USA approaches to Mathematical Modelling

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‘The Committee [CoC] restated its views, published in its guidelines in 1991, that use of mathematical models to evaluate the dose-response for carcinogens, namely that extrapolation of the dose-response curve below the lowest experimental data points, taken from animal bioassay data, gave an impression of precision which cannot be justified from the approximations and assumptions used.’

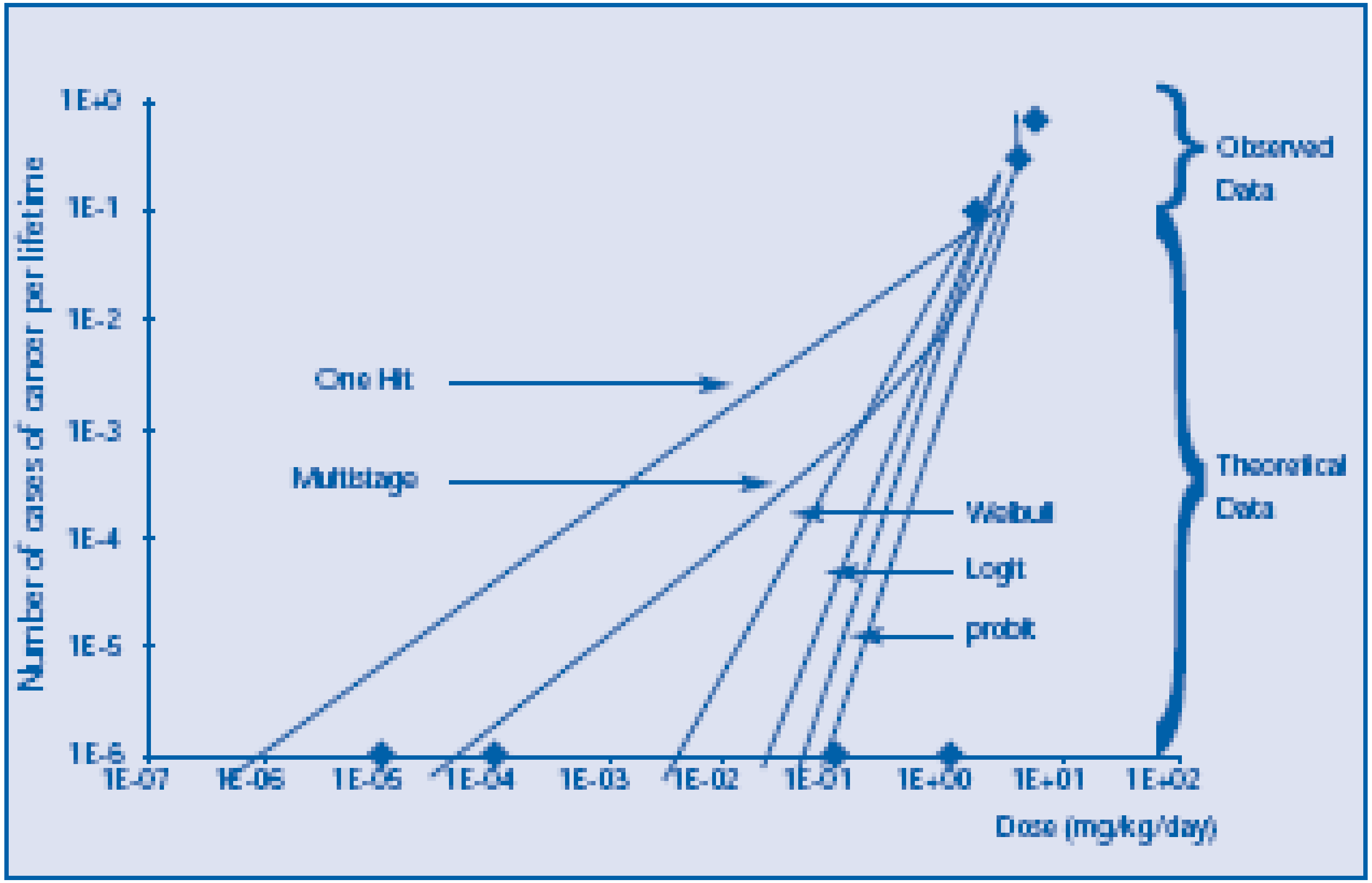
(COC September 2003)

‘American agencies seem prepared to use mathematical models to estimate risks in situations where UK experts either view the risk as insignificant or the technology of extrapolation as unproven. From the standpoint of the British regulatory process, the discussion of quantitative risk assessment remains largely academic …’.

Jasanoff (1986)

History of modelling

- 1958 Delaney Clause ‘no safe level of carcinogen’
- 1970s FDA began using quantitative risk assessment for environmental contaminants
- 1973 Modified Mantel-Bryan method
- 1980 EPA adopted linearized multistage model
- 1983 NAC/NRC ‘Risk Assessment in the Federal Government: Managing the Process
- 1986 EPA/CAG use upper 95% confidence limit of linearized multistage model



Variance of models when modelling the same data set (redrawn from 1991 Guidelines and Cothern 1985)

The US National Academy of Sciences 'Red Book' Risk Assessment Paradigm

National Research Council. 1983. Risk assessment in the federal government. Managing the process. National Academy Press, Washington, DC.

