
Kanzerogene Stoffe

Das Einstufungssystem von MAK

Prof. Dr. Andrea Hartwig
Technische Universität Berlin
Fachgebiet Lebensmittelchemie und Toxikologie
Vorsitzende der MAK-Kommission

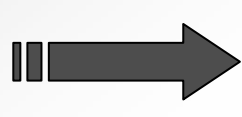
Background

- Many compounds exert carcinogenic/and or DNA damaging activity, however the carcinogenic potentials are quite different

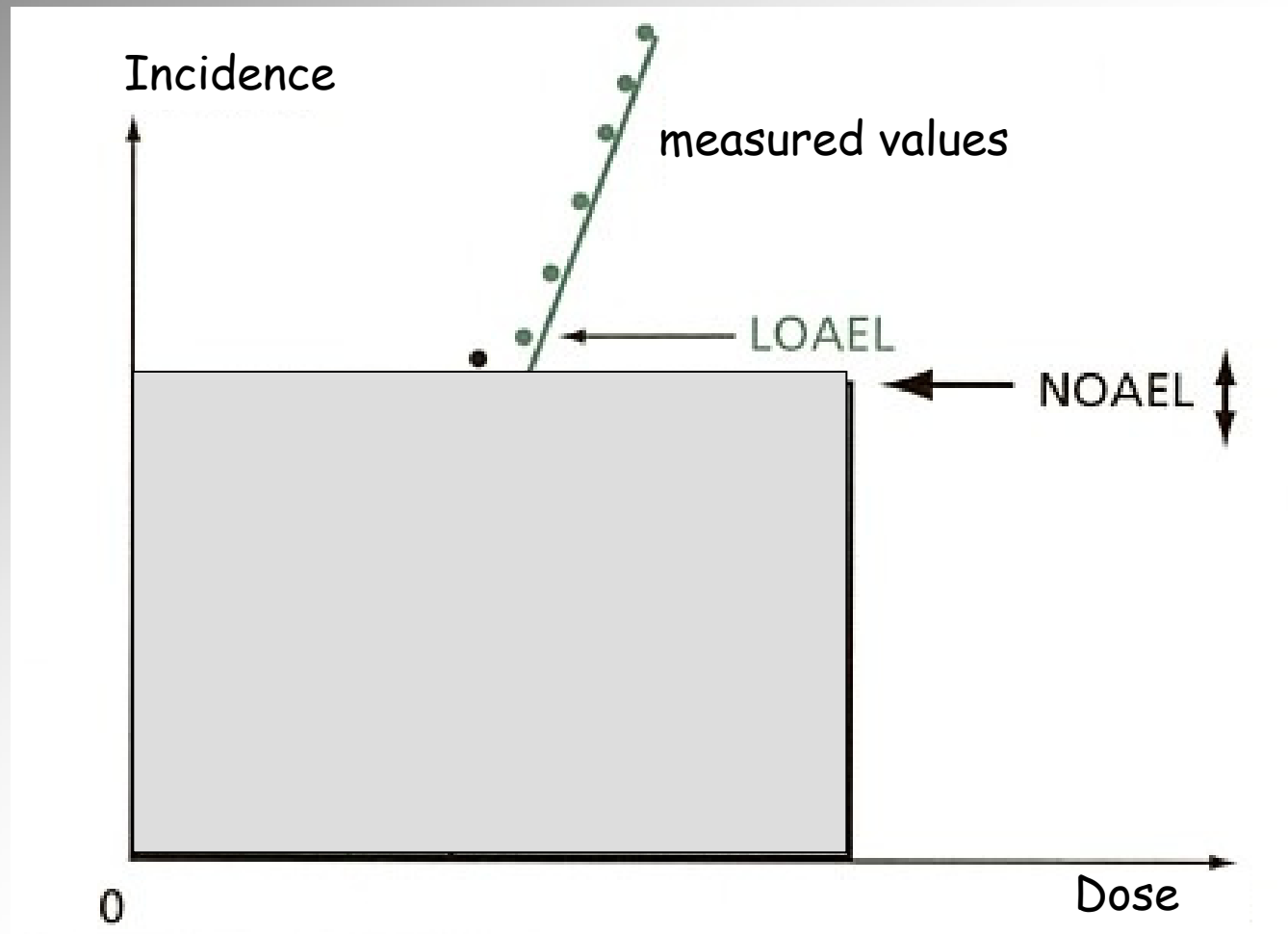
Important question for the MAK Commission:

- Is there a carcinogenic potential relevant under realistic exposure conditions?
- What are the underlying mechanisms involved?
- Is it possible to define MAK values which protect from carcinogenicity?

