Is a Linear Extrapolation of Cancer Risks to Very Low Doses Justified?

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Albuquerque, New Mexico, USA

Daniel J. Strom

Risk Analysis & Health Protection

Pacific Northwest National Laboratory

Richland, Washington

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Overview

- Risk management
- Model contrasted with hypothesis
- Radiation risk models: highly simplistic
- Why *use* models at all?
- The weight of evidence
- Arguments for and against using LNT
  - Scientific
  - Policy
- Brown's 3 uses of risk assessments
- *Mis*uses of radiation risk models

Risk Management

- Science is only one input
- Must be practical
- Must be politically acceptable
- Stakeholder involvement inevitable

Model or hypothesis?

- Relationship, function, association
- Conjecture, supposition, hypothesis
- Theory
- Model
  - climate
  - economics
  - environment
  - nuclear shell
  - dose-response

All models are wrong,
but some are useful.

- George E.P. Box, 1979

Radiation Risk Models Are Highly Simplistic

- Somatic Effects
  - Deterministic
    - » Developmental, teratogenic
  - Stochastic somatic: cancer
- Heritable ill-health ("genetic" effects)
- Dose and "response" are only 2 of 16 dimensions of a very complex problem

Dose and Response Aren't Enough - 1

1. What measure (relative, absolute, severity, frequency, …)?
2. What effect or health endpoint? (heritable ill-health, reproductive health and developmental abnormalities, cancer, deterministic effects)
3. Does the effect happen in the absence of radiation exposure, i.e., what is the background incidence?
4. What species?
5. What sub-species (genetic predisposition)?

Dose and Response Aren't Enough - 2

6. Who's exposed, and who's affected?
7. What is the age at start of irradiation?
8. What is the age at manifestation of effect?
   - » time between exposure and clinical effect
   - » cancer is a disease of old age
9. What is age at death and amount of life lost?
   - » lost life expectancy, LLE
10. What sex?

Dose and Response Aren't Enough - 3

11. What dose?
12. What [instantaneous] dose rate?
    - » inverse dose rate effect
13. What dose fractionation?
14. What portion of organism is irradiated?
15. What radiation "quality?"

Dose and Response Aren't Enough - 4

16. What other effect modifiers are there? Known modifiers include
   - diet
   - temperature
   - infection
   - combined injury: trauma, burns
   - state of organ function
   - other initiators, promoters, tumor progressors [smoking]
   - oxygen
   - dehydration
   - chemicals [antioxidants, free radical scavengers], drugs

The Issues (1)

- the existence of a threshold or a practical threshold
- the shape of the functional relationship (linear; linear-quadratic; hormesis: U-shaped, J-shaped)
- repair of DNA
- adaptive response and hormesis
- latent period for cancer

The Issues (2)

- relevance of in vitro and animal data to human health
- importance of heritable ill-health
- whether and how to extrapolate to doses below the range of statistically significant data
- validity of various epidemiologic methods (in particular the ecologic study design)

The Issues (3)

- whether a threshold for one kind of cancer implies a threshold for all
- what to do in the face of uncertainty or contradiction
- how to extrapolate: if one fits a linear relationship to the data, then one ends up with a linear relationship
- inference of causation from association
- determining what is prudent public policy

The Evidence

- physical
- molecular
- cellular
- in vitro
- animal
- human (epidemiology)

Human Evidence

- Epidemiology: the study of patterns of disease in human populations
- Experiments (clinical trials) versus observational studies
- Observational epidemiology for chronic diseases with long latent periods is an extremely blunt tool

Observational Study Designs

- individual health outcomes correlated with individual exposures
  - case-control
  - cohort
- group health outcomes associated with group exposures (or surrogates)
  - cross-sectional
  - ecological

Inferential Problems in Epidemiology (1)

- Confounding
  - factor associated with both exposure & outcome
  - e.g., diet is associated with ethnic group
- Bias
  - non-representative sample
  - e.g., survey only rich people
- Effect modification
  - variable which changes the effect of exposure
  - e.g., age, immunization, smoking

Inferential Problems in Epidemiology (2)

- Looking for a "small" signal in the noise
- Relative risk (RR) or odds ratio (OR) less than 4 is tricky
- Society wants regulation at RR ≈ 1.000 001
- Which studies are persuasive? http://www.pnl.gov/berc/epub/risk/epidprin.html

Controversial Studies

- Cohen's ecological study: non-persuasive design
- Matanoski's nuclear shipyard study: unhealthy control group
- "Tobacco-company science"
  - begin with the conclusions
  - list only those studies that support your conclusions

Why use models at all?

