CHEMICAL RISK ASSESSMENTS AND THEIR USES IN DECISION-MAKING

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CHEMICAL RISK ASSESSMENTS AND THEIR USES FOR DECISIONS

TOPICS

1 Foundations and Principles
2 Types of Decisions and Risk Assessment Requirements
3 Conduct of Risk Assessments
4 Characterizations of Risk, Including Uncertainties
5 Some Impediments to Risk-Based Decision Making
6 Trends

FOUNDATIONS AND PRINCIPLES I

Origins, **1930's-1970's**

- Many efforts to identify chemical exposures low enough to avoid toxicity
- Most relied heavily on expert judgements and lacked transparency
- Scientific basis not fully described
- Major step forward by FDA scientists in 1950's, in response to much new legislation.
- No clear approach to dealing with carcinogens.

FOUNDATIONS AND PRINCIPLES II

Driving Forces, **1970's**

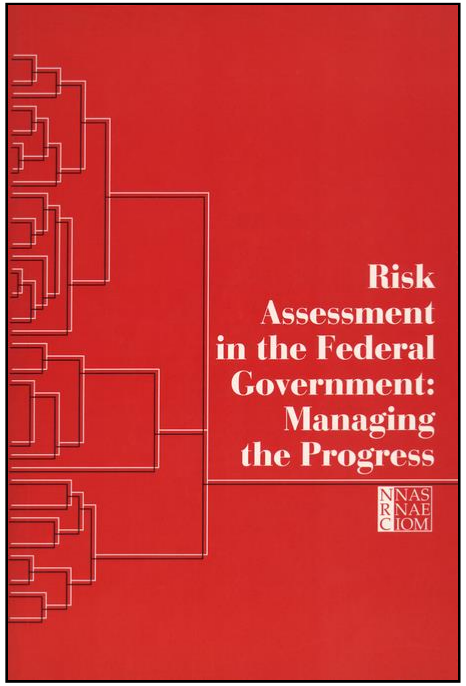
- Many new federal laws and the coming of EPA and OSHA.
- Rapidly increasing amounts of data on toxicity, including carcinogenicity
- Even more rapid increases in identifying chemicals in the environment, at lower and lower levels.
- Regulatory requirements for complete transparency in the science behind regulation.
- Increasing amounts of scholarly literature on the concept of risk, including the notion that "safety" is never a purely scientific determination.

FOUNDATIONS AND PRINCIPLES III

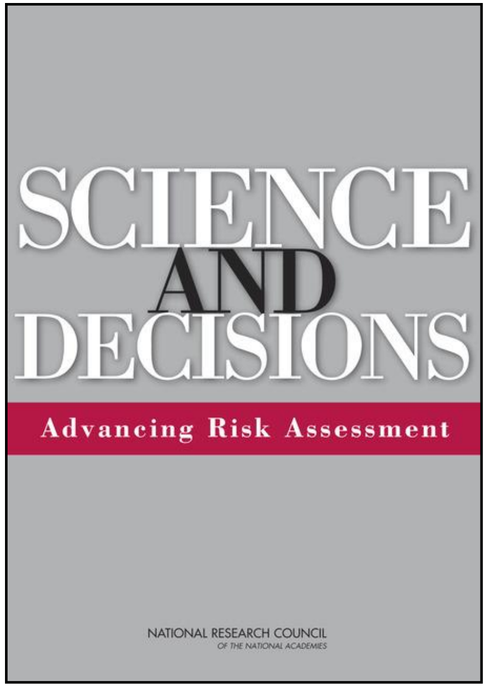
The National Academy of Sciences Steps In, **1983**

- In response to many concerns about regulatory approaches to evaluating chemical risk the NAS was asked for advice.
- A committee on "Risk Assessment in the Federal Government" produced a report that…
  - Established a framework for risk assessment;
  - Defined key terms;
  - Set forth critical concepts and principles.
- This report was and remains highly influential.