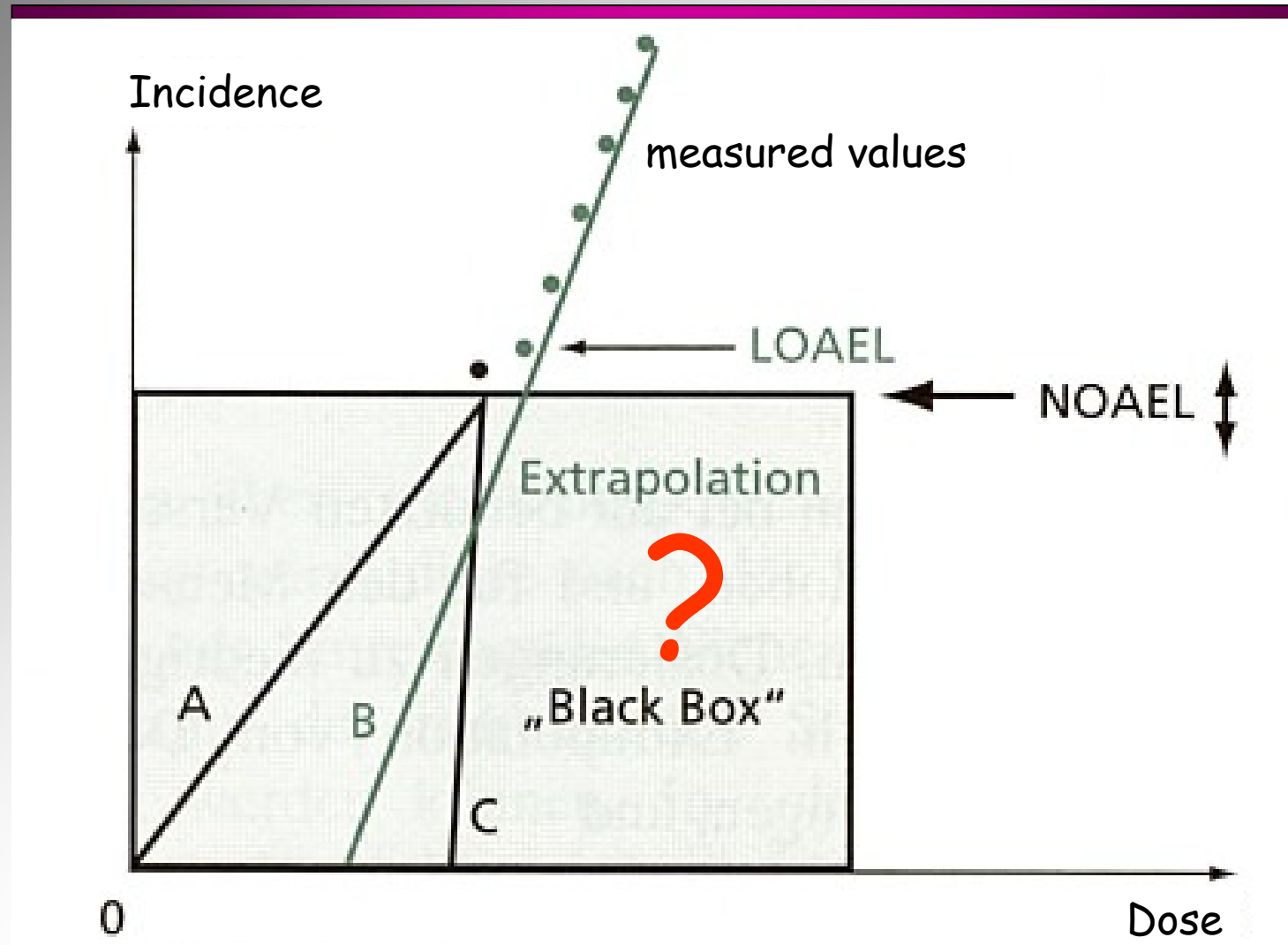
 Hazard identification vs. risk estimation

 Health based exposure limits for carcinogens also required by the german legislation („Gefahrstoffverordnung“)

The problem of dose-response-relationships in case of carcinogenic compounds...



The problem of dose-response-relationships in case of carcinogenic compounds...



Data base

- Data collection
 - Published literature with respect to
 - epidemiological data,
 - occupational medical reports,
 - toxicological properties
 - other relevant information
 - Company reports, if full study report available, handled confidentially
- Data evaluation
 - relevance for current assessment
 - validity of the studies (e.g., according to OECD guidelines if possible, otherwise expert judgement)

Categories for carcinogenic substances

1. Substances that **cause cancer in humans** and can be assumed to make a **significant contribution to cancer risk** (adequate epidemiological evidence or limited epidemiological evidence and mode of action relevant to humans)

Examples:

- Arsenic and inorganic arsenic compounds
- Asbestos
- Benzene
- Beryllium
- Cadmium
- Hard metals (containing tungsten carbide and cobalt)
- Nickel and nickel compounds
- Vinyl chloride

Categories for carcinogenic substances

2. Substances that are considered to be carcinogenic in humans based on sufficient data from long-term animal studies or limited evidence from animal studies, substantiated by evidence from epidemiological studies and/or supported by mode of action (in vitro tests, short-term animal studies)

Examples:

- Acrylamide
- Antimony and its inorganic compounds
- Ceramic fibres (fibrous dust)
- Cobalt and cobalt compounds
- Ethylene oxide
- Lead
- Various N-nitroso compounds
- ...

