

Dose-Response Assessment for Carcinogens

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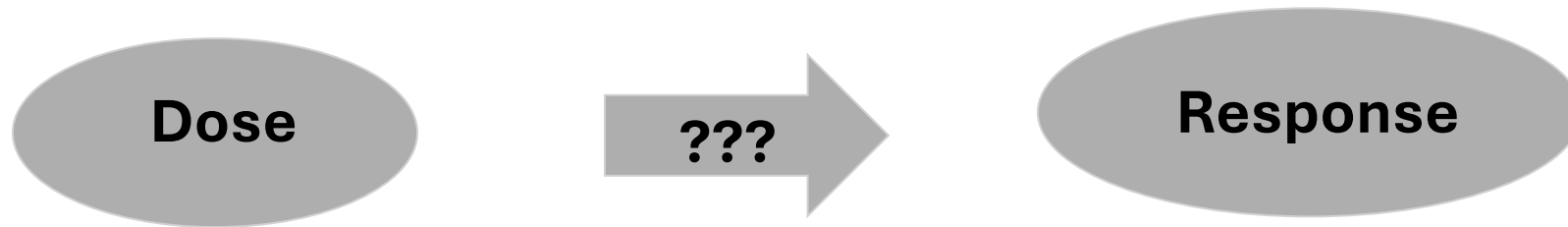
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Overview

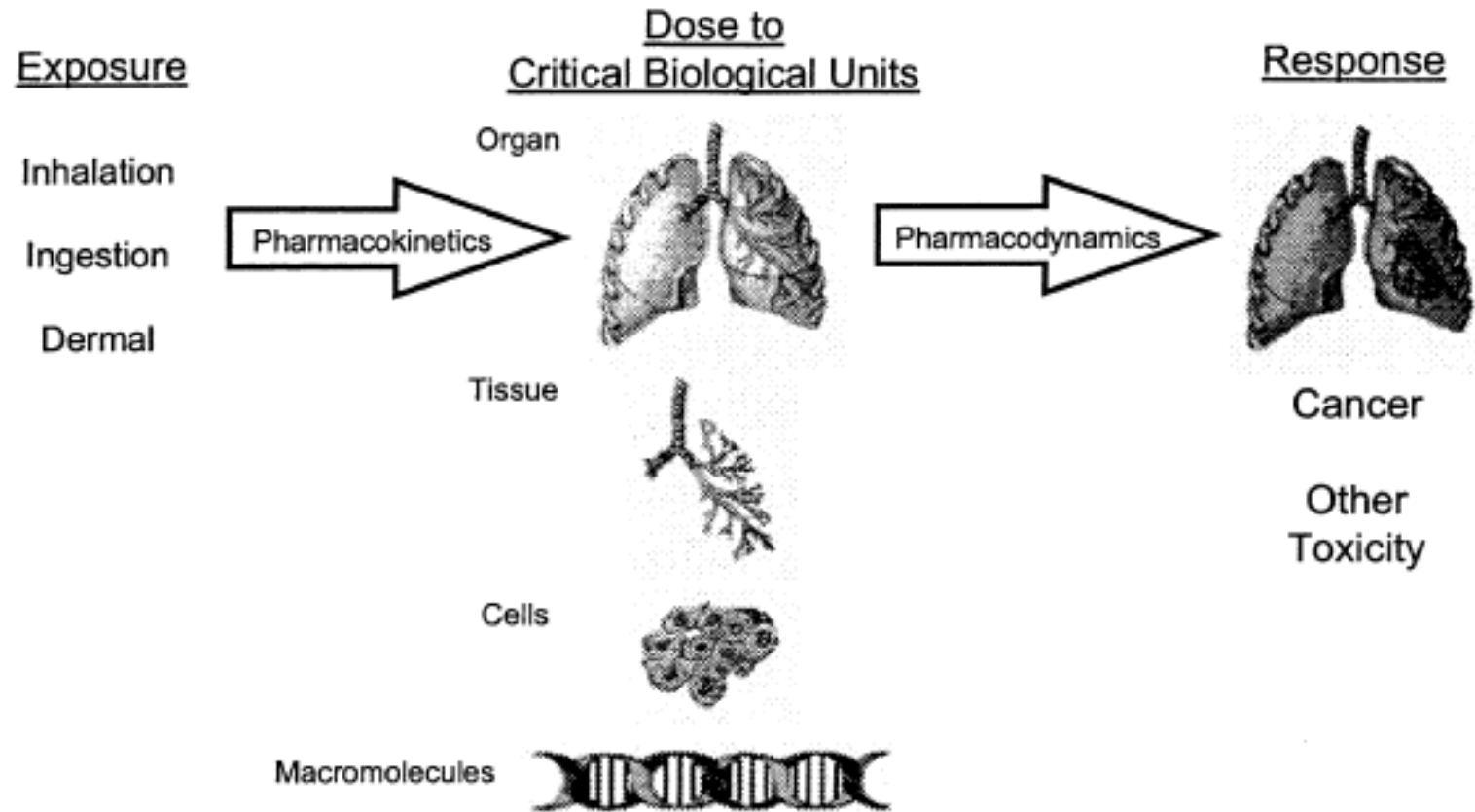
- Definition
- History of Cancer Risk Assessment
- History of Cancer Biology and Toxicology
- Cancer Dose Response Assessment; how has it worked?
- What are the shortcomings?
- Impact on Rule Making
- Recent court decision on LMS and methylene chloride
- What are the options going forward
- Final thoughts

Dose-Response Assessment



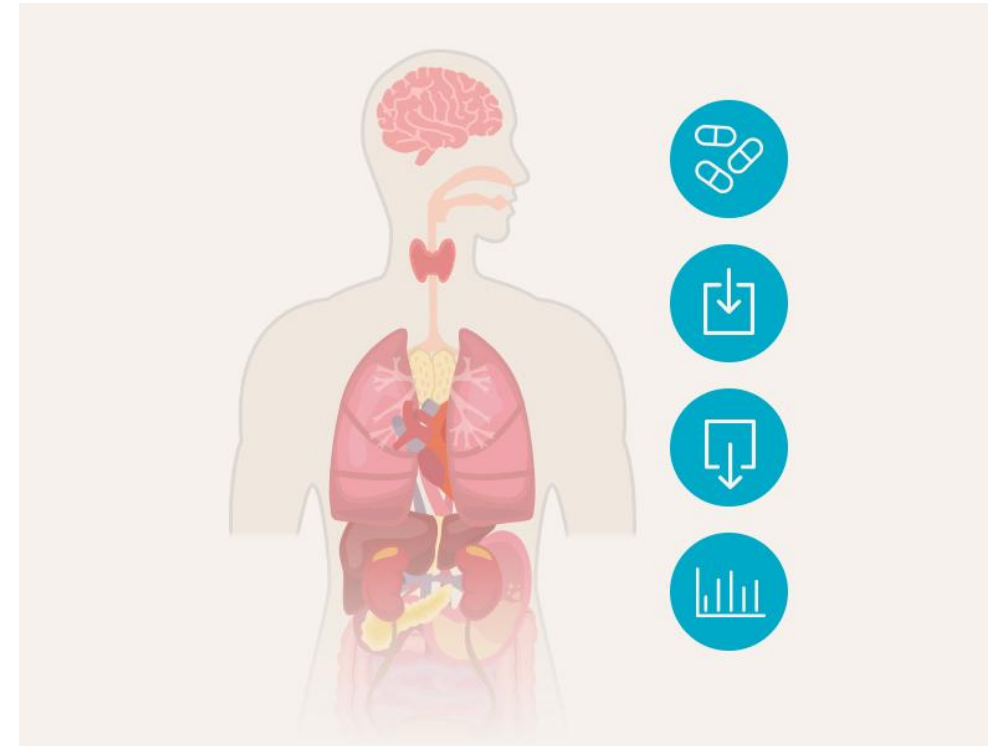
The quantitative evaluation of the potential for developing adverse health effects as a result of exposure to a chemical.

