Uncertainty analysis in human effects assessment

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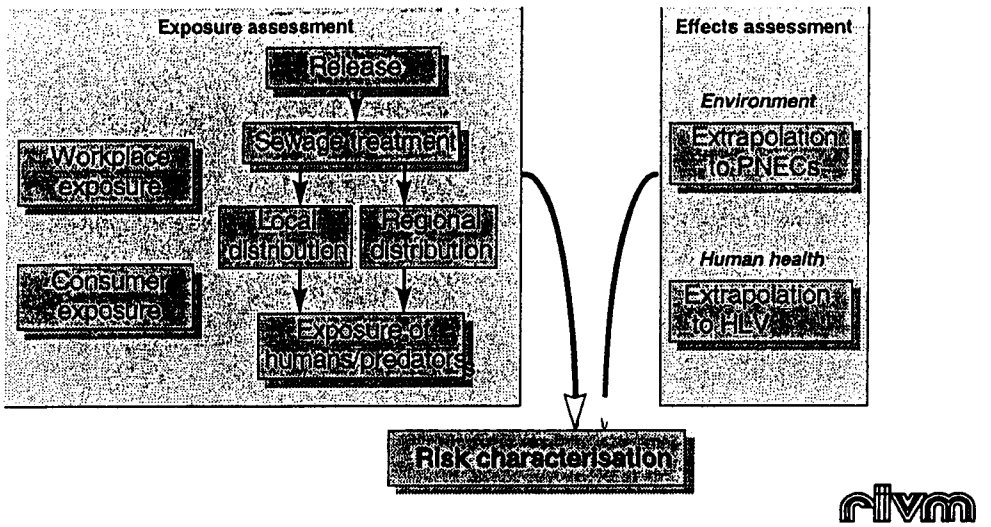
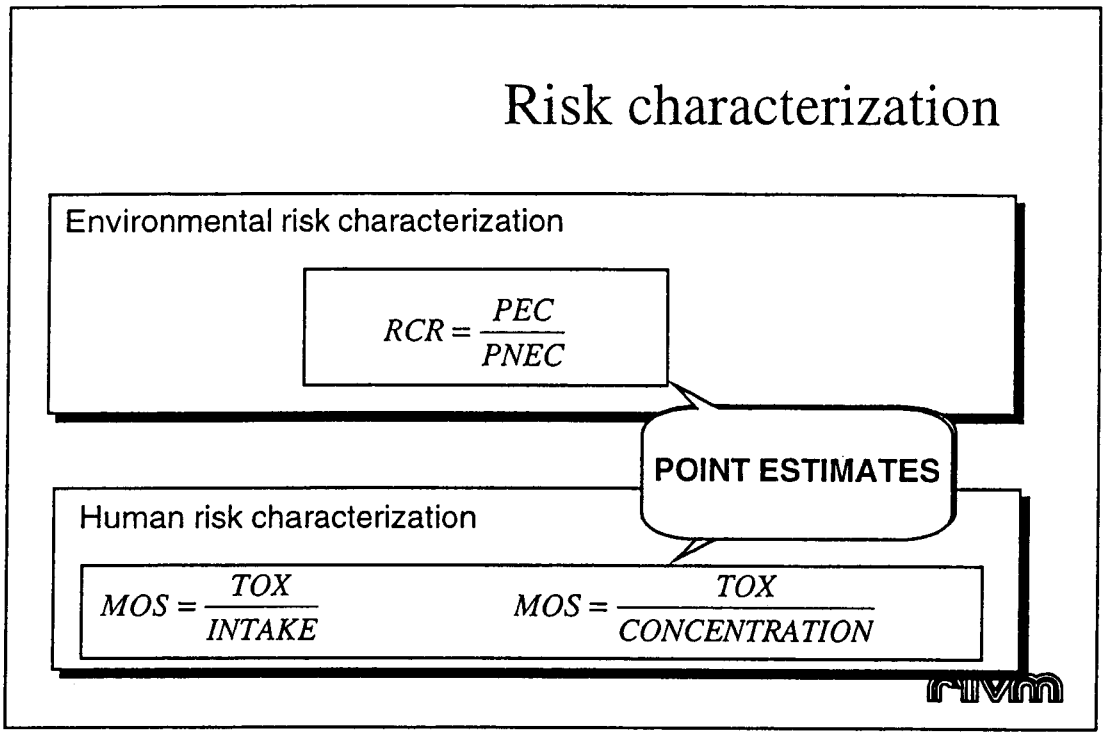
The general goal of this discussion paper is to contribute towards further harmonization of the human health risk assessment. First, it discusses the development of a formal, harmonized set of assessment factors. The status quo with regard to assessment factors is reviewed: i.e.. the type of factors to be identified, the range of values assigned as well as the presence or absence of a scientific basis for these values. Options are presented for a set of default values and probabilistic distributions for assessment factors based on the state of the art. Methods of combining default values or probabilistic distributions of assessment factors are also described. Secondly, the effect parameter, the No-Observed-Adverse-Effect Level (NOAEL), is discussed. This NOAEL as selected from the toxicological database may be a poor substitute for the unknown, true No-Adverse-Effect level (NAEL). New developments are presented with regard to the estimation of the NAEL. Finally, a strategy is proposed for implementation of the new developments into human health risk assessments.