Fit a curve to data of the form:

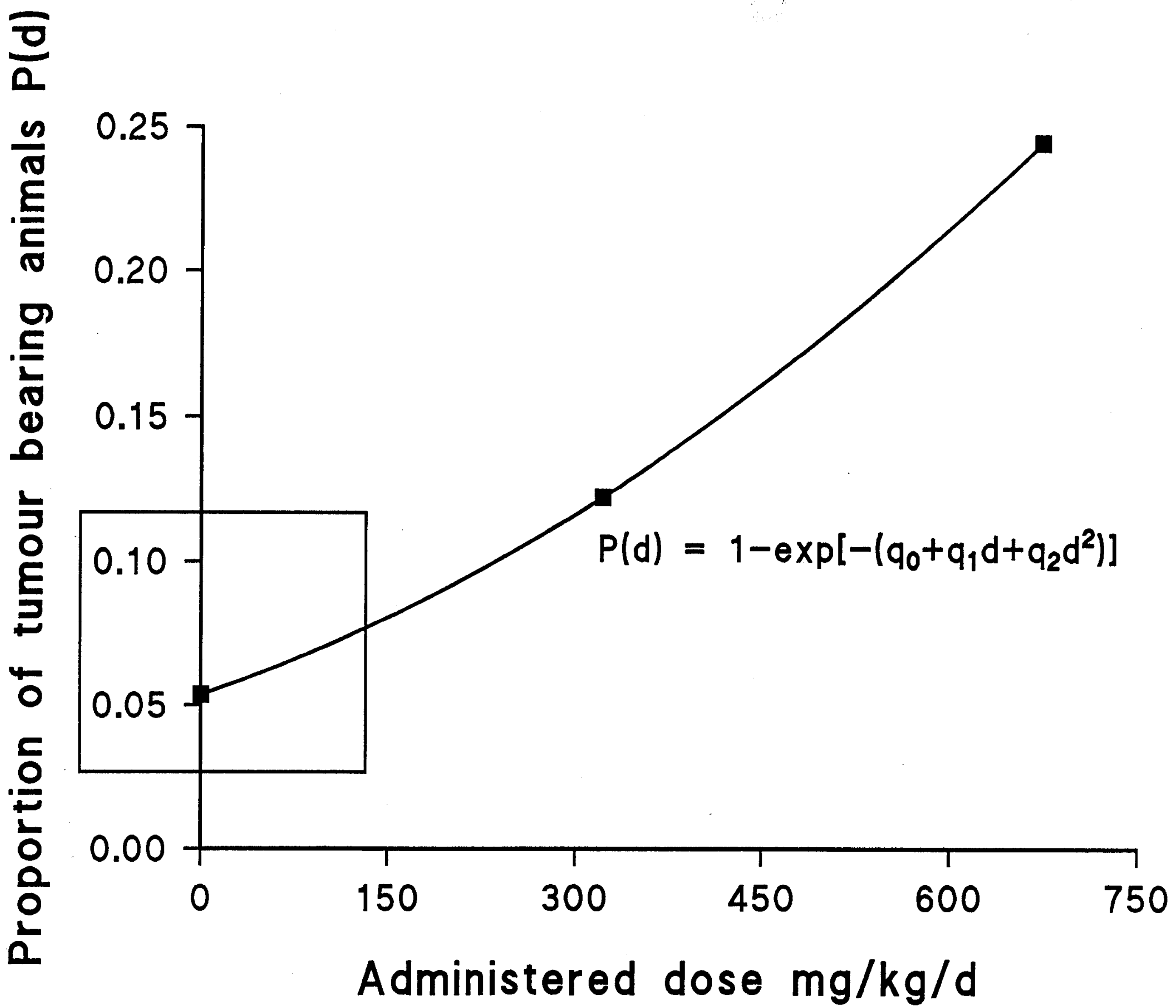
$$P(d) = 1 - \exp[-q_0 + q_1 d + q_2 d^2 + q_3 d^3 \ldots)]$$

Where P(d) is the proportion of animals with a tumour (Cancer risk) and d is a measure of dose

