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Classification systems and approaches of risk assessment for carcinogenic substances

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Genotoxic/ carcinogenic substances: Background

In spite of manifold approaches to substitute carcinogens, there are many carcinogens present in the environment, in food and at workplaces:

- Combustion products
- Carcinogenic metal compounds
- Natural bioactive food ingredients
- Substances generated during storage and preparation of food (mycotoxins, acrylamide, nitrosamines, heterocyclic aromatic amines, benzo[a]pyrene....)
- …

Hazard-based classifications

ECHA CLP, based on principal carcinogenic properties of the substances:

- **Category 1A**: known to have carcinogenic potential for humans, largely based on human evidence
- **Category 1B**: presumed to have carcinogenic potential for humans, largely based on animal evidence
- **Category 2**: Suspected human carcinogens

IARC:

- **Group 1:** Carcinogenic to humans
- **Group 2A:** Probably carcinogenic to humans
- **Group 2B:** Possibly carcinogenic to humans
- **Group 3:** Not classifiable as to its carcinogenicity to humans

Hazard- vs. risk-based approaches

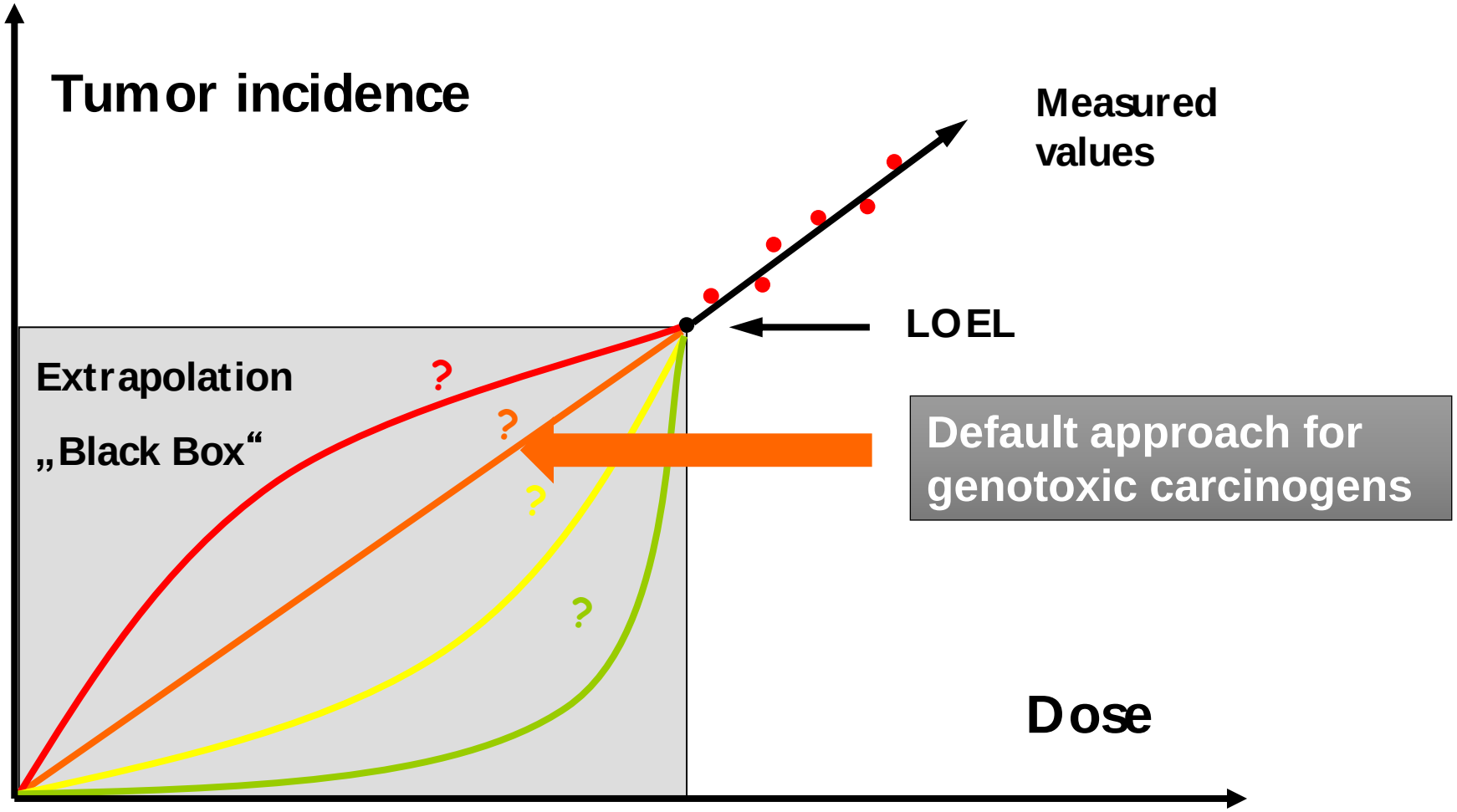
- **Risk-based approaches:** take into account the mode of action (MoA)

