Occupational exposure limits (OEL) at the national level

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Abstract

The "DFG Commission for the Investigation of Health Hazards of chemical compounds in the Work Area" ("MAK Commission") is a scientific commission dealing with manifold aspects of evaluation and classification of hazardous substances at the work place. One main activity consists in the establishment of MAK and BAT values. They are based on published literature with respect to epidemiological data, occupational medical reports, toxicological properties as well as other relevant information. Company studies are considered as well if full study reports are available. For substances without genotoxic and/or carcinogenic properties, MAK and BAT values are derived from the "no observed adverse effect level" (NOAEL) of the most sensitive endpoint of toxicological concern, taking into account local and systemic affects. Available data are checked for validity of the respective studies and evaluated on a case-by-case basis, considering all relevant endpoints, including toxicokinetic and toxicodynamic properties, chemical reactivity as well as structure-activity relationships. This applies also to other classifications and notations, such as germ cell mutagenicity, pregnancy groups, sensitizing effects and danger of percutaneous absorption. Minimum requirements on scientific data will be presented; in case of missing crucial information substances are listed in group IIb and no value will be stated. Consideration will be also given to the analytical surveillance of MAK and BAT values, accompanied by the development of methods for analysis in air and biological materials. With respect to carcinogenic compounds, substances are grouped into five categories, based on epidemiological evidence, animal data and mechanistic information, considering also the potential risk at exposure conditions on which the MAK values are observed. Extrapolation from animal data and margin between NOAEL and MAK/BAT values is done by expert judgement, not by general extrapolation factors. Exposure limits, notations and classifications are published anually in the List of MAK and BAT values. Furthermore, a detailed scientific documentation of each decision is published in the „Toxikologisch-arbeits-medizinische Begründungen", available also in an English translation.

Occupational exposure limits (OEL) at the national level…..

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Chair: Prof. Dr. Andrea Hartwig, Berlin

MAK and BAT values….

- derived by the „DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area" (MAK-Commission)
- published anually in the List of MAK and BAT values
- documented in the „Toxikologisch-arbeitsmedizinische Begründungen", available also in an English translation
- Prior to final publication: 6 months time for scientific comments

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Derivation of MAK values

Endpoints (animal/human):

- **Acute toxicity** *(inhalative, oral, dermal)*
- **Toxicity after repeated exposure** *(inhalative, oral, dermal)*
- **Irritation** *(skin, eye)*
- **Sensitization** *(skin, respiratory tract)*
- **Reproductive toxicity** *(fertility, developmental toxicity)*
- **Genotoxicity in vitro and in vivo** *(somatic cells, germ cells)*
- **Carcinogenicity**

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Derivation of MAK values: General approach

- **Identification of the most sensitive parameter related to the exposure of a given substance, taking into account**
  - **local effects** (mucous membranes of respiratory tract and eyes)
  - **systemic effects**
- **Decision on „adversity" by expert judgement**
- **Identification of a „no observed adverse effect level" (NOAEL) for the most sensitive and relevant parameter for substances without genotoxic/ carcinogenic properties**

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Derivation of MAK values: Data base

- Data collection
  - Published literature with respect to
    - epidemiological data,
    - occupational medical reports,
    - toxicological properties
    - other relevant information
  - Company reports, if full study report available, handled confidentially
- Data evaluation
  - relevance for current assessment
  - validity of the studies (e.g., according to OECD guidelines if possible, otherwise expert judgement)

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Derivation of MAK values for substances without genotoxic/carcinogenic properties

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Derivation of MAK values: Effects in humans

- **Occupational medical and epidemiological studies**
  - **Preferentially longitudinal studies with repeated determination and documentation of past and present external and internal exposure**
- **Human volunteer studies**
  - **Exposed under controlled conditions**
  - **Establishment of NOAEL and dose-effect relationship**

⇒ In case of good quality data MAK value is established at the level of the NOAEL (preferred value approach: 1,2,5 ppm or mg/m³ etc……)

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Derivation of MAK values: Effects in animals

- **Minimum requirements:**
  - Valid 90-day inhalation study for assessment of local and systemic effects, or
  - Valid 90-day study with oral application for assessment of systemic effects, accompanied by information about the local effects of a substance, especially on the respiratory tract
- **Establishment of NOAEL**

⇒ Assessment of potential differences in sensitivity of humans evaluating especially toxicokinetic and toxicodynamic data

⇒ If not suggested otherwise by these data, MAK value is established at the level of **half the NOAEL** (preferred value approach: 1, 2, 5 ppm or mg/m³ etc…)