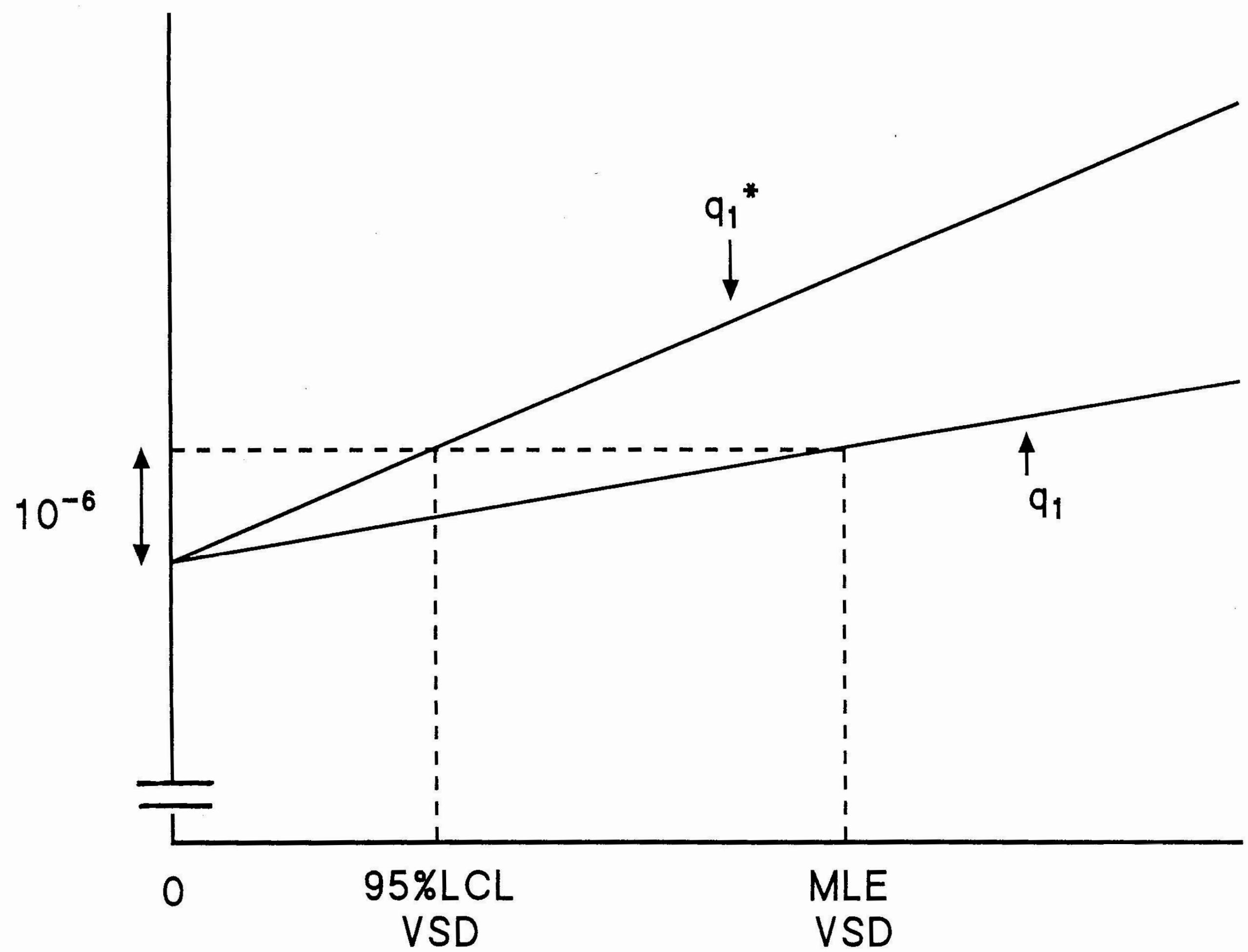
Estimates of $q_{0,}$ $q_{1,}$ $q_{2,}$ q_3 are produced by maximum likelihood methods

‘In the absence of adequate information to the contrary the linearized multistage procedure will be employed’

‘Considerable uncertainty will remain concerning responses at low doses; therefore in most cases an upper-bound risk estimate using the linearized multistage model should be presented’



Proportion of tumour bearing animals P(d)
0.25
0.20
0.15
0.10
0.05
0.00
0
150
300
450
600
750
Administered dose mg/kg/d
$P(d) = 1-\exp[-(q_0+q_1d+q_2d^2)]$



q_1^*
q_1
10^{-6}
0
95%LCL
VSD
MLE
VSD

Slope factor

An upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent.

This estimate, usually expressed in units of proportion (of a population) affected per mg/kg-day, is generally reserved for use in the low-dose region of the dose-response relationship, that is, for exposures corresponding to risks less than 1 in 100.

(US EPA Glossary)

Unit Risk

The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/L$ in water, or 1 $\mu g/m^3$ in air.

The interpretation of unit risk would be as follows: if unit risk = 1.5×10^{-6} $\mu g/L$, 1.5 excess tumors are expected to develop per 1,000,000 people if exposed daily for a lifetime to 1 μg of the chemical in 1 liter of drinking water.

(US EPA/IRIS)

Summary of limitations of LMS

- q_1 is unstable, can be zero
- q_1^* invariant despite data
- q_1^* closely related to MTD
- q_1^* larger if top dose data dropped
- Low dose data carries little weight
- VSD is approx. equivalent to MTD / 500,000

Example of a prediction that VSD is MTD/500,000

Safrole Male Mouse q_1^*

mg/kg/day	affected
0	3/40
15	3/40
75	3/40
150	8/40
750	14/47

Prediction: VSD = MTD / 500,000 1.5μg/kg/d

Using MSTAGE

$q_1 = 3.997 \times 10^{-4}$

$q_1^* = 6.601 \times 10^{-4}$

$\mathrm{VSD} = 10^{-6} / q_1^*$ = 1.515 x 10-3 mg/kg/d

= 1.515 μg/kg/d

EPA: Risk Assessment Forum - Guidelines for Carcinogen Risk Assessment (2005) - Windows Internet Explorer

http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=116283

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Guidelines for Carcinogen Risk Assessment (2005)

In an effort to update key scientific risk assessment methodologies, EPA has published the revised **Guidelines for Carcinogen Risk Assessment 2005 (PDF, 166p, 461K, about PDF)**.The Guidelines provide a framework to EPA scientists for assessing possible cancer risks from exposures to pollutants or other agents in the environment. They will also inform Agency decision makers and the public about these recommended procedures. Revisions to the Cancer Guidelines are intended to make greater use of the increasing scientific understanding of processes of cancer development. (See also the companion document, Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens).

