2. Sankt Augustiner Expertentreff „Gefahrstoffe“

Bad Neuenahr, 5./6. Juli 2011

Ableitung von Grenzwerten im internationalen Vergleich

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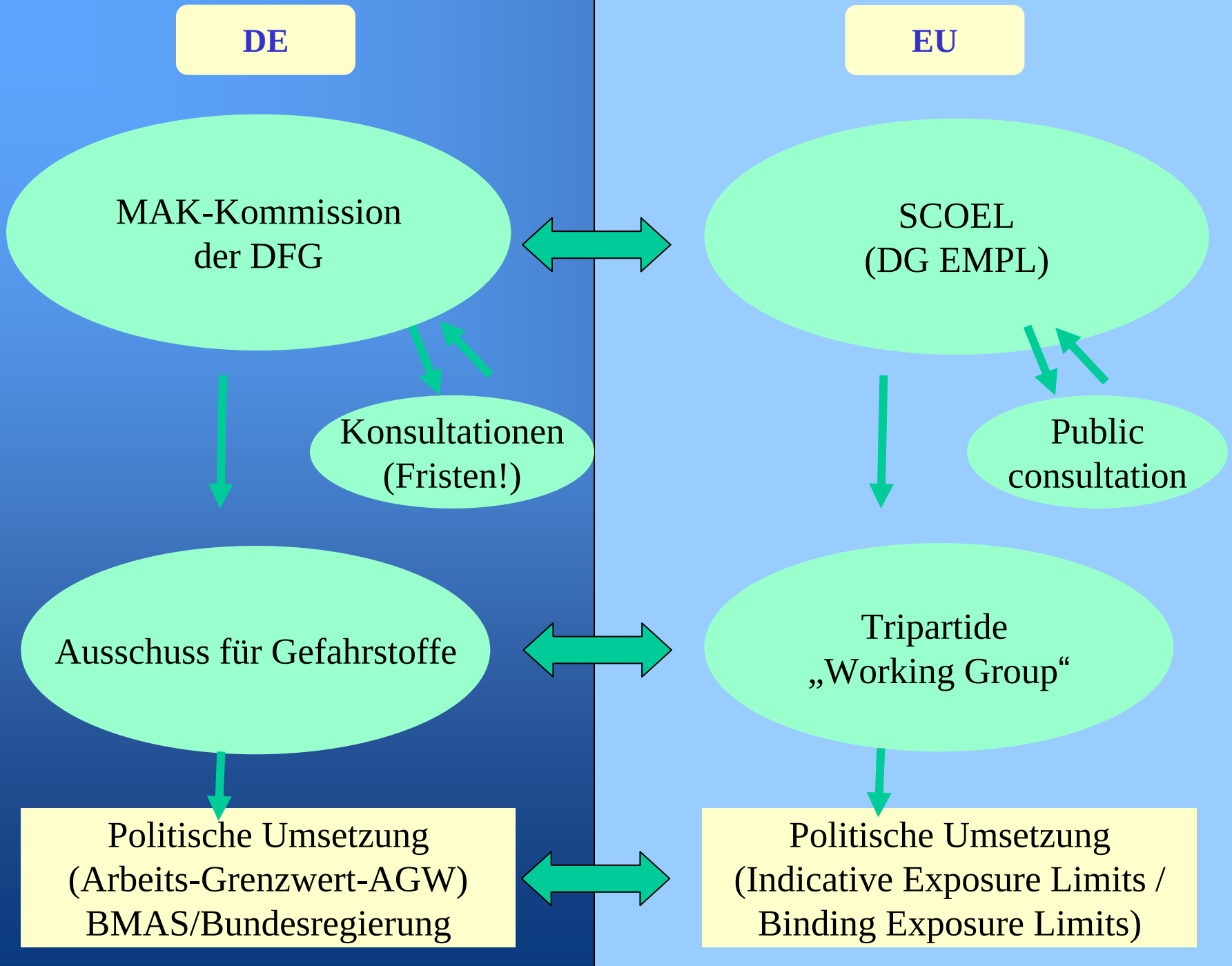
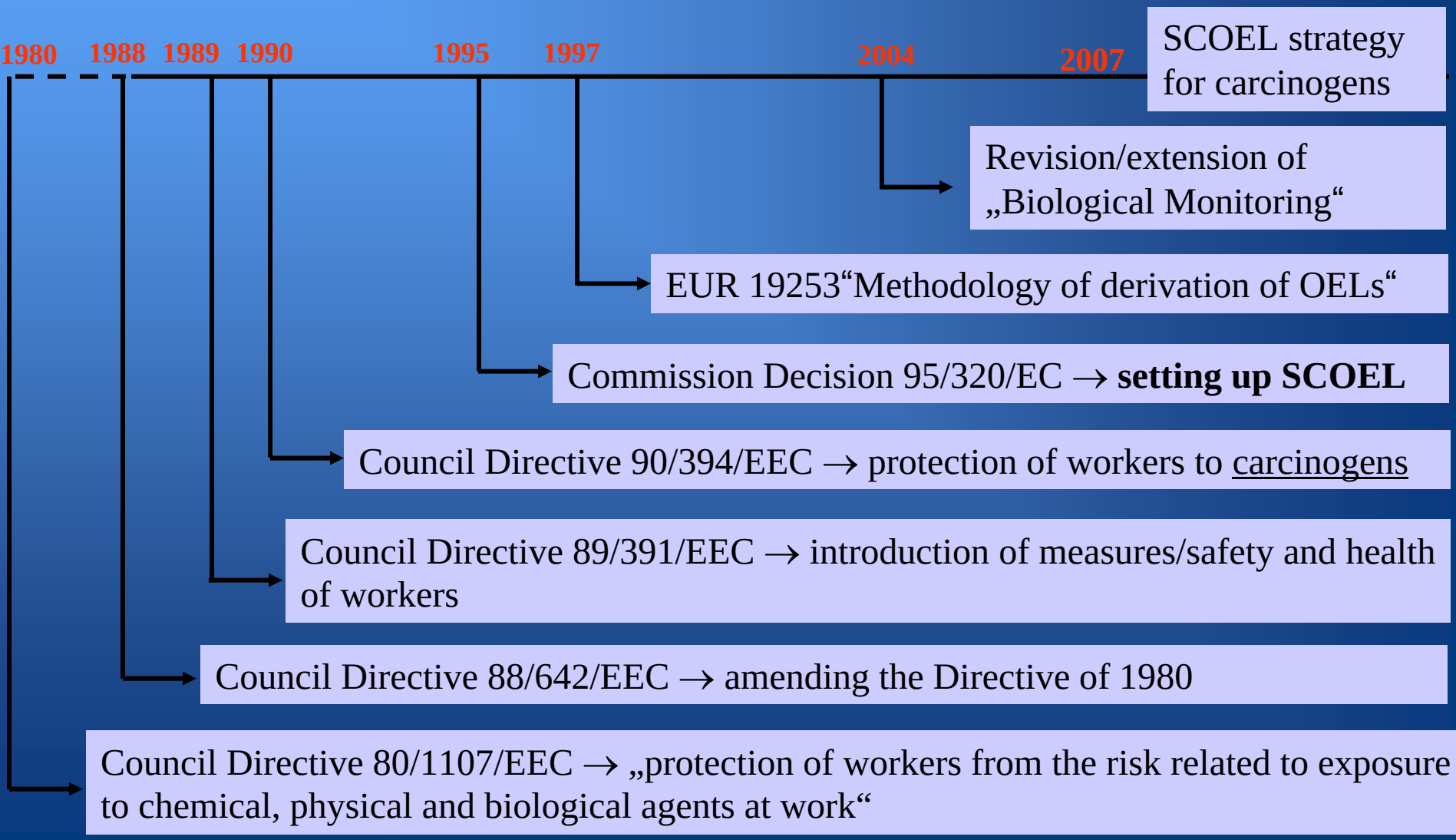
Interaktions-Geflecht (international sehr ähnlich)