Categories for carcinogenic substances

3. Substances that cause **concern** that they could be carcinogenic to humans but **cannot be assessed conclusively because of lack of data**. The classification in Category 3 is provisional.

- B. Substances for which in vitro or animal studies have yielded **evidence of carcinogenic effects, but not sufficient for classification of the substance in one of the other categories** (further studies are required). A MAK or BAT value can be established in the absence of genotoxicity.

Categories for carcinogenic substances

Examples for category 3 B:

- Carbon black
- Diethanolamine
- Ozone
- Phenol
- Selenium and its inorganic compounds
- ...

Categories for carcinogenic substances

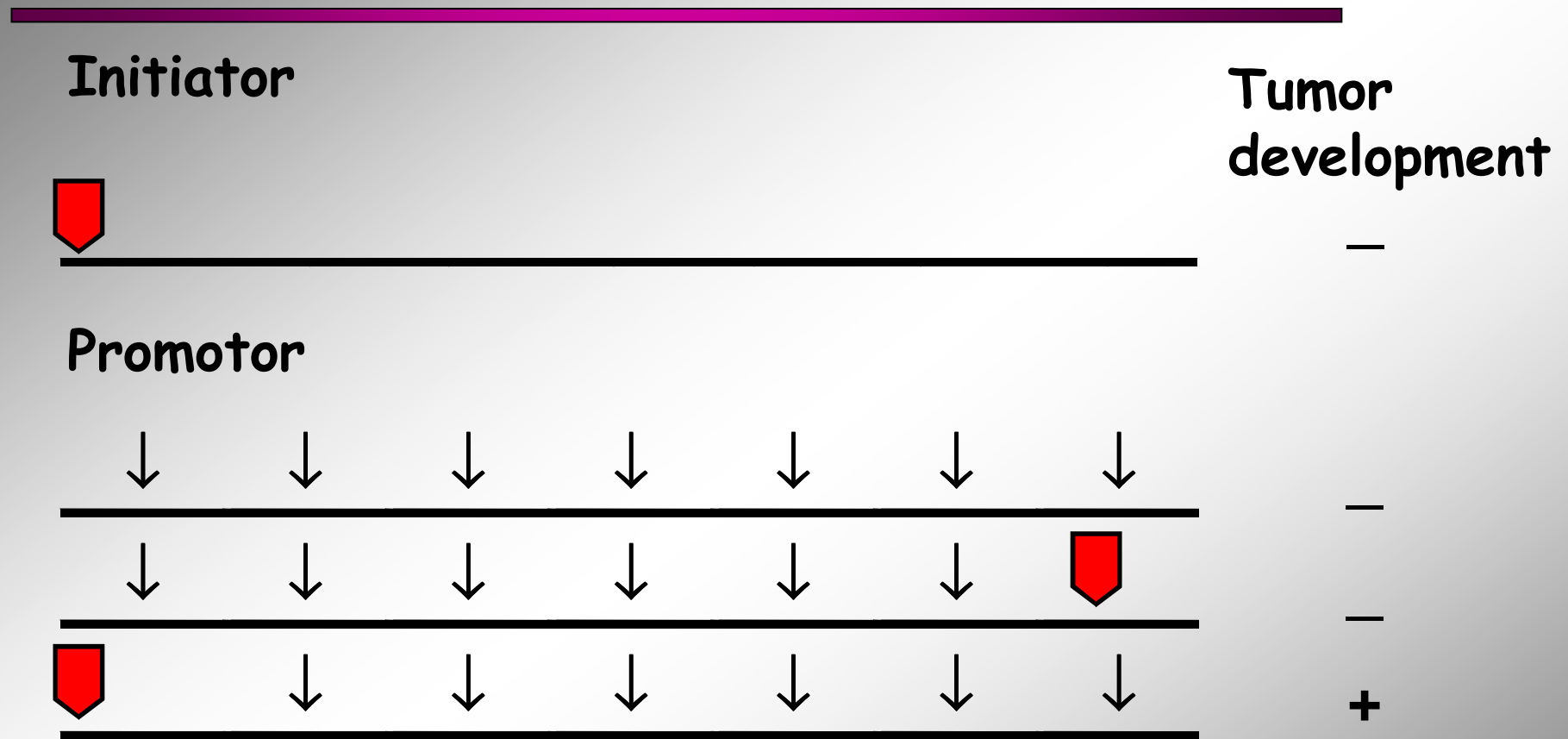
4. Substances with carcinogenic potential for which a non-genotoxic mode of action is of prime importance; **no significant** contribution to human cancer risk is expected at exposure observing MAK and BAT values
 - mode of action well understood
 - related for example to increases in cellular proliferation, inhibition of apoptosis or disturbances in cellular differentiation

Categories for carcinogenic substances

Examples for category 4:

- Aniline
- Formaldehyde
- Hydrogen peroxide
- Sulfuric acid
- 2,3,7,8 - TCDD
- ...