Elements of Dose-Response



Elements of Dose-Response

- Pharmacokinetics (PK) relates exposure to tissue dose
- Pharmacodynamics (PD) relates tissue dose to response
- When these are incorporated, the confidence in the predictions are greater



Dose-Response Concepts

Mode of Action - In a broad fashion, the key steps involved in the causation of specific biological responses.

Dosimetry - Estimation of the target tissue exposure to the form of the chemical that is most directly related to the adverse effect.

Mode of Action Statement - Describes the biological basis of the response and the active form of the chemical involved in causing the response.

Low-Dose Assessment for Carcinogens

- 1955-2025: Assessments were based on the assumption that there was no threshold for the carcinogenic response; based on ionizing radiation data from Hiroshima
- This prompted development of approaches for extrapolating to doses well below the range of experimental observation
 - “Linearized Multistage Model” (LMS) was developed to estimate statistical upper bound on low-dose potency (q^{1*}) consistent with tumor incidence
 - Assumed low-dose linearity (Crump et al. 1976) and a response at every dose
- For 50 years, no other approach gained traction due to support by special interests, including EPA, OSHA, NRC, and trial lawyers

“All models are wrong, but some are useful.”
- George Box

“Models are **always** an oversimplification.”
- Virgil Andersen

Science, Risk, and Public Policy

“A climate of fear now dominates the discussion of environmental issues. The scientific community can help alleviate this fear by making a greater effort to explain to the public the uncertainties involved in estimates of risk.”

- Ruckelshaus, 1983

Until about 1985, all carcinogens were considered similar...

- Most chemical carcinogens were assumed to be genotoxic (much like ionizing radiation)
- The early and potent occupational carcinogens were genotoxic, but it was apparent by about 1985 that many, if not most, were not
- Due to regulatory policy and a desire to “not under-predict the risks to human health”, as well as pressure due by environmental groups and trial lawyers, no one has successfully “moved the needle” to support another approach

Early Historical Approach Remains in Place

- Mantel and Bryan (1961): Proposed the LMS approach
- Crump et al (1976): Simplified their approach by writing an easy-to-use computer program and clear documentation
- The LMS proposed by Crump et al. (1976) remains the “default” approach....right up until Sept. 2026

The Linearized Multistage Model (LMS)... How It Works And Why It Can't Reliably Estimate The Likely (Plausible) Incidence of Cancer in Humans

How the LNT Functions?

1. Begins with animal or human data
2. There should be at least three doses and the associated response rate
3. To begin, for insight, select the best fit or the maximum likelihood estimate (MLE)
4. One can also choose to ask it to fit to the highest estimated “plausible response” or the upper bound (the regulatory approach)
5. In both cases, the LNT assumes low dose linearity
6. It also assumes no safe dose (e.g., the response must go through zero)

Limitations of Cancer Models

1. Assumes delivered dose at target organ to be linear with exposure... which is rarely true
2. Do not account for biologic repair mechanisms
3. Assumes that all “hits” are biologically important
4. Most assume “no safe dose” (e.g., no threshold)
5. Are often fragile unless the data set is substantial
6. It assumes that any exposure to a carcinogen is added to the background rate of cancer; which is highly unlikely

Traditional Approach To Identifying A Tolerable, If Not Safe, Dose

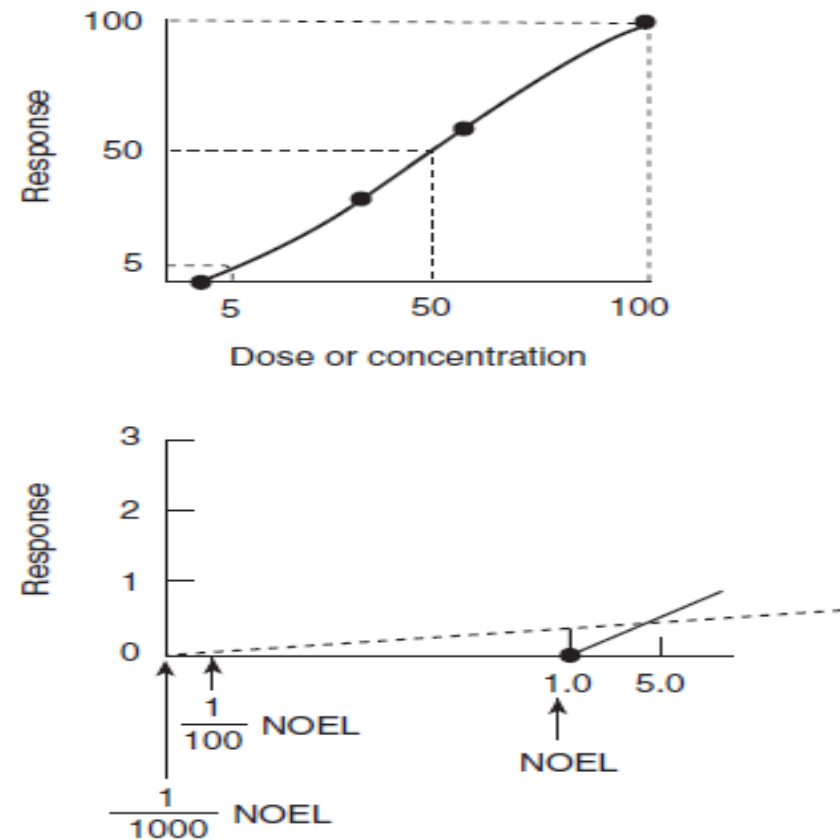


Figure 4.4 Illustration of the region in which mathematical models are used to estimate the likely response at doses 1/100th and 1/1000th the no-observed-effect level (NOEL). The upper plot represents the best fit for the four doses that were evaluated. In the lower plot, the intersection of the x-axis at 1.0 mg/kg-day is the NOEL dose. This plot illustrates how one estimates a safe dose for humans (e.g., 1/100 or 1/1000 of the NOEL). It is assumed that there is no risk of a response below 1/100 or 1/1000 of the upper bound of the NOEL for non-carcinogens and non-genotoxic carcinogens.

Illustration Of How The BMD 10% Dose Is Identified... And The Impact Of The Bounding Approach

