



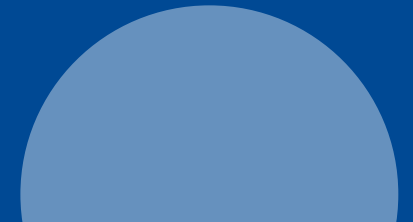
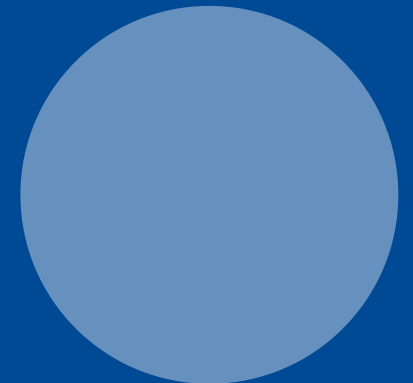
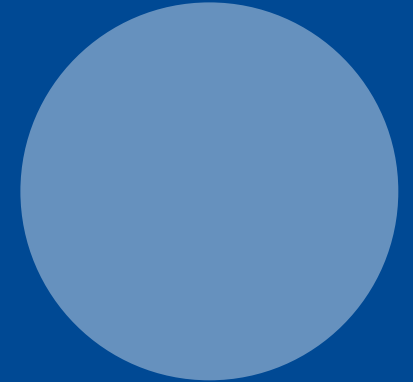
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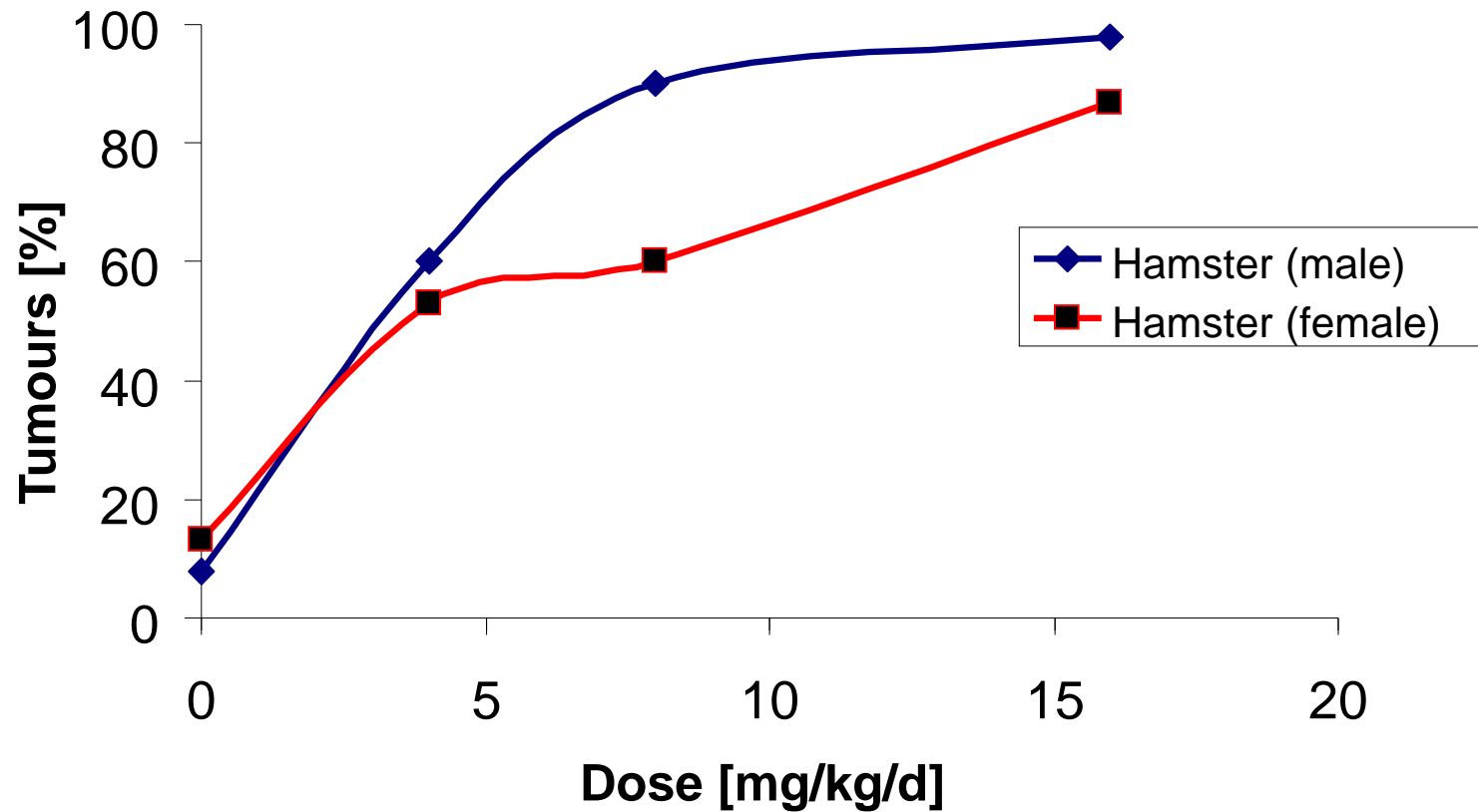
# Different Approaches to the Deriving of Occupational Exposure Limits for Carcinogenic Substances