DE
EU
MAK-Kommission der DFG
SCOEL (DG EMPL)
Konsultationen (Fristen!)
Public consultation
Ausschuss für Gefahrstoffe
Tripartide „Working Group“
Politische Umsetzung (Arbeits-Grenzwert-AGW) BMAS/Bundesregierung
Politische Umsetzung (Indicative Exposure Limits / Binding Exposure Limits)

Zeitliche Entwicklung des Mandates von SCOEL

(Scientific Committee for Occupational Exposure Limits)



Commission Decision (95/320/EC) of 12 July 1995, setting up a Scientific Committee for Occupational Exposure Limits to Chemical Agents (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.“

Review: European aspects of standard setting in occupational hygiene and medicine. *Rev.Environ.Health 16:81-86*

Gesetzlicher Hintergrund

Complete and coherent legislation in the EU regarding OSH (Chemical risk). Limit values.

Social dialog

ACHSW

WP-C

Treaty:
Art.137,138,139,140

Directives

89/ 391/CE (Framework) Minimal req.
98/24/CE (CAD)
2000/39/CE (first list IOELV)
2006/15/CE (second list IOELV)
2009/?/CE (third list IOELV)
2004/37/CE (Carcinogens and mutagens)
2003/18/CE (Asbestos)

1991/322/CEE

Decision 95/320/EC
(2006/275/EC)

SCOEL
SLIC

Technical guides

„Indicative Values“ - „Binding Values“

Two ways to establish limit values

- D 98/24/CE on chemical agents (indicative and binding values)
- D 2004/37/CE on carcinogens and mutagens (only binding)

- IOELVs : Based on health criteria, derived from the assessment of updated and validated scientific data

Below this exposure no adverse effects are expected.

- BOELVs : Take also into account practical and socio-economical factors and the risk accepted by society

They are considered “political-type” values*.

*** Political decision: to define “acceptable” *versus* “non-acceptable” risk**

Formale Prozeduren

Development of limit values

- Prioritization of chemicals
- Collection of existing data (contractor)

- **Evaluation of scientific data**
- **Recommendation of limit value(s)**
- **Scientific discussion (including 6 months consultation) and final recommendation (including analytical methods)**

- Consultation of social partners
- Adoption (Commission/EP + Council)
- Transposition (national) and use

Rahmen des Auftrages

Role of SCOEL

- Scientific assessment to the EC (**D 95/320/CE**), especifically in relation to the legislation (98/24/CE + 2004/37/CE) foreseen to set occupational exposure limits (**OEL**s)
- Identification of available scientific data
- Evaluation of the relationship **exposure/effects**

- Recommendation of "OELs" : **8-h TWA**, **15-min STEL**, **BLVs** and **"notations"** (eg. skin absorption, sensibilization, carcinogen category) based on own **methodology**

Berufung von SCOEL

Practicalities

- **21 independent Members** (to cover different specialities in chemistry, toxicology, epidemiology, occupational medicine and hygiene) elected among nominations from the MS
- **Mandate for 3 years** (list published in the OJ)
- **4 meetings/ year**
- **Eventual invitation of** external experts
- **Chair** (+2 **Vice**-) elected among and by SCOEL
- **Secretariat** by the staff of F4 Unit from DG EMPL of the EC

Methodik

Methodology

- **Evaluations on a “case by case“ basis**
- **Recommendations with clear justifications**
- **Critical effects and mechanisms of action as described as detailed as possible**
- **NOAEL and/or LOAEL explicit, as well as the extrapolation model used and agreed quatitative considerations cuantitativas**
- **Systematic update of key scientific factors and criteria (e.g. genotoxicity)**

Methodik

Methodology

- Developed by the Committee parallel to its work (started 1990 as SEG)
- Published in 1999 and partially updated
- Includes criteria on:
  - **General principles**
  - **Uncertainty factors**
  - **Time-weighted (8-hours) average values (TWA)**
  - **Short term exposure (generally 15min) levels (STEL)**
  - **Absorption through the skin**
  - **Toxicity to reproduction**
  - **Respiratory sensitizers**
  - **BLVs**
  - **Carcinogenic and mutagenic substances**

Offizieller Zwischenstand 2008

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

- 3 Binding values:
  - Benzene
  - VCM
  - Wood dust

  } D 2004/37/CE

Other routes:

- Lead — D 98/24/CE
- Asbestos — D2003/18/CE

Krebserzeugende Stoffe - Konzepte

Zeitmarken: Wissenschaft

- **1950/60** Frühphase experimenteller Entwicklungen;
  Analogie zu ionisierenden Strahlen
- **1970**er Jahre:
  - Ames et al. (1973)
  - Standardisierung Tierversuch
  - ED_{01}-Studie („Megamaus“)
  - „Multi-hit“- Konzepte
- **1980**er Jahre:
  - Beginn diff. Überlegungen, z.B. „Formaldehyd-Bericht“, 1.10.1984
  - Entwicklung Molekularbiologie!
- Ab **2000**: Verstärkte internationale Diskussion zu „MoA“ und Dosisschwellen

