Descriptive vs Quantitative Risk Assessment: Is there a Best practice?

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Standard setting (workplace and environment): Discussions of ionising radiation vs. chemicals

- European Academy Bad Neuenahr-Ahrweiler, 1996-1999
  “Umweltstandards“
  (Streffer, Bücker, Cansier, Cansier, Gethmann, Guderian, Hanekamp, Henschler, Pöch, Rehbinder, Renn, Slesina, Wuttke, Springer, 1999)

- European Academy Bad Neuenahr-Ahrweiler, 2001-2003
  „Low Dose Exposures in the Environment“

- Main differences between radiation and toxicology:
  (i) Exposure assessment at target tissue, and
  (ii) Metabolic activation/inactivation in toxicology!

- Mechanisms/modes of action of key importance
Discussions of Thresholds in Genetic Toxicity Within the European Scientific Community

- **ECETOC-EEMS Symposium on Dose-Response and Threshold Mediated Mechanisms in Mutagenesis**
  Salzburg, Sept. 1998

- **EUROTOX Speciality Section Carcinogenesis, 2001-2005**
  (Toxicol Lett 151:29-41, 2004; Toxicol Sci 81:3-6, 2004; Arh Hig Rada Toksikol 56:165-173, 2005)

- **European Academy Bad Neuenahr-Ahrweiler, 2001-2003**

- **Leading to SCOEL Discussions** → SCOEL /INF/739A (May 2006)
  (Bolt & Huici-Montagud, Arch Toxicol 82: 61-64, 2008)

*Mechanisms of action should be considered in a much better way!*
The classical paradigm (since the 1970s)

*Based on epidemiological and/or experimental data on a given chemical:*

- Categorisation as carcinogenic in **humans** (cat. 1) or **animals** (cat. 2), may be carcinogenic (cat. 3), non-carcinogenic/no data („cat. 0“)

- Cat.1/cat.2 compounds: no determination of NOAEL (No Observed Adverse Effect Level) -> **descriptive element**

- **Quantitative risk assessment** (by regulatory agencies)

- Cat. 3 compounds: strategy varies between different official bodies

- Non-carcinogenic compounds: NOAEL -> determination of safe exposure limits
Indirect Genotoxicity Mechanisms and Possible Criteria for Threshold Effects
(Discussions since 2000)

- Induction of aneuploidy
- Topoisomerase II poisons
- Oxidative stress
- Inhibition of DNA synthesis
- Steep dose-effect curve, cytotoxicity involved
- Endogenous compounds (?)
  (on SCOEL agenda: ethylene oxide)
- Clastogens (?)

Kirsch-Volders et. al: Mutation Res. 464:3-11, 2000
Madle et. al: Mutation Res. 464:117-121, 2000

„The dose-response relationship for a number of such agents is generally accepted to show a threshold, however, the degree of acceptance of the threshold effect differs in different EU regulatory systems.“
**Dose-Effect Relations in the Low Dose Range and Risk Evaluation**

*(Concept adopted by SCOEL - see Archives of Toxicology 82: 61-64, 2008)*

- **Chemical carcinogen**, causing tumours in humans and/or experimental animals
  - **Genotoxic**
    - DNA reactive, causing mutations
    - Clearly DNA-reactive & initiating
      - **A**: No threshold, LNT model to apply
    - Borderline cases
      - **B**: Situation not clear → LNT as default
      - **C**: Practical/apparent threshold likely
    - Weak genotoxin, secondary mechanisms important
      - **D**: Perfect/statistical threshold likely
  - **Non-genotoxic**
    - Genotoxicity only on chromosome level (e.g. spindle, topoisomerase)
    - Numerical risk assessment, → risk management procedures
    - NOAEL → health-based exposure limits
Results of SCOEL Discussions (2009)

A. No threshold, LNT (Linear Non-Threshold) model to apply:
- vinyl chloride / vinyl bromide (risk assessment)
- dimethyl / diethyl sulfate
- 1,3-butadiene (risk assessment)

B. LNT as default assumption:
- acrylonitrile
- benzene (provisional assignment)
- naphthalene
- hexavalent chromium
- wood dust
- o-anisidine; 2,6-dimethylaniline (insuff. data)
- naphthalene

C. Practical/apparent threshold:
- formaldehyde
- vinyl acetate
- nitrobenzene
- pyridine
- silica
- lead (provisional OEL); lead chromate
- TRI
- DCM
- Ni (being discussed)
- glyceryl trinitrate (being discussed)

D. Perfect/statistical threshold:
- carbon tetrachloride
- chloroform

Distinction between B and C is most important!
1973: Vinyl chloride disease in PVC workers

Vinyl chloride (regarded as non-toxic)

Recommended for anaesthesia

Carcinogenic
In humans

Liver/spleen changes

Haemangio-sarcoma

(Haemangio-endothelioma)