This work is a collaboration between TNO (Nutrition and Food Research Institute) and RIVM (National Institute of Public Health and the Environment).

Risk assessment: an overview



Shown is the EU(European Union) Risk Assessment scheme for new and existing substances. The risk assessment methodology is laid out in Technical Guidance Documents and implemented in a PC-program EUSES European Union System for the Evaluation of Substances).



The measure of risk RCR (Risk Characterization Ratio) often is a point estimate: e.g.. PEC/PNEC for the environment (Predicted Environmental Concentration/Predicted No-Effect Concentration) and a MOS (Margin of Safety) for human populations.

TOX = Toxicity parameter such as the NOAEL (No-Observed-Adverse-Effect Level) of LOAEL (Lowest-Observed-Adverse-Effect Level)

INTAKE = a measured or predicted daily exposure dose which can be taken up via the skin or orally

The MOS is evaluated taking into account all uncertainties (intraspecies, interspecies, route-to-route, subchronic to chronic, LOAEL to NOAEL, inadequacies in database). At this point in time there is no harmonization at international/EU level with regard to quantification of uncertainties(extrapolation/assessment factors).

Disadvantages of point estimates

(Thompson & Graham, Hum. Ecol. Risk Assessm. 2: 1008-1034)

1. It is generally not possible to determine precisely where a point estimate lies in the range of possibilities.
2. Use of point estimates may mislead risk managers by producing falsely precise estimates.
3. Use of point estimates may lead to non-optimal decisions.
4. Use of point estimates eliminates the incentives for conducting research that might reduce uncertainty.
5. Use of point estimates ignores variability in the population and thus precludes discussion and consideration of inequity in the distribution of risk in the exposed population.

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This sheet highlights disadvantages of the use of point estimates for risk characterization.

Uncertainty =

1. Uncertainty due to natural variability in time or space. Uncertainty caused by variability cannot be reduced by further research.
2. Uncertainty due to ignorance.
3. Uncertainty due to error.
4. Uncertainty due to choices

Advantages of probabilistic RA

Burmaster, Hum.Ecol. Risk Assess. 2:25-29

The probabilistic framework of risk (Burmaster, 1996):

1. Honours the definition of risk.
2. Includes all information available about uncertainty and variability inherent in the assessment.
3. Reveals the compounded conservatism in the deterministic framework. Risk managers and the general public can see the full range of possibilities.
4. Reveals the nature and the extent of professional judgement in a risk assessment.
5. Can indicate the main sources of uncertainty in the final result, thereby offering an efficient way to refine the assessment.
6. Re-establishes the now blurred boundary between risk assessment and risk management. Too often risk assessors use exaggerated point values so the risk manager can ignore the complexities and cost-effectiveness of measures. Allows the risk manager to make a trade-off between the costs of type I errors (rejecting a harmless substance) and type II errors (accepting a harmful substance).
7. Ultimately saves money as the results are generally less conservative, yet fully protective.
8. Is closer to the truth. The output is a distribution of potential risk. Getting closer to the truth is preferable to the world of fiction created when distributions are replaced by single numbers.

And additionally:

9. Allows for comparing chemicals with different degrees of uncertainty.
10. Acts to reward the input of measured data. Even when additional data lead to higher PEC/PNEC ratios, their uncertainty may be lower which may therefore result in an assessment with greater confidence.

