Occupational Exposure Limits

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The Positioning of Advisory Bodies

- The general discourse and interplays leading to OEL/BLV regulations are similar at national and EU levels:

  - Political authorities
  - Legislation on occupational standards
  - Scientific experts
  - Social partners: employers/industry, trade unions
Chemical disasters with long-term influence on policy and legislation on chemicals in the EU

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>Event Description</th>
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</thead>
<tbody>
<tr>
<td>1974</td>
<td>Flixborough/UK</td>
<td>Cyclohexane explosion: 28 deaths, 89 wounded</td>
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<tr>
<td>1976</td>
<td>Seveso/Italy</td>
<td>TCDD disaster</td>
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<tr>
<td>1984</td>
<td>Bhopal/India</td>
<td>Methylisocyanate disaster</td>
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<tr>
<td>1986</td>
<td>Schweizerhalle/CH</td>
<td>Environmental disaster; Rhine pollution</td>
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<tr>
<td>1993</td>
<td>Frankfurt-Höchst/Deutschland</td>
<td>Accidents: communication disaster</td>
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<tr>
<td>2000</td>
<td>Baia Mare/Romania</td>
<td>Cyanide (50-100 t) in Tisa and Danube</td>
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<tr>
<td>2000</td>
<td>Enschede/Netherlands</td>
<td>Explosion: 23 deaths, 947 wounded</td>
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<tr>
<td>2001</td>
<td>Toulouse/France</td>
<td>Ammonium nitrate explosion: 31 deaths</td>
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</tbody>
</table>

http://www.sust-chem.ethz.ch/teaching/courses/MaterialCuG/Unfaelle.pdf (modified)
OELs and BLVs: Development of the SCOEL Mandate


Council Directive 80/1107/EEC → protection of workers from the risk related to exposure to chemical, physical and biological agents at work


Commission Decision 95/320/EC → setting up SCOEL

EUR 19253 “Methodology of derivation of OELs“


Revision/extension of „Biological Monitoring“

SCOEL strategy for carcinogens

2011: New mandate

SCOEL strategy for carcinogens

Methodology of derivation of OELs

Commission Decision 95/320/EC → setting up SCOEL
Article 2 (1)

... „The Committee shall in particular give advice on the setting of Occupational Exposure Limits (OELs) based on scientific data and, where appropriate, shall propose values which may include:

- the eight-hour time-weighted average (TWA),
- short-term limits/excursion limits (STEL),
- biological limit values.

The OELs may be supplemented, as appropriate, by further notations. The Committee shall advise on any absorption of the substance in question via other routes (such as skin and/or mucous membranes) which is likely to occur.“ [Nota bene: no explicit reference to carcinogens!]

Methodology

- Evaluations on a “case by case” basis
- Recommendations with clear justifications
- Critical effects and mechanisms of action to be described as detailed as possible
- NOAEL and/or LOAEL, extrapolation model used and quantitative considerations
- Systematic update of key scientific criteria (e.g. genotoxicity)
7

Official performance data in 2008

- 156 Recommendations in total
- 18 Carcinogens
- 96 IOELVs (+10) D2000/39/CE & D2006/15/CE (91/322/CE)

“Binding Values”:

- Benzene
- VCM
- Wood dust
- Lead
- Asbestos

D 2004/37/CE
D 98/24/CE
D2003/18/CE
Triggering Discussions for new Criteria (2000-2007)
(Threshold Effects for Carcinogens ?)

- Induction of aneuploidy
- Topoisomerase II poisons
- Oxidative stress
- Inhibition of DNA synthesis
- Steep dose-effect curve, cytotoxicity involved
- Endogenous carcinogens, within limits of homeostasis
- Clastogens (being discussed)

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
    - Numerical risk assessment, risk management procedures

- Genotoxicity only on chromosome level (e.g. spindle, topoisomerase)
  - Borderline cases
    - **B**: Situation not clear
      - LNT as default

Non-genotoxic
- Weak genotoxin, secondary mechanisms important
  - **C**: Practical/apparent threshold likely
    - NOAEL
      - health-based exposure limits

- **D**: Perfect/statistical threshold likely
Summary of the SCOEL Strategy for Carcinogens

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

- Such a mechanism-based assignment is independent of the formal classification of carcinogens (i.e., former EU categories 1, 2 or 3, equivalent to GHS categories 1A, 1B, 2)!

- 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.
Results of SCOEL Discussions (Examples)

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)
- arsenic
- naphthalene
- hexavalent chromium
- o-anisidine
- 2,6-dimethylaniline (insuff. Data)

C. Practical/apparent threshold:
- vinyl acetate
- nitrobenzene
- pyridine
- lead (provisional OEL); lead chromate
- TRI
- DCM
- glycercyl trinitrate

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

Distinction between B and C is most important!
SCOEL: Formaldehyde - B oder C?

Major points of general discussion

- Classical case since the 1980s of nasal tumours in rats
- Sublinear dose-response curve (accepted since the 1980s)
- Cytotoxicity as relevant/necessary influencing factor
- IARC (2005): Sufficient evidence of human nasopharyngeal carcinomas (local effect in humans)

Discussions by SCOEL (2005-2007):

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

Group C: Carcinogen with practical threshold
Local carcinogenicity requires cell proliferation. Irritancy on the upper respiratory tract is therefore a precondition that must be avoided.