Important question:

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

Health-based vs. risk-based limit values

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



Health- and/or risk-based approaches

- **Distinction of carcinogens** in view of low dose extrapolation and potential proposal of health-based occupational exposure limits:

- **Comprehensive evaluation** of **epidemiological data (preferred)**, **animal carcinogenicity studies** and **„Mode of Action“ information** is critical for either
  - *Health-based OEL proposal*
  - *Numerical risk estimates or*
  - *Neither OEL proposal nor numerical risk estimates*

Past and current approaches for workplace carcinogens

TRK-Values (technical guidance concentration)

- Strictly based on **technological considerations**; valid until 2005
- **Since 2005: Requirement for setting health-based exposure limits also for carcinogens**

Since 2005 in Germany two different approaches:

- **Exposure-Risk-Relationships** (Expositions-Risiko-Beziehungen; ERB) established by Ausschuss für Gefahrstoffe **(AGS):**
  - **Tolerated or accepted risks:** 4:1,000 (tolerated risk); 4:10,000 (accepted risk 2013); 4:100,000; accepted risk 2018 at the latest)
- **MAK categories 4 and 5** (since 1998; **similar approach by SCOEL since 2008 and by ECHA since 2019)**

In the meantime considerably lower threshold values for many carcinogens, e.g., metal compounds !

Germany: MAK categories for genotoxic/ carcinogenic substances

1. Substances that **cause cancer in humans** and can be **assumed to contribute to cancer risk**

2. Substances that are **considered to be carcinogenic in humans** based on **sufficient data from long-term animal studies** …. **supported by mode of action**

   → **No MAK or BAT value established**

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.

   → **No MAK or BAT value established**

MAK categories for genotoxic/ carcinogenic substances

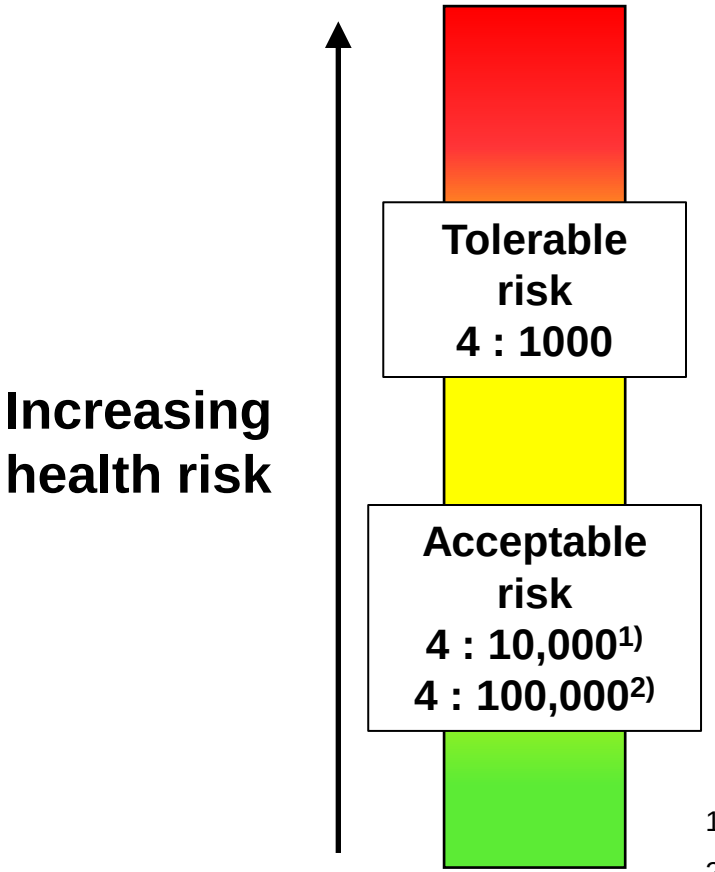
4. Substances **that cause cancer in humans or animals** ... and for which a MAK value can be derived. A **non-genotoxic mode of action is of prime importance**; **no contribution to human cancer risk is expected** at exposure observing **MAK and BAT values**