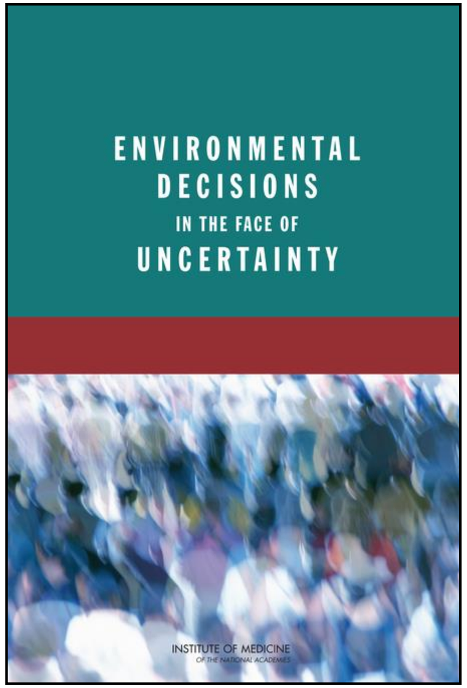
Chemical Risk Assessments have been guided by many reports from the NAS, including:



1983



2009



2013

Guidance from the **National Academy of Sciences**

etc. etc. etc.

KEY GUIDING PRINCIPLES THAT EMERGE FROM NAS

1. Risk assessments need to be both *scientifically rigorous* and *useful* for decision (up-front planning)
2. Although assessments need to be guided by risk management (policy) needs, they should be conducted without the intrusion of management.
3. Assessments are based on scientific evidence, but cannot be completed without the use of some assumptions ("defaults") that have not been fully verified.
4. Because of (3), regulators should develop and rely upon written guidelines for risk assessment
5. Critical uncertainties should be described in ways useful for decisions.

THE KEY ELEMENTS OF RISK ANALYSIS

RESEARCH

Toxic or other hazardous properties of environmental agents*

Human and environmental exposures

→

RISK ASSESSMENT

(see next slide)

→

RISK MANAGEMENT

Decisions to protect health, environment

- Restrictions on exposures
- Warnings
- Education
- Required technical controls

*Agents can be chemical, biological or physical.

RISK COMMUNICATION

THE STANDARDIZED FOUR-STEP FRAMEWORK FOR RISK ASSESSMENT (NAS, 1983)

STEP 1

Hazard Identification

What adverse health effects may result from exposure to the chemical of interest?

STEP 2

Dose-Response Assessment

What is the relationship between dose of the chemical and the probability of adverse effects (risk) in the range of doses occurring in populations?

STEP 3

Human Exposure Assessment

What doses of the chemical are occurring in exposed populations?

STEP 4

Risk Characterization

- What is the risk of toxicity (adverse health effects) in exposed populations?
- What are the significant uncertainties?

GUIDING PRINCIPLES FOR RISK-BASED DECISIONS

1 Virtually all chemicals can cause toxicity at sufficiently high doses
2 Hazard: the term applied to those toxic properties
3 The rate of occurrence and severity of a chemical’s hazards increase as exposure (dose) increases
4 Methods are available to identify doses at which hazards are unlikely to be expressed

i.e., doses at which the **RISK** that the **HAZARDS** will be expressed is negligible; “SAFE DOSES”

TYPES OF DATA AND EVIDENCE USED IN RISK ASSESSMENT

HAZARD INFORMATION	DOSE-RESPONSE INFORMATION	HUMAN EXPOSURE INFORMATION
Data from toxicology and epidemiology studies that reveal the types of toxic effects a chemical can cause	Data from toxicology and epidemiology studies that reveal how the frequency and severity of toxic effects change as the dose of the toxic agent changes	Data from analysis of chemicals present in relevant environmental media (e.g., air, water, food) and on rates of human contact with and exposure to those media

EVIDENCE REGARDING HAZARDS AND DOSE-RESPONSE DERIVES PRINCIPALLY FROM:

1. **OBSERVATIONAL EPIDEMIOLOGY STUDIES**
   - Cohort/case-control
2. **EXPERIMENTAL STUDIES**
   - Whole animal, in vitro, in silico, and other types of mechanistic studies