For this effect, the database is insufficient to establish an OEL.

The database is much better for eye irritation. Avoidance of eye irritation also avoids irritancy on the upper respiratory tract and provides an additional safety margin.
Evaluation by Paustenbach et al. (1997): at 0.3 ppm “practically all workers“ protected against eye irritation

DECOS/Nordic (2003): 0.24 ppm as LOAEL
(difference to Paustenbach: interpretation of 2 studies from Scandinavia)

Lang et al. (2008): NOAEL for eye irritation at 0.5 ppm, or 0.3 ppm with peaks of 0.6 ppm
Proposal of an OEL of 0.2 ppm (TWA) and 0.4 ppm (STEL), because:

• Consideration of particularly sensitive persons

• Safety margin to the onset of irritation-induced cytotoxicity / cell proliferation necessary
Proposal of an OEL of 0.3 ppm (TWA) because:

- DPX and cell proliferation in nasal epithelia experimentally increased only at > 2 ppm
- Consideration of CIIT (1999) risk assessment: at 0.3 ppm -> risk for non-smokers $1.3 \times 10^{-8}$, for smokers $3.8 \times 10^{-7}$ (as secondary argument)
- Evaluation of Paustenbach et al (1997): practical NOAEL for irritation (workers) of 0.3 ppm
# OEL Recommendations for Formaldehyde

<table>
<thead>
<tr>
<th></th>
<th>TWA (ppm)</th>
<th>STEL (ppm)</th>
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</thead>
<tbody>
<tr>
<td>ACGIH (USA, 2006)</td>
<td>-</td>
<td>0.3</td>
</tr>
<tr>
<td>DECOS (NL)+Nordic (2003)</td>
<td>0.12</td>
<td>0.42</td>
</tr>
<tr>
<td>DFG/MAK (D, 2006)</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>SCOEL (EU, 2006)</td>
<td>0.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*(Health-based OELs recommended)*
It may be concluded:

There has been significant progress in research on modes of carcinogenic action.

The recognition of genotoxic and carcinogenic thresholds will allow the assignment of health-based limit values for an increasing number of relevant carcinogens.
Further examples: Recent SCOEL recommendations on inorganic compounds

A (no threshold): Cr(VI) - numerical risk assessment

B (situation not clear): Be – no OEL recommended

C (practical threshold):
• Crystalline silica, resp. dust: OEL = 50 µg/m³
• Cd: OEL = 4 µg/m³; BLV = 2 µg/g creatinine
• Ni: OEL = 10 µg/m³ inh., 5 µg/m³ resp. dust; BLV = 3 µg/L

D (perfect threshold): RCF; OEL = 0.3 fibres/mL
Minimizing silicosis will minimize cancer risk

Sigmoidal dose-response for silicosis

0.05 mg/m³ will reduce ILO 1/1 to less than 5%

OEL should be below 0.05 mg/m³ respirable dust

Example: Silica, crystalline, respirable dust

[Carcinogen with threshold, category C]
**Example: Threshold Arguments for Cd**

- Experimentally: tumours at 12.5 µg/m³ (inhal.)
- Epidemiological risk assessment difficult (co-exposures!)
- Indirect mechanisms of genotoxicity likely
- Genotoxicity threshold in workers: 25 µg/m³ for 40 years exp.
- No cancer excess in workers at exposures without lung/renal toxicity

**Recommendation:** Carcinogenicity group C (practical threshold)

- OEL: 4 µg Cd/m³
- BLV: 2 µg Cd/g creatinine
**Most recent example:** Nickel and inorganic Ni compounds (I)

SCOEL/SUM 85 [2011]

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**Basic features of Ni**

- At low concentrations Ni-ions do not directly interact with DNA
- Indirect genotoxic effects by interference with DNA repair and DNA methylation, leading to clastogenicity and genomic instability

**Increased chromosomal aberrations in humans at exposure levels >0.5 mg/m$^3$**

- Cancer risk in lung and nasal cavity; inflammatory responses/fibrosis in the lung

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**Indirect genotoxicity of Ni$^{2+}$**
Example: Ni and Ni compounds (II)

Metallic Ni: no positive evidence of carcinogenicity, but clear inflammation response in rats at 0.1 mg/m$^3$

NOAEL for Ni-sulfate; local inflammation: 0.03 mg/m$^3$

Carcinogenicity group C (practical threshold)

Proposed OELs:
0.01 mg Ni/m$^3$ (inhalable fraction)
0.005 mg/m$^3$ (respirable fraction)

BLV: 3 µg Ni/l urine
General conclusions:

There has been consistent progress in research on modes of carcinogenic action. Secondary genotoxicity is receiving more attention!

The recognition of genotoxic and carcinogenic thresholds will allow the assignment of health-based limit values for an increasing number of relevant carcinogens.

Discussions on formaldehyde have been a key for the treatment of other chemicals!