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Food for Thought …
Uncertainty of Testing Methods – What Do We (Want to) Know?

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ALTEX 2013, 30

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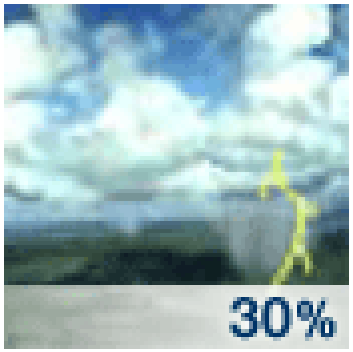

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A **chance of** showers and thunderstorms **after** 1pm. **Mostly** sunny, with a high **near** 91 that **feels like** 85. **Chance** of precipitation is **30%**... amounts **less than** a tenth of an inch, except **higher amounts possible** in thunderstorms

Is that good science?

Uncertainties of testing methods

What do we (want to) know?

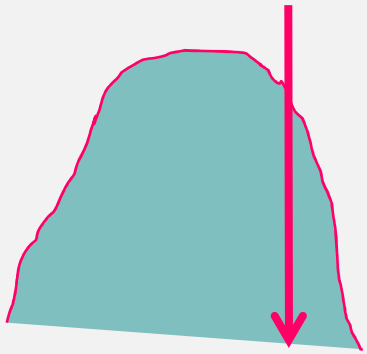
Interpretation of complex study results, statistics, p-values?

Relevance of endpoints analysed?

e.g. 95th percentile

High – low dose extrapolation?

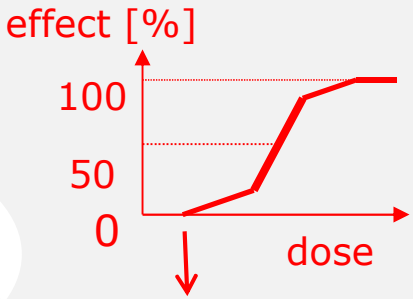
What is an adverse effect?



Route to route Extrapolation?

exposure
time

Ignorance?



animal-Δ-human
human-Δ-human
NOAEL/100

Exposure ⟷ **AEL** ← **NOAEL**

Margin of Safety

quality of data
severity of effect

Distance of dose levels?

Exposure scenario, model, parameter uncertainty

Relevance of inbred strain, sex, age?

Reproducibility of standard animal tests?

Mode of action relevant for humans?

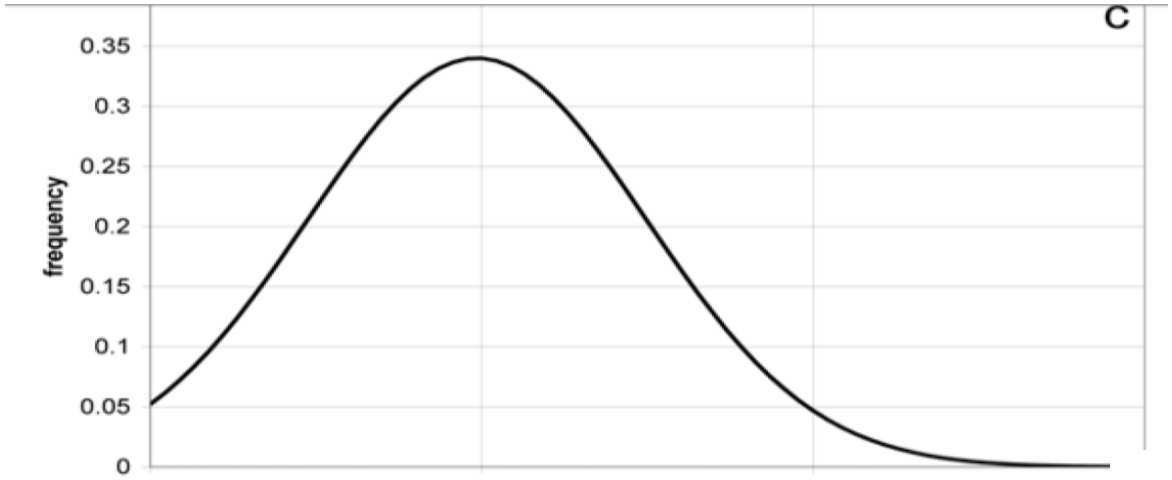
Animal to animal and strain to strain variability?