Zeitmarken: Regulatorische Konzepte

- **1958/59**: „Delaney Clause“
- *Später:* Folgediskussionen, besonders zu Cyclamat / Sacharin
- Ab **1970**: Klassifizierung nach Art der Evidenz (3 Gruppen)
  [Human / experim./ Verdacht]
- Ab **1980**: Differenzierung der Verdachtsstoffe *[Kat. 3a/b]*
- **2000**: MAK-Konzept mit 5 Kategorien
  (mit/ohne Dosisschwelle)
- **2007**: SCOEL-Konzept mit 4 Kategorien
  (mit/ohne Dosisschwelle)

Diskurs zu Schwellen in der Gentoxizität und Karzinogenität in Europa (1998-2006)

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

- **EUROTOX Speciality Section Carcinogenesis, 2001-2005**
  Budapest, Sept. 2002 → Antalya, Oct. 2003 → Crakow, Sept. 2005
  (Toxicol Lett 151:29-41, 2004; Toxicol Sci 81:3-6, 2004; Arh Hig Rada Toksikol 56:165-173, 2005)

- **Europäische Akademie Bad Neuenahr-Ahrweiler, 2001-2003**
  (Streffer, Bolt, Føllesdal, Hall, Hengstler, Jakob, Oughton, Rehbinder, Swaton: Low-Dose Exposures in the Environment, Springer, 2003)

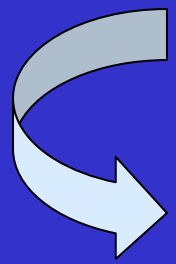
- **SCOEL-Diskusionen** → SCOEL /INF/739A (May 2006)
  Presentation: EU OEL/Carcinogen Workshop, Luxemburg, 25 Oct 2006
  (Bolt & Huici-Montagud, Arch Toxicol 82: 61-64,2008)

Wirkungsmechanismen sind sehr viel stärker als bisher zu betrachten!

"Indirekte" Mechanismen der Gentoxizität und mögliche Kriterien für Schwelleneffekte

(Besondere Diskussionspunkte seit 2000)

- Induktion von Aneuploidie
- Topoisomerase II Inhibitoren
- Oxidativer Stress *[z.B. Metalle!]*
- Inhibition der DNA Synthese
- Steilheit von Dosis-Wirkungs-kurven und Beteiligung von Mechanismen der Zytotoxizität
- Endogene Stoffe *(z.B. Isopren, Ethylenoxid, Acetaldehyd, etc.)*
- Beurteilung von Klastogenen, besonders in Beziehung zu oxid. Stress