Current (simplified) model of carcinogenesis



Comparison Tumor initiators/ Tumor promoters

Typical initiators:

- Directly (or after metabolization) DNA reactive substances like aflatoxins, benzo[a]pyrene, dimethylnitrosamine

Typical promoters:

- Irritants and inflammatory substances; increase cell proliferation, such as chloroform, man-made mineral fibres, dioxine (TCDD), DDT, PCBs, formaldehyde, titanium dioxide

Tumor promoters

- Usually long-term exposure required
- Reversible effect
- Examples for mechanisms:
 - Hormonal effects in target tissue(s)
 - Chronic stimulation of proliferation (toxicity, inflammation)
- Non-linear dose-response-relationship

Sulfuric acid (category 4)

- Human carcinogen due to strong irritation, no genotoxicity

- Irritation: Man: LOEL 0.3 mg/m³

- Rabbits: LOEC 0.05 mg/m³

Systemic effects: not relevant due to strong irritation

MAK: 0.1 mg/m³ STEL: 0.2 mg/m³ **Category 4 carcinogen**

- In volunteers at 0.3 mg/m³ (1-4x10 min) consistent impairment of mucociliary clearance & reduction of pH in mucus expected. No long-term studies in humans: preliminary MAK.

- In rabbits increased clearance at 0.25 and 0.5 mg/m³ , 1 year at 0.125 mg/m³ (2 hrs, 5 d/w) slight reversible bronchiolar hyperplasia

Hydrogen peroxide (category 4)

- Local carcinogenic effects in rats and mice at high exposure conditions, depending also on catalase activity (small intestine, stomach, skin)
- Genotoxic in subcellular and bacterial test systems; mammalian cells more resistant
- No genotoxicity in vivo (UDS, chromosomal aberrations, micronuclei)
- Mechanisms of carcinogenicity:
 - Local irritation, tissue damage
 - Genotoxicity in case of limited detoxification (e.g., catalase)