Federal Register Notices

- FR Notice: April 7, 2005
- FR Notice: November 29, 2001

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Background

In 1983, the National Academy of Sciences (NAS)/National Research Council (NRC) published its report entitled *Risk Assessment in the Federal Government: Managing the Process*. In that report, the NRC recommended that Federal regulatory agencies establish "inference guidelines" to promote consistency and technical quality in risk assessments and to ensure that the risk assessment process was maintained as a scientific effort separate from risk management. EPA responded to this recommendation by publishing a set of risk assessment guidelines in 1986, including Guidelines for Carcinogen Risk Assessment (51 FR 33992, September 24, 1986).

EPA began revising the 1986 cancer guidelines in light of significant advances in our understanding of the processes of carcinogenesis and the modes of actions of disease at the cellular level. Revising the cancer guidelines is in keeping with EPA's original intent when it issued the first set of final risk assessment guidelines in 1986. The risk assessment guidelines were meant to be dynamic, flexible documents that would evolve to reflect the current state of the science and risk assessment practices.

Major issues considered in finalizing revisions to the Cancer Guidelines were:

- beginning with an analysis of available information, and invoking defaults if needed to address uncertainty or the absence of critical information;
- emphasizing key events and processes, starting with the interaction of an agent with a cell, through functional and

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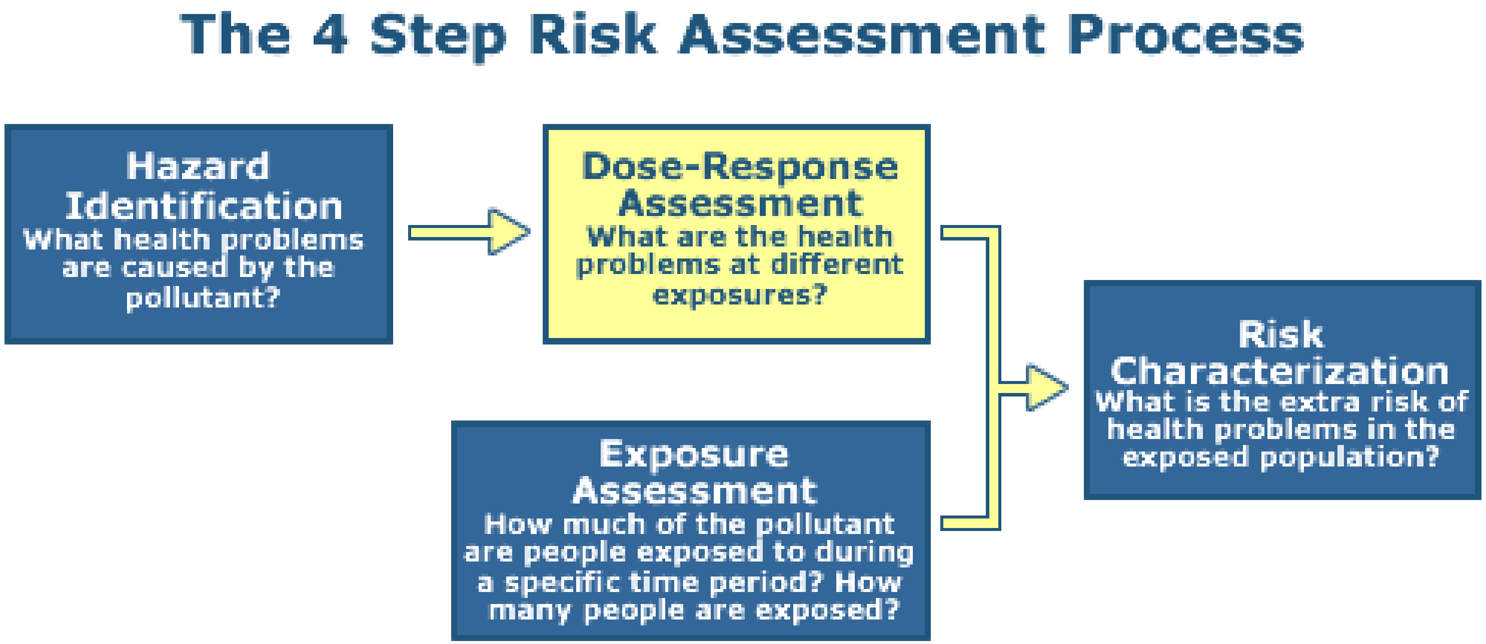
U.S. EPA, 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001B, March 2005)


The 4 Step Risk Assessment Process
Hazard Identification
What health problems are caused by the pollutant?
Dose-Response Assessment
What are the health problems at different exposures?
Exposure Assessment
How much of the pollutant are people exposed to during a specific time period? How many people are exposed?
Risk Characterization
What is the extra risk of health problems in the exposed population?