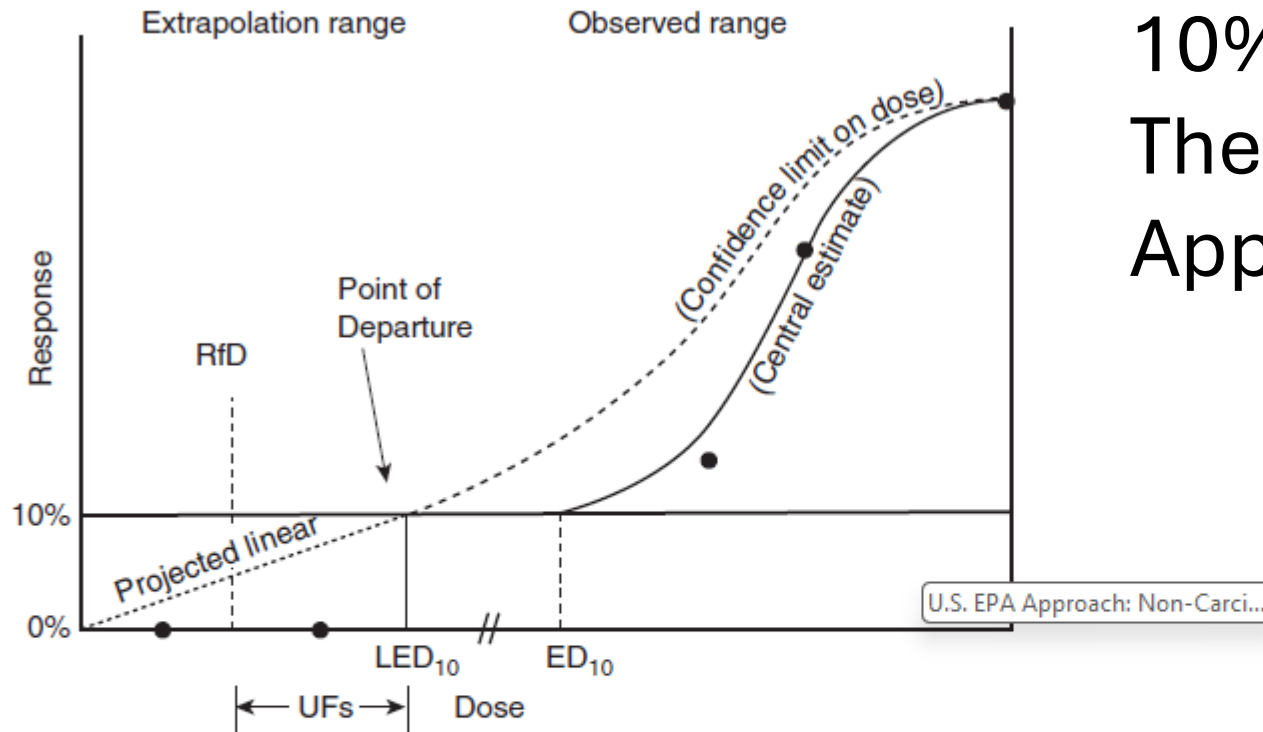


Figure 4.3 Estimated hypothetical cancer risks from chemical exposures where the benchmark dose approach is applied. This approach uses an upper bound estimate of the response, much like the linear low dose models, for responses above 10%. The large dots represent the observed response rates for the doses that were used in the study. Responses with the estimated upper bound are considered stable or a reliable estimate of the likely true response. Since there is less confidence below 10%, uncertainty factors are added to the 10% response level to estimate the true likely zero responses. In this approach, the point of Departure (POD) is the dose to which uncertainty factors (UF) are applied. Normally, an uncertainty factor between 100 and 500 is applied to the 10 or 20% response (POD) to identify the acceptable dose (RfD) or the acceptable intake (AI). ED₁₀ is defined as the dose reflecting the best estimate of likely 10% response of the study. LED₁₀ is the lower bound risk estimate for a 10% response. *Source: Adapted from EPA (2005).*

The LMS Relies on At Least Three Key Assumptions (Crump et al. 1976)

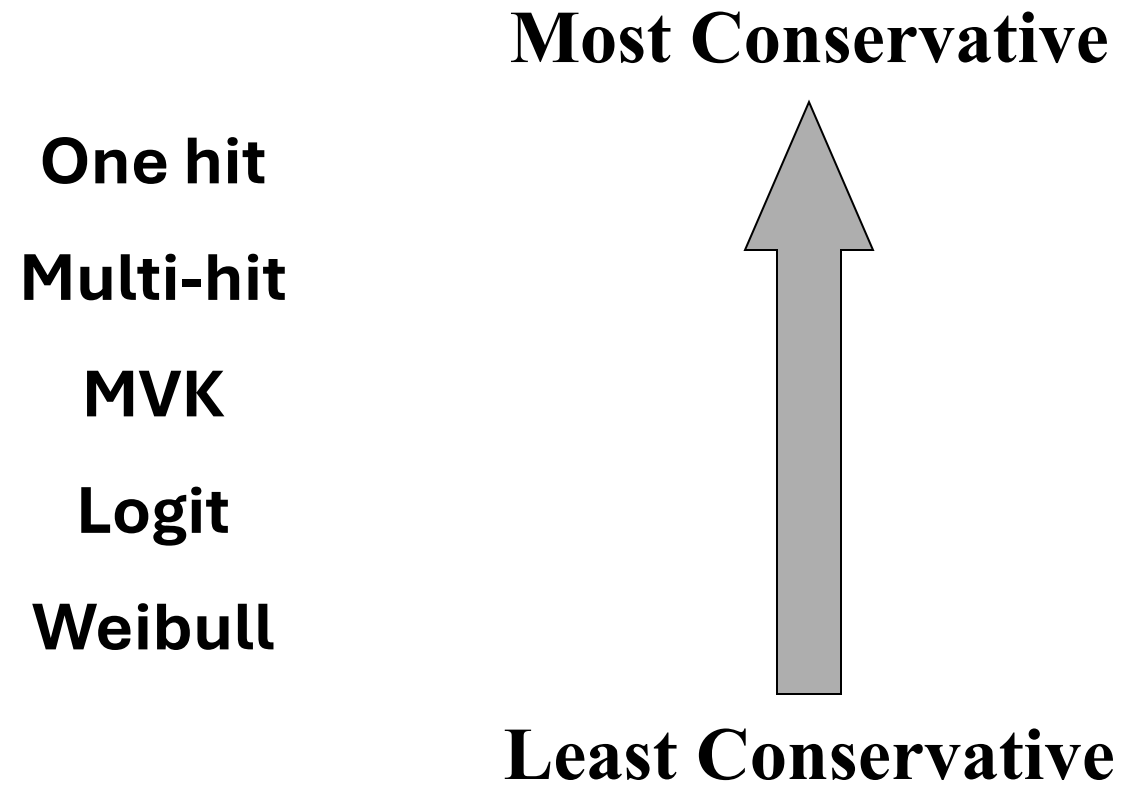
- Epidemiology data of the 1960-1980 era were relied upon (they did not see a dose with zero response in Hiroshima).
- The bounding approach attempted to account for biological variability among persons and statistical uncertainty in the data. That is, the model attempted to estimate the response if 1,000 or 10,000 animals were tested, instead of the 100 animals per dose.
- The model assumed that any exposure to a carcinogen was additive to the background cancer rate....a bold assumption.

Other Shortcomings: The Low-Dose Models Can Not Incorporate Most of the Biological Information

- Number of assays that showed no increased risk
- Relevance of tumor site
- Age of onset (time-to-tumor)
- Type of mechanism that caused the cancer
- Dose at target tissue (pharmacodynamics)
- The role of metabolism
- Quantitatively address the difference between animals and humans
- Mutagenic potency
- Nongenotoxic etiology