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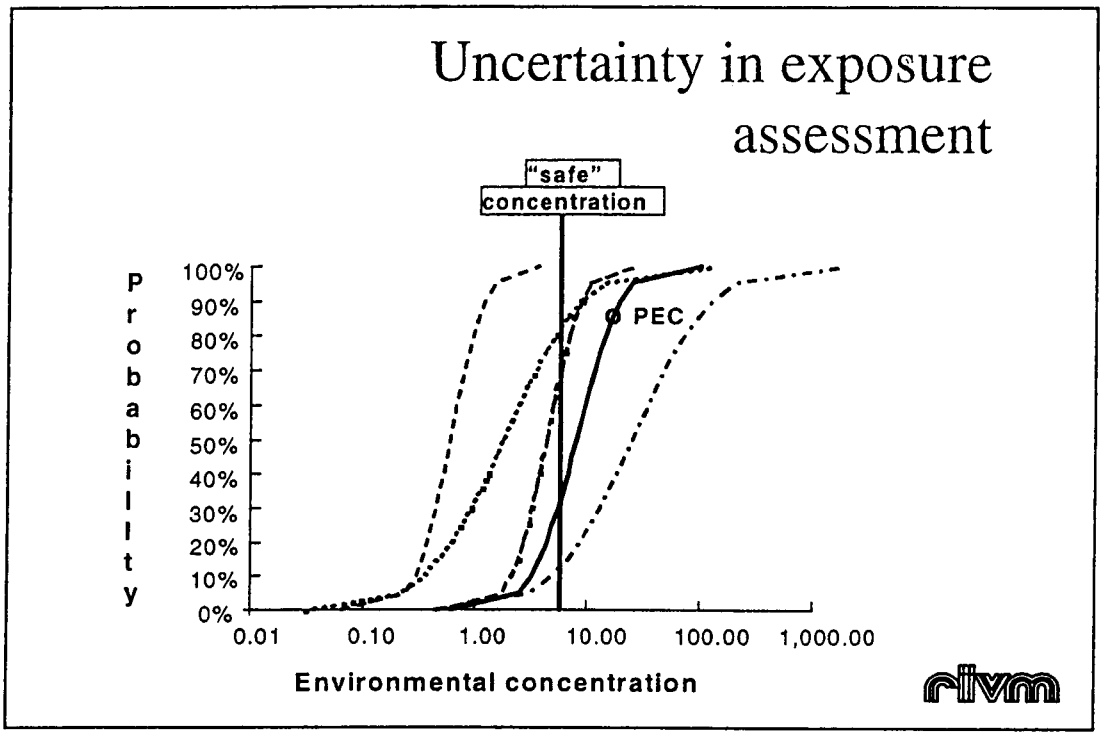
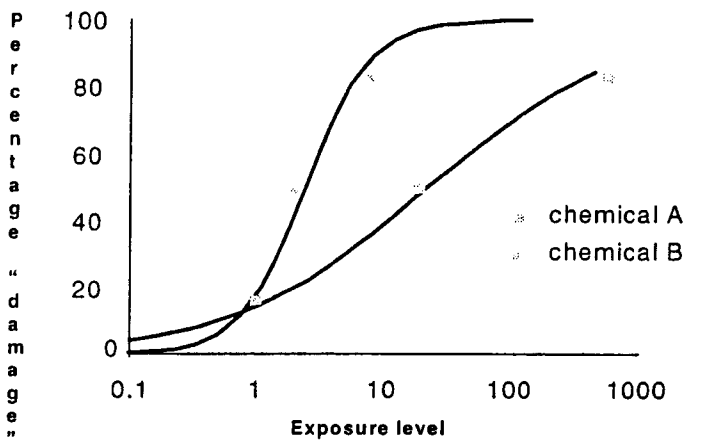
This sheet highlights the advantages of probabilistic risk assessment.



Example od uncertainty analysis in exposure assessment. The PEC is the point estimate of exposure. Alternatively this PEC could be a predicted dose.The PEC shown is on the "unsafe" side. Due to uncertainty there is a 30% probability that the PEC is "safe". Environmental variability is represented by alternative distributions.

Uncertainty in effects assessment



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We cannot usually estimate a risk because impacts are not properly defined. Currently a no-effect level is estimated by applying assessment factors (10 - 1000) on the results of laboratory tests. The impact of exceedance of this safe level remains unknown. The diagram shows the desired result of risk assessment as a hypothetical fraction of the population (humans) or species (environment) which is exposed above their no-effect level. This result can be achieved by taking uncertainty and variability into account as will be discussed further in this presentation.