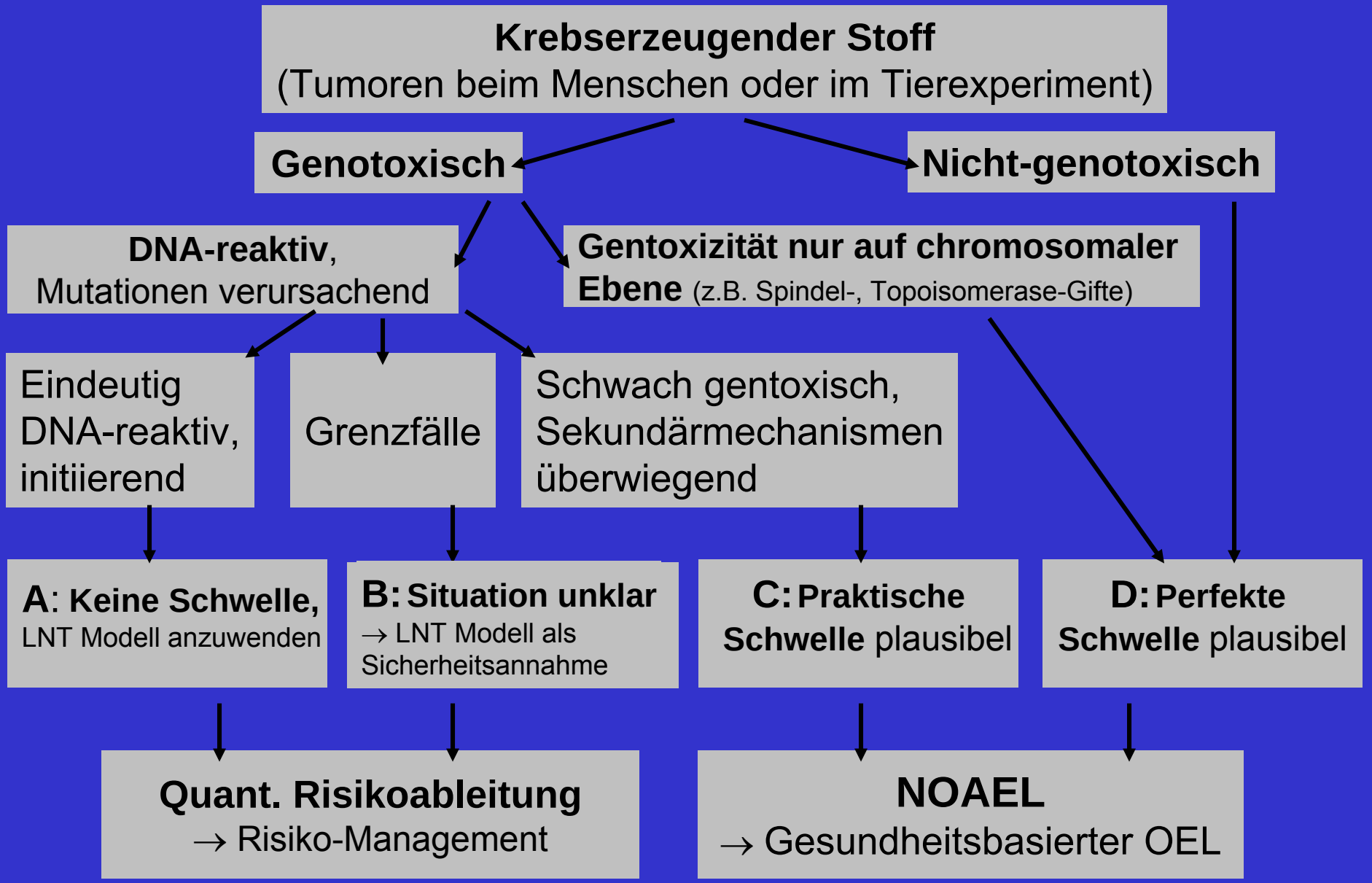


Kirsch-Volders et. al: Mutation Res. 464:3-11, 2000
Madle et. al: Mutation Res. 464:117-121, 2000
Pratt & Baron: Toxicol. Lett. 140/141: 53-62, 2003

„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."

SCOEL-Konzept zur Bewertung krebserzeugender Stoffe

(Archives of Toxicology 82: 61-64, 2008)



Ergebnisse bei SCOEL *(Stand: 2009)*

(publiziert und im Stadium „public consultation“)

A **No threshold, LNT (Linear Non-Threshold) model to apply:**

- vinyl chloride / vinyl bromide (risk assessment)
- MDA
- 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)*
- naphthalene

C **Practical/apparent threshold:**

- formaldehyde
- vinyl acetate
- nitrobenzene
- pyridine
- silica
- lead *(provisional OEL)*; lead chromate
- TRI
- DCM
- Ni
- glyceryl trinitrate

D **Perfect/statistical threshold:**

- carbon tetrachloride
- chloroform

Unterscheidung B und C ist entscheidend!

Fall 1: Formaldehyd, B oder C ?