- **Clinical trials may reveal adverse effects**
- **Case reports often difficult to interpret**

COMMON ASSUMPTIONS UNDERLYING THE USE OF ANIMAL DATA [SCIENCE POLICY]

- Adverse effects identified in animal studies are assumed to be relevant to humans unless there is, in specific cases, a convincing scientific basis to believe they are not.
- It is appropriate to use animal data even when the data may not predict specific human health effects.
- Results obtained at very high doses are relevant to low dose intakes in humans unless there is, in specific cases, a convincing scientific basis to believe they are not.
- Animal studies cannot be used to identify subjective indictors of adverse effects, and are highly limited in their capacity to detect allergies, idiosyncratic reactions, and adverse effects on behavior or cognitive development.

DECISION CONTEXTS DICTATE THE CURRENT APPROACH TO EXPRESSING RISK ASSESSMENT RESULTS

APPROACH A

Estimate the maximum conditions of population exposure (**dose**) at which toxic effects of a chemical are not likely to occur
(**“safe” doses**)

OR

APPROACH B

Estimate the probabilities that the toxic effects of a chemical will occur in populations exposed under various conditions
(**risk per unit of dose**)

APPROACH A: THE TRADITIONAL "BRIGHT LINE" DECISION MODEL

- Results from hazard/dose-response assessments are expressed as ADIs, RfDs, TDIs, ULs, etc.
- These values are all expressed as doses and are treated as "bright lines" between safe and unsafe intakes.
- Their derivation is viewed as a strictly scientific activity.
- These are routinely used for all forms of toxicity except cancer and other effects not likely to exhibit a clear threshold.*

TYPICAL DEFINITIONS:

Exposure at the ADI is

"likely to be without deleterious effects"

"practical certainty of no harm"