- Extrapolation to low doses (<50 mGy), low dose rates (<50 mGy/y), and both
- Below the range of statistical significance, effects may still be significant:
  - LNT model predicts that ~1% of all deaths are cancer deaths due to background & technologically-enhanced radiation
  - another 20-25% of all deaths are cancer deaths unrelated to radiation

Scientific Arguments for LNT

- Monoclonal origin of tumors
- Perturbation theory
  - Crump, K.S. et al. Cancer Research 36:2973-2979; 1976
  - Heitzmann, M.; Wilson, R. BELLE Newsletter 6(1):2-8; 1997.
- Miner, JPN bomb survivor, and many other human studies are consistent for most cancer endpoints
- Heritable ill-health probably LNT

Scientific Arguments Against LNT

- Some cogent radiation data contradict LNT for a few cancer endpoints
- No statistically significant heritable ill-health in JPN bomb survivors

Specious Arguments Against LNT (1)

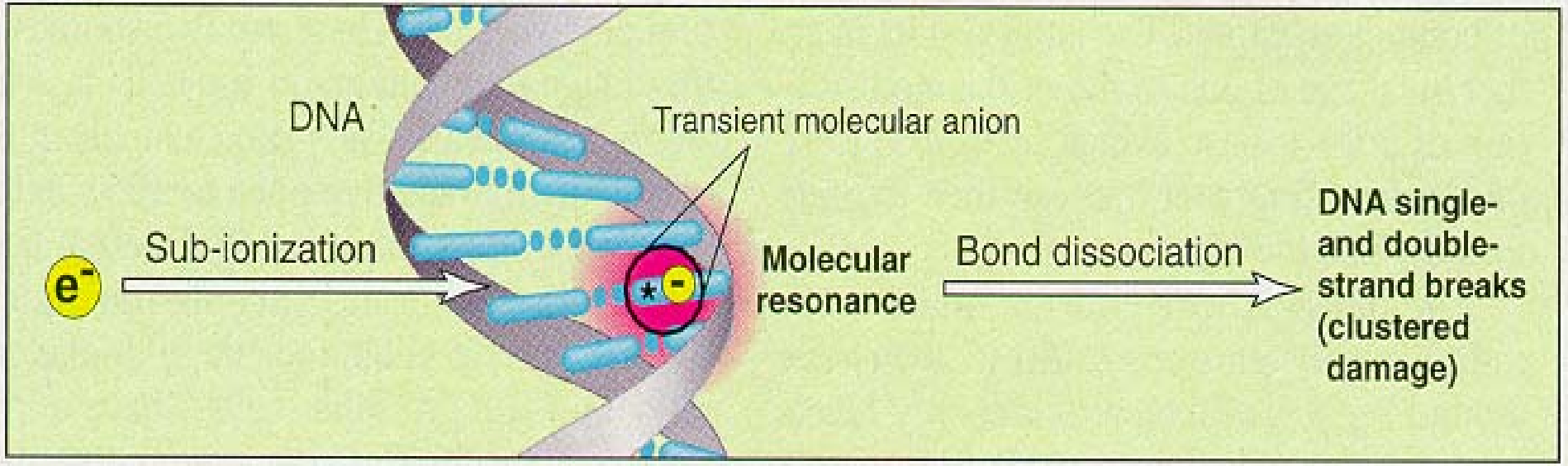
- If you can't see it, it isn't there
  - a signal-to-noise problem
- If you can't see it, it is of no concern
  - huge effects (e.g., 14,000 lung cancers/y) can't be seen
- Bomb survivors & miners are "high dose" studies
  - recent analyses have focused on low doses of concern
- Adaptive response
- Oxidative damage same for radiation & chemicals
  - ***no*** chemical can do what an α–particle or electron at the end of its track can do to DNA

Ionization Clusters (Goodhead 1992)

Initial cluster (in or very near DNA)		DNA damage	Repair	Biological importance
Sparse ionization	~10-20 eV	ssb or base	~100%	~none
Moderate cluster	~100 eV in 2-3nm	dsb + Some extra damage	Moderate	Mainly determines low-LET effects
Large cluster	~400 eV in 5-10nm	dsb(s) + much associated damage (nucleosome?)	~None	Mainly determines high-LET effects
Gross cluster	~800eV in 5-10nm	gross damage to DNA and surrounds	None	Some effects unique to high-LET?

Sub-Ionization Effects?

- Boudaïffa et al. Resonant Formation of DNA Strand Breaks by Low-Energy (3 to 20 eV) Electrons. *Science* 287:1658-60; 3 March 2000.
- Michael and O'Neill. A Sting in the Tail of Electron Tracks. *Science* 287:1603-4; 3 March 2000.