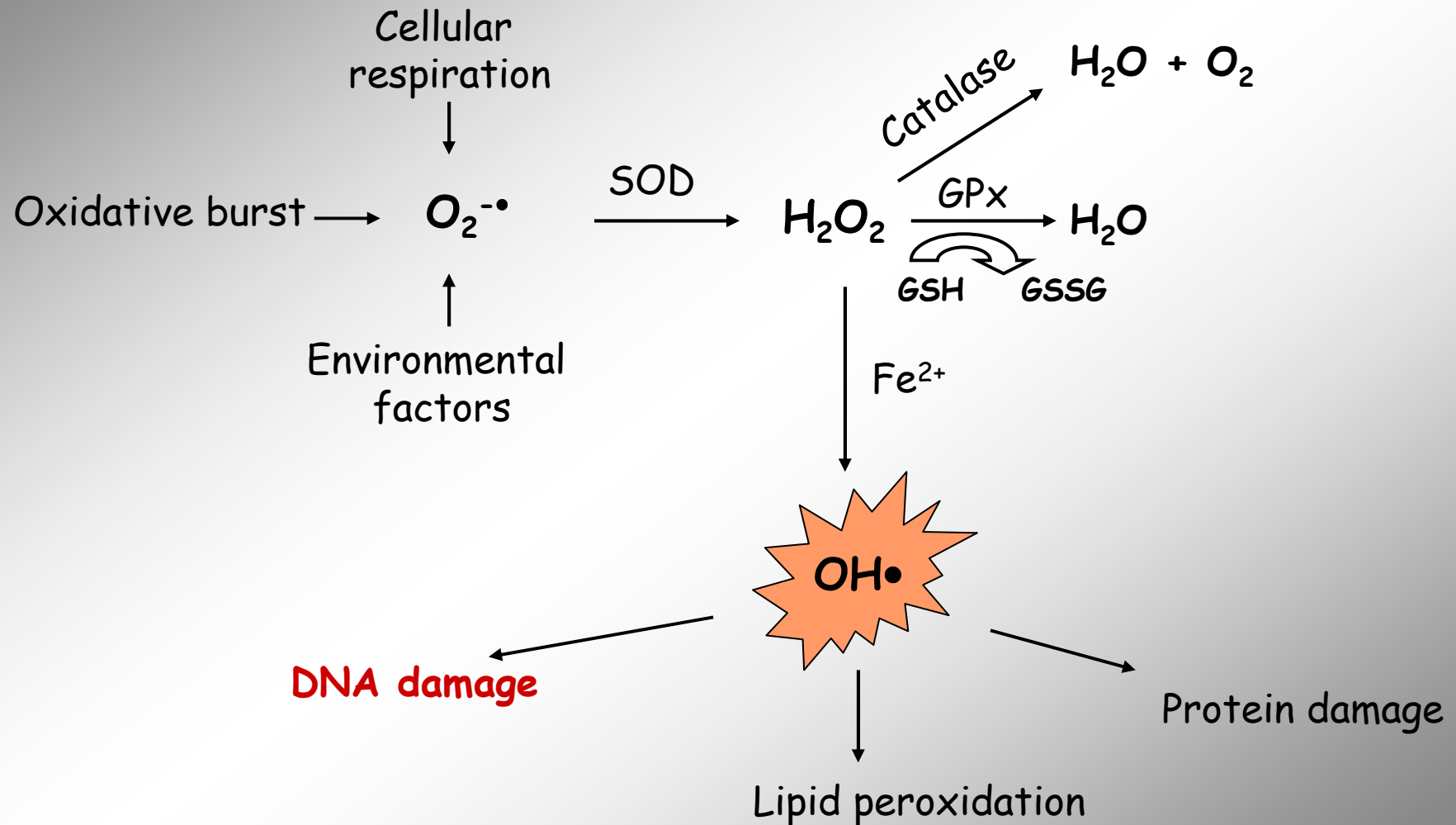


both effects due to increased generation of reactive oxygen species

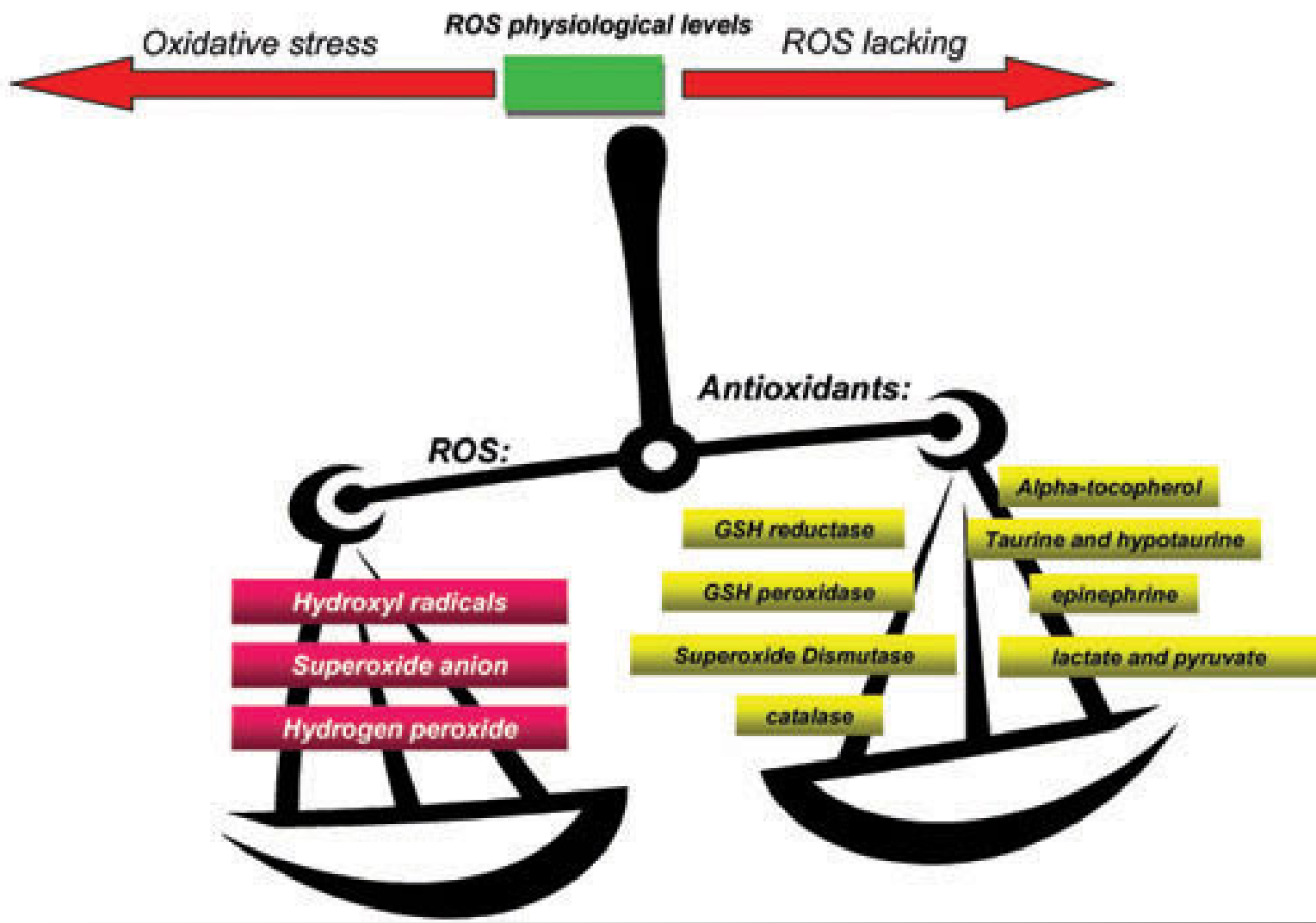


MAK value (0.5 ml/m³) based on the prevention of sensoric irritation should also protect from genotoxicity