Disadvantages

Table 1 Disadvantages or costs of probabilistic risk assessment.

Explanations for the limited use of probabilistic risk assessment (Thompson & Graham, 1996):

1. Lack of (EPA) guidance.
2. The existence of established point estimates for some inputs (e.g., the Exposure Factors Handbook).
3. Inexperience with using probabilistic results.
4. Increased legal challenge.
5. Mistrust and suspicion. Risk managers may suspect that outcome will favour industry (perhaps just by delaying decisions by endless discussion) or may be worried that the assessment contains hidden assumptions or hard-to-detect errors.
6. Difficulties in risk communication.

Costs of probabilistic risk assessment (Burmaster, 1996):

1. Probabilistic methods need more measured data to estimate the variability or uncertainty in a stochastic variable.
2. Probabilistic methods need many input distributions.
3. To work in the probabilistic framework, risk assessors, toxicologists and regulators need to learn new skills. It takes serious study to learn how to develop, manipulate, and interpret stochastic variables and equations.
4. Risk management decisions are harder to make. The risk manager must consider the character, location, and spread of the whole distribution of risk.
5. Risk communication hinges on the continued development of visual and graphical tools to convey the results.
6. Risk assessors must make sure that guidance manuals do not impede the growth and advancement of their discipline.

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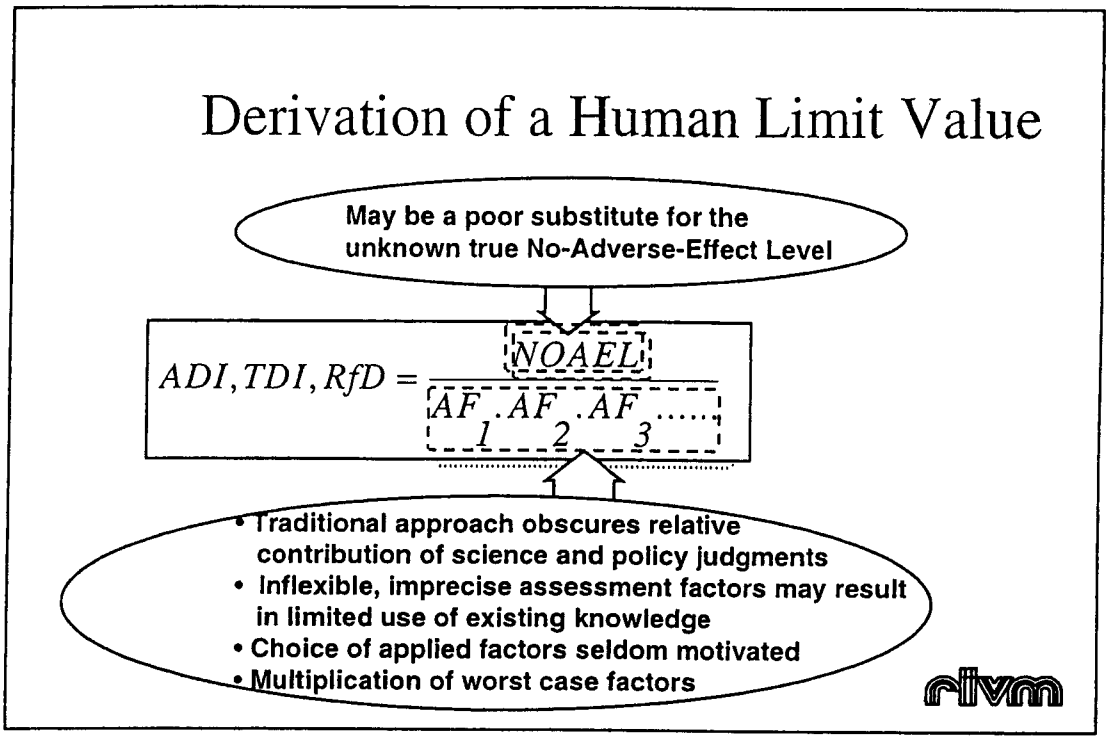
This sheet summarize disadvantages or costs of probabilistic risk assessment.

Risk assessors and managers should discuss advantages and disadvantages to come to a decision on implementation of such methods.It must be demonstrated how decision making can benefit from the extra effort needed to perform probabilistic risk assessment.