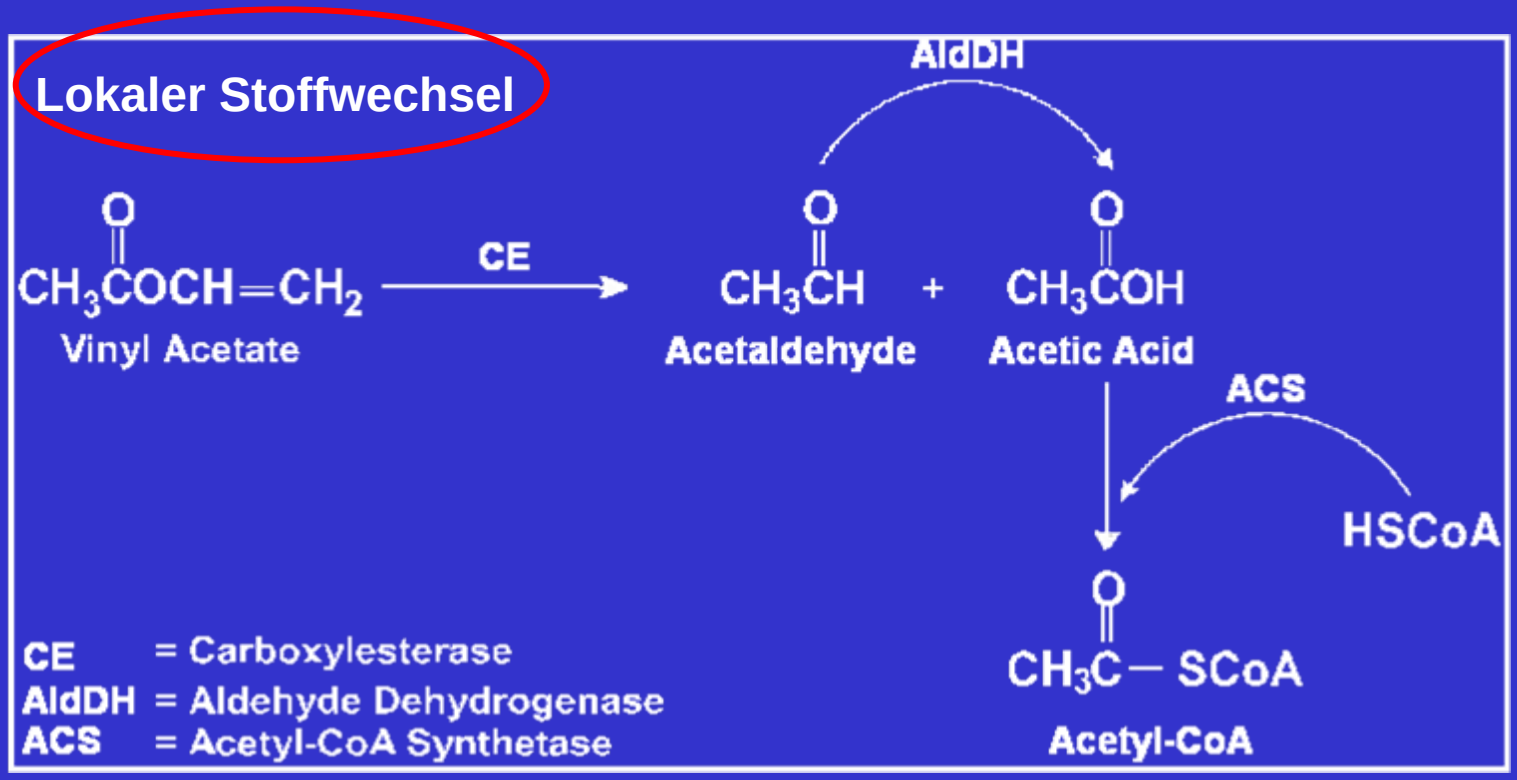
- Klassischer Fall: Nasenepitheltumoren bei Ratten
- Sublineare Dosis-Wirkungs-Kurve
- Zytotoxizität als quantitativ bestimmender Faktor
- IARC (2005): „*Sufficient evidence of human nasopharyngeal carcinomas*“

Argumentationen von SCOEL (2005-2007):

- Zellproliferation/Irritation notwendig für Tumorentstehung
- Keine einleuchtende Erklärung für systemische Effekte

→ **Gruppe C: OEL von 0.2 ppm empfohlen**

Fall 2: Vinylacetat *(SCOEL 2005/2006):*



- Alter TLV-Wert bei 10 ppm (lokale Irritation)
- Lokale Tumoren an der Eintrittspforte in den Organismus
- Keine systemische Bioverfügbarkeit bei Inhalation!

Fall-Diskussion: Vinylacetat, B oder C ?

- Lokale Tumoren nach Inhalation und Trinkwasser-Applikation
- Lokale Hydrolyse zu Acetaldehyd und Essigsäure
- Lokale Gentoxizität des Acetaldehyds *plus* Zytotoxizität durch Zell-Ansäuerung *(M. Bogdanffy, EUROTOX Budapest 2002)*

Argumentationen von SCOEL (2005)

- Zellproliferation/Irritation notwendig für die Tumorbildung
- Kein Beleg für systemische Effekte

→ **Gruppe C: OEL von 5 ppm vorgeschlagen**

Fall 3: Acrylnitril, B or C ?

- Krebserzeugend bei Ratten (orale und Inhalations-Studien)
- Schwach mutagen in vitro, aber mutagener Epoxid-Metabolit

Argumentationen zu Hirntumoren, diskutiert von SCOEL:

- Keine DNA-Addukte im Gehirn
- Oxidative DNA-Schaden in Astrocyten in vitro
- Reversibler Schaden an „gap junctions“ bei exponierten Astrocyten
- Dosis-Wirkungs-Kurve sublinear
- Gentoxizität in vivo nicht eindeutig belegt

→ Aber: Multi-Organ Karzinogen
[Hirn, Rückenmark, Zymbaldrüse, Magen-Darm-Trakt (orale Gabe), Brustdrüse]

→ Starke akute Toxizität durch die Bildung von Zyanid!