Cellular damage by reactive oxygen species

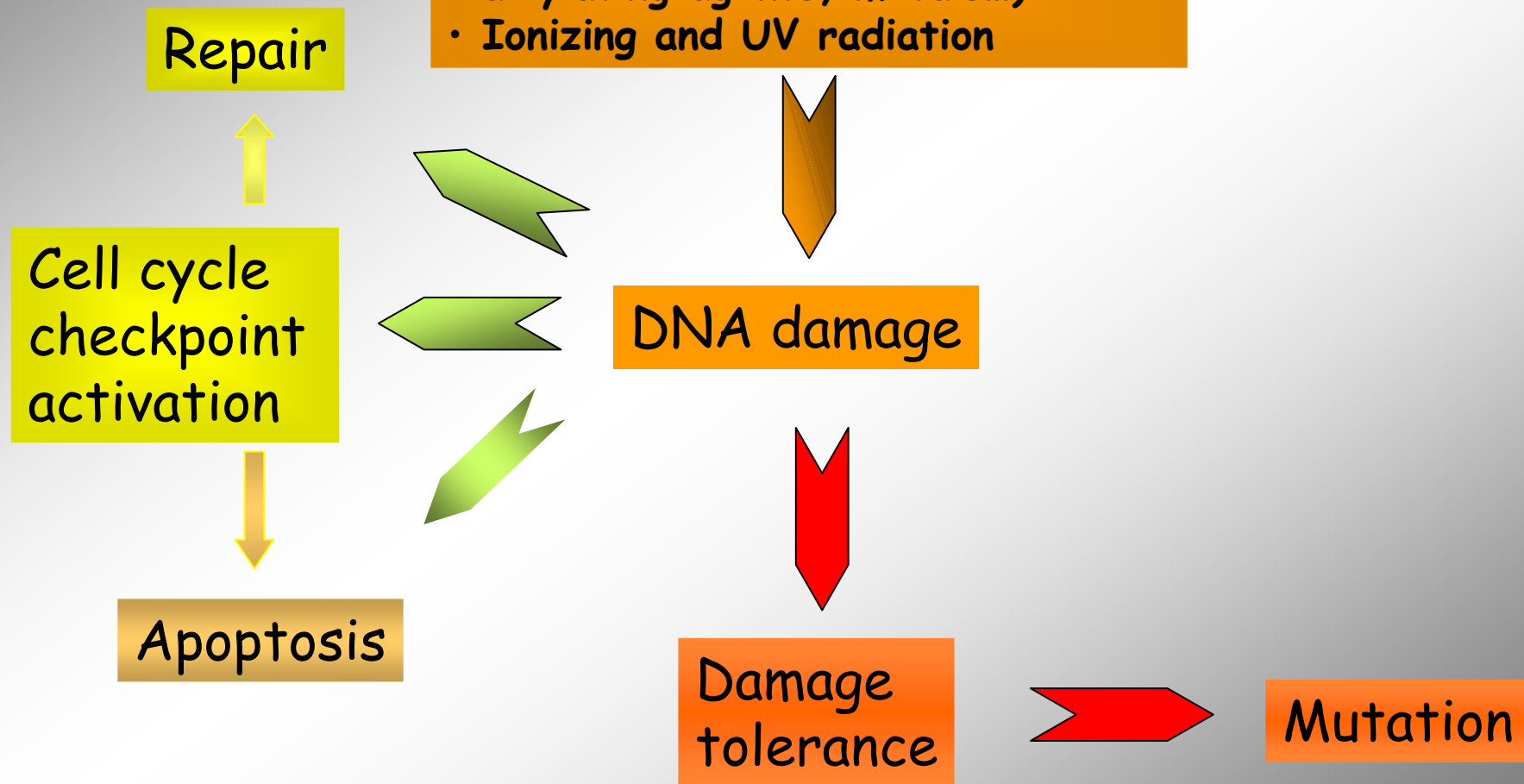


Oxidative stress



Some substances affect genomic stability by indirect mechanisms, such as the cellular response to DNA damage...

- Endogenous processes (ROS, DNA base elimination...)
- Environmental mutagens (BaP, alkylating agents, metals...)
- Ionizing and UV radiation



Categories for carcinogenic substances

5. Substances with **carcinogenic and genotoxic effects**, the potency of which is considered to be so low that, provided the MAK and BAT values are observed, **no significant contribution to human cancer risk is to be expected** (must be supported by information on the **mode of action**, dose-dependence and toxicokinetic data pertinent to species comparison)

Up to now only four substances listed:

- Acetaldehyde
- Ethanol
- Isoprene
- Styrene

Example Ethanol (Category 5)

- **Human carcinogen; critical metabolite acetaldehyde**
- **Concentration of ethanol in blood over time determines the internal body burden of the critical metabolite acetaldehyde**
- **Humans are physiologically exposed to ethanol due to endogenous ethanol production**
 - **amount and range of internal life-time body burden are known**
 - **correlation of external ethanol concentration with ethanol concentration in blood is also known**
 - **at an exposure of 500 ml ethanol/m³ during the entire working life, the average life-time body burden of ethanol is still within the range of variation of the endogenous body burden**