Mixture effects and reaction products in products/environment

Effects not detectable with standard animal tests?

Housing and care?

✓ **Probabilistic** animal-human inter-species assessment factors



e.g. rat –human GM = 5; P95 = 40

Bokkers et Slob 2007

✓ **Probabilistic** human-human intra-species assessment factors

e.g. for P95 of individuals: GM 1+3.82;GSD~4; P95=43.8; P99=117

Schneider et al. 2005

Reproducibility of animal test standard data?

sub-chronic and 2-generation studies; NOAELs range =10 ?
Janer at al. 2007

carcinogenicity; concordance ~ 57% ?
Gottmann et al. 2001

acute fish toxicity; 96 hours LC50 range ~ 3 log units ?
Hrovat et al. 2009

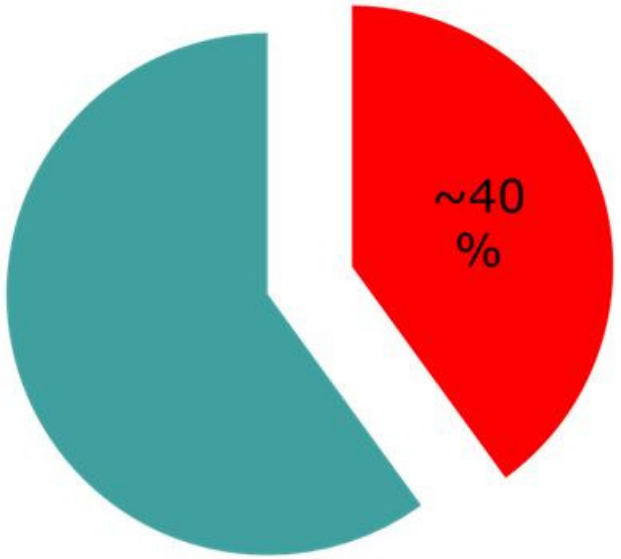
acute rodent toxicity
90% probability that 44% of substances
fall in two adjacent categories

Hoffmann et al. 2010

Complexity-uncertainty

e.g. for 23 of 57 substances:

different ADI derived by EFSA und JMPR



EFSA supporting publication 2013, EN413

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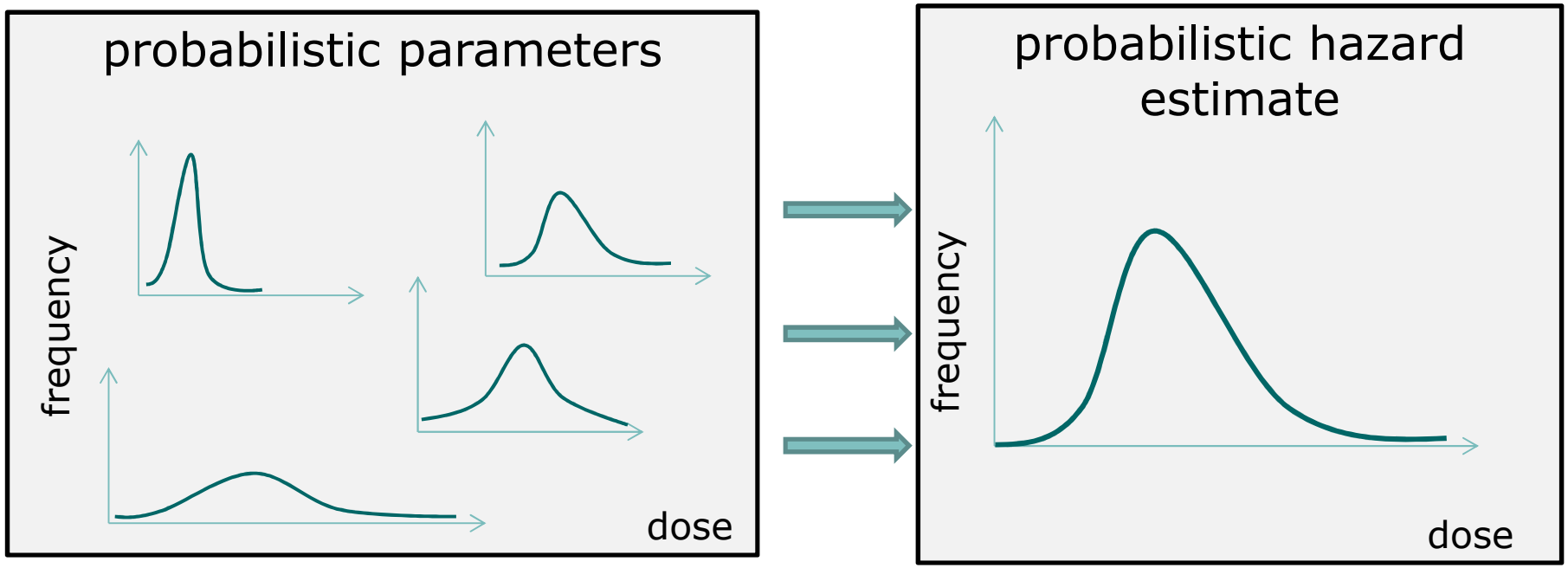
quantitatively?	
inter-& intra-species, time, no effect level	+++
inconsistent data, reproducibility	+
qualitatively?	
species-specific effects, exposure-route, nano-tox, ED, mixture tox, epigenetics, complexity...	+

