MAK value for glass wool with low biopersistency – no carcinogenic effect at low concentrations –

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Glass wool with half-life < 40 days after intratrachial administration

- **Carcinogenicity: Reclassification from MAK Category 2 to Category 4**
- **MAK value: 0.1 mg/m³ respirable fraction (fibrous and granular components)**

Inhalation of fibres (Hartwig 2019)
(long half-life and repeated exposure)
↓
lungs, larynx, pleura, peritoneum
↓
inflammatory reactions, fibrosis, tumours

Fibres biopersistence measurement (TRGS 905, AGS 2021):

- repeated 0,5 mg i.tr. instillation of fibres in the rat for 4 days
- fibre lung burden determination on days 2, 14, 28 and 90

→ **half-life < 40 days = not classified as carcinogen**

Toxicological data: **no** inhalation studies with glass wool, half-life < 40 days
as a **worst case:** inhalation studies with glass fibres MMVF10 and MMVF11 (half-life > 40 days)

2-year inhalation study (rats) (Hesterberg et al. 1993, 1996)

Exposure	Findings
3 mg MMVF10/m³	**beginning inflammatory effects in the lung (Wagner score 2.5)** **decreased lung clearance, lung weight increased**
4.8 mg MMVF11/m³	beginning inflammatory effects in the lung (Wagner score 2.5) lung clearance: no information
16 mg MMVF10/m³	inflammation (Wagner score 3)
16 mg MMVF11/m³	inflammation (Wagner score 3)

Wagner pathology grading scale

Cellular change		
normal	1	no lesion
minimal	2	macrophage response
mild	3	bronchioloization, inflammation
Fibrosis		
minimal	4	minimal
mild	5	linking of fibrosis
moderate	6	consolidation
severe	7	marked fibrosis and consolidation
	8	complete obstruction of most airways

(Hesterberg et al. 1993)

Two possibilities of MAK value calculation

A. **LOAEC** 3 mg/m³:
: 3 (NAEC, no adverse effect concentration)
: 3 (lung **deposition** ratio rat/human) (Nielsen & Koponen 2018)
: 3 (lung **clearance** ratio rat/human)
= 0.111 mg/m³ → MAK value **0.1 mg/m³**

B. HEC-calculation **LOAEC** 3 or 4.8 mg/m³:
MPPD model: lung **deposition** ratio rat/human:
MMVF10: 0.055 & MMVF11: 0.2
HEC = 0.008 (exposure time and respiratory volume ratios animal/human) × 192,7 (ratio lung surface animal/human) × lung deposition ratio rat/human × 1/3 (clearance ratio rat/human and solubility) x LOAEC rat x 1/3 (NAEC)

MMVF10: 0.029 mg/m³
MMVF11: 0.164 mg/m³
Mean ≅ **0.1 mg /m³ =** MAK value

Carcinogenicity of fibres

overload mechanisms or chronic inflammation → **tumour**
fibres in pleura or peritoneum → mesothelioma
mesothelioma: - small fibre amounts
- long latency periods

Long-term inhalation animal studies: not always representative for carcinogenic potential for humans

intraperitoneal injection (very sensitive for fibres):
> 1 × 10⁹ fibres glass wool (half-life < 40 days):
small number of mesotheliomas

Classifications of the MAK Commission (2024)
MAK value : **0.1 mg/m³ R**
Peak limitation : **II (excursion factor 8)**
Carcinogenicity : **4** (Carcinogenic in humans and/or experimental animals; based on the mode of action, no additional cancer risk is expected provided that the MAK value is observed.)
Prenatal toxicity : **Pregnancy Risk Group D** (no data)

References: AGS 2021 (TRGS 905) https://www.baua.de/DE/Angebote/Regelwerk/TRGS/pdf/TRGS-905; Hartwig (2019) Fibrous dust, inorganic https://DOI: 10.1002/3527600418.mb0243fase6519; Hesterberg et al. (1993) Fundam Appl Toxicol 20(4): 464–476; Hesterberg et al. (1996) Fundam Appl Toxicol 32(1): 31–44; Nielsen & Koponen (2018) Regul Toxicol Pharmacol 94: 252-270

All authors confirm that there is no conflict of interest.

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