→ **Gruppe B; kein gesundheitsbasierter OEL**

Fall 4: Acrylamid, B oder C ?

- Krebserzeugend bei Ratten (*ähnlich zu Acrylonitril*)
- Schwach mutagen in vitro, aber mutagener Epoxid-Metabolit

Argumentationen in der Diskussion bei SCOEL:

→ *Ähnlichkeit zu Acrylnitril*: Multi-Organ Karzinogen
[Gehirn, Brustdrüse, Peritoneal-Mesotheliome]

Starke Neurotoxizität!

→ **Gruppe B; kein gesundheitsbasierter OEL**

→ *Aber: Aufzeigen von Expositionsbereichen, die die Neurotoxizität des Stoffes vermeiden*

Fall 5: Trichlorethylen, B oder C ?

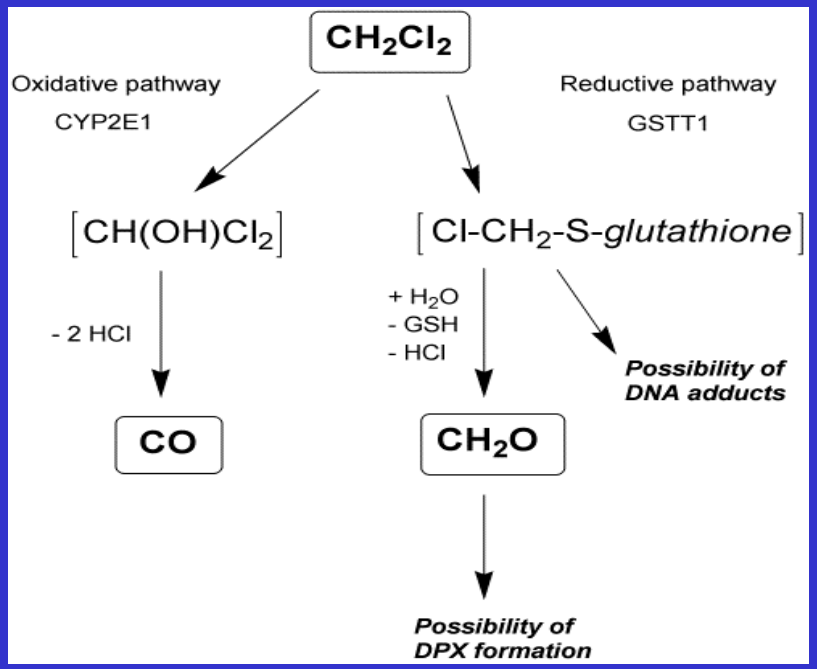
- Nierenzellkarzinome bei Arbeitern nach häufigen und hohen Spitzen-Konzentrationen (Studien in Deutschland und Frankreich)
- β-Lyase Metabolismusweg beteiligt in der lokalen Aktivierung
- Spezifische VHL Mutationsmuster bei hochexponierten Personen
- Nephrotoxizität beteiligt (α_1-Microglobulin, GSTα, weitere Marker)

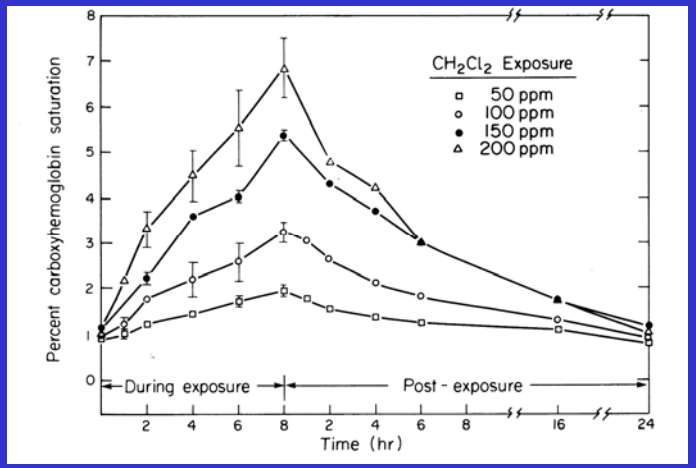
SCOEL-Empfehlung

Gruppe C: Vorschlag eines OEL von10 ppm,
basierend auf der Vermeidung von Nierenschäden

Siehe auch: Toxicol. Lett. 140-141: 43-51, 2003

Fall 6: Methylenchlorid (Dichlormethan)