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Derivation of MAK values: Effects in animals

In some cases, the MAK value is derived from the NOAEL of a 28-day study:

- if critical effect is irritation (e.g., SAR, Draize-test, pH-value); usually no time-extrapolation required unless structure-activity-relationship to other compounds indicate the time-dependence of irritation
- if critical effect is systemic and SAR data are available

→ otherwise no MAK-value → II b

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Derivation of MAK values: Effects in animals

If no NOAEL, but dose-response curve for critical effect available:

- Expert judgement
  - severity of effect
  - steepness of dose-response-curve
- Benchmark-dose calculation if data suitable

→ otherwise no MAK-value → II b

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Example for the derivation of MAK values in case of data supporting higher sensitivity of humans as compared to experimental animals

Diethylene glycol:

- **higher sensitivity of humans compared to rats based on acute intoxiciatons was used to set MAK value at 10 ppm**
- **systemic NOAEL in rats: 50 mg/kg bw, 10 ppm = 6 mg/kg bw**

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Genotoxic/ Carcinogenic substances

Categories for carcinogenic substances

1. Substances that **cause cancer in humans** and can be assumed to make a **significant contribution to cancer risk** (adaquate epidemiological evidence or limited epidemiological evidence and mode of action relevant to humans)
2. Substances that are **considered to be carcinogenic in humans** based on **sufficient data from long-term animal studies** or limited evidence from animal studies, substantiated by evidence from epidemiological studies and/or **supported by mode of action** (in vitro tests, short-term animal studies)

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Genotoxic/ Carcinogenic substances

Categories for carcinogenic substances

3. Substances that cause **concern** that they could be carcinogenic to humans but **cannot be assessed conclusively because of lack of data.** The classification in Category 3 is provisional.

a. Substances for which the **criteria for classification in category 4 or 5 are fulfilled** but for which the **database is insufficient** for the establishment of a MAK or BAT value.

b. Substances for which in vitro or animal studies have yielded **evidence of carcinogenic effects, but not sufficient for classification** of the substance **in one of the other categories** (further studies are required). A MAK or BAT value can be established in the absence of genotoxicity.

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Genotoxic/ Carcinogenic substances

Categories for carcinogenic substances

4. Substances with **carcinogenic potential for which a non-genotoxic mode of action is of prime importance; no significant contribution to human cancer risk is expected** at exposure observing **MAK and BAT values (mode of action well understood,** related for example to increases in cellular proliferation, inhibition of apoptosis or disturbances in cellular differentiation)

5. Substances with **carcinogenic and genotoxic effects**, the potency of which is considered to be so low that, provided the MAK and BAT values are observed, **no significant contribution to human cancer risk is to be expected** (must be supported by information on the **mode of action**, dose-dependence and toxicokinetic data pertinent to species comparison)

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Genotoxic/ Carcinogenic substances

Currently:

- Working group on **„New Mechanisms in Carcinogenicity"**

Aim:

- development of **concepts for integrating the manifold mechanisms of carcinogenicity** including current knowledge of cell biology **into risk assessment ond classification** of carcinogens

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Other relevant aspects….

- **Germ cell mutagenicity**
- **Pregnancy groups**
- **Sensitizing effects (skin, respiratory tract) "Sa, Sh, Sah"**
- **Danger of percutaneous absorption „H"**
- **Limitation of exposure peaks**
- **Biological Tolerance (BAT), exposure equivalents established for carcinogenic substances (EKA) and BLW values established in case of insufficient data for setting a BAT value**
- **Consideration of surveillance of respective exposure and development of methods for analyses in air and biological materials**

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Substances requiring special consideration: Example carcinogenic metal compounds

- Metals are **frequently listed as the element "and its inorganic compounds"**
- **For individual compounds of most metals**, the **available data** from animal studies or from known effects on man are **insufficient for evaluation**.

All available **epidemiological, animal and mechanistic data** for the metal and its compounds are used to decide on classification and whether or not they are assigned to the same category

