

表1 既定の不確実性係数について

## MOS Workshop

### *Default Uncertainty Factors (UFs)*

- are pragmatic, generic values for possible use by risk assessors in the absence of relevant & essential data
- are *not* intended to be applied universally & routinely
- are *not* intended to be binding or rigid
- should serve as “interim guides”
- should reflect the current state-of-the-science
- should avoid integration of science and policy in a composite value
- should be based on transparent assumptions

# SHORTCOMINGS OF MATHEMATICAL MODELS

- ◆ OVERSIMPLIFICATION OF  
COMPLEX PROCESSES.
- ◆ MECHANISM OFTEN NEGLECTED
- ◆ EXTRAPOLATION OUTSIDE RANGE  
OF OBSERVATION
- ◆ FALSE IMPRESSION OF ACCURACY

表3 動物間のサイズによる代謝速度など比例計算手法の長所と短所

## Scaling: pros and cons

### PRO

takes account of metabolic rates: detoxification, bioactivation and excretion scale with  $BW^{0.67-0.75}$

scaling used in dose calculation for inhalation exposure

many biological functions related to energy production and use scale with  $BW^{0.75}$

validation done for acute effects (Travis 91/92) and carcinogenicity (EPA 92)

### CON

metabolism of xenobiotics often organ-specific

humans do not eat according to caloric demand

allometric scaling and experimental exposure period not independent

not all effects correlate to metabolism (e.g. local effects)

size independent factors: e.g. absorption, protein binding, bile excretion

図1 暴露から毒性影響に至るデータの入手可能性に基づく

定量的な評価の種々な方法

Different databases quantitative risk assessment may be required (Renwick, 2000)