- Krebs bei Mäusen, nicht bei Ratten und Hamstern
- Große Speziesdifferenzen im GSH-abhängigen Metabolismus (GSTT1-1)
- Konventionelle *(konservativ)* Risikoabschätzung:
  100 ppm ➡ 4.9×10^{-5}
- Empfohlener OEL:
  100 ppm [->3% CO-Hb]

➡ **Gruppe C**

Zusammenfassung zu SCOEL / Karzinogene

- Seit den 1950er Jahren: Kontinuierliche Entwicklung wissenschaftlicher Konzepte zur chemischen Karzinogenese

- Derzeitige Konzepte zur Einstufung und Grenzwertsetzung krebserzeugender Stoffe beruhen noch weitgehend auf dem wissenschaftlichen Stand der 1970er Jahre.

- Seit den späten 1990er Jahren: Bemühungen (europäische Ebene und weltweit), stoffbezogene Wirkungsmechanismen (“MoA”) verstärkt in der Regulation zu berücksichtigen

- Stoffbeispiele hierzu aus der laufenden Arbeit von SCOEL

- Fazit: ***Differenzierte Erkenntnisse zu Krebsmechanismen erfordern differenzierte regulatorisache Konsequenzen!***

Europäische Interaktionen:

Beispiel Holzstaub (Wood Dust)

SCOEL Discussions on Wood Dust (I)

- Starting point: Evaluation by IARC (1995)
- European Commission asking for a statement in 1996
  (inclusion of wood dust in Annex of the Carcinogens Directive?)

Joint Wood Dust Working Group (May 7, 1997)

- Evidence of human carcinogenicity for dusts of oak and beech , particularly for adenocarcinomas
- Evidence for other types of wood less convincing, but some evidence also for softwood dusts
  (sino-nasal squameous cell carcinomas)
- Definitions of „hard“ and „soft“ not universally agreed

→ *Basis of discussion: Demers et al. Am J Ind Med 31: 385ff (1997)*

SCOEL Discussions on Wood Dust (II)

- SCOEL statement on wood dust to the Commission in 1997
- Dusts of oak and beech „intended to be included“ in Carcinogens Directive, Annex III

Argumentation and steps by the Commission

- A most frequently accepted maximum workplace value was 5 mg/m^3.
- Based on such existing values, the Commission proposed a TWA of 5 mg/m^3, and inserted a clause on re-assessment over the subsequent 5 years (as für vinyl chloride).
- The temporary limit value is not scientifically health-based.

„ An evaluation by SCOEL will be requested at some time in the next 5 years, and could include other types of wood dust.“

2nd Ammendment of Carcinogens Directive (1999)

- **Political decision made to include the term „hardwood dust“, using the IARC definition**

- **„Pragmatic value“ set, but the Council required a scientifically based proposel of an OEL within 2 years**

SCOEL Discussions on Wood Dust (III)

Discussions in France, see Carton M, Goldberg M, Luce D: Rev Epidemiol Sante Publique 50: 159-178 (2002)

Preparation of a draft statement by SCOEL (2001/2002)

In addition to carcinogenicity:

- Inclusion of **non-malignant respiratory effects** at low concentrations
- Discussion of sensitizing effects

SUM document for public consultation in March 2002

SCOEL Discussions on Wood Dust (IV)

- *Results of public consultation:*
  Most comments referred to problems of measurement of wood dust.

Discussion of final SCOEL recommendation (SUM 102, Dec. 2003))

- Although effects may differ according to particle size, not realistic to suggest different particle size-selective limits
- Most studies refer only to „total dust“ measurements.
- Differentiation of hard and softwood difficult (mixed exposures)

Elements of the SCOEL SUM/102 Recommendation

(available via http://ec.europa.eu/social)

- Quantitative cancer risk assessment not realistic – lack of quantitative data on exposure levels and associated risks
- No adequate information for setting a health-based OEL
- Impairment of respiratory function and increased prevalence of pulmonary symptoms at exposures > 0.5 mg/m^3
- **This level of 0.5 mg/m^3 (total dust) „is probably below the levels to which the cases of sino-nasal cancers had been exposed“.**

Present state - what does it mean?

- The value of 0.5 mg/m^3 (total dust) refers to all types of wood dust.
- It is not health-based in a very strict sense, because it does not exclude any adverse health effect.
- It is meant as a means towards risk reduction, and represents therefore a „pragmatic“ value.
- In terms of carcinogenicity, a threshold appears plausible, although there is no definite proof.

This implies that a revision/amendment will be required as relevant new data become available.