EPA Dose-Response Assessment

“Generally, the dose-response assessment consists of two parts: the evaluation of data in the observable range, and the extrapolation from the observable range to low doses/risks. Recent terminology refers to the result of analysis in the observable range as the "point of departure" from which extrapolation begins. The approaches used for evaluation in the observable range are similar for all types of effects, but EPA's current extrapolation methods differ considerably for cancer and noncancer effects.”

Point of Departure

A "*point of departure*" (POD) marks the beginning of extrapolation to lower doses. The POD is an estimated dose (usually expressed in human-equivalent terms) near the lower end of the observed range, without significant extrapolation to lower doses.

US EPA Carcinogenicity Guidelines

Mode of Action (MOA)

- EPA 2005
- Genotoxic direct DNA-reactive MOA: low-dose linear response
- Non-mutagenic MOA carcinogen: non-linear dose-response

EPA ideally wants a robust, biologically based model

- "If there are sufficient quantitative data and adequate understanding of the carcinogenic process, a biologically based model may be developed to relate dose and response data on an agent-specific basis."

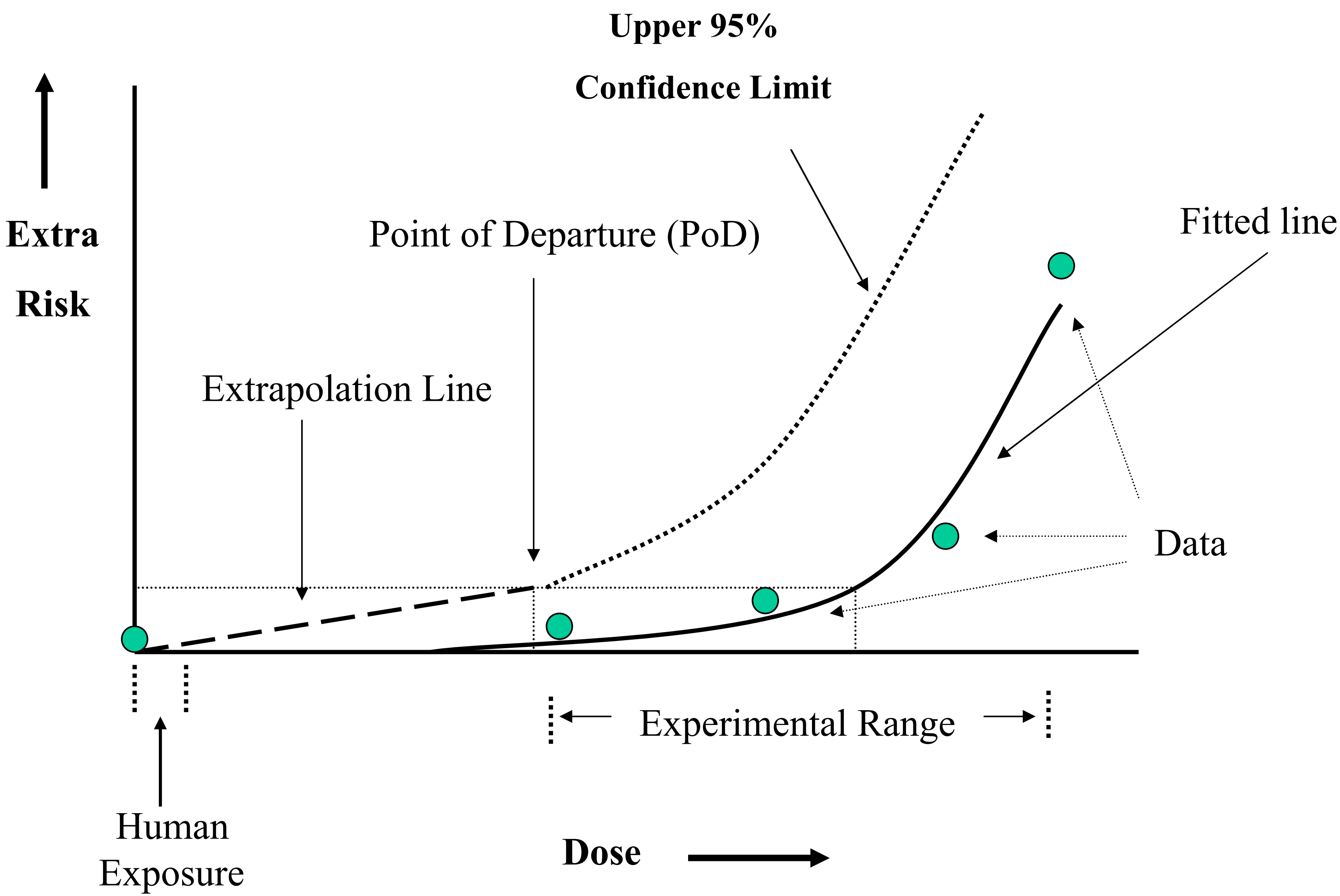
- "When a toxicodynamic model is not available or when the purpose of the assessment does not warrant developing such a model, empirical modeling (sometimes called "curve fitting") should be used in the range of observation."

- "Goodness-of-fit to the experimental observations is not by itself an effective means of discriminating among models that adequately fit the data."

- "The lowest POD is used that is adequately supported by the data."