How could be describe uncertainties?

A) Probabilistic description of quantify-able uncertainties



B) … amended with semi-quantitative or qualitative description of non-quantifyable uncertainties:

source	Influence on hazard estimate
e.g. subset of human population not respected	-
e.g. qualitative differences	-/+
…	…

How could be describe uncertainties?

e.g. AEL=daily exposure of human population causing, with a

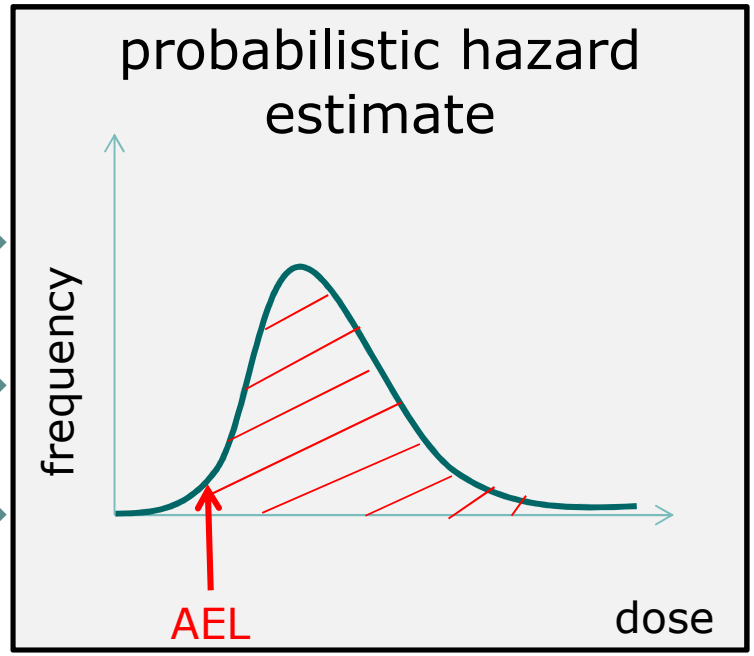
probability of 95% and considering the qualitative uncertainties xyz,

for just 1% of population

more than 5% reduction in RBC

residual hazard at any dose, also with "threshold-effects"!

tify-able uncertainties



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…	…

Let´s improve probabilistic knowledge and thinking in toxicology!

- **risk communication**
  - ✓ no 100% protection, whatever method

- **testing methods**
  - ✓ change, adaption to technical progress
  - ✓ correct use of in vivo reference data for validation

- **regulatory science**
  - ✓ risk management based on informative assessment
  - ✓ tool for precaution and sustainability discussion

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http://www.plasticseurope.org/plastics-and-the-precautionary-principle.aspx