

# **Predictivity of carcinogenicity studies in animals for human cancer risks**

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**Prof. Dr. Wolfgang Dekant  
Department of Toxicology  
University of Würzburg  
Germany**

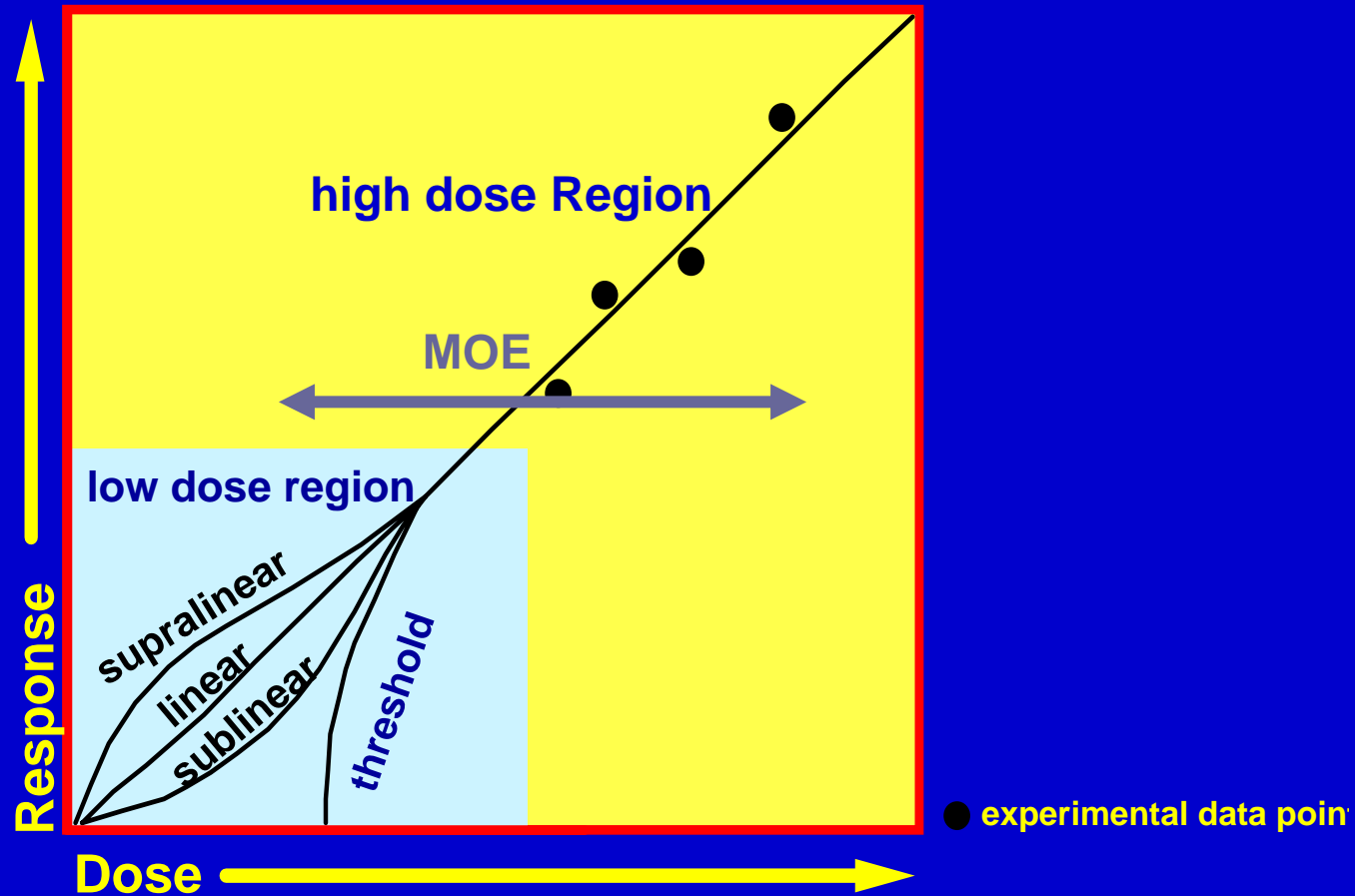
# Extrapolation issues

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**Exposures of animals in toxicity tests is usually orders of magnitude above expected or measured human exposures, therefore extrapolations are needed**

