009

George Kowalczyk, Health Protection Agency

Chemical Hazards and Poisons Division (Birmingham)

## FEATURES OF HCVs

- **HCVs are often seen as "Gold Standards" by Risk assessors**
- **Used as point source data in Risk Assessment**
- **Other sources of uncertainty are identified in Risk assessment – confidence in HCVs rarely challenged**
- **Sources of Uncertainties not visible**

## MAIN SOURCES OF UNCERTAINTYIN SETTING HCVs

**MAIN UNCERTAINTIES**

- **Quality of the toxicological data**
- **Gaps in the tox data set**
- **Relevance of the end point (animals to man)**
- **Variability in response**

**(Toxicokinetic and Toxicodynamic factors for latter two )**

## Default approach (Threshold substances)

Identify toxic endpoint (usually a NOAEL, or LOAEL) – **"point of departure"**

Apply factors to cover key uncertainties

Usually 2 **Uncertainty Factors each of 10** are applied to NOAEL in most sensitive species to cover

- o species differences
- o human variability
- o**Composite uncertainty = 100**
- oAdditional factors for other uncertainties

Output is TDI, ADI RfD etc -each of which can be basis of setting an HCV.

## Are Default Uncertainty Factors Valid - have they worked?

**Some evidence that factors of 10 are protective**

**Paracetamol**
A factor of 10 is sufficiently protective. Most sensitive species (rat NOAEL 200mg/kg/d) and man (NOAEL 150mg/kg/d)
(nb least sensitive species = mouse (NOAEL 2000mg/kg/d))

**Methyl mercury**
Current PTWI = 3.6µg/kg bw/wk (from human epi data)
PTWI based on rat NOAEL/100 = 0.7 µg/kg bw/wk
UF of 100 sufficiently protective

Overprotective?? - can we do better?

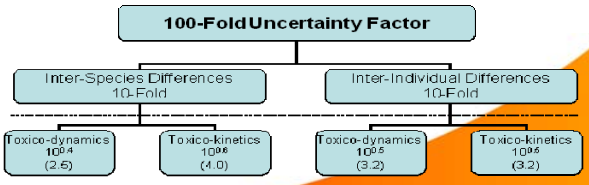
## REDUCING UNCERTAINTIES – Improving HCVs

- **Can we improve on default values of 10 by 10?**
- **Can we improve point of departure estimate?**
- **Are there other (better?) ways of arriving at HCVs**

## IMPROVING DEFAULT FACTORS KINETIC AND DYNAMIC SUBFACTORS

Each factor of 10 has a both **kinetic** and **dynamic** component

**TOXICODYNAMICS** – **effect** of critical agent at the target
**TOXICOKINETICS** – **amount** of critical agent at the target




## WEIGHTINGS GIVEN TO SUBFACTORS

**INTERSPECIES DIFFERENCES (UF 10)**
Dynamics (UF **2.5**) x Kinetics (**UF 4**) = UF **10**
(unequal due to inherent physiological differences eg blood flows)

**HUMAN VARIABILITY (UF 10)**
Dynamics (UF **3.2**) x Kinetics (UF **3.2**) = UF**10**
(equal weighting -analysis of data of therapeutic drugs)

Can reduce uncertainty by using chemical specific assessment factor (CSAF) to replace defaults
(nb CoT endorsed as part of RA process)

## CSAF EXAMPLE - DIOXIN

**USUALLY (2.5 x 4) x (3.2 x 3.2) =100**

**DIOXIN CSAFs**
Dose expressed as modelled steady state body burden (mg/kg bw) not as intake (mg/kg/d) Do not need an interspecies factor
– ie **kinetic UF = 1** (not 4)

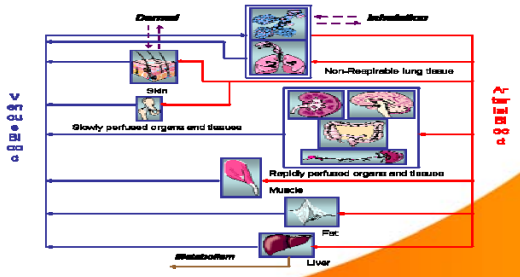
Considered no differences in tissue response between most sensitive human and test species
Inter and intra species **dynamic UFs =1** (not 2.5 and 3.2)

**TOTAL UF = (1 x 1) x (1 x 3.2 [human kinetics variability]) = 3.2**

**UF = 3.2** - applied to steady state animal body burden to derive human body burden (mg/kg) then converted to TDI (mg/kg/d)
Extensive database on dioxins provided 3 CSAFs

## PBPK modelling

can provide comparative estimates of concentrations of key agent at target tissues
– can improve default **interspecies kinetic factors** .