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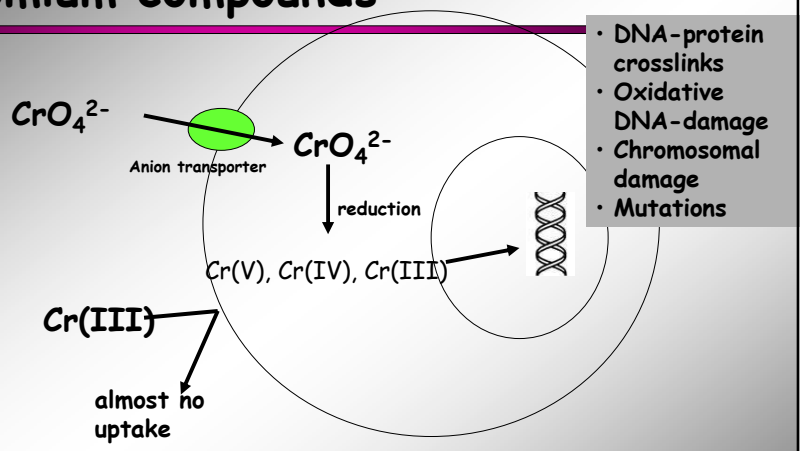
Chromium compounds



- DNA-protein crosslinks
- Oxidative DNA-damage
- Chromosomal damage
- Mutations

- Classification of Cr(VI) compounds as carcinogenic (category 2)

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Nickel compounds

- Soluble and insoluble particulate nickel compounds carcinogenic to humans; metallic nickel some evidence

Main mechanisms of genotoxicity/carcinogenicity:

- Oxidative DNA damage
- Interactions with DNA repair proocesses

- Toxic species: Ni^{2+}
- No differentiation between water soluble, largely water insoluble and metallic nickel
- Classified as carcinogenic, category 1

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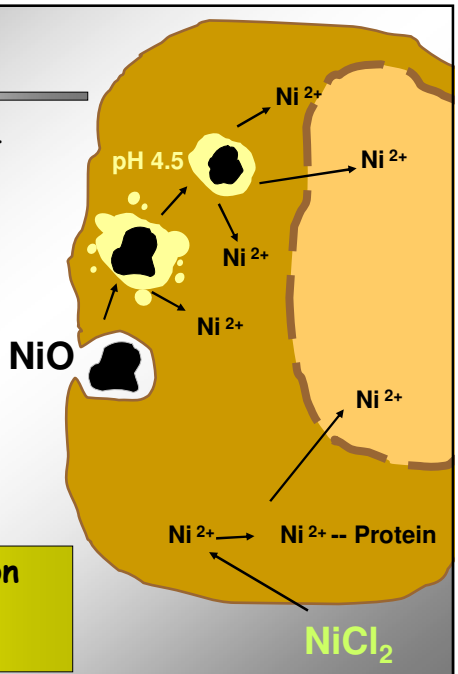
Nickel compounds

- insoluble particles very potent carcinogens (Ni_3S_2, NiO)
- oxidative DNA damage
- DNA repair inhibitions



- Toxic species Ni^{2+}

- Extent of damage depends on bioavailability and biological half live

MAK values and pregnancy

- **Necessity to assess the risk for embryo or fetus if pregnant women are exposed to substances at the MAK value**
- **Human data are mostly not available, and if so, they cannot be used for a quantitative risk assessment**

  ➔ **risk assessment has to be based on animal data: developmental toxicity**

(studies preferably conducted according to OECD Test Guidelines 414 (prenatal toxicity), 415 (perinatal and postnatal toxicity, 416 (two-generation study), 421, 422 (screening test))

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MAK values and pregnancy

- Evaluation of the **effects** observed at the LOAEC of developmental toxicity studies in the most relevant species
- Evaluation of the **margin** between

MAK/BAT Value ➔ ➔ NOAEC

of developmental toxicity studies in the most relevant species

- **Classification** in one of the pregnancy groups, depending on severity of effects on a **case-by-case** basis (usually at least factor 10 in case of teratogenic effects)

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Assignment of pregnancy groups to substances with MAK and BAT values

Group A: **Damage** to the embryo or foetus **in humans** has been **unequivocally demonstrated** and is to be expected even when MAK and BAT values are observed.

Group B: According to currently available information **damage** to the embryo or foetus **must be expected** even when MAK and BAT values are observed.

Group C: There is **no reason to fear damage** to the embryo or foetus when MAK and BAT values are observed.

Group D: Either there are **no data** for an assessment of damage to the embryo or foetus **or** the currently available **data** are **not sufficient** for classification in one of the groups A – C.

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Conclusion

- **MAK and BAT values are derived from the NOAEL of the most sensitive endpoints of toxicological concern.**
- **Available data are evaluated on a case-by-case basis, taking into account**
  - **all relevant endpoints, including toxicokinetic and toxicodynamic considerations**
  - **chemical reactivity**
  - **structure-activity relationships**
- **This applies also to other classifications and notations.**
- **Extrapolation from animal data and margin between NOAEL and MAK/BAT values is done by expert judgement, not by general extrapolation factors.**

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