- **Dose extrapolation: high to low**
- **Species extrapolation: rodent to humans**

## Possible slopes of dose-response curves in the very low dose range below the ability of experimental determination in cancer bioassays



# Principles of carcinogenicity testing

## Basic procedures of rodent carcinogenicity testing

species	Rats and mice
age of animals at start	four to six weeks
numbers	Min. of 50 per sex per dose for carcinogenicity
doses	maximum tolerated dose (MTD) intermediate dose non-toxic dose controls
duration	24 months
dosing	gavage, feed, drinking water, inhalation
toxicologic pathology	histopathology of all tissues

# Identification of human carcinogens

Often based on increased tumor incidences in occupationally exposed populations, individuals with specific habits such as smoking, or after medical treatment

- **Low sensitivity due to small groups sizes or high background**
- **Often insufficient characterization of exposure, many confounders possible**

# Human and Animal carcinogenicity of selected agents

Agent	Carcinogenic in humans	Induces carcinoma in animal experiments
4-Aminobiphenyl	+	+
Arsenic and arsenic compounds	+	+
Asbestos	+	+
Azathioprine	+	+
Benzene	+	+
Benzidine	+	+
Benzo[a]pyrene	+	+
Beryllium	+	+
Bis(chloromethyl)ether	+	+
1,3-Butadiene	+	+
Cadmium and cadmium compounds	+	+
Chloromethyl methyl ether	+	+
Chromium[VI]	+	+/-
Diethylstilboestrol	+	+
Erionite	+	+
Ethylene oxide	+	+

Agent	Carcinogenic in humans	Induces carcinoma in animal experiments
Etoposide	+	nd
Formaldehyde	+	+
Gallium arsenide	+	+
8-Methoxypsoralen (Methoxsalen)	+	+
Methylenebis(chloroaniline) (MOCA)	+	+
Mustard gas (Sulfur mustard)	+	+/-
2-Naphthylamine	+	+
Nickel compounds	+	+
N'-Nitrosoornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)	+	+
Silica, crystalline	+	+
2,3,7,8-Tetrachlorodibenzo-para-dioxin	+	+
ortho-Toluidine	+	+
Vinyl chloride	+	+

## Animal testing alone may be “overpredictive” of human cancer risks and improved hazard characterization requires more information on mode-of-action

<b>Data set</b>	<b>Example of information required</b>
<b>Evidence of genotoxicity</b>	<b>DNA-adduct formation, mutagenicity, bioactivation</b>
<b>Effects on the expression of genes relevant in the process of carcinogenesis</b>	<b>alterations of the structure or quantity of product of a proto-oncogene or suppressor gene</b>
<b>Effects on cell behavior</b>	<b>mitogenesis, cell proliferation, hyperplasia,</b>
<b>Time and dose-response relationships and interactions</b>	<b>initiation, promotion, progression,</b>

# Progress in classification of cancer hazards (MAK)

## ■ **Category 1**

- ◆ Substances that cause cancer in man and can be assumed to make a significant contribution to cancer risk

## ■ **Category 2**

- ◆ Substances that are considered to be carcinogenic for man because sufficient data from long-term animal studies or limited evidence from animal studies substantiated by evidence from epidemiological studies indicate that they can make a significant contribution to cancer risk

## ■ **Category 3**

- ◆ Substances that cause concern that they could be carcinogenic for man but cannot be assessed conclusively of lack of data

## ■ **Category 4**

- ◆ Substances with carcinogenic potential for which genotoxicity plays no or at most a minor role. No significant contribution to human cancer is expected provided the MAK value is observed

## ■ **Category 5**

- ◆ Substances with carcinogenic and genotoxic potential, the potency of which is considered to be so low that, provided the MAK value is observed, no significant contribution to human cancer risk is to be expected

# Conclusions

- Animal studies using accepted protocols are highly predictive for human carcinogenicity
- There may be some overprediction of cancer hazards in animal experiments due to high dose toxicity or rodent specific mechanisms of tumor formation
- Therefore, additional information on genetic toxicology and mode-of-action are needed in hazard characterization applying a weight-of-evidence approach
- Epidemiology has significant limits in identifying human carcinogens with low exposures