

## Formaldehyde releasers: The assessment procedure of the MAK Commission

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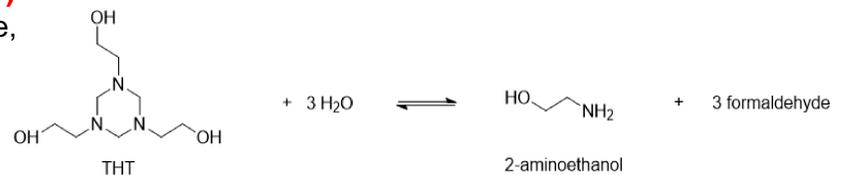
### Introduction

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 chemicals to provide information to occupational safety professionals and researchers and to give scientific policy advice.

Formaldehyde releasers (FARs) are compounds that release formaldehyde (FA) upon hydrolysis. They are used in e.g. metalworking fluids and cosmetics for biocide purposes. FA can cause irritation as well as acute and chronic toxicity e.g. to the eyes, respiratory tract, and skin. FA is a local carcinogen following inhalation exposure. Mechanistic data indicate that FA does not promote increased cell proliferation at non-cytotoxic concentrations in the respiratory epithelium and tumors do not develop. Therefore, FA is classified as a Category 4 carcinogen. FARs are presumed to have the same qualitative effect as FA. Key factor determining their carcinogenicity is the rate of FA release within the respiratory tract characterized by the half-life of the FAR. If FARs are present as an aerosol (vapour pressure: 0.001-1 Pa), effects will be more severe due to aerosol impaction and analogy with the MAK value of FA (vapour) is not possible. Consequently, the respective FAR will be assigned to Carcinogen Category 2.

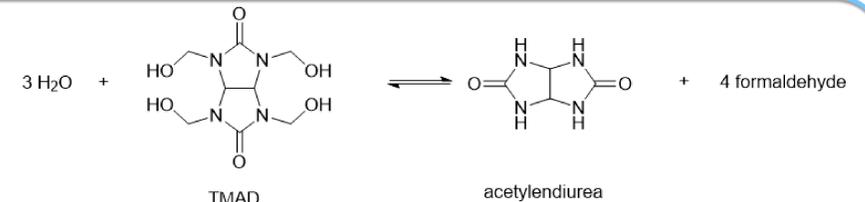
### N,N',N''-Tris(β-hydroxyethyl)hexahydro-1,3,5-triazine (THT)

- NOAEC, MAK value in analogy to gaseous formaldehyde not derivable, (28 d inhalation: effects exacerbated by aerosol impaction)
  - THT causes multifocal squamous metaplasia (larynx, nose), degeneration of the bronchial epithelium at 3 mg/m<sup>3</sup>
  - NOAEC (FA) = 2 ml/m<sup>3</sup>; NOAEC (2-aminoethanol) = 10 mg/m<sup>3</sup>
  - THT vapor phase at 3 mg/m<sup>3</sup>: only formaldehyde detected; hydrolysis only after reaching the respiratory tract (aqueous environment)
- THT induces stronger local effects than formaldehyde or 2-aminoethanol (aerosol impaction)  
→ Assignment to Carcinogen Category 2 with the footnote "Prerequisite for Category 4 in principle fulfilled, but insufficient data available for the establishment of a MAK or BAT value" (Hartwig and MAK Commission 2023a)



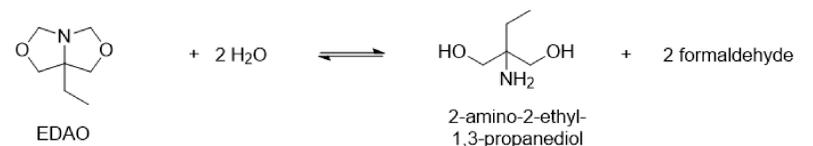
### Tetramethylol acetylenediurea (TMAD)