- "It (the POD) uses information from the model(s) a small distance below the observed range rather than discarding this information and using extrapolation procedures in a range where the model(s) can provide some useful information."

EPA approach



Linear v. non-linear

Linear v. non-linear

- Straight line v. curved line
- Linear regression v. non-linear regression
- General linear modelling

- Non-linear does not mean a threshold
- A system in which the output is not a uniform relationship to the input
- Disproportionate in cause and effect

- Shape of D-R can be changed by scale of graph

A footnote:

The term “*nonlinear*” is used here in a narrower sense than its usual meaning in the field of mathematical modeling. In these cancer guidelines, the term “*nonlinear*” refers to threshold models (which show no response over a range of low doses that include zero) and some nonthreshold models (e.g., a quadractic model, which shows some response at all doses above zero). In these cancer guidelines, a nonlinear model is one whose slope is zero at (and perhaps above) a dose of zero. A *low-dose-linear* model is one whose slope is greater than zero at a dose of zero. A low-dose-linear model approximates a straight line only at very low doses; at higher doses near the observed data, a low-dose-linear model can display curvature. The term “*low-dose-linear*” is often abbreviated “linear,” although a low-dose-linear model is not linear at all doses. Use of nonlinear approaches does not imply a biological threshold dose below which the response is zero. Estimating thresholds can be problematic; for example, a response that is not statistically significant can be consistent with a small risk that falls below an experiment’s power of detection.

LMS no longer mentioned in EPA Guidelines

- “The guidelines are prospective only and will apply to the agency's current and future risk assessments of environmental pollutants.”
- Old methods can still be used.
- LMS approach in sets of data e.g. IRIS

Compare IRIS Values Results | IRIS | US EPA - Windows Internet Explorer

http://cfpub.epa.gov/ncea/iris/compare_results.cfm?RequestTimeout=180

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Acetophenone	98-86-2	**Not Assessed under the IRIS program.**					QuickView IRIS Summary
Acifluorfen, sodium	62476-59-9	**Not Assessed under the IRIS program.**					QuickView IRIS Summary
Acrolein	107-02-8	**Not Assessed under the IRIS program.**					QuickView IRIS Summary Toxicological Review (PDF)
Acrylamide	79-06-1	CNS, mammary and thyroid glands, uterus, oral cavity (combined)	4.5 per mg/kg-day	Linearized multistage procedure, extra risk	$1.3x10^{-4}$ per ug/L	Oral, drinking water	QuickView IRIS Summary
Acrylic acid	79-10-7	**Not Assessed under the IRIS program.**					QuickView IRIS Summary
Acrylonitrile	107-13-1	Brain and spinal cord astrocytomas, Zymbal gland carcinomas and stomach papillomas/ carcinomas	$5.4x10^{-1}$ per mg/kg-day	Linearized multistage procedure, extra risk	$1.5x10^{-5}$ per ug/L	Oral, Drinking water	QuickView IRIS Summary
Adiponitrile	111-69-3	**Not Assessed under the IRIS program.**					QuickView IRIS Summary
Alachlor	15972-60-8	**Not Assessed under the IRIS program.**					QuickView IRIS Summary
Alar	1596-84-5	**Not Assessed under the IRIS program.**					QuickView IRIS Summary
Aldicarb	116-06-3	**Not Assessed under the IRIS program.**					QuickView IRIS Summary
Aldicarb sulfone	1646-88-4	**Not Assessed under the IRIS program.**					QuickView IRIS Summary
Aldrin	309-00-2	Liver carcinoma	$1.7x10^{1}$ per mg/kg-day	Linearized multistage procedure, extra risk	$4.9x10^{-4}$ per ug/L	Oral, Drin	QuickView IRIS Summary
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Approaches to extrapolation below the observed data

- Model–dependent
  - Empirical multi-stage model (LMS)
  - BBDR
- Model-independent
  - Linear from PoD
  - Reference Doses/concentrations (RfD/RfC) from PoD using Uncertainty Factors
- Combination approaches
  - PoD determined by model then linear