**Eberhard Nies**

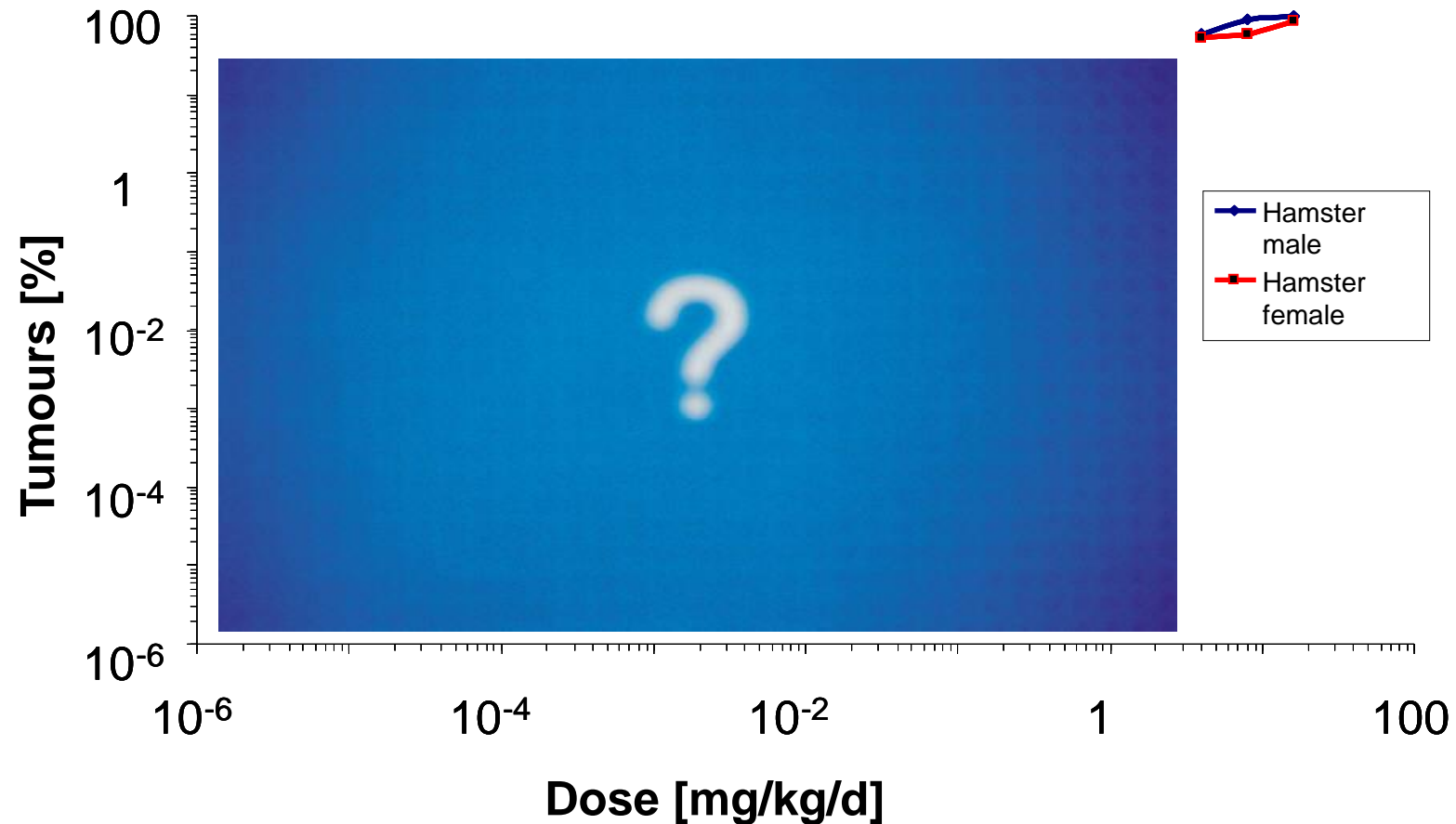
Institute for Occupational Safety and Health  
of the German Social Accident Insurance (IFA)