## IMPROVING "POINT OF DEPARTURE"

**Benchmark dose (BMD)**
Dose producing a predetermined incidence (eg 5% or !0%) of an adverse effect/response (eg liver weight) - take lower confidence limit (BMDL) as POINT of DEPARURE

- Makes use of all dose response data (NOAEL does not!)
- NOAEL depends on study design and size – data above NOAEL not utilised
- Can apply usual UFs (or CSAFs) to BMDL
- nb depends on statistics and model used

## NEW HCVs – UNCERTAINTY REDUCED?

| HCVs (2009) | Basis | Possible Impact on Uncertainty |
|---|---|---|
| **Numerically Increased HCVs** | | |
| ↑ Benzene $_{inhal}$ | Changed air quality regulatory limit | None |
| ↑ Toluene $_{inhal}$ | Better human data | Reduced |
| ↑Ethylbenzene $_{inhal}$ | Better animal data | Reduced |
| ↑Mercury inorg $_{oral}$ | Better animal data | Reduced |
| ↑ Selenium $_{oral}$ | New interpretation of key epi study | ? |
| ↑ Nickel $_{oral}$ | Changed WHO water regulatory limit | ? |
| **Numerically reduced HCVs** | | |
| ↓ Cadmium $_{oral}$ | Improved precision in risk estimate | Reduced |
| ↓Mercury $Hg^{0}_{inhal}$ | Revised risk estimates | Reduced |
| **New HCV** | | |
| Phenol $_{inhal}$ | New data – new HCV | Reduced |

## WHY UNDERSTANDING UNCERTAINTY IS IMPORTANT

Can inform understanding of the health significance of exceeding an HCV (SGV) for health

For threshold substances, exceeding an SGV "erodes" uncertainty factors –

- oCould mean that health effects more possible for all exposed populations (eroding interspecies UF)
- OR
- o fewer people are fully protected (instead of 95-98% protected _ perhaps 90% protected) (reduced allowance for human variability)
- OR
- A MIXTURE OF BOTH!

Transparency of uncertainty and its origins are important to make this judgement

## TOXICOLOGICAL UNCERTAINTY AND STATUTORY GUIDANCE

- Mentioned in context of exceeding SGV and SPOSH – ie where there is "little uncertainty" in the toxicology
- "little uncertainty" - not defined but would need to consider
  - oEvidence from human data (eg arsenic + asbestos)
  - oAnimal data – same toxic end point as in humans (eg not naphthalene)
  - oToxic mechanism known (very few substances)
  - oLittle variability in human response (-ie not much polymorphism)

## REDUCING TOXICOLOGICAL UNCERTAINTY

- **Data gaps** - better test methods to detect hazards of some areas of concern – endocrine disruption, developmental neurotoxicity
- **Refine UFs** - use of PBPK modelling
- **Improve PoD** – Replace NOAEL by BMDL
- Better identification of **vulnerable subgroups**
- Understanding of **genetic factors** (polymorphism)
- Understanding impacts of **exposures at different stages of life**? (eg early life)
- **Other approaches** (probabilistic, body weight scaling, margin of exposure etc )

## IMPROVING RISK ASSESSMENT

**Transparency of Toxicological inputs into risk estimates**

- Clear identification of PoD and its origin (why some studies discarded)
- Uncertainty factors used should be
  - visible
  - assumptions justified
  - chemical specific

## FURTHER READING

**CoT report 2007**
*"Variability and Uncertainty in Toxicology of Chemicals in Food, Consumer Products and the Environment"*
*CoT website*

**IGHRC (Interdepartmental Group on Health Risks from Chemicals) report 2003**
*"Uncertainty factors : their use in human health risk assessments by UK Government"*
*Institute of Environment and Health (IEH), Cranfield website*

**Thanks for listening any questions?**