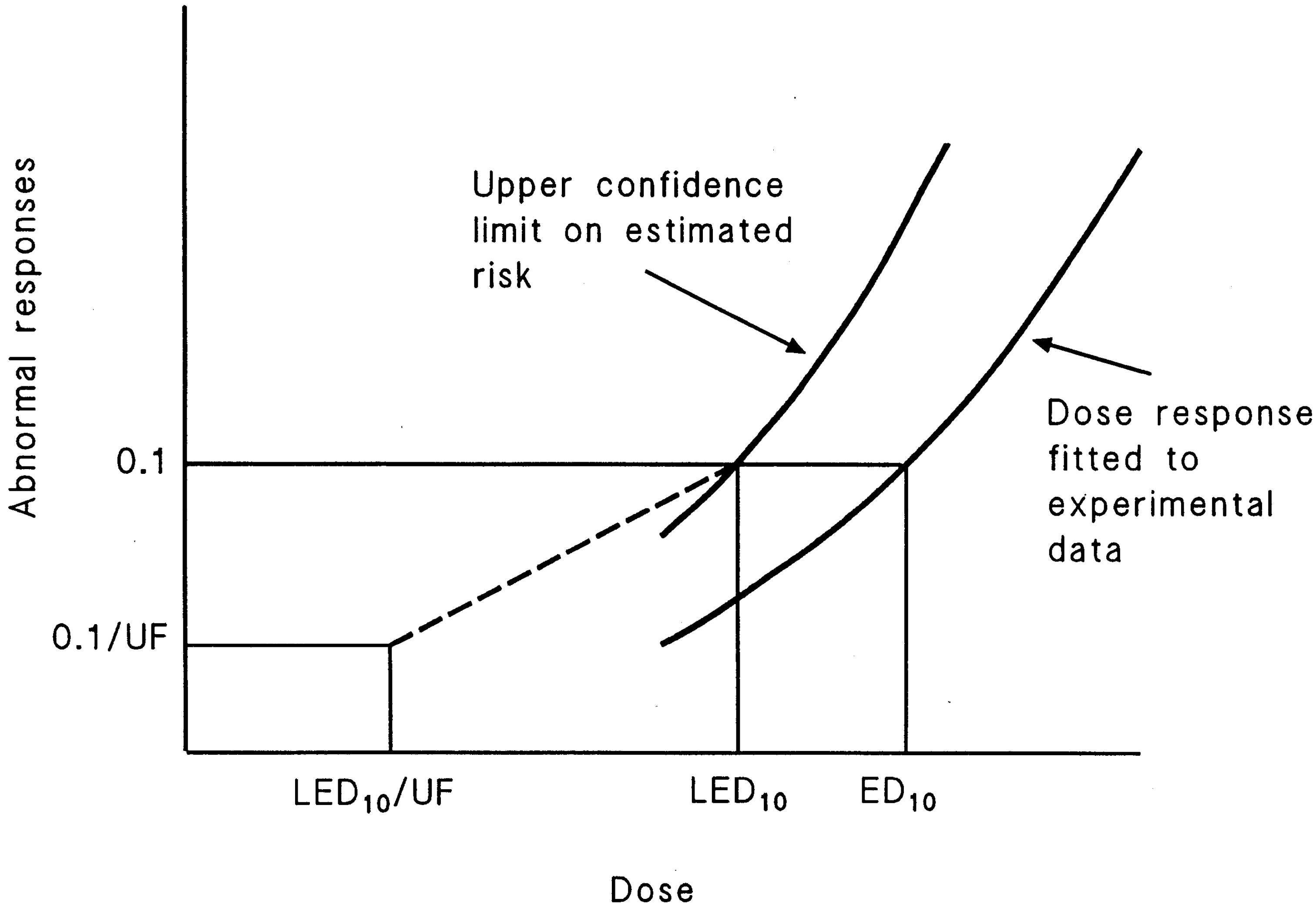
Benchmark Dose

Benchmark Dose (BMD) or Concentration (BMC): A dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background.

BMDL or BMCL: A statistical lower confidence limit on the dose or concentration at the BMD or BMC, respectively.

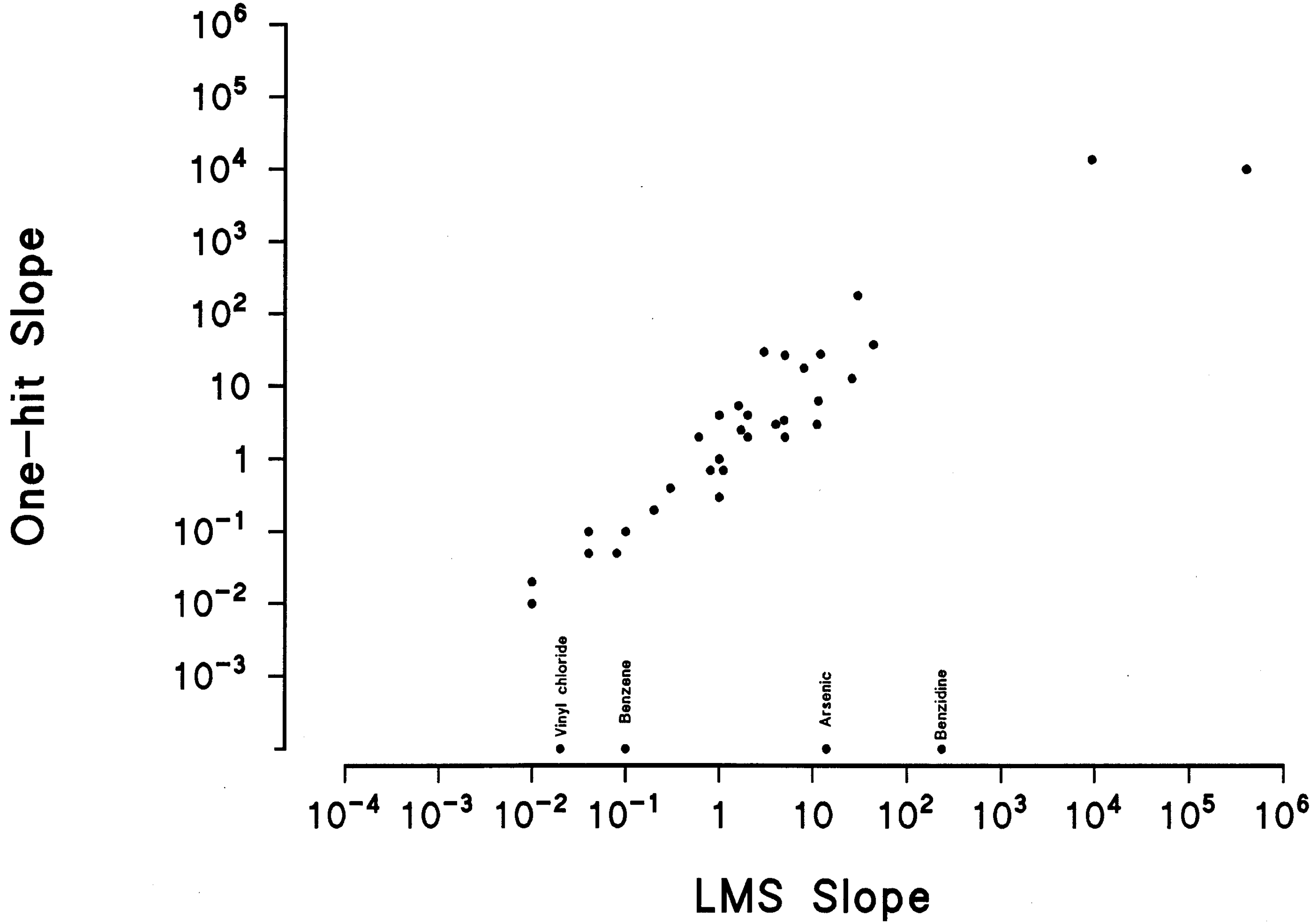
Benchmark response (BMR): An adverse effect, used to define a benchmark dose from which an RfD (or RfC) can be developed. The change in response rate over background of the BMR is usually in the range of 5-10%, which is the limit of responses typically observed in well-conducted animal experiments.