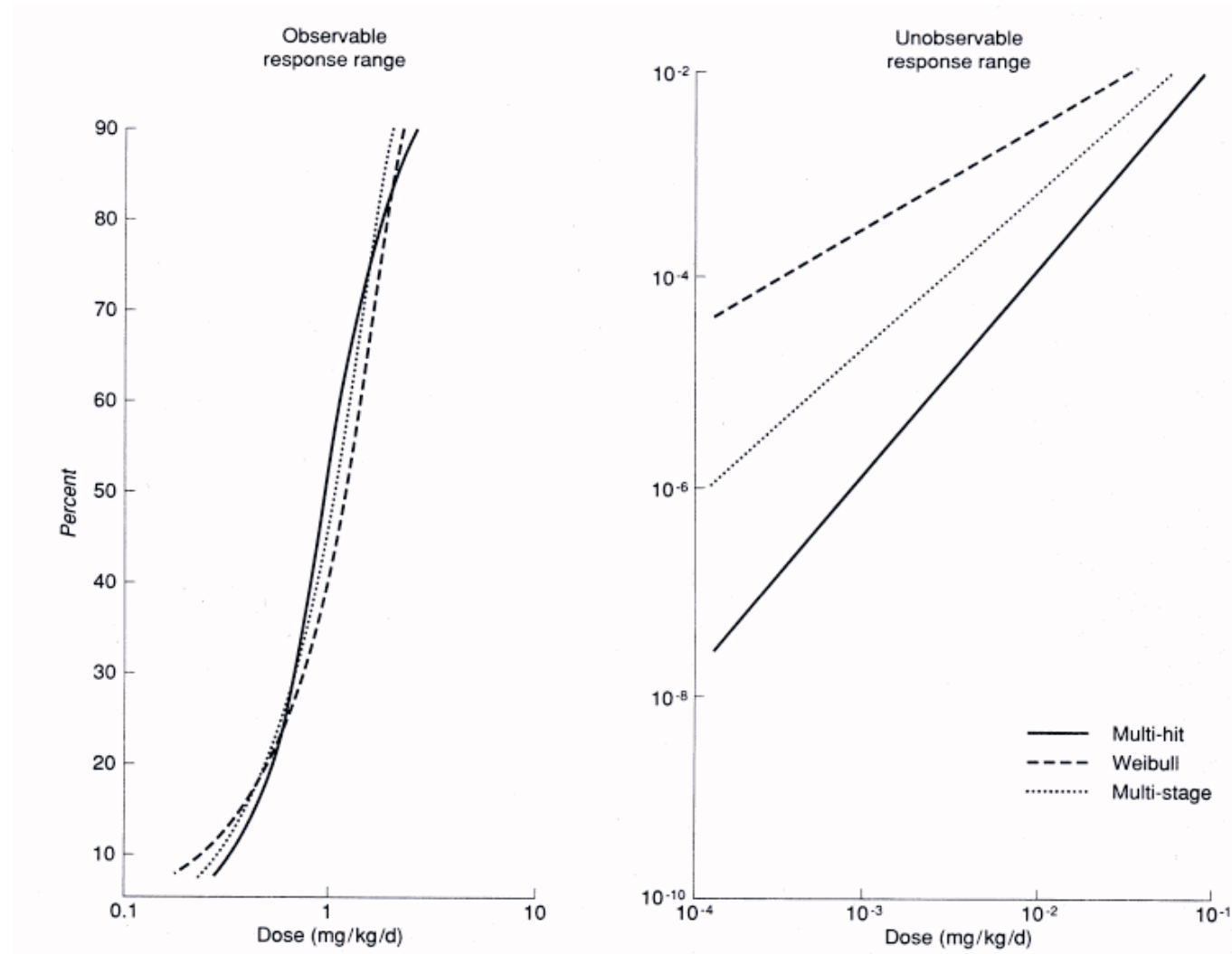
The LMS is not the only low dose model... but
the others fell by the wayside in the 1980s

We Used to Discuss Various Models

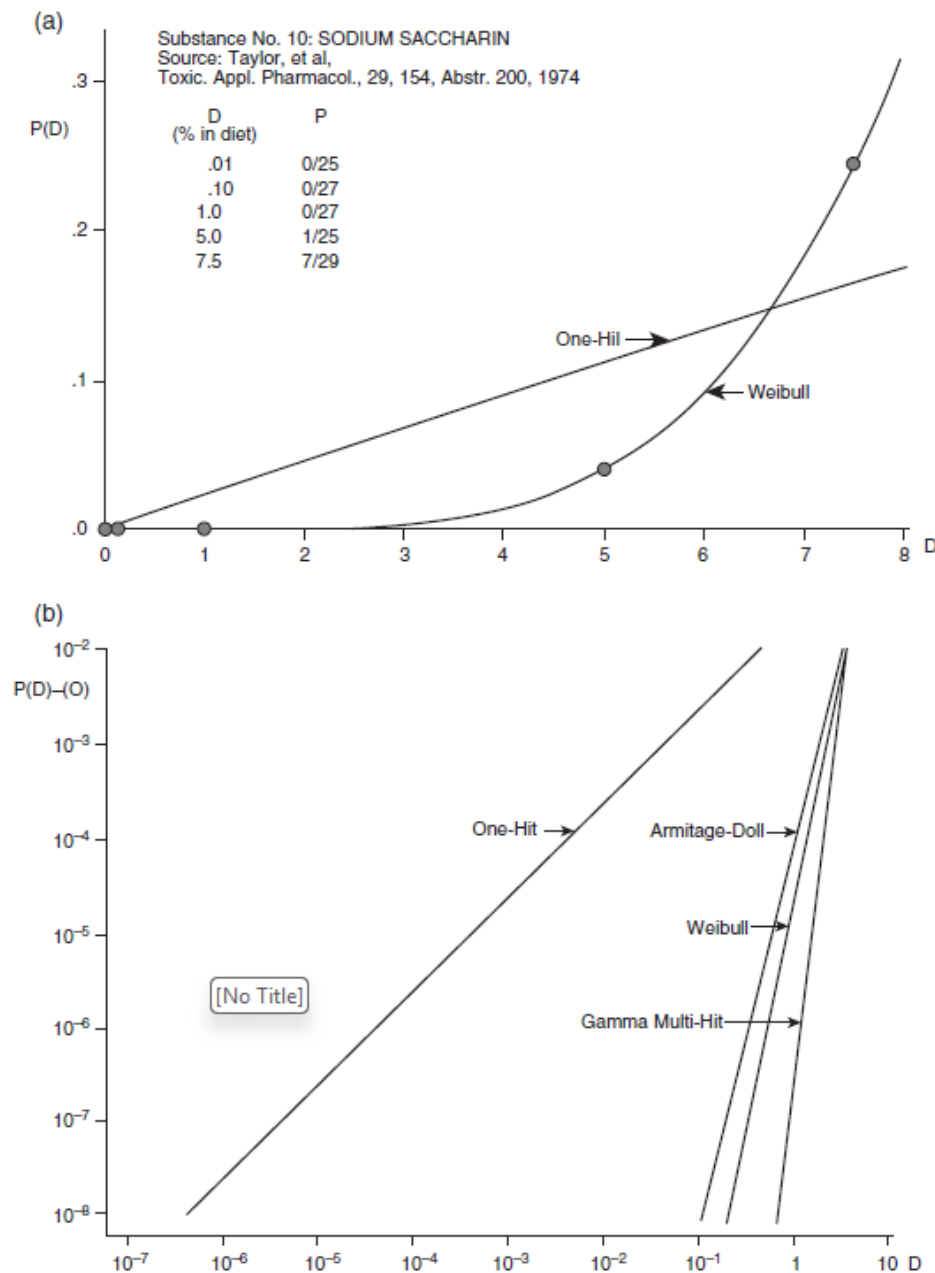


Various models yielded
markedly different results

Reasonable Models Yield Widely Different Responses (up to 1000-fold different at the 1 in a 1,000,000-risk level)



Look at the fit
when four doses
are available...