Example: Granular biopersistant dust (GBD) (inert dust without additional specific toxicity)

→ **Carcinogenic at high concentrations; MAK value protects from chronic inflammation** on conditions of overload and diminished clearance

5. Substances **that cause cancer in humans or animals** ... and for which a MAK value can be derived. A **genotoxic mode of action is of prime importance** but is **considered to contribute only very slightly to human cancer risk**, provided the MAK and BAT values are observed (Acetaldehyde, Ethanol, Isoprene, Styrene, Dichloromethane)

The risk-based concept for carcinogenic substances applied by the Ausschuss für Gefahrstoffe (AGS)



Red: Stop! (Hazard area)

Health risk not tolerable – prohibition of use unless exposure is reduced significantly

Yellow: Attention! (Area of concern)

Unwanted risk – provide for active risk

Green: Go! (Area of basic safety precautions)

Health risk acceptable – duty of care remains

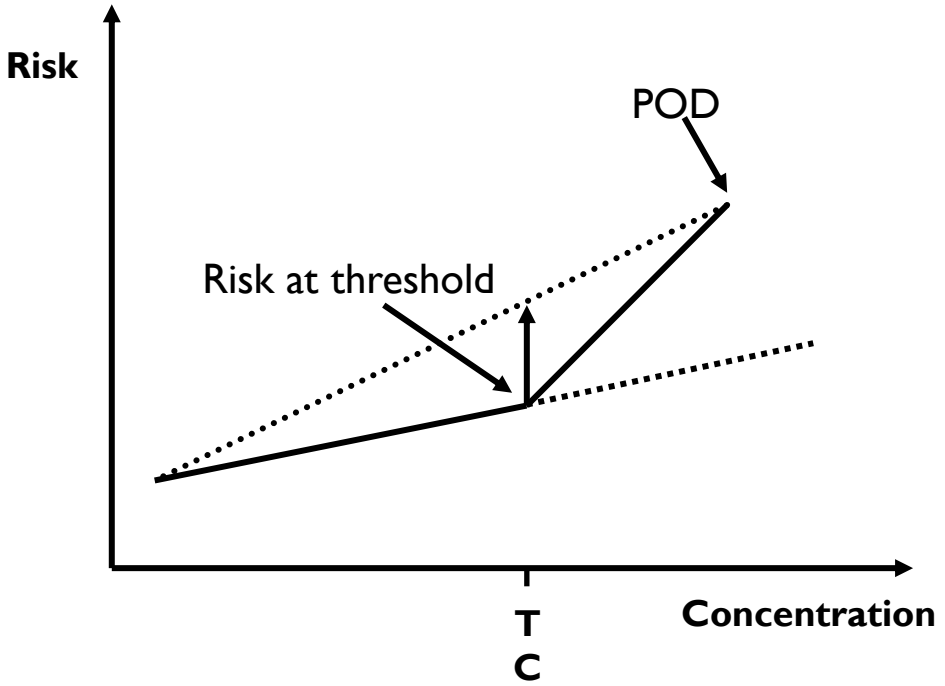
[1)] until 2013
[2)] until 2018

BAuA (2013) The risk-based concept for carcinogenic substances developed by the Committee for Hazardous Substances, From limit-value orientation to an action-oriented approach

The risk-based concept for carcinogenic substances applied by the Ausschuss für Gefahrstoffe (AGS)

Exposure-Risk-Relationships (ERR) of carcinogenic substances

- refer to the **relation between the substance concentration (inhalation) and the statistical probability of developing cancer**
- based on data from **animal studies or** derived from human data
- **extrapolation** in the area of low risks **linear or sublinear**, depending on the mode of action
- **the acceptable/tolerable concentration** is a **substance-specific value** corresponding to the risk according to the ERR