Note: residual risk at ADI is <u>not quantified</u>

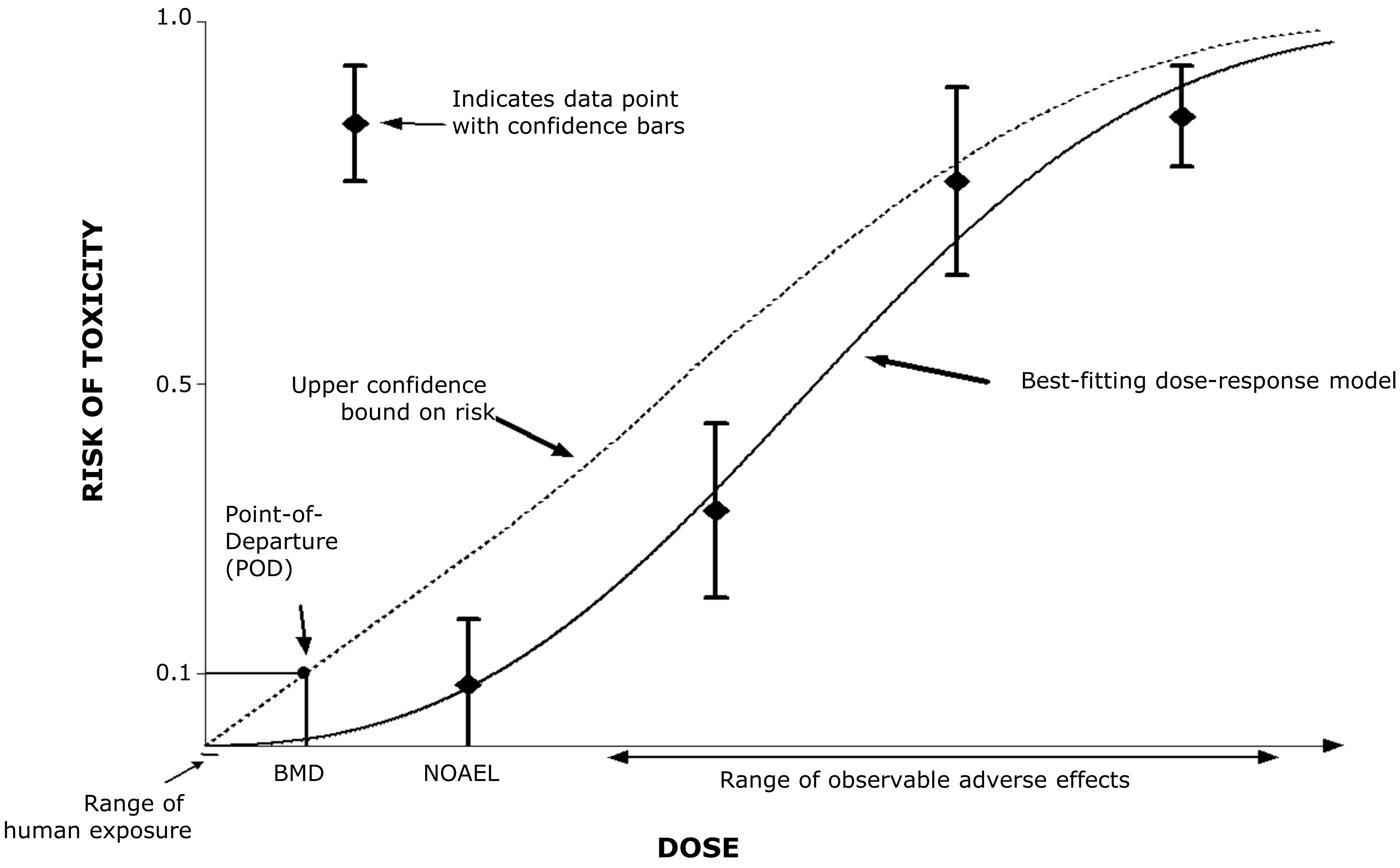
*** At least in the USA**

DEVELOPING ADIs

Steps 1 & 2 of Risk Assessment

1. All available toxicology and epidemiology studies on the chemical are collected.
2. Experts review each study, determine quality and describe what each study shows and the uncertainties.
3. Identify the types of toxicity associated with the chemical, and the strength of the scientific evidence for each type.
4. Identify the subchronic, chronic, or reproductive study showing toxicity at the **lowest dose.**
5. Determine which the quality of the study is adequate. If not, choose another study.
6. Determine which the chosen study also includes a "NO EFFECT" dose (next slide).

DERIVING SAFE DOSE BEGINS WITH OBSERVED DOSE-RESPONSE RELATIONSHIP



DEFAULT ASSUMPTIONS FOR DERIVING ADIs (Acceptable Daily Intakes)

1. The Benchmark Dose (BMD) or No-Observed Adverse Effect Level is a **THRESHOLD DOSE** for toxicity in the most sensitive animal species/study.
2. The average human is **10 times** more sensitive than experimental animals.
3. The most sensitive humans are **10 times** more sensitive than average humans.

These factors have some scientific basis, but are not certain.
They are nevertheless widely used.

ADI

The factors of 10 are called uncertainty factors (UF)

- UF_{AH} (animal to human)
- UF_{HH} (within human population)

THUS

$$ADI = \frac{NOAEL\ (mg/kg/day)}{UF_{AH} \times UF_{HH}} = \frac{NOAEL\ (mg/kg/day)}{10 \times 10}$$

OTHER UNCERTAINTIES ARE OFTEN FOUND

1. A **UF** is added if there are no studies involving lifetime exposures.
2. A **UF** may be added if the toxicology data base is deficient in other ways.
3. A **UF** is added if the critical study does not identify a NOAEL.

ADI

The ADI is expressed as the daily dose (mg/kg/day) that can be considered “safe.”

Intakes less than the ADI are accepted as “safe.”

Exceedances of the ADI are not necessarily unsafe, but there is no way to know this.

The ADI is not known to be “risk-free,” but at present no attempts are made to quantify risks at or near it.

ADIs are not established for **CARCINOGENS,** at least in the USA.