Acro-osteolysis
Case: Vinyl chloride

- Clearly carcinogenic in humans and in rodents (cat.1)

- SCOEL: Quantitative risk assessment performed (SCOEL group A)
  
  (SCOEL//SUM/109, Nov 2004)

<table>
<thead>
<tr>
<th>Exposure for working lifetime</th>
<th>Derived angiosarcoma risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ppm</td>
<td>3 x 10^{-4}</td>
</tr>
<tr>
<td>2 ppm</td>
<td>6 x 10^{-4}</td>
</tr>
<tr>
<td>3 ppm</td>
<td>9 x 10^{-4}</td>
</tr>
</tbody>
</table>
Case: Acrylonitrile, B or C?

- Carcinogenic to rats (oral and inhalation studies)
- Weakly mutagenic in vitro, but mutagenic epoxide metabolite

Argumentations for brain tumours discussed by SCOEL:

- Absence of DNA adducts in brain
- Oxidative DNA damage in astrocytes in vitro
- Reversible loss of gap junction communication in exposed astrocytes
- Dose-response curve sublinear
- Genotoxicity in vivo not straightforward

But: multi-organ carcinogen
[brain, spinal cord, Zymbal gland, GI tract (upon oral dosing), mammary gland]

High acute toxicity, due to cyanide formation!

Group B; no health-based OEL
**Case: Acrylamide, B or C?**

- Carcinogenic to rats (*similar to acrylonitrile*)
- Weakly mutagenic in vitro, but mutagenic epoxide metabolite

**Argumentations discussed by SCOEL:**

*Similar to acrylonitrile*: multi-organ carcinogen  
[brain, mammary gland, mesotheliomas]

High neurotoxicity!

**Group B; no health-based OEL**

But: *derivation of an OEL and BLV to prevent neurotoxicity!*
Case: Formaldehyde, B oder C?

- Classical case, nasal tumours in rats
- Sublinear dose-response curve
- Cytotoxicity as relevant influencing factor
- IARC (2005): Sufficient evidence of human nasopharyngeal carcinomas

Argumentations by SCOEL (2005-2007):

- Cell proliferation/irritation necessary for tumour formation
- No straightforward evidence for systemic effects

Group C: OEL of 0.2 ppm recommended
Case: Vinyl Acetate (SCOEL 2005/2006):

- Old TLV value of 10 ppm, based on avoidance of irritancy
- Local tumors at the site of contact with the organism
- No systemic bioavailability upon inhalation!
Case Discussion: Vinyl Acetate, B oder C?

- Local carcinogenesis upon inhalation and drinking water application
- Locally hydrolysed to acetaldehyde and acetic acid
- Local genotoxicity of acetaldehyde plus cytotoxicity due to acidification of cells (M. Bogdanffy, EUROTOX Budapest 2002)

Argumentations by SCOEL (2005)

- Cell proliferation/irritation necessary for tumour formation
- No straightforward evidence for systemic effects

Group C: OEL of 5 ppm recommended
**Case: Trichlorethylene, B oder C?**

- Renal cell carcinomas in humans exposed to very high peak concentrations over several years (studies in Germany and France)
- $\beta$-Lyase pathway involved in local bioactivation
- Specific VHL mutation patterns in highly exposed persons
- Nephrotoxicity involved ($\alpha_1$-microglobulin, GST$\alpha$, other markers)

**SCOEL Recommendation** *(for public consultation)*

*Group C: Proposal of an OEL of 10 ppm based on avoidance of nephrotoxicity*

*Toxicol. Lett. 140-141: 43-51, 2003*
Case: Methylene Chloride

- Cancers in mice, not in rats or hamsters
- Large species differences in GSH-dependent metabolism (GSTT1-1)
- Risk estimate: 100 ppm leads to $4.9 \times 10^{-5}$ cancer risk in humans
- Recommended OEL (100 ppm) leads to 3% CO-Hb

Group C
Summary 1: SCOEL strategy for carcinogens

- The scientific development allows to identify carcinogens with a threshold-type mode of action. For such compounds health based OELs (and BLVs, where appropriate) can be derived.

- When derivation of a health-based OEL/BLV is not possible, SCOEL assesses the quantitative cancer risk, whenever data are sufficient.

- When data are not sufficient for a risk assessment, SCOEL gives recommendations on possible strategies for risk minimisation, if possible.
Summary 2: Descriptive vs. quantitative risk assessment

• Quantitative risk assessment:
  For genotoxic carcinogens without threshold mechanism (group A)

• Quantitative risk assessment based on epidemiological and experimental data, when possible. For extrapolations across species: PB-PK models important!

• No sufficient data for quantitative risk assessment:
  Description and narrative approach

• Carcinogens with threshold mechanism:
  NOAEL and proposal of a health-based OEL