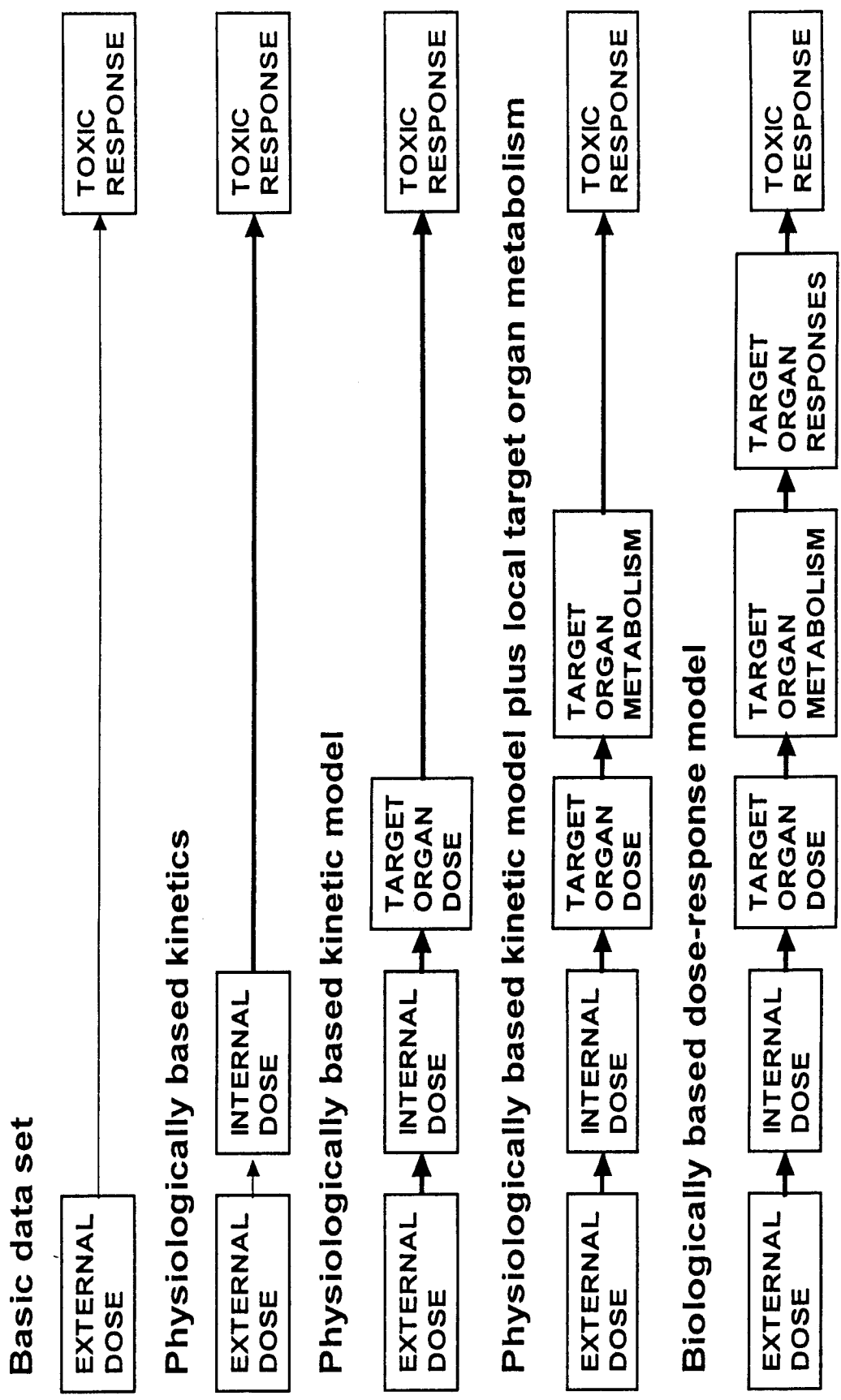
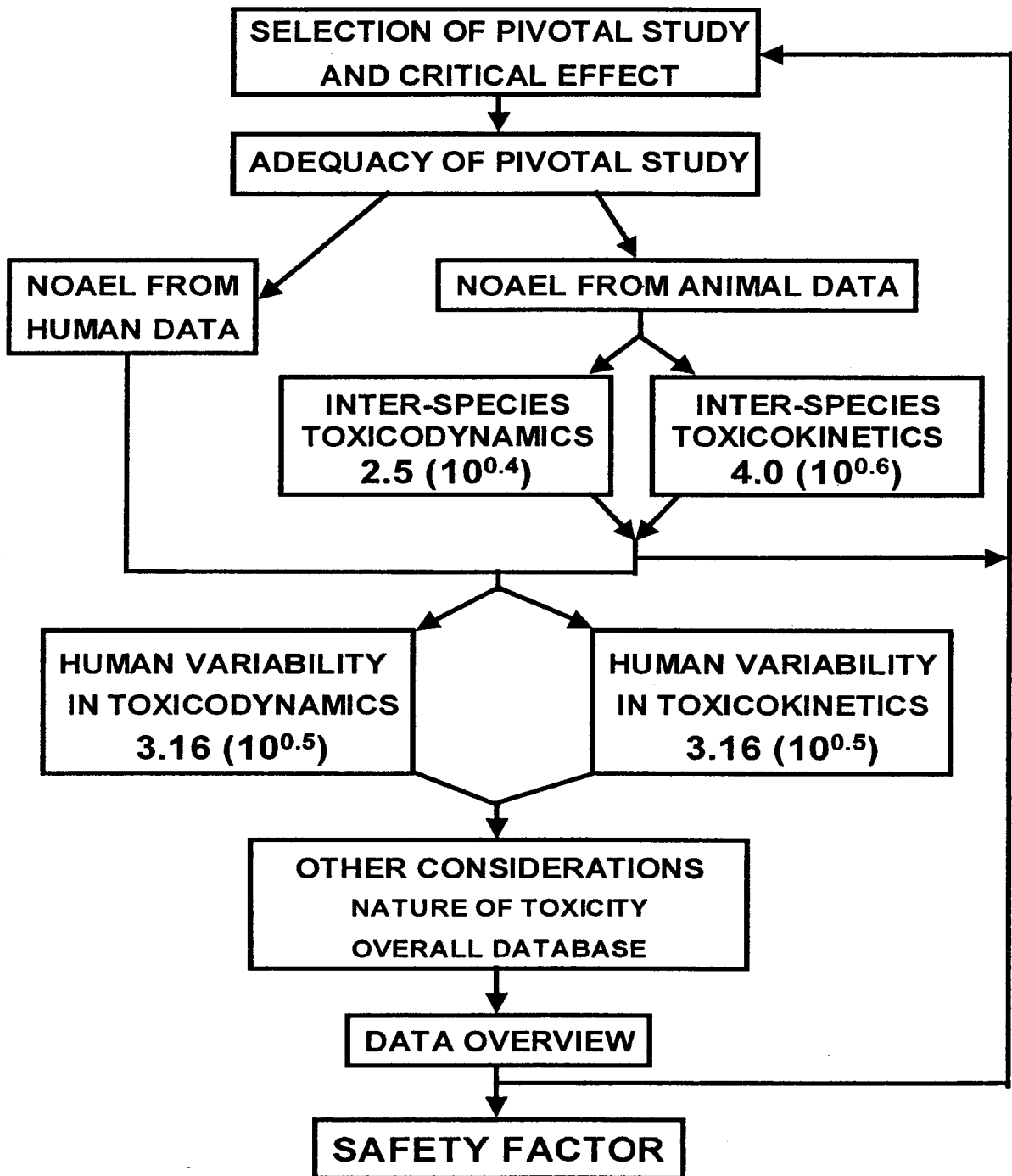