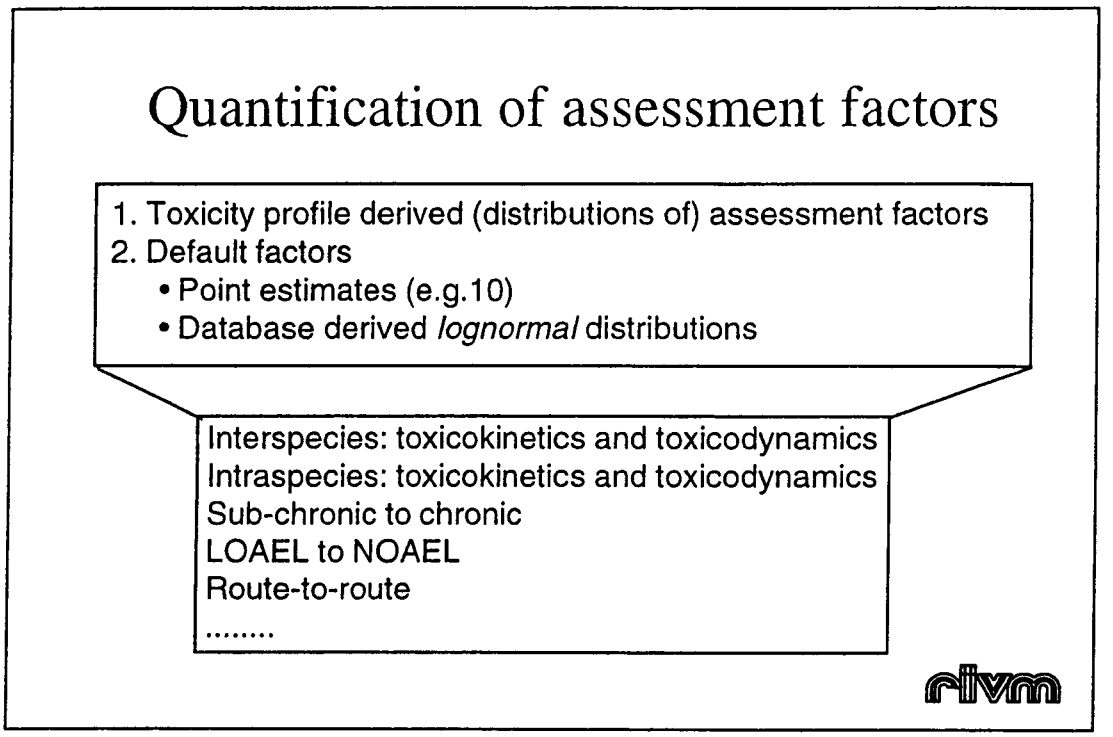
The classical derivation of Human Limit Values (HLVs) such as Acceptable Daily Intakes (ADI), Tolerable Daily Intakes (TDI) and Reference Doses or Concentrations (RfD, RfC) has several shortcomings.

Assessment factors

Few approaches are based on scientific data, but most methods basically rely on the arbitrary imprecise 100-fold factor used to derive the Acceptable Daily Intake (ADI).

The NOAEL

The NOAEL selected from the toxicological database may be a poor substitute for the unknown, true NAEL..



Toxicity derived (distributions of) assessment factors are always preferred above default factors.

With regard to default factors it is recommended to investigate the probabilistic nature of assessment factorsby trying to describe their entire distribution.

Lognormality is assumed for these distributions (based on empirical evidence and on theoretical grounds)

Interspecies factor: scaling

$$Y = aW^n$$

Y = physiological/toxicological characteristic
a = constant
W = body size (weight, surface area)
n = 1 (BW) or 0.75 (caloric demand), 0.67 (surface area)

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For extrapolation of data from animal studies to humans account should be taken of species-specific differences between animals and humans. These interspecies differences can be divided in differences in metabolic size and remaining species-specific differences. To account for differences in metabolic size three methods are used in practice: extrapolation based on body weight, surface area, and caloric demand. These methods can be described by an allometric equation: for that purpose body weight has to be raised to the power 1, 0.67, and 0.75, respectively.

For inhalation NOAELs for systemic effects no correction is made for differences in metabolic size, because extrapolation is already based on toxicological equivalence of a concentration of a substance in the air; animals and humans breath at a rate depending on their caloric requirements