- TMAD causes slight irritation in the larynx at 21.7 mg/m<sup>3</sup> (= LOAEC), in the nasal cavities at 96 mg/m<sup>3</sup> (rats, 28 d inhalation)
  - Acetylenediurea: not responsible for effects (not irritating to eyes/skin, non-toxic up to 1000 mg/kg bw per day)
  - MAK value derived by an empirical approach (Brüning et al. 2014) for substances with critical effect on the upper respiratory tract
- MAK value of 0.5 mg/m<sup>3</sup> and assignment to Carcinogen Category 4 (Hartwig and MAK Commission 2023b)



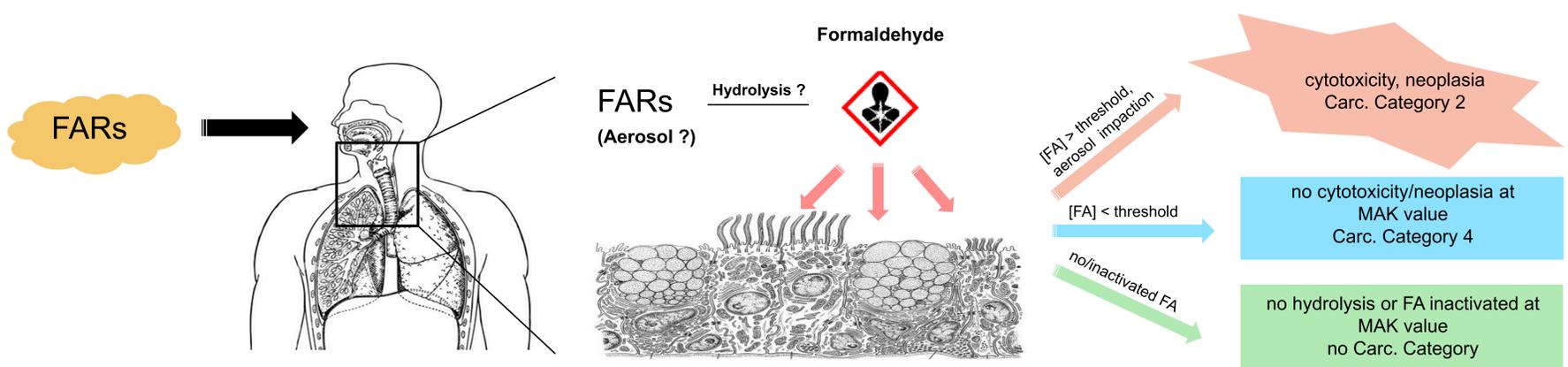
### 5-Ethyl-3,7-dioxa-1-azabicyclo[3.3.0]octane (EDAO)

- EDAO: causes irritation to skin/eyes (stronger than 2-amino-2-ethyl-1,3-propanediol)
  - EDAO: no inhalation data, but no aerosol formation due to a vapour pressure of 0.606 hPa
  - Worst case assumption: EDAO undergoes complete hydrolysis; 2-amino-2-ethyl-1,3-propanediol: no additional irritation
- MAK value of 0.15 ml/m<sup>3</sup> derived for EDAO (in analogy to formaldehyde: 0.3 ml/m<sup>3</sup>) and assignment to Carcinogen Category 4 (Hartwig and MAK Commission 2025)



### Hexamethylenetetramine

- causes very slight skin irritation and no eye irritation; releases formaldehyde only under acidic conditions
  - expected to undergo very limited hydrolysis in the nasal mucosa (mucous pH 6.5; half-life at a pH of 5.8 = 13.6 hours)
  - Hydrolysis products neutralize mucus (reduction of further hydrolysis), detoxification capacity (nasal tissue) not exceeded
- No classification as a carcinogen. MAK value of 20 mg/m<sup>3</sup> derived (Hartwig and MAK Commission 2026)



#### References:

Hartwig A, MAK Commission (2023a) N,N',N''-Tris(β-hydroxyethyl)hexahydro-1,3,5-triazin. MAK-Begründung, Nachtrag. MAK Collect Occup Health Saf 8:1-7. [https://doi.org/10.34865/mb471904kskd8\\_3ad](https://doi.org/10.34865/mb471904kskd8_3ad)  
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