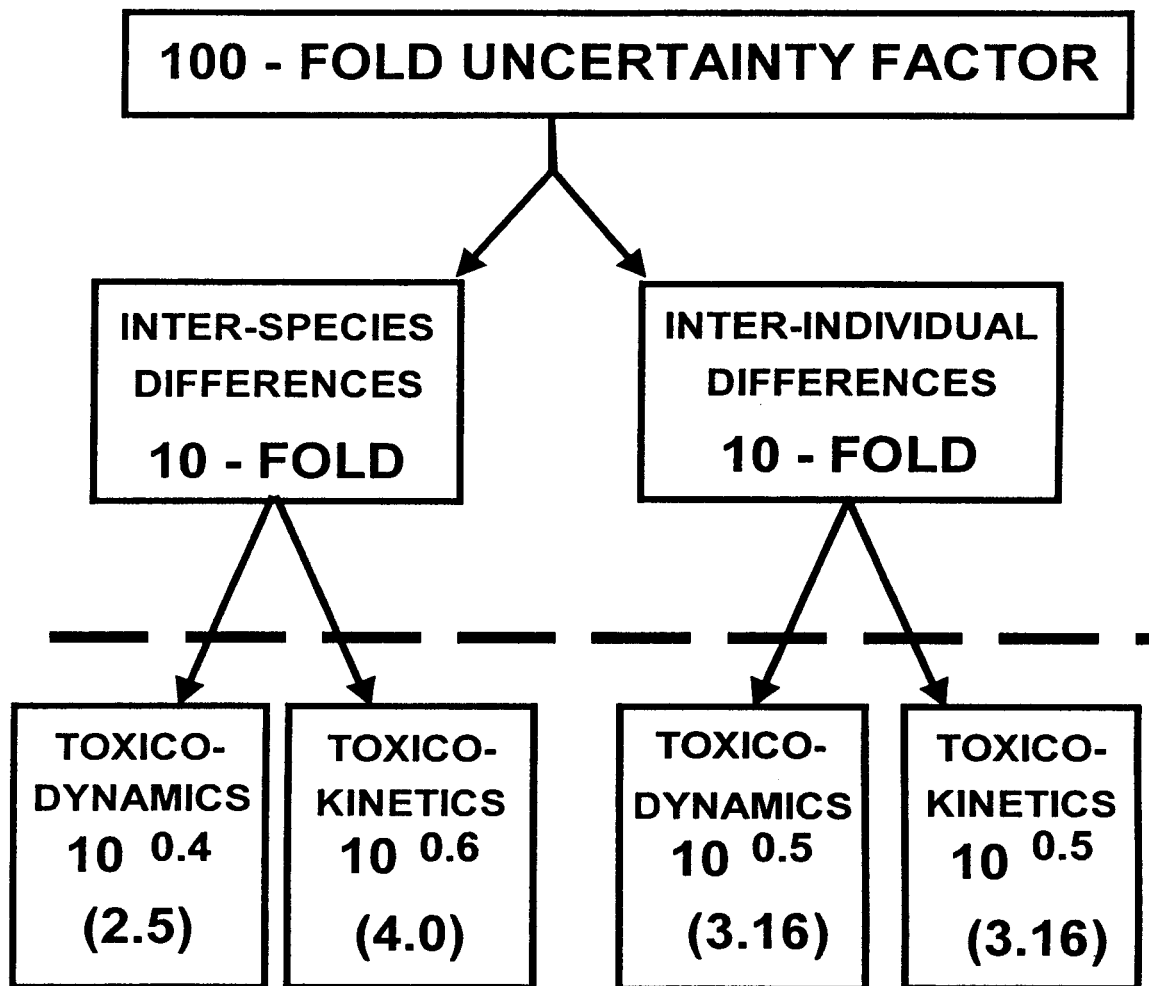