When eleven doses are available... the model is still not very responsive

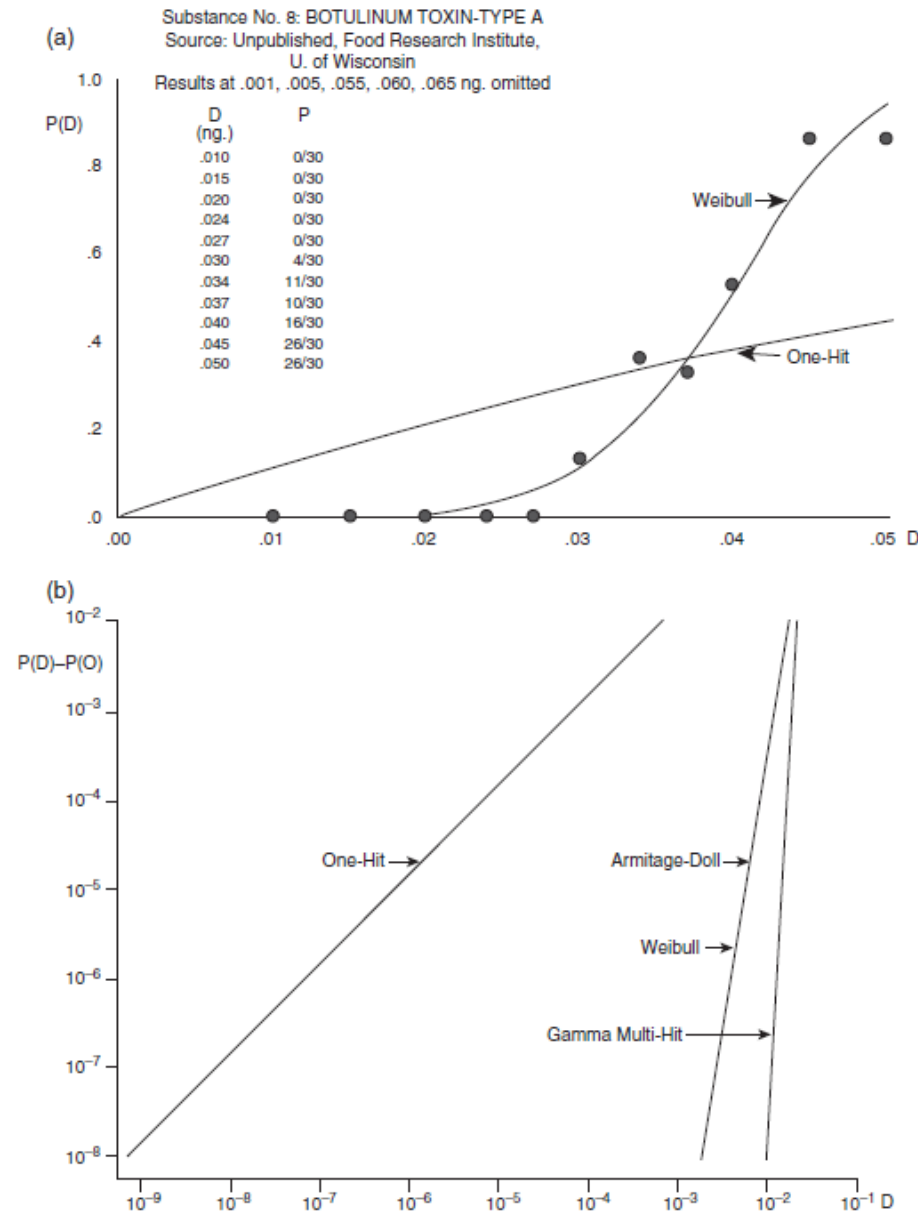


Figure 4.9 This plot is the dose-response curves for Botulinum toxin. Source: Adapted from Food Safety Council (1980). This study is unusual because 11 doses (rather than 3 or 4) were evaluated in a rodent bioassay. Note how the risk estimates for the one-hit model are dramatically higher (by almost 1000,000-fold at relatively low doses) when compared to the Weibull, gamma multi-hit, and Armitage-Doll results.

For thirty-five years, some have questioned the reasonableness of the statistical approach to estimating the upper and lower bounds

The aggressiveness of the bounding approach
has rarely been discussed, except in one
paper by Sielken (1987), which studied
2,3,7,8-TCDD

The Confidence Intervals On The Extrapolation Are Huge...

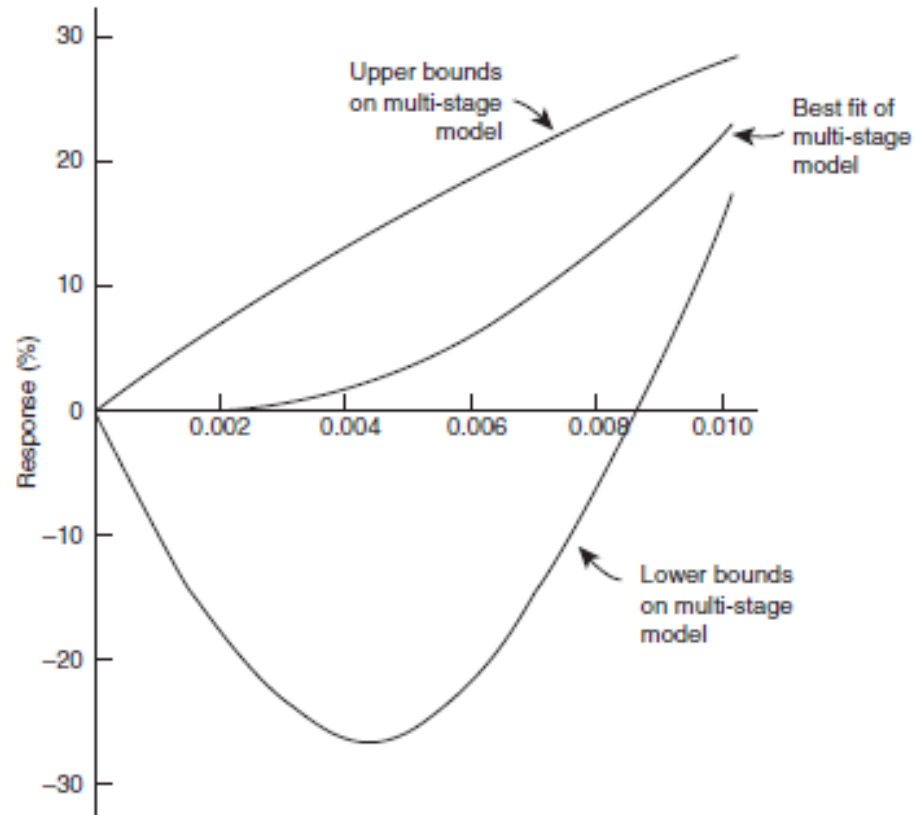


Figure 4.10 Description of historical approach to low-dose extrapolation process. This plot illustrates the range of plausible risks using bounding techniques in the Linearized Multistage Model. The point of this plot is to show just how much conservatism exists in the procedure. *Source: Adapted from Sielken Jr (1985a).*

The Linearized Multistage Model (LMS) Can Be Overly Sensitive

A Simple Case Study Illustrating The Lack of Sturdiness

Tumor Response		
Dose ($\mu\text{g/kg}$)	San Francisco Study	Los Angeles Study
10	10/50	10/50
3	2/50*	1/50
0	0/50	0/55

*One more rat within the low dose group (3 $\mu\text{g/kg}$) group in San Francisco developed a tumor

Impact Of One More Tumor In A Study Of 300 Animals Can Dramatically Influence The Results