HUMAN EXPOSURE ASSESSMENT – CHEMICALS PRESENT IN FOOD

DATA AND EVALUATION NEEDS

1. Quantitative data on the concentrations of chemicals present
2. Statistical analysis to identify average and 90^{th} or 95^{th} percentile concentrations
3. Quantitative data on the rates of human consumption of each food in which the chemical is present: average rates and 90^{th} or 95^{th} percentile rates

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Estimated Daily Intake: EDI

SAFETY (FOR NON-CARCINOGENS)

EDI < ADI

USES AND LIMITATIONS OF "BRIGHT LINE" DECISION MODELS

- Adequate for decisions regarding substances **intentionally introduced** (food additives, pesticides, etc.)
- Although these measures are acknowledged **not to be risk free**, their current methods of derivation reveal nothing about the magnitudes of risks being tolerated.
- **Not useful** for many important decisions involving "trade-offs."
  - Risk – Risk
  - Risk – Technological limitations

THE INTRODUCTION OF CARCINOGEN RISK ASSESSMENT

1970s

USEPA and USFDA began adopting methods to estimate low-dose cancer risks.

- The **no-threshold** assumption was adopted.
- A **linear dose-response** model was adopted.
- **Upper bounds** on low-dose cancer risk were developed.

- Carcinogens would be regulated based on quantitative measures of risk.
- No fixed definition of safety.

This model remains in place today.