(US EPA Glossary)

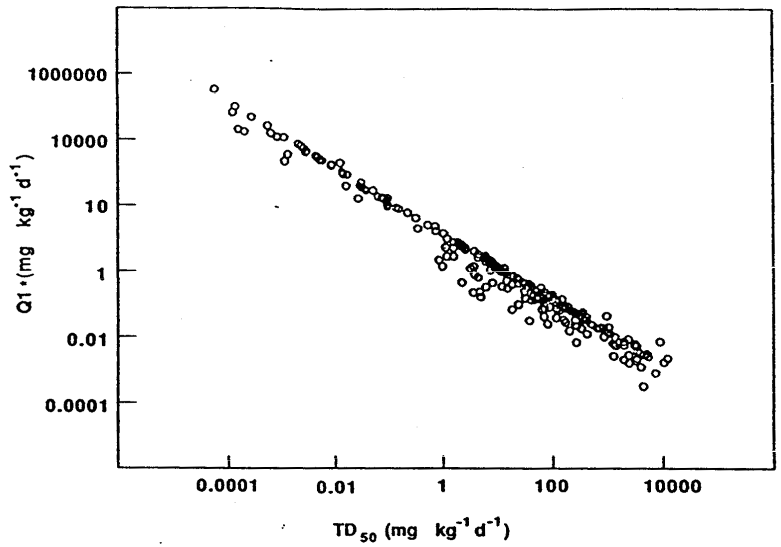


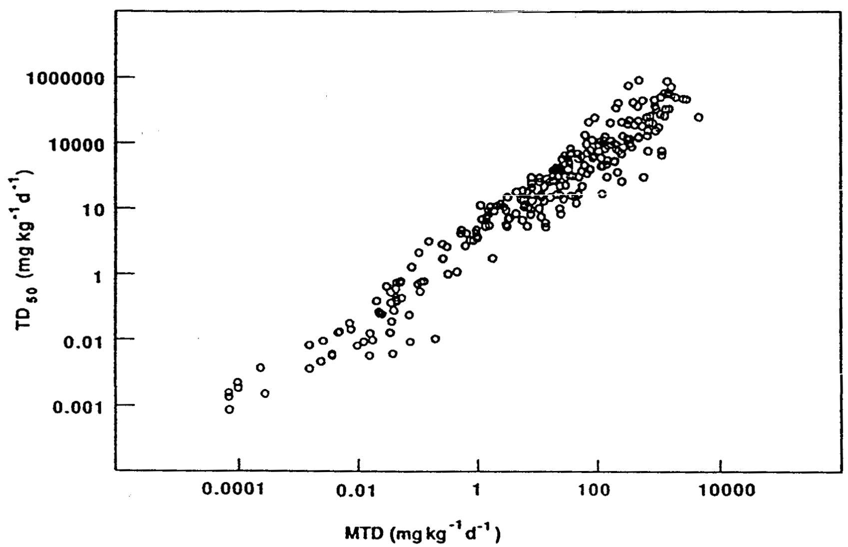
Abnormal responses
0.1
0.1/UF
Upper confidence limit on estimated risk
Dose response fitted to experimental data
LED10/UF
LED10
ED10
Dose

Relationship between the measures



One-hit Slope
LMS Slope
Vinyl chloride
Benzene
Arsenic
Benzidine





Relationship of TD50, MTD and q1* (Krewski et al)

"It should be noted that the straight line extrapolation from the LED10 and the LMS procedure produce similar results."

(Wiltse & Dellarco, 1996)