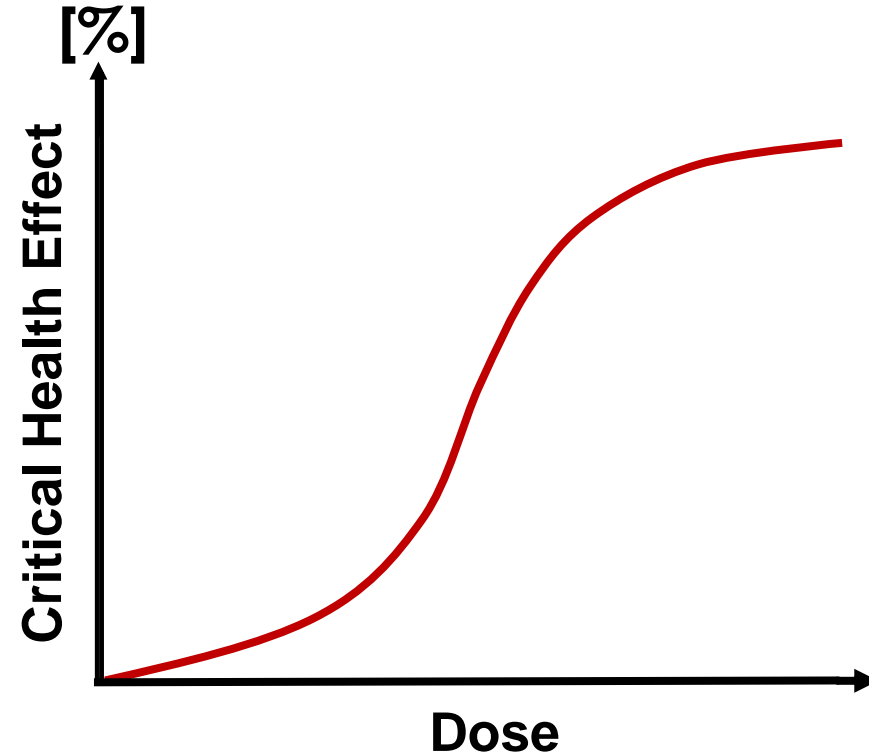
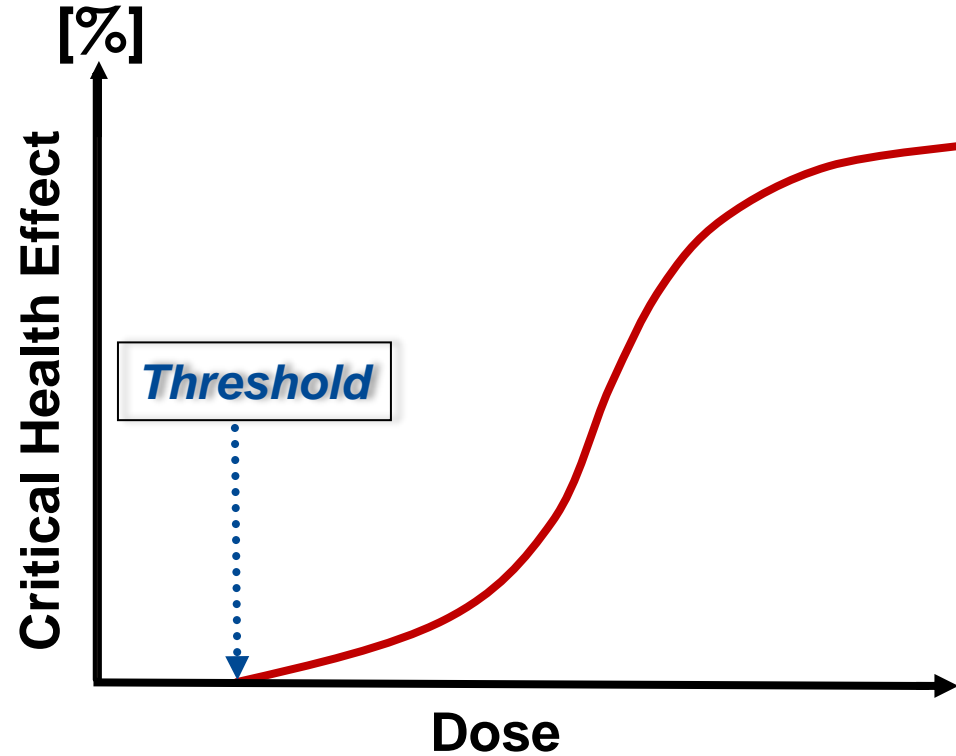
# Hexachlorobenzene: dose-effect diagram



