Differences between humans and rats in chloroform-induced effects on the olfactory epithelium ?

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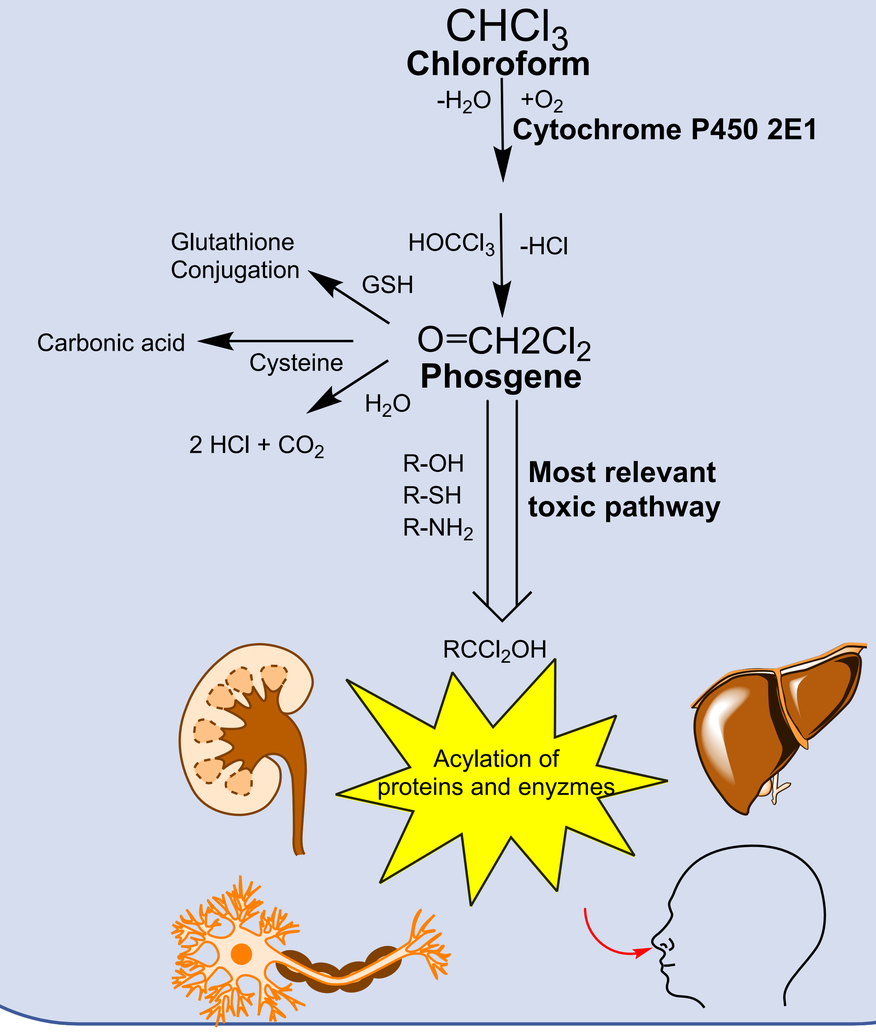
Introduction

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 in order to provide comprehensive information for workplace safety professionals and researchers and to give scientific policy advice. Members and contributors of the MAK Commission come from different scientific fields like toxicology, epidemiology, occupational medicine, veterinary medicine, biochemistry, molecular biology, analytical chemistry, dermatology, pathology and statistics. Recently, the MAK Commission re-evaluated the hazard of chloroform at the workplace.

Chloroform was used as an inhalation narcotic until the end of the 19th century before its harmful effects on the liver and kidneys were recognized. Nowadays, it is used as a solvent and in chemical synthesis. Furthermore, chloroform is contained in cleaning and disinfecting agents and large amounts are produced as by-products in the chlorination of drinking water.

Oxidative Metabolism



Objectives

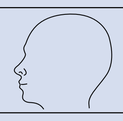
- Chloroform affects the central nervous system, liver and kidneys after oral and inhalation exposure
- In 1999: a NOAEC (no observed adverse effect concentration) of 5 ml/m³ in a 13-week inhalation study was determined
  → based on increased cell proliferation in the kidneys and liver of rats and mice
  → A **MAK value of 0.5 ml/m³** was established
- New: 2-year inhalation study in rats and mice → nasal lesions play a major role in chloroform-induced toxicity
- However: differences in anatomy, physiology and air flow dynamics in the nasal cavity between humans and rodents
- **Question: Are rodents more sensitive for effects in the olfactory epithelium (OE)?**

Methods

A comprehensive literature search on the toxicity of chloroform was performed. Reviews by other regulatory bodies and original studies on inhalation toxicity and metabolism were discussed and evaluated within an expert committee of the MAK Commission.

Results

In the new 2-year inhalation study, thickening of the bone in the nasal cavity and respiratory metaplasia of the OE were observed at 10 ml chloroform/m³ in rats. The pathomechanism of thickening of the bone is due to a degeneration of the Bowman's glands, which are located in the OE. However, there are differences in anatomy, physiology, and air flow dynamics between humans and rats:

		
breathing	obligate nose	nasal and oral
average percentage of OE	50 %	3 %
air flow over OE	15 %	7 %
enzyme activity of CYP2E1 in OE[a]	↑↑	no

- Substances that cause effects in the Bowman's glands of the OE are therefore particularly toxic for rodents
- As CYP2E1 is the key enzyme that metabolizes chloroform to the toxic phosgene, it is assumed that rodents are more sensitive than humans

a: Green T, Lee R, Toghill A, Meadowcroft S, Lund V, Foster J (2001) The toxicity of styrene to the nasal epithelium of mice and rats: studies on the mode of action and relevance to humans. Chem Biol Interact 137(2): 185–202

MAK value derivation and conclusion

- **LOAEC: 10 ml chloroform/m³ due to effects on the OE in rats**
- **Since humans are less sensitive than rodents, no factor is needed for the extrapolation of the animal data to humans**
- **MAK value derived from effects in the nose would correspond to 1 ml/m³**
- **Kidney and liver effects correspond to 0.5 ml/m³**

The present MAK value of 0.5 ml/m³ thus protects also against effects in the nose