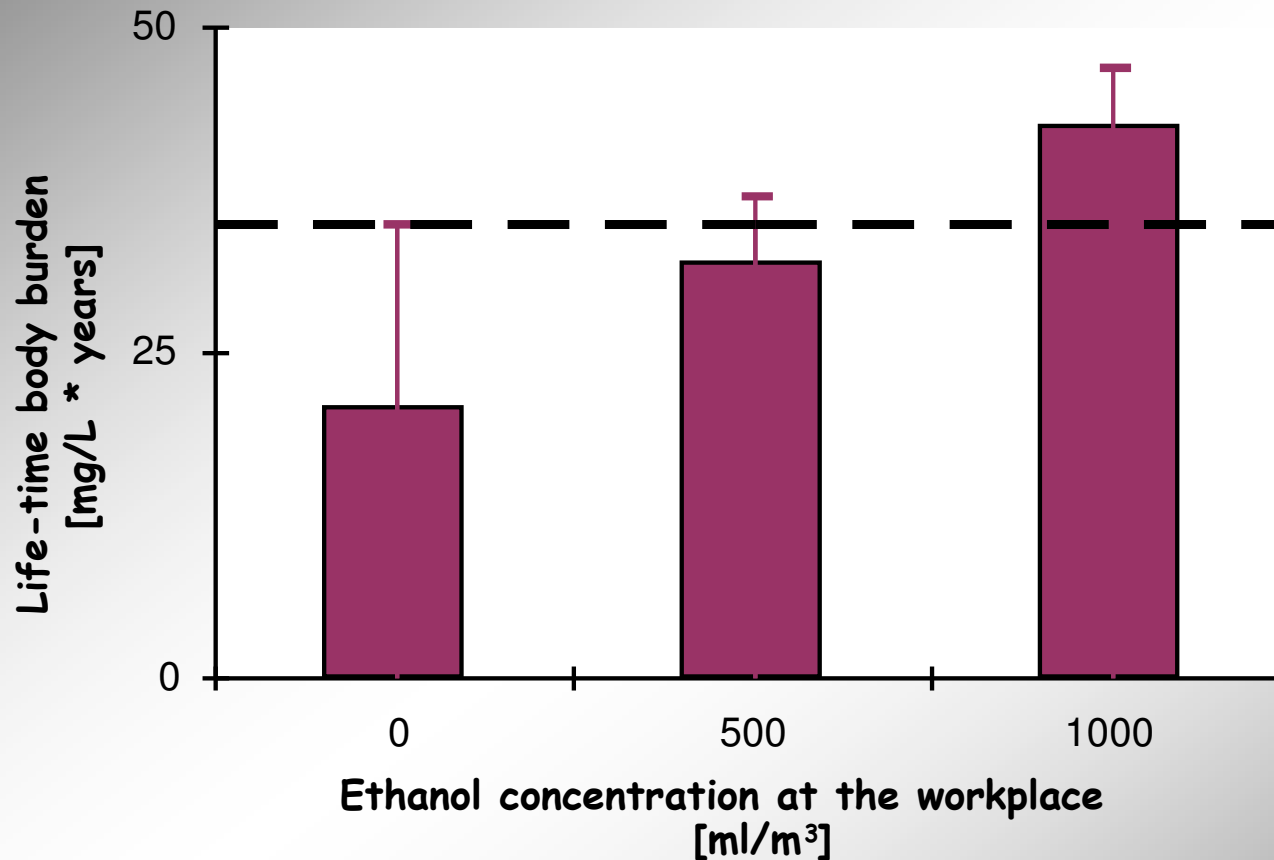
Metabolism of ethanol



* Alkohol dehydrogenase

** Aldehyde dehydrogenase

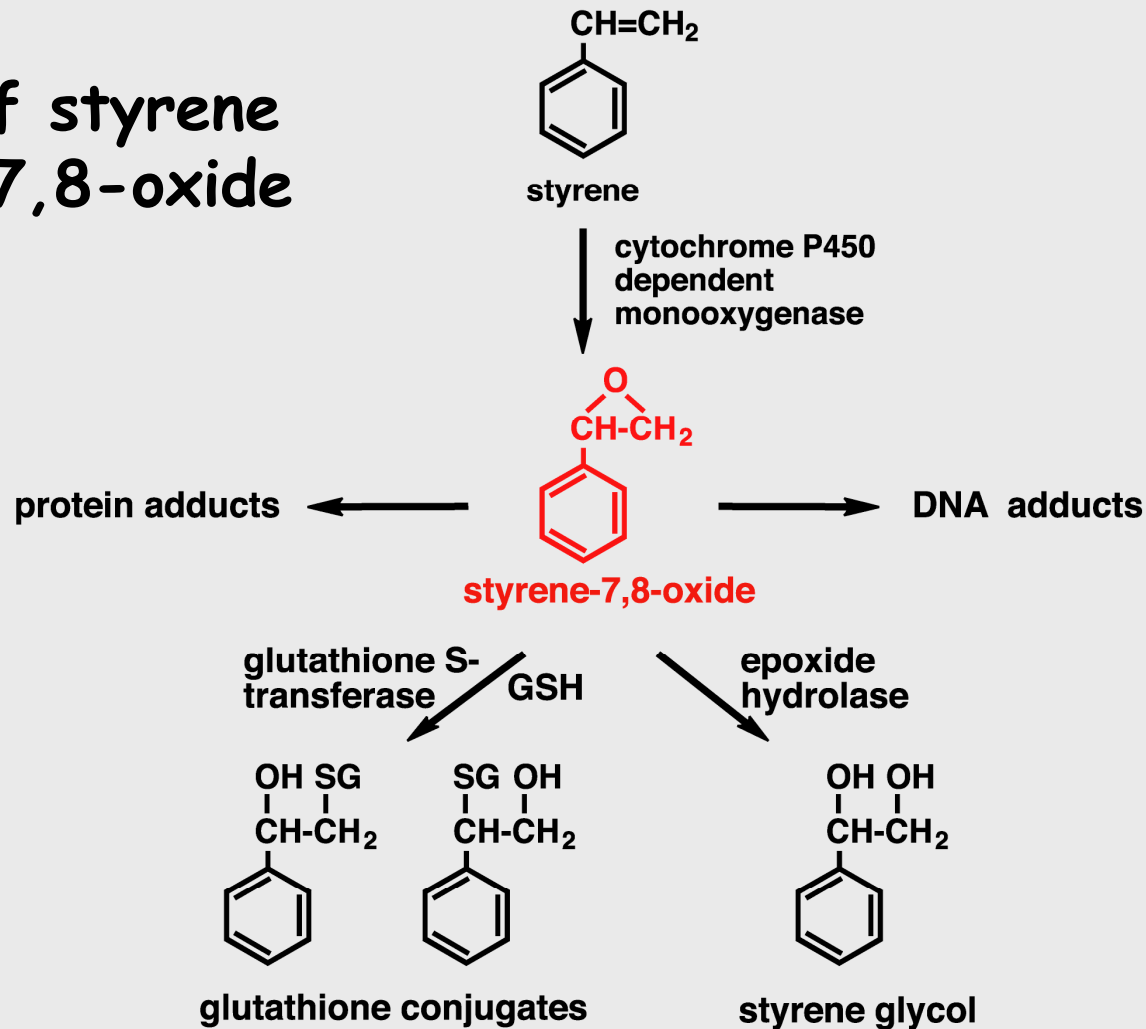
Life-time body burden of ethanol without and with occupational exposure



→ workplace exposures to concentrations up to 500 ml/m³ do not result in a significant contribution to cancer risk

Styrene (Category 5)

Metabolism of styrene and styrene-7,8-oxide



Metabolism of styrene and styrene-7,8-oxide

- Critical metabolite formed by mouse, rat and man
- Extent assessed by biochemical marker Hb-adducts:
Mouse 1 → Rat 1/2 - 1/3 → Man 1/20 - 1/50
- Carcinogenic risk calculation for systemic styrene exposure
- Based on the positive oral studies in mice (lung tumors) and oral study with styrene oxide in rats (maximal statistic tumor incidence of 3 %)
- Exposure at the workplace (40 years, 8 hrs per day, 5 days per week, 48 weeks per year) at
20 ppm results in a risk of about 1 : 20 000,
which is well below the risk of endogeneous epoxides (for
example, ethylene oxide)



Category 5, MAK 20 ppm

Categories for carcinogenic substances

3. Substances that cause **concern** that they could be carcinogenic to humans but **cannot be assessed conclusively because of lack of data**. The classification in Category 3 is provisional.
 - a. Substances for which the **criteria for classification in category 4 or 5 are fulfilled** but for which the **database is insufficient** for the establishment of a MAK or BAT value.