BENZENE

VINYL CHLORIDE

AFLATOXIN

DIMETHYLNITROSAMINES

DES

ASBESTOS

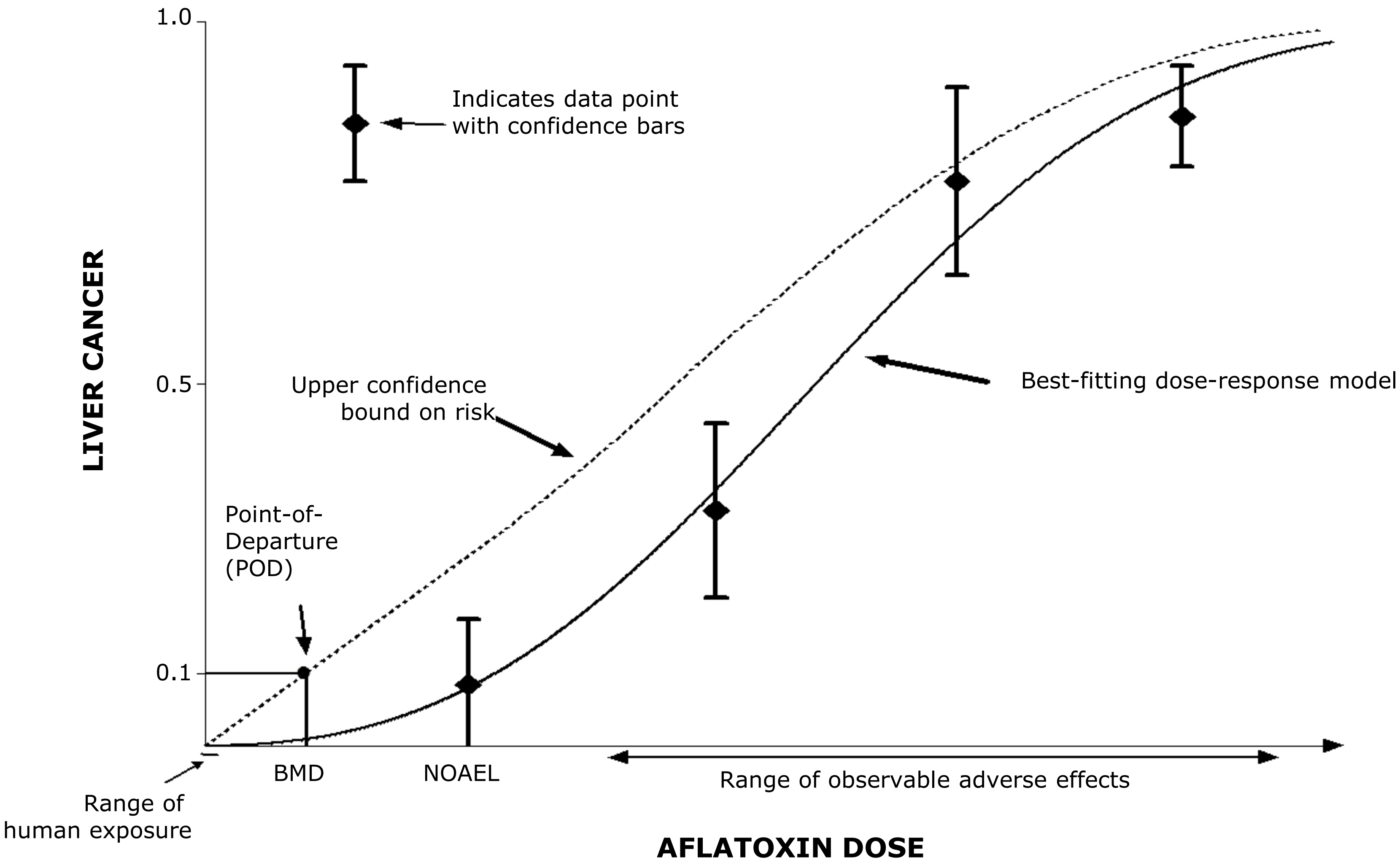
PAHs

DOSE-RESPONSE RELATIONSHIP FOR AFLATOXIN-INDUCED LIVER TUMORS IN RATS

DOSE* (MG/KG DIET)	LIFETIME TUMOR INCIDENCE	LIFETIME RISK
0	1/20	0.05
1	2/20	0.10
5	2/20	0.10
15	4/20	0.20
50	16/20	0.80
100	20/20	1.00

*Typical levels in human diet (USA) are in nanogram/kg range.

DOSE-RESPONSE RELATIONSHIP FOR AFLATOXIN-INDUCED LIVER CANCER IN RATS



QUANTIFICATION OF RISK

The approach to cancer risk assessment results in a statement regarding the lifetime probability of cancer development per unit of lifetime average daily dose.

- based on linear extrapolation into very low dose range

- not known to be accurate, but actual risk not likely to be greater.

