

# TOXICOLOGY OF FORMALDEHYDE

## BASIC DATA and FORMACARE RESEARCH

H.P. Gelbke, Sept. 2007

# LOCAL TUMORS

# BASIC ANIMAL DATA

- Nasal tumors in rats significantly increased after inhalation exposure
    - starting between 5.6 and 10 ppm with a steep non-linear increase
    - at 15 ppm nearly 50% tumor incidence
    - cytotoxic irritation and cell proliferation already at 2 ppm
  - In mice a small non-significant nasal tumor incidence (ca. 1%) at 15 ppm
    - cell proliferation at 5.6 ppm and above
  - In hamsters at 10 (5 d/w) of 36 ppm (1 d/w) no respiratory tract tumors
    - only minimal hyperplasia and metaplasia
- Clear differences in species sensitivity

# BASIC MECHANISTIC DATA

## In vitro:

- Genotoxicity / mutagenicity test systems
- Generally associated with cytotoxicity

## In vivo:

- Genotoxic (DNA-protein cross-links) at site of direct contact (predominantly nasal mucosa)
- No genotoxicity at distant sites in animals (weight of evidence)
- Cytotoxicity and increased regenerative cell proliferation in tissues with direct contact

# PROPOSED MODE OF ACTION

- Cytotoxic irritation leading to
- compensatory cell replication in combination with
- genotoxicity manifested as DNA-protein binding
- in tissue with direct contact to formaldehyde

Cytotoxicity and increased cell proliferation play the predominant role in comparison to DNA-protein binding

Extremely steep dose-response curve for tumor incidence and precursor effects

## CLASSIFICATION BY GERMAN MAK-COMMISSION

- By this mode of action the MAK-commission decided to classify formaldehyde as category 4 carcinogen
- Definition of category 4:  
„Substances with carcinogenic potential for which a non-genotoxic mode of action is of prime importance and genotoxic effects play no or at most a minor part provided the MAK and BAT values are observed. Under these conditions no significant contribution to human cancer risk is expected.“
- Under this definition the MAK-value was set at 0.3 ppm with an excursion factor of 2 for peak exposures

## EU-CRITERIA TO DIFFERENTIATE BETWEEN CAT. 2/3

- Tumors only in organs susceptible to high spontaneous tumor formation → no
- Tumors only at site of application in very sensitive test systems (e.g. i.p. or s.c.) → no
- Species-specific mechanism → no
- Exceeding “maximal tolerated dose” → **no for systemic, but yes for local MTD**
- Lack of genotoxicity → **no, but genotox. always associated with cytotox.**
- Secondary mechanism with practical threshold (e.g. chronic stimulation of cell proliferation) → **yes**

# RESEARCH RELATED TO LOCAL TUMORS (1)

## Micronuclei formation in nasal and buccal cells of exposed humans ?

- Background: Some published data indicate to such effects
- Critical review of literature (Speit)
- MNs in buccal cells of human volunteers ? (Speit, Triebig)

## RESEARCH RELATED TO LOCAL TUMORS (2)

### Genotoxicity / Mutagenicity / Cytotoxicity

- Relationship of these endpoints in permanent cell lines (Speit)
- Relationship of these endpoints in normal / transformed / malignant human keratinocytes (Grafström)
- Relationship of these endpoints after inhalation in rats (Speit)
- Highly sensitive determination of DPX in local tissues (Swenberg)
- Adaptative protection after repeated DPX formation in vitro (Speit)

# SYSTEMIC TUMORS (LEUKEMIA)

# BASIC DATA (1)

- Indication for (myloid) leukemia
  - in studies of Hauptmann and Pinkerton
  - but not of Coggon
  - but negative meta-analysis of Collins and Lineker
- But no sound biological basis for induction of leukemia:
  - no indication for leukemia in rat inhalation studies
  - formaldehyde will only act on tissues of first contact
  - no (reliable) indication for genotoxicity apart from tissues of first contact in animal experiments
  - rapid metabolism prevents distribution of formaldehyde throughout organism

## BASIC DATA (2)

- No systemic tumors in a well documented oral study, but indication for leukemia in another one with deficiencies
- No increase in formaldehyde blood levels after inhalation in rats and humans
- No DPX and protein adducts in bone marrow even after GSH-depletion in rats
- No cytogenetic effects in bone marrow of rats after inhalation up to 15 ppm
- But: conflicting cytogenetic findings in humans at the workplace and one group reported protein associated DNA

# RESEARCH RELATED TO LEUKEMIA

- Stability of DPX in human blood cells in vitro (Speit)
- MN and Comet assay in blood / bone marrow of rats after prolonged inhalation (Speit)
- Comparison of local and systemic DPX formation by highly sensitive method in rats after inhalation (Swenberg)
- Reevaluation of CIIT inhalation studies for leukemia (Woutersen)