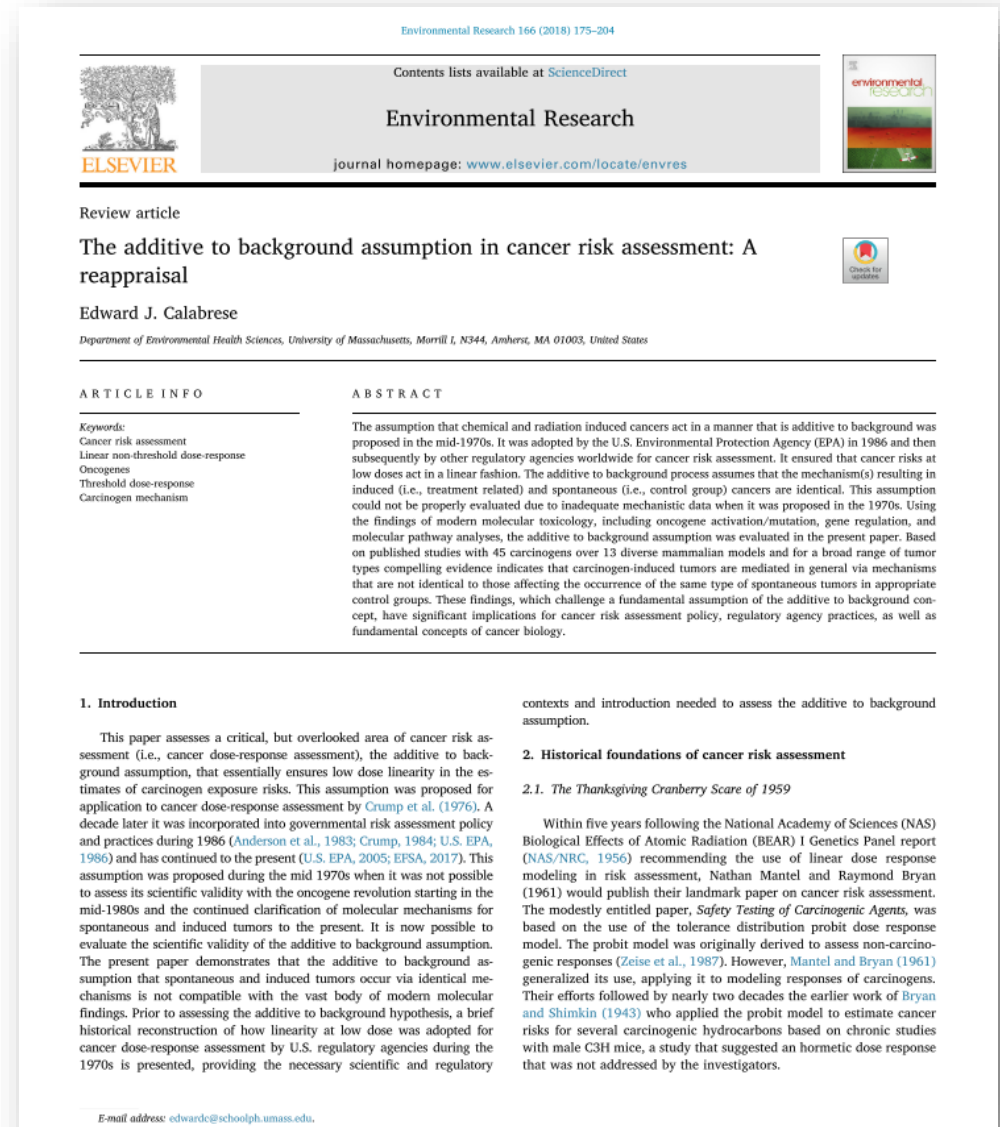
Dose (mg/kg)	San Francisco	Los Angeles
3	0.04	0.02
1	0.01	0.002
0.1	1/1,000	3/100,000
0.01	1/10,000	1/1,000,000

The Big Assumption – Additive to Background

Calabrese (2018) has studied the “additive to background” assumption and he believes the time has come to drop it. His paper evaluating 40+ studies “feels convincing”.

Calabrese (2018)

- His basic claim is that there are at least 15 different modes of action for carcinogens
- Since each chemical has only one mechanism of action, it is highly unlikely those which cause cancer in the background populations are the same as those causing tumors due to xenobiotics (e.g., industrial chemicals)



His Data Indicate that the “Additive to Background” Assumption Is Probably Not Appropriate

- LNT fundamentally assumes that all carcinogens act through the same mechanism (their dose)
- The consequences are the assumption of low-dose linearity in the response to chemicals in our diet, ambient air, and workplace
- Background tumors don’t usually act through the same mechanism as an industrial chemical
- DNA repair is now known to be significant (so assuming no safe dose is highly unlikely); this was not understood in 1976

Calabrese (2018) Conclusions

- “Based on published studies with 45 carcinogens over 13 diverse mammalian models and for a broad range of tumor types compelling evidence indicates that carcinogen-induced tumors are mediated in general via mechanisms that are not identical to those affecting the occurrence of the same type of spontaneous tumors in appropriate control groups”
- He claimed that if one accepts these data, it would dramatically alter how agencies estimate risks associated with low doses
- A screening analysis suggests that, if you drop the additivity option in the LMS, in general, it usually overestimates the true risk by a factor of 100-1,000, or greater, in the vicinity of the 1 in 1,000,000 risk level

How our understanding of cancer has changed over 40 years... just evaluate what has been said in Casarett and Doull's textbook over 9 editions

Casarett and Doull (1980)

- Their chapter on carcinogens listed two major categories of carcinogens
 - (1) Genotoxic
 - (2) Epigenic
 - Solid state
 - Hormones
 - Immunosuppressants
 - Co-carcinogens
 - Promoters

Casarett and Doull (2000) (5th Edition)

- The carcinogens listed at least 9 categories of modes of action:
 - Inorganic carcinogens
 - Fiber carcinogens
 - Hormonal carcinogens
 - Mixtures
 - Solid state
 - Hormones
 - Immunosuppressants
 - Co-carcinogens
 - Promoters

Casarett and Doull (2020) (8th Edition)

- The chapter on carcinogens listed nine mechanisms:
 - Genotoxic Carcinogen
 - Nongenotoxic
 - Non-mutagenic
 - Threshold, reversible
 - Promoters
 - Peroxisome proliferators
 - Receptive mediated
 - Hormonal
 - DNA methylation
 - Oxidative stress
 - Oxidative damage

In the 2024 Edition, there were at least 15 categories of chemical carcinogens

1. Direct genotoxicity
2. Mode of Action (non-genotoxic)
 1. Cytotoxicity
 2. Ox globulin binding
 3. Receptor mediated
 4. Hormonal
 5. DNA methylators
 6. microRNA
 7. Immunosuppressants
 8. Oxidative stress
 9. Oxidative DNA damage
 10. Stress and cell growth regulation
3. Gap Junction
4. Inorganic Carcinogens
 1. Metals
5. Proto-oncogenes and tumor suppressor genes
 1. Retroviruses
 2. DNA viruses

Today, the LMS continues to be used by all Federal agencies for all categories of carcinogens (except those clearly non-genotoxic)

Over the years, there have been those who believe the LMS is entirely appropriate

- U.S. EPA and OSHA have agreed for 30 years that the LMS can drastically overestimate the true cancer risk at low doses.
- Adam Finkel, a risk scholar, thinks our understanding of biology is so poor that we can't claim objectively that we are always over-estimating the true risk.