AGS (2014) Technical Rule for Hazardous Substances 910, Risk-related concept of measures for activities involving carcinogenic hazardous substances

Recent publication of a joint working group of the German MAK commission and SKLM

Archives of Toxicology (2020) 94:1787–1877
https://doi.org/10.1007/s00204-020-02733-2

REVIEW ARTICLE

Mode of action-based risk assessment of genotoxic carcinogens

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Aim:

Development of **concepts for integrating the manifold mechanisms of carcinogenicity** including current knowledge of cell biology **into risk assessment and classification** of carcinogens

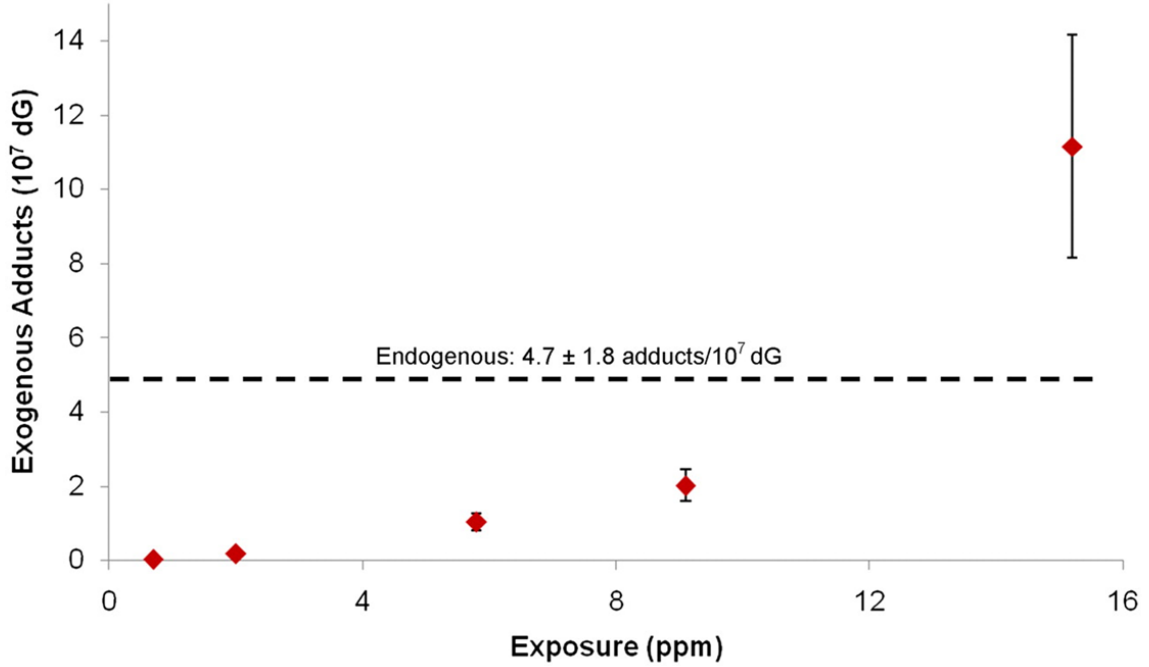
Example Formaldehyde

- Induces **DNA base damage, DNA-protein cross-links** (DPX) as well as **DNA-DNA cross-links**
- Application of stable isotopes ($^{13}CD_2$-formaldehyde, combined with MS analysis), allows the **distinction between endogenously and exogenously induced N^2-hydroxymethyl-dG** adducts (Swenberg et al., 2011), measured in human blood and tissues, predominantly generated as an intermediate of the amino acid metabolism.
- **Risk estimate of exposure via food: Formaldehyde uptake from food accounts for only 0.1 % compared to endogenous turnover** (EFSA 2014)
- **Risk estimate of workplace exposure:** Exposure levels > 10 ppm are required to exceed levels of endogenous internal DNA lesions:
  - Induction of leukemia unlikely
  - However, with regard to nose tumors, local levels are decisive → accelerated cell devision needs to be prevented (MAK value: 0.3 ppm)

