Karlsruhe Institute of Technology

Deutsche Forschungsgemeinschaft

**Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area:**

# N,N-Dimethylformamide (DMF), a high dose carcinogen

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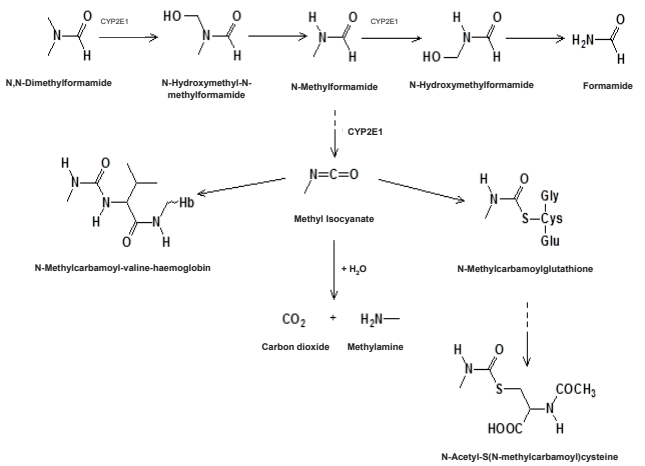
## Introduction

The DFG 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 and recommends further classifications. This poster illustrates the recent evaluation of the carcinogenic potential of dimethylformamide (DMF) and its classification in Carcinogen Category 4. This category contains compounds with carcinogenic properties for which a non-genotoxic mode of action is of prime importance and for which a threshold value and consequently a MAK and/or BAT value can be established. Under these conditions no contribution to human cancer risk is expected.

## Metabolism




## Mechanism for the development of tumors in liver

- Liver-specific enzymes ↑chron. hepatocellular hyperplasia , necrotic and degenerative lesions

  ➔ liver tumors, hepatic adenomas, carcinomas, hepatoblastomas only at doses that also cause necrotic effects

➢ **Mechanism: nongenotoxic, cytotoxic-proliferative effect**

## Prenatal developmental toxicity

| | Inhalation (ml/m³) | Margin to MAK-value of 5 ml/m³ | oral application (converted to ml/m³) [1] | Margin to MAK-value of 5 ml/m³ | Dermal application (converted to ml/m³) [2] | Margin to MAK-value of 5 ml/m³ |
|---|---|---|---|---|---|---|
| **rat** | NOAEC 31<br>LOAEC 297<br>(fetal weight ↓) | **6**<br>59 | NOAEL ≙ 32<br>LOAEL ≙ 58<br>(fetal weight ↓) | **6**<br>**11** | LOAEL ≙ 61<br>(ribs and vertebrae variations ↑) | **12** |
| **rabbit** | NOAEC 50<br>LOAEC 150<br>(umbilical hernia ↑) | 10<br>30 | LOAEL ≙ 47<br>(Hydrocephalus internus) | **9** | NOAEL ≙ ca. 200<br>LOAEL ≙ ca. 400<br>(malformations ↑) | 20<br>40 |
| **mouse** | no data | | LOAEL ≙ 67<br>(fetal weight ↓, malformations ↑) | **13** | no data | |

**NOAEC/L**: no observed adverse effect concentration /level;
**LOAEC/L**: lowest observed adverse effect concentration /level;

[1]: for conversion from mg/kg body weight/day to ml/m³ following assumptions are used: toxikokinetic correction factor 1:4 (rat), 1:7 (mouse), 1:2,4 (rabbit); 100% oral absorption by animals, substance-specific 90% inhalative absorption by humans, 70 kg body weight, breathing volume of 10 m³ per 8 hours

[2]: for rats experimental derived100% dermal absorption, for rabbits assumption of 100% dermal absorption, further assumptions, see [1]

**References: www. dfg.de/en/mak**

## The chemical DMF

DMF is used as an industrial solvent and in the production of fibers, films, and surface coatings. This colorless liquid is miscible with water and the majority of organic liquids. DMF was identified as a Substance of Very High Concern by the European Commission. The amount of DMF manufactured and/or imported into the EU is in the range of 10 000-100 000 t/y.