An Interpretation Of Finkel's Beliefs (1997)

- It is folly to think we understand the variability in response across different persons
- Finkel's Main Beliefs:
 1. Uncertainty is unavoidable in risk assessment
 2. The costs of regulations regarding carcinogens are often overestimated
 3. Risk assessment does not always overestimate risks
 4. People respond differently to toxic chemicals
 5. Risk assessment should focus on protecting public health

Disconnect Brain and Repeat after Me: "Risk Assessment Is Too Conservative"^a

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My first task is to make some amends for the sarcastic title of this talk. I do intend to explore in a detailed manner the half-truths and untruths that form the foundation of the growing "conventional wisdom" about risk assessment—that it deliberately and invariably produces widely exaggerated or "conservative" estimates of harm. I do believe that many of the critics leading the charge against conservatism, having discovered that they can get away with making pronouncements based at best on anecdotes and more often on pure speculation, have in effect disconnected some of their faculties and are making exaggeration of risk into a mantra rather than a theorem. I do not mean to suggest, however, that anyone who inveighs against conservative aspects of risk assessment has abandoned critical thinking in favor of propaganda. To the contrary—the arguments do contain kernels of truth, and risk assessors and policy makers ignore them at their own peril. The title is also meant to be cautionary. Those of us who believe the facts support a different conclusion—that risk assessment often *underestimates* risk and that more stringent regulation would often be needed before costs were in danger of exceeding benefits—must guard against responding to half-baked arguments with reflexive and simplistic counters of our own. No matter how overwrought the criticism may be, "no it's not" is hardly an adequate response. My goal in this discussion is to trace the evolution of the attacks on the alleged conservatism of risk assessment (especially as practiced by federal environmental, health, and safety regulatory agencies); to suggest two unifying ideas that persons truly interested in improving the performance of regulatory risk assessment ought to keep in mind; and to dissect, as time permits, ten separate flaws in the summation denunciation of risk assessment as a tool of exaggeration and overregulation.

THE STAKES ARE HIGH

The furor over whether current methods of risk assessment exaggerate risk is more than an arcane scientific debate; it has repercussions in virtually every aspect

^aThe opinions expressed here are those of the author and do not necessarily reflect the views of the United States Occupational Safety and Health Administration. This article is an edited version of remarks delivered at the Rammazzini Symposium.

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“The actual risk is unlikely to be higher than the estimated risk and could be as low as zero” (EPA 1986)

Common Disputes about the LNT

First Point vs. Counterpoint

- **Point:** In general, epi studies will identify a dose which produces no increased risk, so why do low-dose models often predict a significant risk at the NOEL?
- **Counterpoint:** Epi studies usually have weak exposure data and the number of persons is small, so it is appropriate to apply an aggressive bounding procedure. This is why risks are anticipated far below the NOEL.

Second Point vs. Counterpoint

- **Point:** When you observe no increased risk in several epi studies, it seems unscientific to revert to a statistical model.
- **Counterpoint:** Differences in susceptibility among persons can be vast and we can't quantitatively describe it... so we need to use an aggressive statistical bounding procedure.

Third Point vs. Counterpoint

- **Point:** There are at least 15 different modes of action for producing a tumor. It does not make sense that, for example, a new pharmaceutical will add to the overall cancer risk if it acts through a different mechanism than cancers due to background (e.g., aging, lifestyle, genetic predisposition)
- **Counterpoint:** We have little or no toxicology or epi data which “shows” that all individual chemicals do not add to background (although Calabrese 2018 puts that into question).

Maybe more pharmacodynamic models are
needed

PB-PK Approach for Vinyl Chloride (Reitz et al, 1996)

- This team built a PB-PK model for the rat used in the bioassay
- They accurately “scaled-up” the rat model to humans
- It successfully predicted the circulating blood concentrations in humans (from rat data)... pharmacokinetics
- They successfully scaled up the metabolism and binding in the human liver... pharmacodynamics
- The results were impressive

The incidence of liver angiosarcoma was reasonably well predicted in humans (validated by the epi data on workers)

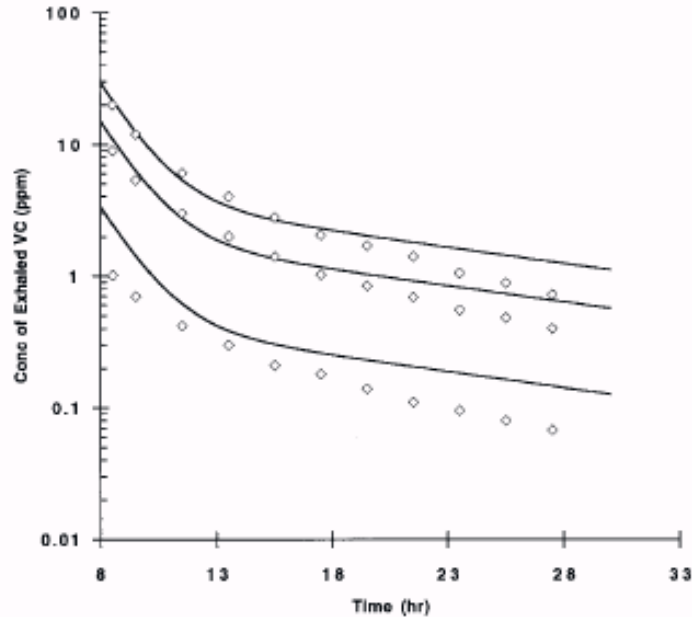


FIG. 4. Predicted (solid line) and observed (open symbols) concentrations of vinyl chloride exhaled by human subjects following 7.5 hr of exposure to vinyl chloride concentrations of 59, 261, or 492 ppm. Data are taken from Baretta *et al.* (1969).

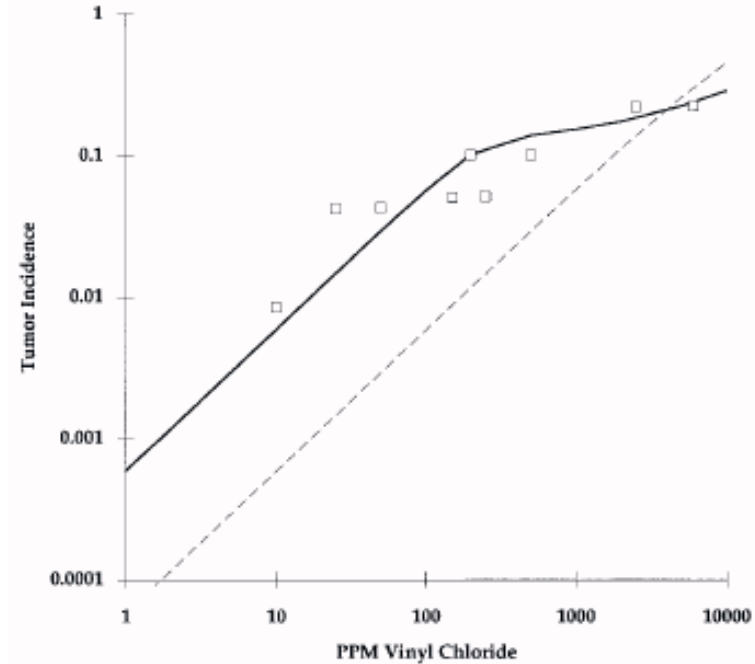


FIG. 5. Predicted (solid line) and observed (open symbols) incidences of liver angiosarcoma in rats following exposure to various concentrations of vinyl chloride for 4 hr/day, 5 days/week, for 12 months (animals held until death for observation of tumor incidence). The dotted line represents the type of risk extrapolation that might have been prepared by EPA if the only data available for VC had been from two high VC concentrations but does not correspond to the actual EPA risk assessment (HEAST, 1993). Data are taken from Maltoni *et al.* (1974).