# Carcinogens: risk extrapolation to low-dose region



## Toxicological threshold or risk continuum?

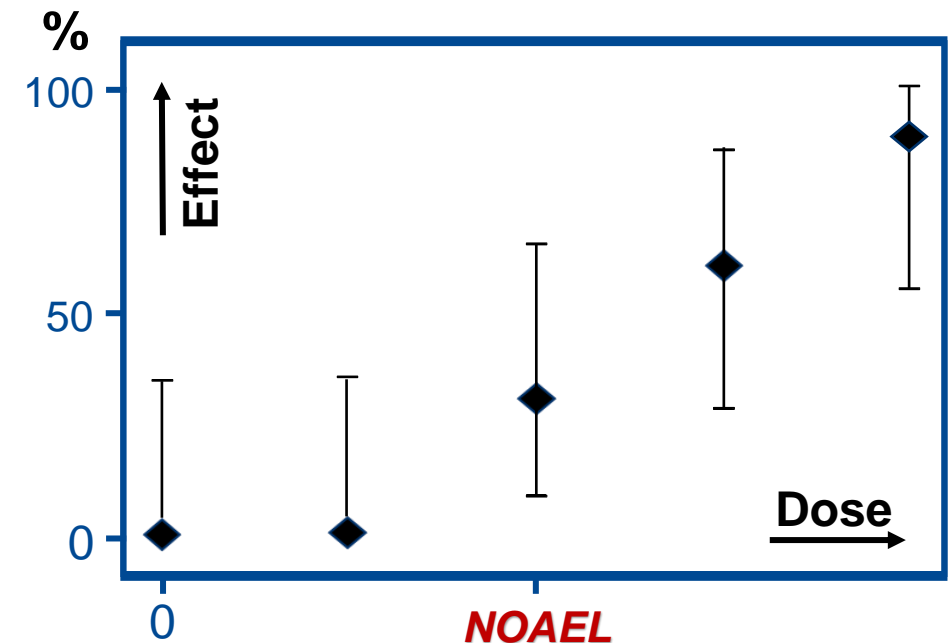


## Threshold carcinogens: NOAEL as point of departure

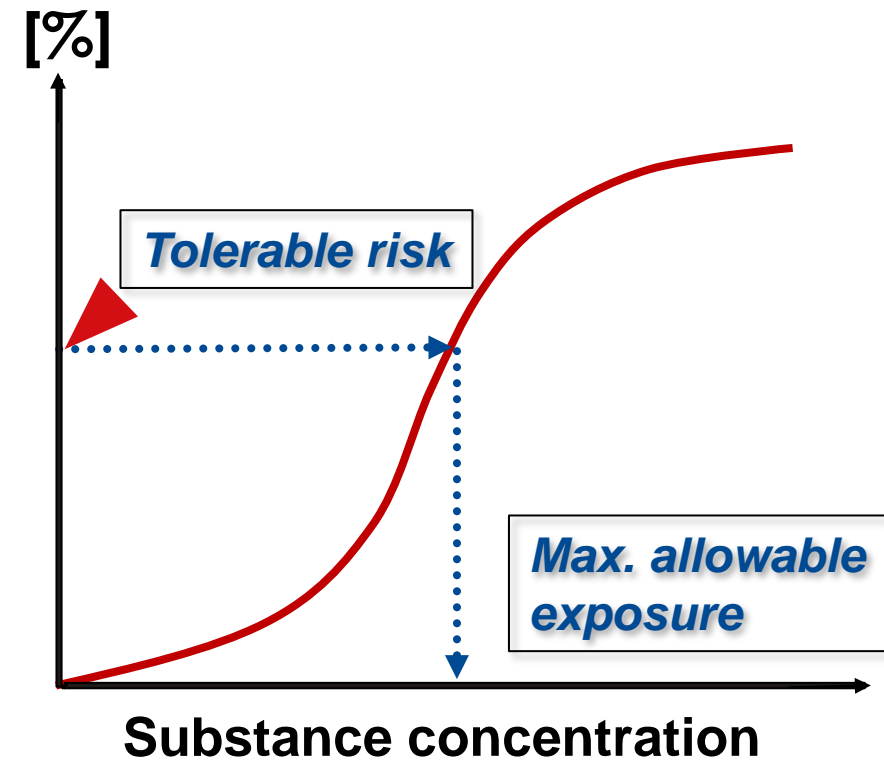
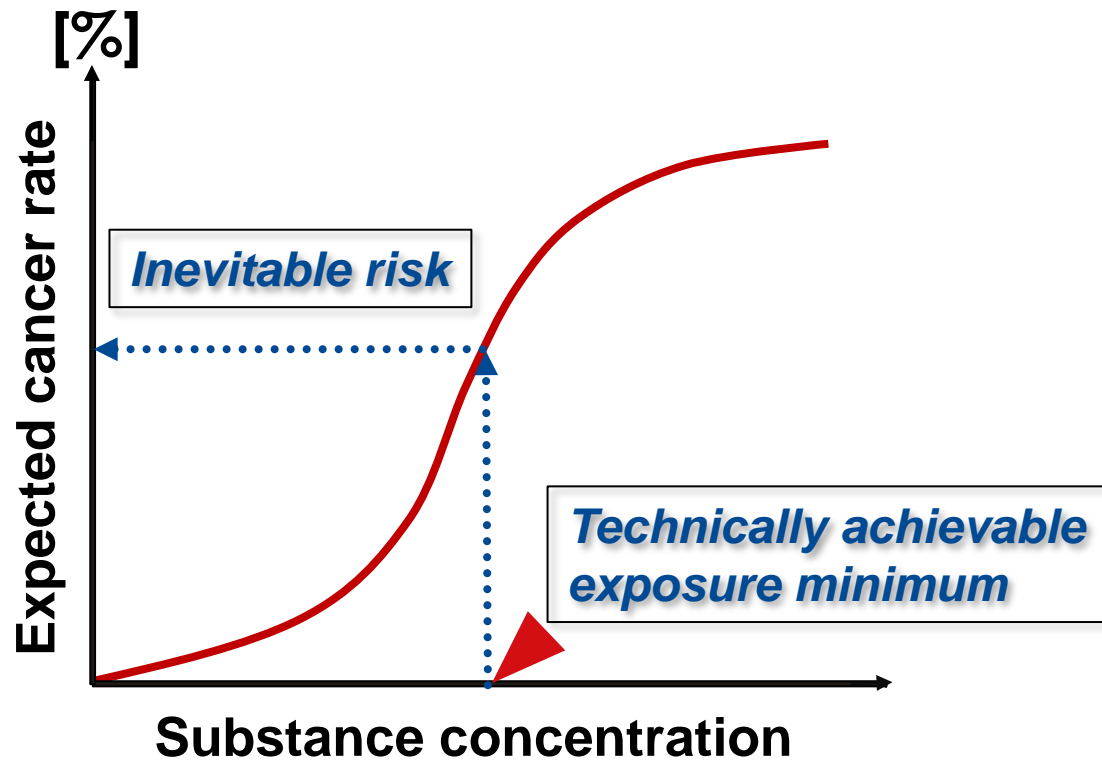
- NOAEL (No Observed Adverse Effect Level)  
= the level of exposure at which there is **no statistically significant increase** in the frequency or severity of any adverse health effects in comparison to a control group

$$OEL = \frac{NOAEL}{UF_1 * UF_2 * UF_3 * \dots * UF_n * MF}$$

- Uncertainty Factors (UF)
  - Interspecies differences/intraspecies differences
  - Differences in duration of exposure
  - ...
- Modifying Factor (MF)
  - Database quality, severity of health effect, ...