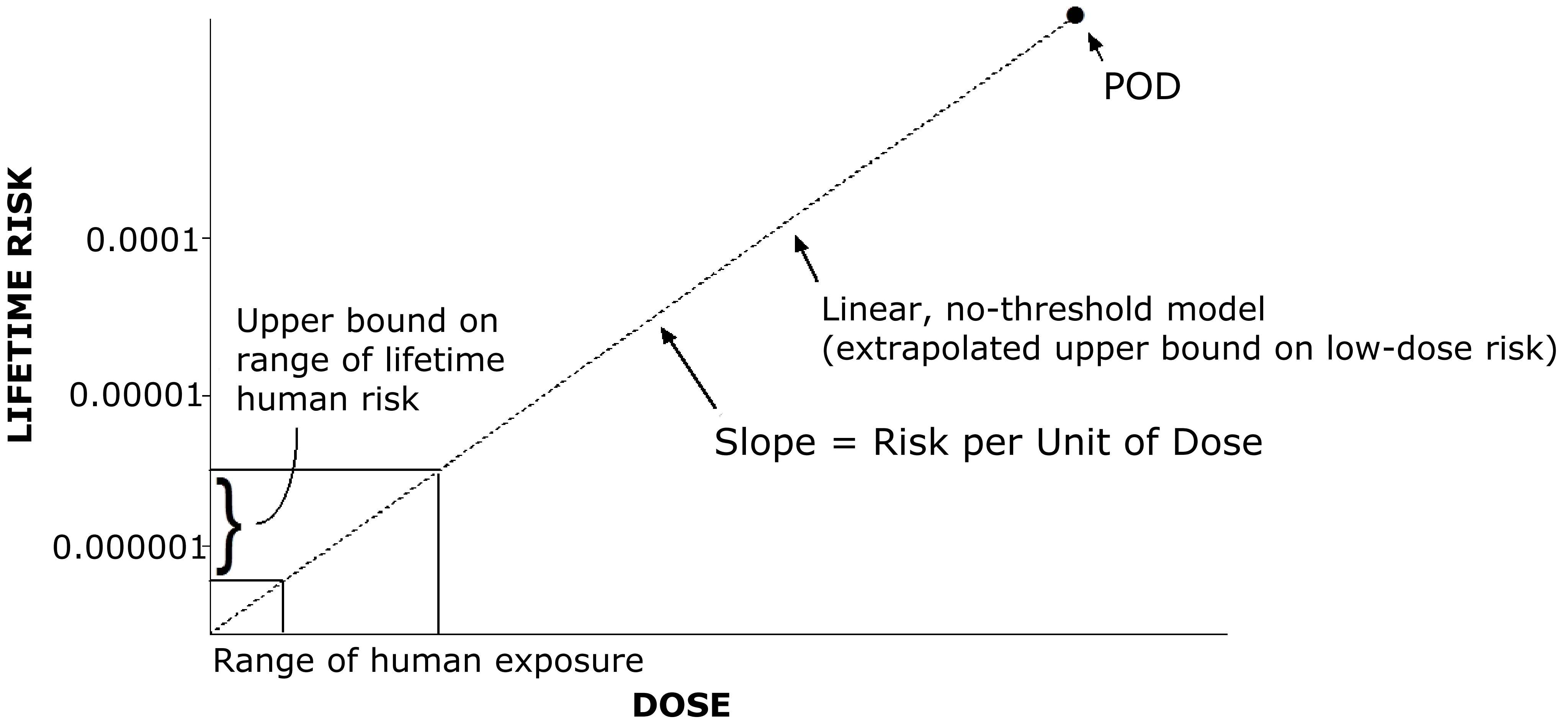
Risk assessment expressed as…

"upper bound on excess lifetime risk of cancer per unit of dose."

<u>CANCER SLOPE FACTORS</u>

THE CURRENT APPROACH TO CARCINOGEN RISK ASSESSMENT

CLOSE-UP OF EXTRAPOLATION INTO LOW-DOSE REGION



AFLATOXIN SLOPE FACTOR

- **0.00021 per µg/kg/day** (JEFCA, 1998).

- Assume present in food at 15 µg/kg
  - Assume 0.05 kg food intake/day for 70 kg person.

Daily human dose = 0.01 µg/kg/day.

Lifetime Cancer Risk (Upper Bound)

  - **0.00021** × **0.01** = **2.1×10^{-6}**

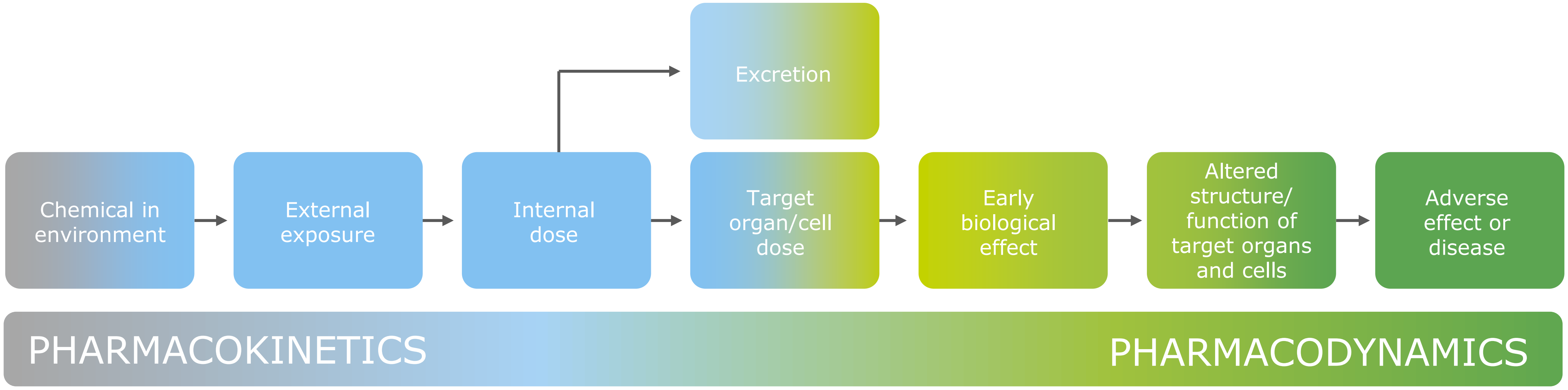
THE QUANTITATIVE RISK MODEL IS MOST USEFUL FOR DECISIONS REGARDING "TRADE-OFFS"