Example Formaldehyde

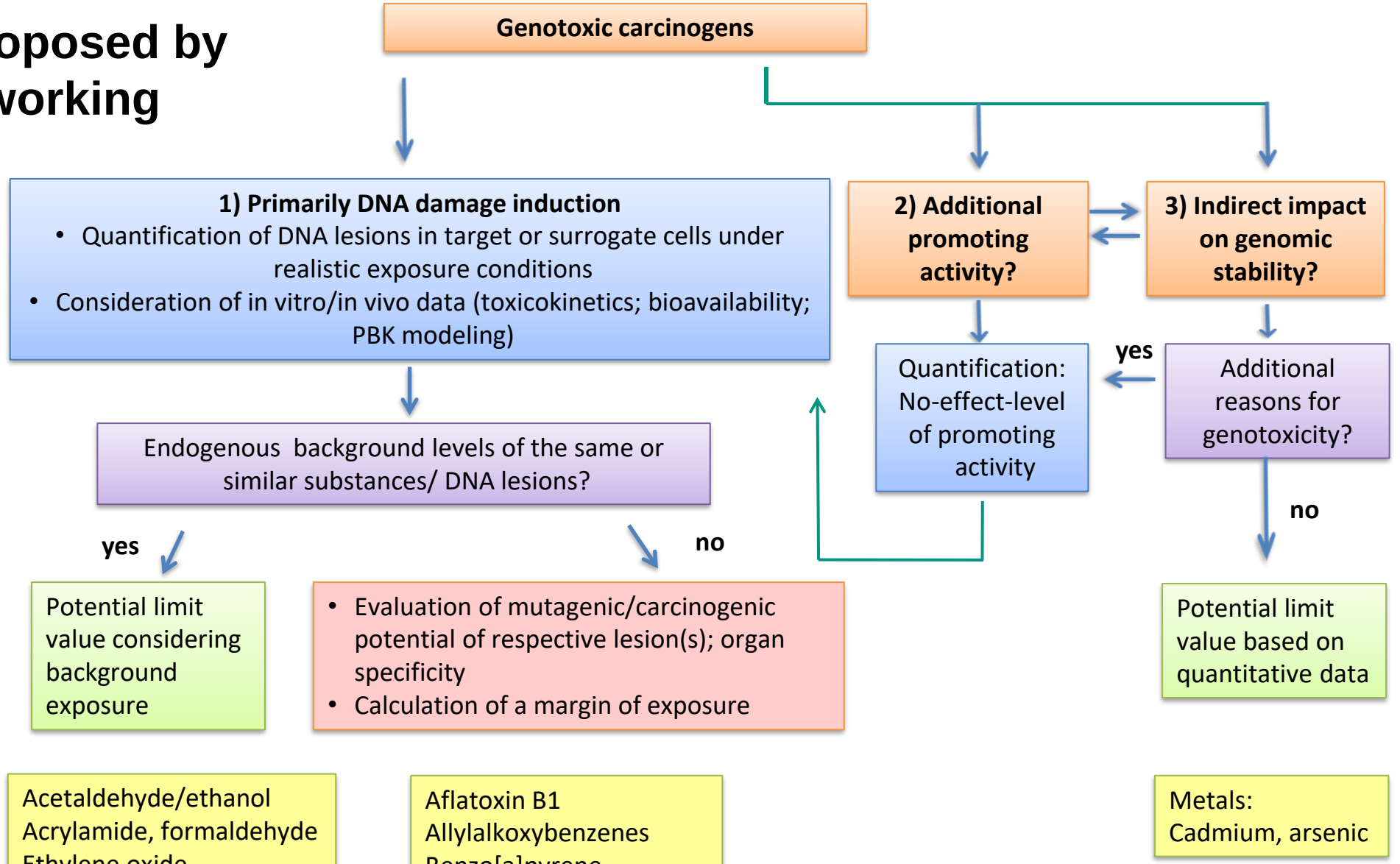
***In vivo* (rats):**

- Exogenous N2-hydroxymethyl-dG-adducts after inhalation in nasal epithelium
- Non-linear dose-response relationship after 6 h inhalation of 0.7; 2; 9.1 or 15.2



from Swenberg et al., 2011

Approach proposed by MAK/SKLM working group



Hartwig et al., (2020), Arch. of Toxicol., 94, 1787 - 1877

Thank you very much for your attention!