# Non-threshold carcinogens: risk-based approaches



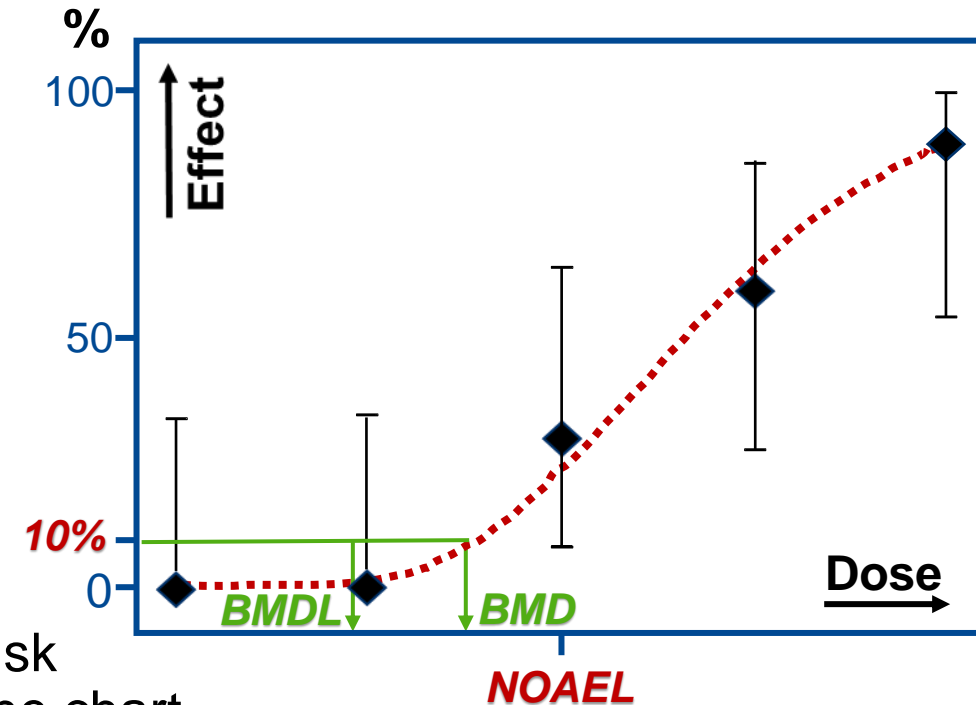
## SCOEL's categories (Bolt & Huici-Montagud, 2008)

- **Non-genotoxic carcinogens and non-DNA-reactive carcinogens:**
  - True (“perfect”) threshold, associated with a clearly substantiated NOAEL
- **Non-threshold genotoxic carcinogens:**
  - Linear non-threshold (LNT) model
  - Risk management based on ALARA principle, technical feasibility, or other socio-political considerations
- **Genotoxic carcinogens for which the existence of a threshold cannot be sufficiently supported:**
  - LNT model as a default assumption, based on the scientific uncertainty
- **Genotoxic carcinogens with a practical threshold** (supported by mode of action or toxicokinetics):
  - Health-based exposure limit based on an established NOAEL (no observed adverse effect level)

## Margin of Exposure (EFSA etc.)

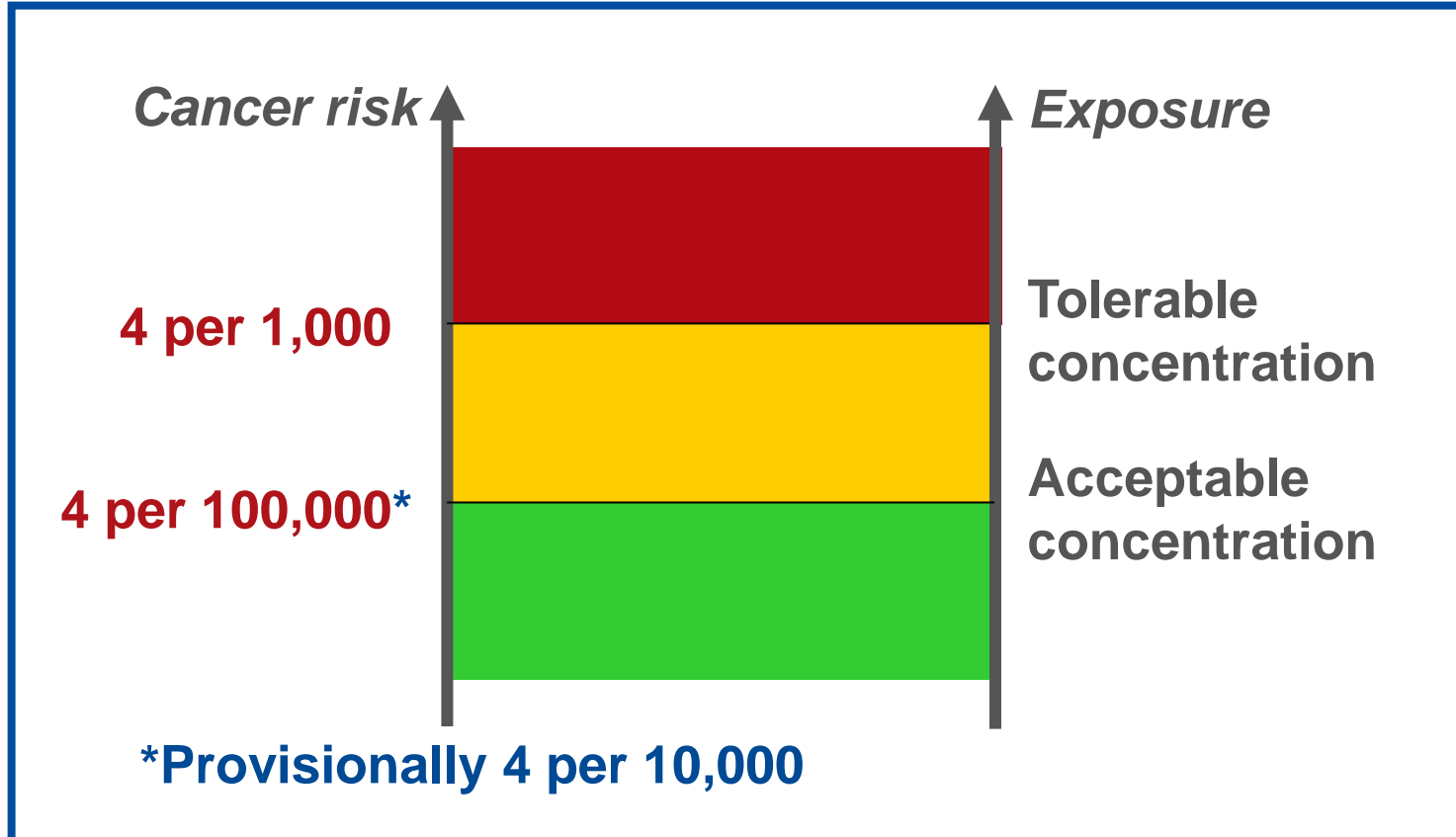
### General Procedure:

- Model the dose-response curve by a special “Benchmark Dose” (BMD) software application (U.S. EPA, RIVM)
  - Select a response of (usually) 10% additional cancer risk and determine the corresponding dose ( $BMD_{10}$ ) from the chart
  - As a point of departure use this benchmark dose’s lower bound ( $BMDL_{10}$ ), describing the lower (preferably 95%) one-sided confidence limit of the  $BMD_{10}$
  - Divide the  $BMDL_{10}$  by at least 10,000 (i.e. “margin of exposure” =  $BMDL_{10}/10,000$ )
- The resulting dose is considered to be of low concern from a public health point of view.





## German “Traffic Light Model”



- Similar approaches are in place e.g. in the Netherlands and Poland

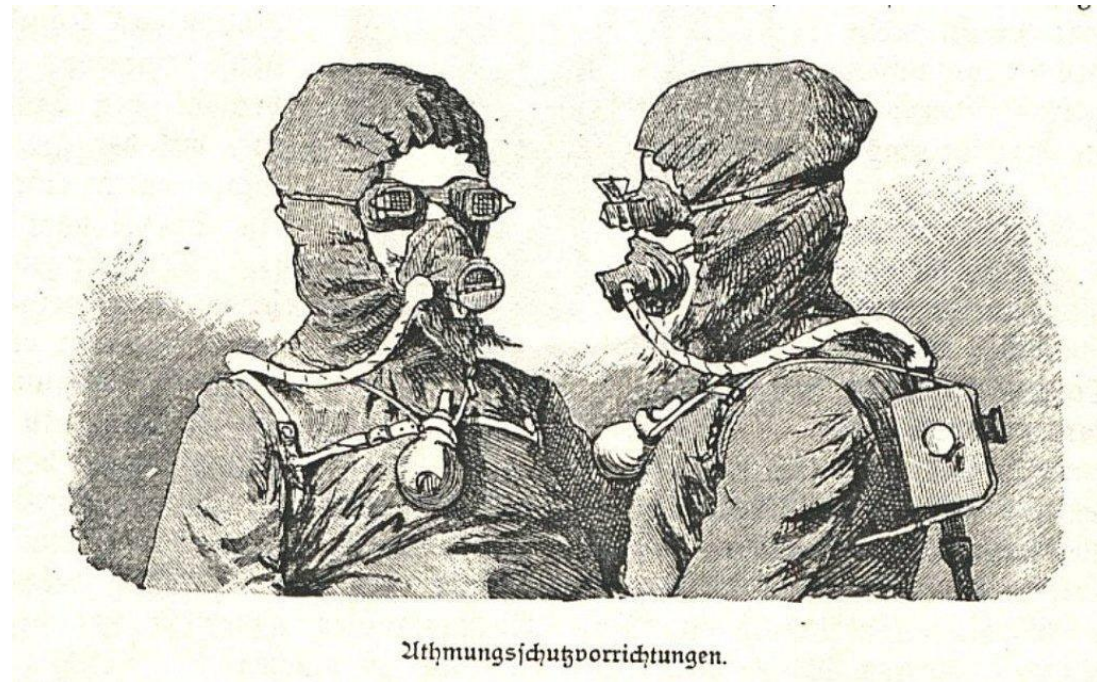
## Measures according to the German Technical Rules

- The “Traffic Light Model” is linked to a concept of tiered control measures for **minimal**, **medium** or **high** risks.