図2 閾値を有する毒性影響の定量的リスク評価



## Risk Assessment for Threshold Toxicants (IPCS, 1994)

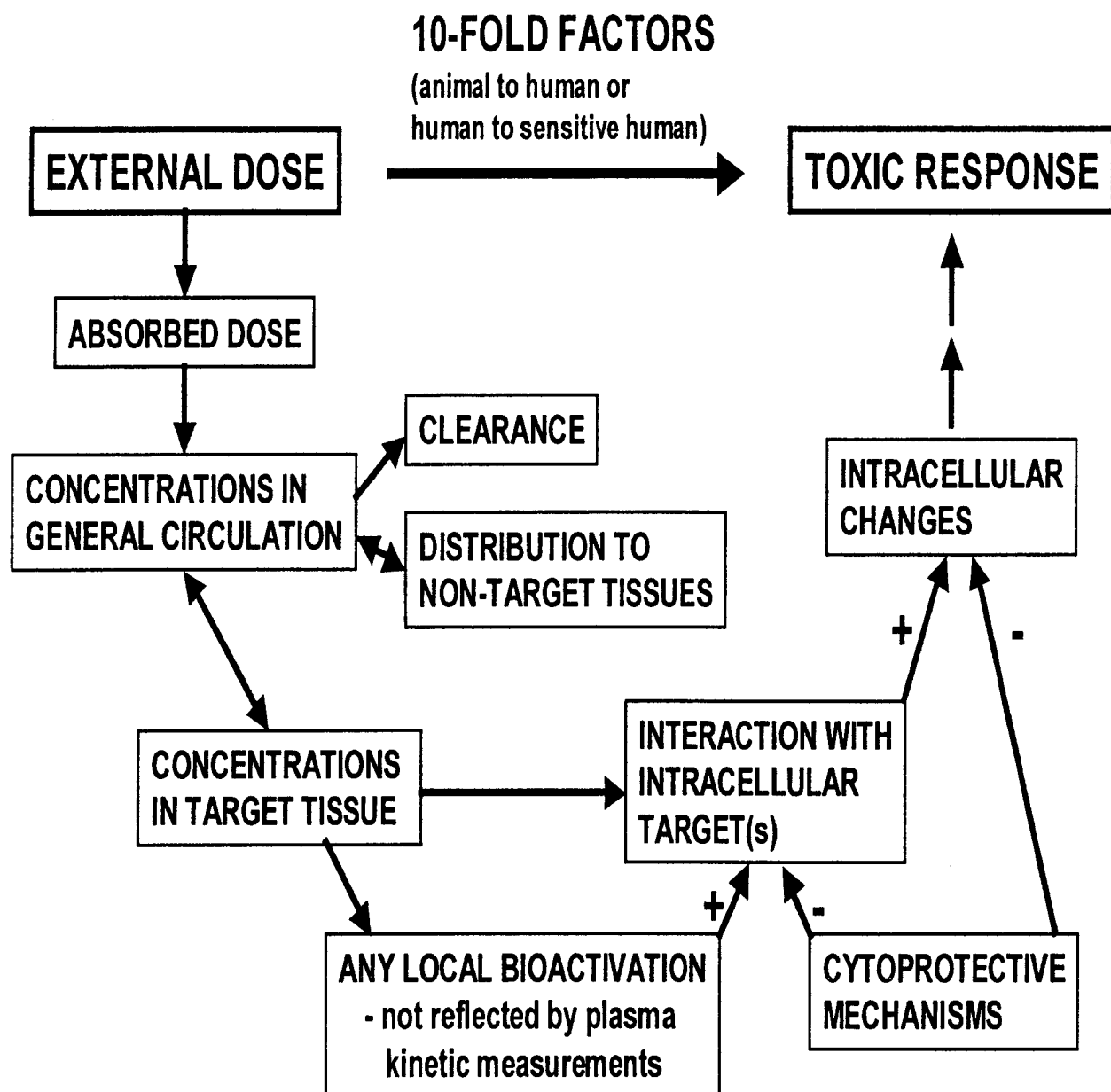
図3 トキシコキネティクスとトキシコダイナミクスのデータに基づく種差と個体差の評価 (IPCS, 1999)



**Subdivision of uncertainty factors (IPCS, 1999)**

図4 外部暴露値から毒性影響の間に介在するプロセス

(Renwick, 2000)



Note – “CONCENTRATIONS” refers to the relevant active form delivered by the general circulation and may be the parent compound, or an active metabolite produced in another tissue and delivered to the target tissue/organ

**Processes involved in the conversion of an external dose into a toxic response (Renwick, 2000)**

図5 種差と個体差を説明する要素としての

トキシコキネチクス、トキシコダイナミックスデータ

**EXAMPLES OF DATA WHICH ARE SUITABLE FOR THE  
REPLACEMENT OF DEFAULT UNCERTAINTY FACTORS**

**INTER-SPECIES**

**KINETICS**

PHYSIOLOGICALLY BASED  
KINETIC PARAMETERS  
PB-PK MODELS

**DYNAMICS**

IN VITRO RESPONSE DATA  
ACTIVATION/CYTOPROTECTION  
IN VIVO PK-PD MODELLING

**INTER-INDIVIDUAL**

**KINETICS**

PHYSIOLOGICALLY BASED  
KINETIC PARAMETERS  
PB-PK MODELS

**DYNAMICS**

IN VITRO RESPONSE DATA  
ACTIVATION/CYTOPROTECTION  
IN VIVO PK-PD MODELLING

**Types of data which may be used to replace a default  
uncertainty factor (Renwick, 2000)**