» It allows estimation of health benefits (risk reductions) gained with different types of risk management interventions.

» It can also be used for "bright line" decisions if a specific risk target is specified (e.g., 10-6 lifetime risk).

FROM EXPOSURE TO ADVERSE EFFECT OR DISEASE

MODE OF ACTION (MOA) FOR TOXICITY IS THE KEY TO THE FUTURE



- It is possible through research to understand these events and to use this knowledge to characterize **LOW-DOSE RISKS**, animal-human and human population **VARIABILITIES**, and **LIFE-STAGE** risks.
- Move toward quantitative expressions of risk for all forms of toxicity.

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UNCERTAINTY

1 Uncertainty is **inherent** in science/risk assessment.

2 Risk assessments are **incomplete** unless the important uncertainties in them are described.

3 Uncertainties in risk assessment should be analyzed and disclosed in ways **useful** to decision makers.

4 The **influence** of uncertainty **varies** among different decisions.

5 Decision documents should make clear how uncertainty **influences** the decision.

6 Risk **communication** is deficient if uncertainties and their influence on decisions are not explicitly discussed.

IMPEDIMENTS TO RISK COMMUNICATION

RISK ASSESSORS	RISK MANAGERS	THE PUBLIC AND VARIOUS INTEREST GROUPS
Reluctant to reveal scientific limitations May sometimes confuse science and policy	Reluctant to acquire all necessary understanding of science Uncomfortable admitting to the acceptance of any risk	Lack of trust in science and in policymakers Costs of compliance are irrelevant to some and highly relevant to others

AND

everyone is influenced by perceptions that do not match technical understanding of risk.

ATTRIBUTES OF RISK THAT INFLUENCE PUBLIC PERCEPTIONS

RISKS EASIER FOR PEOPLE TO TOLERATE	RISKS DIFFICULT FOR PEOPLE TO TOLERATE
Voluntarily assumed	Imposed by others
Personal benefit high	No perceived personal benefit
Scientists agree	Scientists disagree
Not catastrophic	Catastrophic
Natural	Industrial
Hazard not fearsome	Highly dreaded hazard
Common event	Rare event
Equitably distributed	Distribution not equitable

SUMMATION: CHEMICAL RISK ASSESSMENTS

1. Although useful epidemiology evidence is available for many important substances, most risk assessments are based on hazard and dose/response evidence from animal studies.
2. With a few exceptions, THRESHOLD models are assumed for chemical toxicity. Risk assessments yield "safe" intakes that are associated with very small but unspecified risks.
3. Carcinogens are assumed to act through NON-THRESHOLD mechanisms unless convincing evidence exists in specific cases to refute such a mechanism.
4. "Bright line" risk outcomes are most useful for decisions involving intentionally introduced and readily controlled substances.
5. The types of quantitative risk models used for carcinogens are most useful for complex decisions involving substances that are not readily avoidable.
6. Efforts are underway to use detailed mechanistic information to guide risk assessments and to develop quantitative risk estimates for both threshold and non-threshold agents.
7. Careful elucidation of uncertainties in a manner useful for decisions is an underdeveloped but exceedingly important area of work.