These measures include:

- Administration
- Technology
- Organisation
- Occupational medicine
- Substitution

<https://www.baua.de/EN/Service/Legislative-texts-and-technical-rules/Rules/TRGS/TRGS-910.html>





## Bad example: Derived Minimal Effect Levels (DMEL)

- “For those human effects and those environmental spheres for which it was not possible to determine a DNEL or a PNEC [limit values based on the threshold concept], a qualitative assessment of the likelihood that effects are avoided when implementing the exposure scenario shall be carried out” (EU REACH Regulation, Annex I 6.5)
- The registrants of chemicals are advised by guidance documents to establish DMEL (Derived Minimal Effect Levels). These should also be stated in the chemical safety report and the safety data sheet.
- “... the decision point for 'acceptable' lifetime (i.e., a working life of 40 years) cancer risk levels used for **workers** are generally around  $10^{-5}$  but higher or lower levels have been considered to be tolerable under certain circumstances” (ECHA Guidance R.8)
- It is left to the manufacturers/distributors themselves to decide upon their modelling methodology and what risk they intend to consider acceptable and not even compulsory to indicate the cancer risk associated with the reported DMEL.

## Toxicology secondary: European “SHEcan” Project (2009-2011)

- OEL values for a series of substances were either proposed by DG Employment or identified as being “typical” values in EU Member States.
  - Health costs and benefits were calculated for no intervention and separately for the introduction of up to three possible OELs.
  - Compliance costs were estimated for the intervention scenarios and set against the benefits.
- The majority of the EU Binding Occupational Exposure Limit Values for carcinogens are based on these considerations.

**SHEcan** Socioeconomic, health and environmental  
impact of possible amendments to the  
EU Carcinogens and Mutagens Directive

## Philosophical excursus

- **Utilitarian ethics:**

*“It is the greatest happiness of the greatest number that is the measure of right and wrong.” (J. Bentham)*

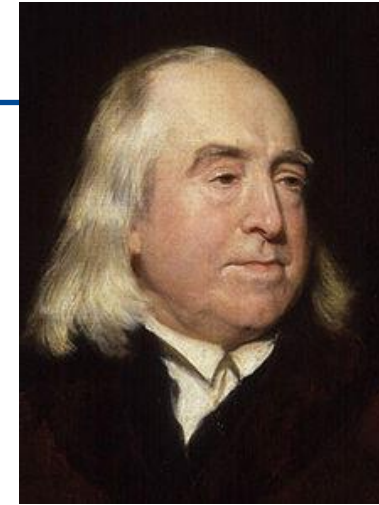
- Years of life lost, suffering caused by disease are to be converted into a monetary value and weighed against exposure reduction measures
- Different treatment of different collectives

- **Deontological ethics:**

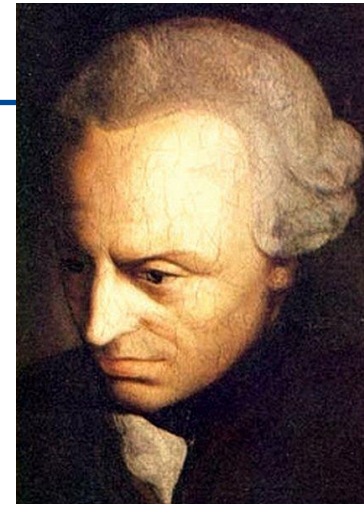
*“Act in such a way that you always use humankind, both in your person and in the person of anyone else, at the same time as an end, never as a means.” (I. Kant)*

- The right to life means that no one may be killed, not that a situation should be optimised for the survival of the greatest number of people.
- Universal Declaration of Human Rights (UN):  
*“All human beings are born free and equal in dignity and rights.”*
- Deontological principles apply which should constrain cost-benefit considerations.

Wikipedia Commons



**Bentham**



**Kant**

# Take-home messages

- For carcinogens without (known) effect threshold toxicologists may derive dose-response relationships – provided a sufficient data base exists.
- In the interests of comparability and reproducibility the methodology of modelling the respective dose-response function should be clearly specified and made transparent.
- The decision upon an “acceptable” cancer risk level should be reached by a socio-political consensus.
- Utilitarian considerations should be strictly constrained by the ethical principle of individual human dignity, which is compromised when the welfare of one person is put at risk in the interest of others.





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**Thank you  
for your attention.**