**Previous evaluation by the MAK Commission:**

- MAK-Value (2005): ml/m³ ≙ 15 mg/m³
- Peak limitation (2011): Cat II, Excursion factor 2
- Carcinogen category: not classified
- Germ cell mutagenicity: no designation
- Prenatal toxicity (2005): Pregnancy Risk Group B
- Sensitising assessment (2005): no Sa/Sh
- Percutaneous absorption (2005): „H"

## Carcinogenicity

Epidemiology: IARC „inadequate evidence"

**Animal studies:**

***1) Senoh et al. 2004:*** *0, 200, 400, 800 ml/m³*

Rat: Hepatocellular carcinomas in ♂ at 800 ml/m³ (highest conc.)
Hepatocellular adenomas in ♂ and ♀ at 400 ml/m³.
Preneoplastic lesions (Spongiosis hepatis) in ♂ at 200 ml/m³

Mouse: Hepatocellular carcinomas at 200 ml/m³ (lowest conc.)

***2) Ohbayashi et al. 2009***:

*0, 800 , 1600 ppm in drinking water; 0, 200, 400 ml/m³ inhalation;*
*in combination: 200 (inh) + 800 (in drinking water) ppm (165 mg/kg bw/day);*
*200 (inh) + 1600 (in drinking water) ppm (205 mg/kg bw/day);*
*400 (inh) + 800 (in drinking water) ppm (289 mg/kg bw/day);*
*400 (inh) + 1600 (in drinking water) ppm (338 mg/kg bw/day)*

Rat ♂: Hepatocellular adenomas and carcinomas at 1600 ppm (in drinking water) (82 mg/kg bw/day)

## MAK-Value

**MAK value (2005): 5 ml/m³**

The basis for the MAK value is a 2-year inhalation study and the effects in the liver (centril. hepat. hypertrophy, necrosis, Kupffer cell hyperplasia)

**NOAEC**: 25 ml/m³ for rats
**LOAEC**: 25 ml/m³ for mice
⇒ calculated BMD is 14.7 ml/m³ and BMDL 7.8 ml/m³

No new data available

## Prenatal toxicity

As a result of:

- the inadequate margins between NOAEC or NOAEL/LOAEL for prenatal toxicity and the MAK-value of 5 ml/m³,
- malformations at higher doses in all 3 species (rat, rabbit, mouse)

➔ Confirmation of the **assignment to Pregnancy Risk Group B,** i.e., damage to the embryo or fetus cannot be excluded after exposure to concentrations at the level of the MAK-value.

## Summary

N,N-Dimethylformamide is a hepatotoxin in humans and rats. The carcinogenicity studies in both mouse and rat were conducted with test material of an acceptable purity and physical form. The critical study involved administration of DMF via inhalation, which is relevant to human exposure. There is conclusive evidence that DMF induces significant increases of hepatocellular carcinomas in rats after exposure to 800 ml/m³ and in mice in response to 200 ml/m³ and higher. Several in vitro and in vivo studies have indicated that DMF is not genotoxic. The results of the long-term studies reveal that the tumors develop in the liver only after toxic , inflammatory and degenerative changes have developed in this organ. It is concluded that the tumors are a result of chronic damage of the liver, as a consequence of very high concentrations. The available evidence suggests that there is a threshold dose for the carcinogenic effects of DMF. Therefore DMF was classified in Carcinogen category 4 with a MAK-value of 5 ml/m³, an exposure concentration which does not induces liver toxicity and as a consequence is not associated with an increased cancer risk. It still remains unclear how predictive the tumours induced in rodents after exposure to high concentrations, which do not occur at the workplace or the environment, are for human carcinogenicity. Pregnancy Risk Group B is confirmed, because at the level of the MAK-value of 5 ml/m³ damage to the embryo or fetus cannot be excluded.