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Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area - An example about the procedure in threshold derivation and classification of chemical substances

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Introduction

The Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) proposes maximum workplace concentrations (MAK values) for volatile chemicals and dusts, biological tolerance values (BAT values), biologische Leitwerte (BLW), biological reference values for workplace substances (BAR) and analytical methods for substances in the air and biological material. Substances which are carcinogenic, germ cell mutagenic, sensitizing or absorbed percutaneously or which pose a risk during pregnancy are classified accordingly. To gain an insight into the procedure of the MAK Commission the present poster provides two examples for the derivation of a MAK value and the allocation in the classification categories.

Manganese & its inorganic compounds

Most sensitive endpoint

- central nervous system after inhalation
- in addition: effects on lung or on cardivascular system

Mode of action

- damage to dopaminergic neurons in the brain stem and basal ganglia
- inhibition of the reverse transport of dopamine to the cells and synapses as well as dopamine release
- cellular level: inhibition of mitochondria oxidative phosphorylation and ATP synthesis
- induction of reactive oxygen species (ROS) and nitrogen monoxide (NO)

Carcinogenicity and germ cell mutagenicity

- not genotoxic
- not carcinogenic

MAK value derivation

- MAK value 1994: 0.5 mg/m³ (inhalable fraction)
- new data → 2011 re-evaluation
- based on: preclinical neurotoxic effects after inhalation in humans
  → Table 1: Studies relevant for MAK value derivation

Table 1: Survey of studies relevant for MAK value derivation

	Inhalable fraction	Respirable fraction	Functional domain affected
	NOAEC/LOAEC		
Lucchini et al. 1997	NOAEC: 0.2 mg/m³ (AM) [T]	–	motor and olfactory
Lucchini et al. 1999	LOAEC: 0.05 (GM) or 0.18 mg/m3 (AM) [T]	LOAEC: 0.02 (GM) or 0.07 mg/m3 (AM)	motor and cognition
Gibbs et al. 1999	NOAEC: 0.1 (GM) or 0.2 mg/m³ (AM) [T]	NOAEC: 0.04 (GM) or 0.07 mg/m³ (AM)	motor and cognition
Dietz et al. 2001	NOAEC: 0.4 mg/m³ (AM) [I]	–	motor and cognition
Myers et al. 2003 a	LOAEC: 0.8 mg/m³ (AM) [I]	–	motor and cognition
Bast-Pettersen et al. 2004	LOAEC: 0.3 (GM) or 0.75 mg/m³ (AM) [I]	LOAEC: 0.04 (GM) or 0.06 mg/m³ (AM)	motor and cognition
Cowan et al. 2009 b	NOAEC: 0.18 mg/m³ (GM) [T]	–	motor and cognition
Young et al. 2005	–	LOAEC: 0.06 mg/m³ (median)	motor and cognition

GM: geometric mean; AM: arithmetic mean; I: inhalable fraction; T: total dust

- **Inhalable fraction:**
  → majority of studies: NOAEC at or above 0.2 mg/m³
  → Lucchini et al. (1999): loss of motor and cognitive performance within this range, however, dose-response analysis casts some doubts
  → conclusion: neurotoxicity not expected at a **MAK value of 0.2 mg/m³**

- **Respirable fraction:**
  → Gibbs et al. (1999): **N**OAEC 0.04 mg/m³ (GM) or 0.07 mg/m³ (AM)
  → Bast-Pettersen et al. (2004), Lucchini et al. (1999) and Young et al. (2005): **L**OAEC values within this range
  → 0.04 mg/m³ (GM) or 0.06 mg/m³ (AM): effects are still present
  → **MAK value: 0.02 mg/m³**

Prenatal toxicity

- oral study (rat) at 32.7 mg/kg bw and day:
  → postimplantation loss
  → delayed development of skeleton and organs
  → visceral and skeletal malformations
  → NOAEL: 25 mg/kg bw/day
- corresponding manganese concentration at the workplace (air): 4.4 mg/m³ taken into account:
  → species-specific correction factor for toxicokinetic differences between rats and humans of 1:4
  → oral absorption (rat): 10%
  → body weight: 70 kg
  → volume inhaled (8 working hours): 10 m³
  → Inhalation absorption (worker): 100%
- conclusion: difference to MAK value sufficiently large → **Pregnancy Risk Group C**

Sensitization and Skin absorption

- no classification with "Sh", "Sa" or "H"

Dichloromethane

Most sensitive endpoint

- central nervous system
- short-term: acute neurotoxic effects in humans
- long-term: carcinogenic in mice

Mode of action

- microsomal oxidative pathway:
  → conversion to carbon monoxide by CYP2E1
  → CO-Hb formation by CO binding to blood hemoglobin
  → oxidative microsomal pathway: saturable
- cytosolic GSH-dependent pathway:
  → conversion by GSH-transferases to genotoxic metabolite (S-chloromethylglutathione)
  → reaction with guanosine and cytidine → adduct formation
  → cytosolic, GSH-dependent pathway: not saturable
- ↑dichloromethane concentration: cytosolic pathway predominant
- saturation of the oxidative metabolism: 500 ml dichloromethane/m³

Somatic and germ cell mutagenicity

- *in vivo* studies in rats and hamsters: negative
- *in vivo* studies in mice (liver cells , bone marrow): positive at ↑ concentrations
- studies in germ cells are not available
  → mouse compare to human GSTT1 isoenzyme is five times more efficient
  → RNA-formaldehyde adducts is seven times less in humans compare to mice
  → human: lower GSTT1 RNA expression in prostate, ovaries and placenta
- conclusion: not expected to be mutagenic in germ cells

Carcinogenicity

- epidemiologic studies: no evidence for carcinogenicity
- studies in rats: benign mammary tumours (adenomas)
- studies in mice: adenomas and carcinomas in the liver and the lung
  → in mice: rapid metabolism of dichloromethane via the GSH-dependent metabolic pathways in liver and lung

Carcinogenic potential in human

- based on:
  → toxicokinetic (PBPK) model (Marino et al. 2006) in mice
  → risk characterization in human (David et al. 2006)
  → 50 ml dichloromethane/m³ (MAK value)
  → working lifetime exposure (14% life time)
- median tumour risk (development of liver and lung tumours): **2.5×10^{-5}** ($0\text{-}6.67 \times 10^{-5}$)

Carcinogen Category

Dichloromethane fulfils the requirements for classification in **carcinogen category 5**:

- genotoxic mode of action is of prime importance and well-known:
  → genotoxic carcinogen
  → tumours in liver and lung of the mouse are due to species-specific sensitivity
  → high activity of GSTT1
- carcinogenic potential in human can be specified
- in compliance with the MAK value: very slightly contribution to human cancer risk

MAK value derivation

- based on: acute behavioral effects indicative for CNS depression
- NAEC: 0.85 mg dichloromethane/L blood
- blood concentration of 0.85 mg dichloromethane/L:
  → after exposure of 100 ml/m³ dichloromethane in resting participants
- however: ↑ higher respiratory rates under working conditions
- extrapolation:
  - inhalation: 50 ml dichloromethane/m³
  - condition: light activity (10m³ breathing volume/8-hour shift)
  → blood level dichloromethane: 0.51 mg/L
- **MAK value: 50 ml/m³**

Prenatal toxicity

- exposure to concentrations at the level of the MAK value:
  → damage to the embryo or foetus cannot be excluded (CO-Hb formation)
  → **Pregnancy Risk Group B**

Sensitization and Skin absorption

- no classification with "Sh", "Sa" or "H"

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References: www. dfg.de/en/mak

www.kit.edu