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An example of the conceptual work on the evaluation and classification of chemical substances:

The evaluation of the human relevance of tumours in animal carcinogenicity studies

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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 and designations.
The conceptual work involved in the evaluation of the human relevance of tumours observed in animal experiments and in the classification of chemical substances is illustrated. There is often no clear evidence of carcinogenic potential, which constitutes borderline cases. The decisions of three borderline cases are given below.

Conclusion

The human relevance must be considered case by case by applying expert knowledge and employing a weight-of-evidence approach

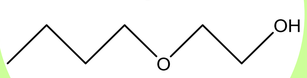
How is the carcinogenicity of borderline cases evaluated?

Borderline cases:
- chemical substances resulting in tumours in animals, but which are not genotoxic or are only genotoxic at cytotoxic concentrations

To be considered:
1. **Occurrence** of the tumours only at or in the vicinity of the **Maximum Tolerated Dose (MTD)**
2. **Mechanism** of the tumour formation
3. **Dose-response** relationship including the overwhelming of the potential for metabolic inactivation of the chemical
4. **Species, strain** and **organ specificity** of tumours and their relevance for humans
5. **Qualitative** and **quantitative differences** between the species
6. **Significance** of high spontaneous tumour rates
7. **Evaluation** of adenomas and their potential for the development of malignancy

Examples

2-Butoxyethanol



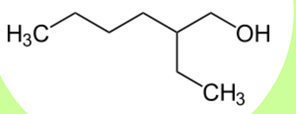
- not genotoxic
- in mice: hepatocellular carcinomas, haemangiosarcomas and forestomach tumours
- in rats: phaeochromocytomas

→ 2006: Carcinogen Category 4* → 2017: withdrawal of classification in Carcinogen Category 4 *

Reasons:
- no human relevance of forestomach tumours in rodents induced by non-genotoxic substances
- hepatic tumours and phaeochromocytomas: consequences of the haemolysis caused by the metabolite butoxyacetic acid
- formation and haemolytic potency of butoxyacetic acid: much lower in humans than in rats
- CNS-depression and irritation occurring at low concentrations are the critical effects in humans at the workplace. Therefore, high 2-butoxyethanol concentrations which might result in significant haemolysis cannot be achieved

no classification

2-Ethylhexanol



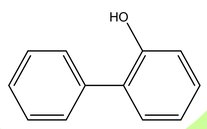
- not genotoxic
- in mice: hepatocellular carcinomas, only females
- in rats: not carcinogenic

→ 2000: not classified as carcinogen

Reasons:
- maximum tolerated dose (MTD) exceeded: liver tumours only in female mice given more than the MTD of 750 mg/kg body weight and day (>10% reduced body weight gains and 15/50 deaths)
- plausible mechanism for the carcinogenic action: toxic effects on the liver, and not peroxisome proliferation, since 500 mg/kg body weight and day in a 90-day study did not cause peroxisome proliferation

no classification

o-Phenylphenol (OPP)



- not primarily genotoxic
- in mice: hepatocellular adenomas
- in rats: bladder carcinomas, only males

→ 2016: Carcinogen Category 4*

Reasons:
- in male rats: mechanism of carcinogenicity presumably a cytotoxic effect in combination with species or gender-specific factors; the effect is seen especially at high dosages at a saturation range in metabolism
  but: cell proliferation maybe triggered by other mechanism besides cytotoxicity, therefore human relevance is not clear

Carcinogen Category 4

*Carcinogen Category 4 - Evidence for carcinogenicity with a threshold mechanism:
a non-genotoxic mode of action is of prime importance and genotoxic effects play no or at most a minor part if the MAK and BAT values are observed.

Further information: www. dfg.de/en/mak

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