Impact Of The LNT On Corporate Decision Making

- EPA's historical view is that "the mechanistic and epi data are not sufficiently convincing" to move away from the LNT
- Corporations threw up their hands beginning around 1995 due to EPA's inflexibility regarding dioxin, formaldehyde, trichloroethylene, perchloroethylene, and methylene chloride.
- The corporations and their consultants felt that all their hundreds of millions of dollars of effort was a waste of time.
- As a result, about 90% of the corporate toxicology labs and research labs for chemical companies, dedicated to understanding chemical carcinogens, were closed between 1995-2015!
- The firms then chose lawyers to deal with EPA and other agencies; a sad state of affair

In spite of all the shortcomings of the current application of the LNT to nearly all animal and human chemical carcinogens, agencies still predict very specific “anticipated deaths” due to low dose exposures

LMS Predicted Lifetime Risk of Death from Cancer Associated with Occupational Exposure at OSHA Permissible Exposure Limits for Selected Substances in Workplace Air (Rodricks et al 1987)

Substance	PEL	Risk/1000
Inorganic arsenic	10 $\mu\text{g}/\text{m}^3$	8
Ethylene oxide	1 ppm	1 – 2
Ethylene dibromide	20 ppm	0.2 – 6
Benzene	1 ppm	5 – 16
Vinyl chloride	1 ppm	4
Dibromochloropropane	1 ppb	2
Asbestos	0.2 fiber/ cm^3	6.7
TCDD	200 pg/m^3	0.357

A Classic Example Of Placing Too Much Value On The LMS (PFAS Rule of 2024)

Table 8-22: Annualized Cases Avoided per 100,000 People by Race/Ethnicity and Income Group, Final Rule (PFOA and PFOS MCLs of 4.0 ppt each, PFHxS, PFNA, HFPO-DA MCLs of 10 ppt each and HI of 1)

Health Endpoint	Race and Ethnicity				Income	
	Non-Hispanic Black	Hispanic	Other	Non-Hispanic White	Below Twice the Poverty Level	Above Twice the Poverty Level
Non-Fatal MI Cases Avoided	2.34	3.78	3.52	2.91	3.09	2.99
Non-Fatal IS Cases Avoided	7.48	5.33	3.87	3.78	4.68	4.45
CVD Deaths Avoided	3.90	1.57	1.29	1.26	1.72	1.62
Non-Fatal RCC Cases Avoided	3.31	4.04	3.04	2.73	3.09	3.02
Fatal RCC Cases Avoided	0.96	1.44	0.86	0.74	0.91	0.88
Birth Weight Gain (total grams)	122,024	167,846	102,190	71,201	100,943	93,366
Birth Weight-Related Deaths Avoided	1.00	0.93	0.47	0.41	0.62	0.55

Abbreviations: CVD – cardiovascular disease; MI – myocardial infarction; IS – ischemic stroke; RCC – renal cell carcinoma.

The EPA PFAS Risk Assessment Sent to OMB Was
Considered Reasonable and The MCL Was
Promulgated At An Amazing Cost To Society

But Most Informed Toxicologists and
Epidemiologists Thought It Was “A Bridge Too Far”

The EPA Predictions On Adverse Effects Around the New PFAS MCL

- EPA offered up seven different health effects that they believed the PFAS rule would impact.
- They predicted that 122,000 per 100,000 babies would have birth weight problems...even though the data was very weak, unvalidated and controversial
- They estimated that 4 persons per 100,000 persons would not suffer a heart attack and die...even though there were no solid data on that adverse effect
- They predicted about 1 per 100,000 of fatal kidney cancer would likely be avoided; in spite of the fact that the epidemiology data don't support that claim

What did the court just tell us about low dose models when evaluating the EPA risk analysis of methylene chloride (Sept. 2026)?

The Court's Key Conclusions (Sept. 2026)

1. Conservative risk estimates must be scientifically justified.
 - The court criticized EPA for stacking conservative assumptions and uncertainty factors without adequately demonstrating that the resulting exposure limits reflected an unreasonable risk
2. Risk assessment must consider all relevant scientific evidence.
 - The court found that EPA relied too heavily on selected animal studies while discounting human epidemiological evidence: mathematical extrapolation cannot replace a balanced evaluation of available evidence
3. Unreasonable risk does not mean zero risk.
 - The court emphasized that TSCA is not a zero-risk statute. EPA must distinguish between theoretical or highly conservative risk estimates and risks that justify regulation

Where do we go from here?

- Accept that DNA repair and other biological processes often eliminate or drastically reduce the cancer risk at low doses (figure out a way to accommodate this fact in a model)?
- Stop assuming that all chemical carcinogens will add to the background cancer rate... tackle this challenge thoughtfully. It will sometimes eliminate the need for the model to be linear at low doses.
- Use a modified benchmark analysis for non-genotoxic chemicals?
- Use a PB-PK model to estimate the delivered dose to “the target organ” at various doses to estimate the cancer risk?

There Is Room For Modifications to the LMS

- Crump left the door open for non-linear behavior if the additive to background assumption is incorrect.
- When this occurs, Crump indicated that when the mechanism is not the same as for cancers in the background, the low dose response need not be linear.
- The challenge, for some chemicals, is that one still has to convince naysayers that the mechanisms are “clearly” different.
- It is unclear that the EPA should have adopted the 95% Upper Confidence Limit approach which virtually insured low dose linearity...some variation is probably more appropriate.

Consider the Following...

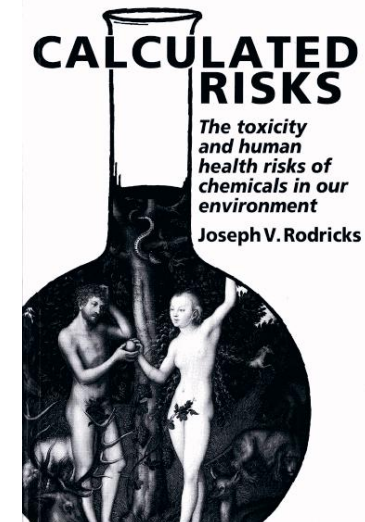
- Transition from LMS to Linear Threshold model
- Adopt limited low dose linearity and allow for a threshold
- Adjust Crump et al. (1976) to remove additivity to background (unless the mechanism requires it)

Table 10. *Risks estimated by Wilson to increase chance of death in any year by 0.000 001 (1 chance in 1 million)*

Activity	Type of Risk
Smoking 1.4 cigarettes	Cancer, heart disease
Spending 1 hour in a coal mine	Black lung disease
Living 2 days in New York or Boston	Air pollution
Traveling 300 miles by car	Accident
Traveling 10 miles by bicycle	Accident
Flying 1,000 miles by jet	Accident
Living 2 months in Denver on vacation from New York	Cancer caused by cosmic radiation
Living 2 months with cigarette smoker	Cancer, heart disease
One chest x-ray taken in a good hospital	Cancer caused by radiation
Eating 40 tbsp. of peanut butter	Liver cancer caused by aflatoxin*
Drinking 30 12-oz cans of diet soda	Cancer caused by saccharin
Living 150 years within 20 miles of a nuclear power plant	Cancer caused by radiation
Risk of accident by living within 5 miles of nuclear reactor for 50 years	Cancer caused by radiation

* Assumes aflatoxin at maximum FDA permitted level; most commercial brands contain much lower levels.

Source: Wilson, R. 1979. Analyzing the risks of daily life. *Technology Review* 81(4), 41–46.



Closing

- There is clearly “more work to be done”... but the door is open for a major change on how to estimate the risks due to carcinogens at low doses
- It genuinely seems like it is time to have some major overhaul of the LMS and seek consensus on a more reasonable approach
- The economic and social costs of unnecessarily low EPA regulatory limits has long been known to be substantial
- Critics say “who cares” because, due to the benefits of the unintended consequence of regulation, it is worth “spinning the scientific dialogue” to put pressure on corporations.

THE END

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