 - b. Substances for which in vitro or animal studies have yielded **evidence of carcinogenic effects**, but not sufficient for classification of the substance in one of the other categories (further studies are required). A MAK or BAT value can be established in the absence of genotoxicity.

Titanium dioxide (Category 3A)

- Carcinogenic in experimental animals
- Generation of reactive oxygen species and DNA damage in *in vitro* systems due to photoreactivity



not relevant under in vivo conditions

- Carcinogenicity due to chronic inflammation (particle effect)



MAK value has to protect from chronic inflammation (has yet to be defined)



Common value for biopersistent particles

Substances requiring special consideration: Example carcinogenic metal compounds

- Metals are frequently listed as the element “and its inorganic compounds”
- For individual compounds of most metals, the available data from animal studies or from known effects on man are insufficient for evaluation.



All available **epidemiological, animal and mechanistic data** for the metal and its compounds are used to decide on classification and whether or not they are assigned to the same category

Perspectives

Currently:

- Working group on „**New Mechanisms in Carcinogenicity**“

Aim:

- Development of **concepts for integrating the manifold mechanisms of carcinogenicity** including current knowledge of cell biology into risk assessment and classification of carcinogens
- Consideration of **biological consequences of diverse DNA adducts**
- Potential **consideration of new toxicogenomic data** into risk assessment (for example, identification of mode of action)



Identification of research need !