Boudaïffa et al. Resonant Formation of DNA Strand Breaks by Low-Energy (3 to 20 eV) Electrons. *Science* 287:1658-60; 3 March 2000.

Resonant Formation of DNA Strand Breaks by Low-Energy (3 to 20 eV) Electrons

Badia Boudaïffa, Pierre Cloutier, Darel Hunting, Michael A. Huels,* Léon Sanche

Most of the energy deposited in cells by ionizing radiation is channeled into the production of abundant free secondary electrons with ballistic energies between 1 and 20 electron volts. Here it is shown that reactions of such electrons, even at energies well below ionization thresholds, induce substantial yields of single- and double-strand breaks in DNA, which are caused by rapid decays of transient molecular resonances localized on the DNA's basic components. This finding presents a fundamental challenge to the traditional notion that genotoxic damage by secondary electrons can only occur at energies above the onset of ionization, or upon solvation when they become a slowly reacting chemical species.

Adaptive Response: Why Not?

- adaptive response seen only for
  - certain endpoints
  - certain intervals after priming
- large priming dose required: 150 mGy
  - excess human cancers seen below this dose
- priming wears off
  - lasts 10 days...

Specious Arguments Against LNT (2)

- Threshold arguments
  - {high, medium, low} applied to {fall, wind, impact}
  - only make sense for hit size, not for dose: big hits exist at any dose
- Hormesis
  - Diet is a powerful risk factor for lifespan
  - "Is it the chemicals or the calories?" (NAS/NRC, Carcinogens & Anti-carcinogens in Diet, 1996)

Specious Arguments Against LNT (3)

- Some chemical carcinogens have thresholds
  - chemicals act through different mechanisms
  - Ames's "mitogenesis is mutagenesis"
  - mutagenic v. non-mutagenic carcinogens (Wilson, J.D. Risk Analysis 17(1):1-3; 1997)
- Energy imparted, not dose, should be independent variable
  - mass of control & coding DNA roughly the same in all people

Policy Arguments for LNT

- Errs on the side of safety (conservative)
- Politically acceptable status quo
- No prospect of direct measurements of effects at doses of interest
- Practical system based on LNT has protected workers

Policy Arguments Against LNT

- Expensive risk management decisions
- Failure to Optimize: the "R" is ignored in ALARA (as low as reasonably achievable)
- 10^{-6} lifetime fatal cancer risk may have insignificant life-shortening
  - Gaylor & Zheng 1997

Specious Policy Arguments

- Other systems won't work
  - tolerance dose system can work
- Conspiracy theories
  - oddly, they're used by both sides!
- Science and "Scientific Method" as only valid inputs to risk management decisions
  - ignores policy, practicality, & social values
- LNT model causes fear
  - where are the data that the fear is caused by the model?

The Real, Hard Question

- What is a *reasonable* value of imposed risk that is acceptable?
  - reasonable = affordable
  - involuntarily imposed without knowledge or prior consent: 1000× *less* acceptable than voluntarily accepted risks
  - acceptable
- We can live with the LNT model if a consensus answer can be found

Uses and Misuses of the LNT Model

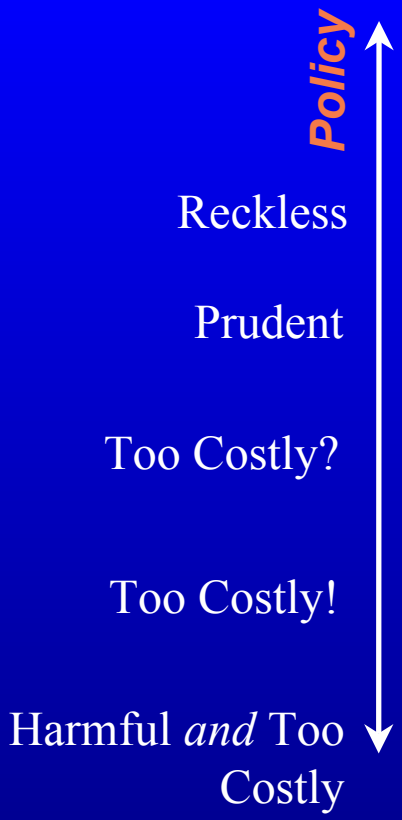
- Linear, no-threshold (LNT) dose response model is simplistic for stochastic effects
- LNT is
  - ok for prevention (standards setting)
  - wrong for individual prediction (e.g., probability of causation)
  - inappropriate for priority-setting
- LNT requires *de minimis* or risk threshold concepts

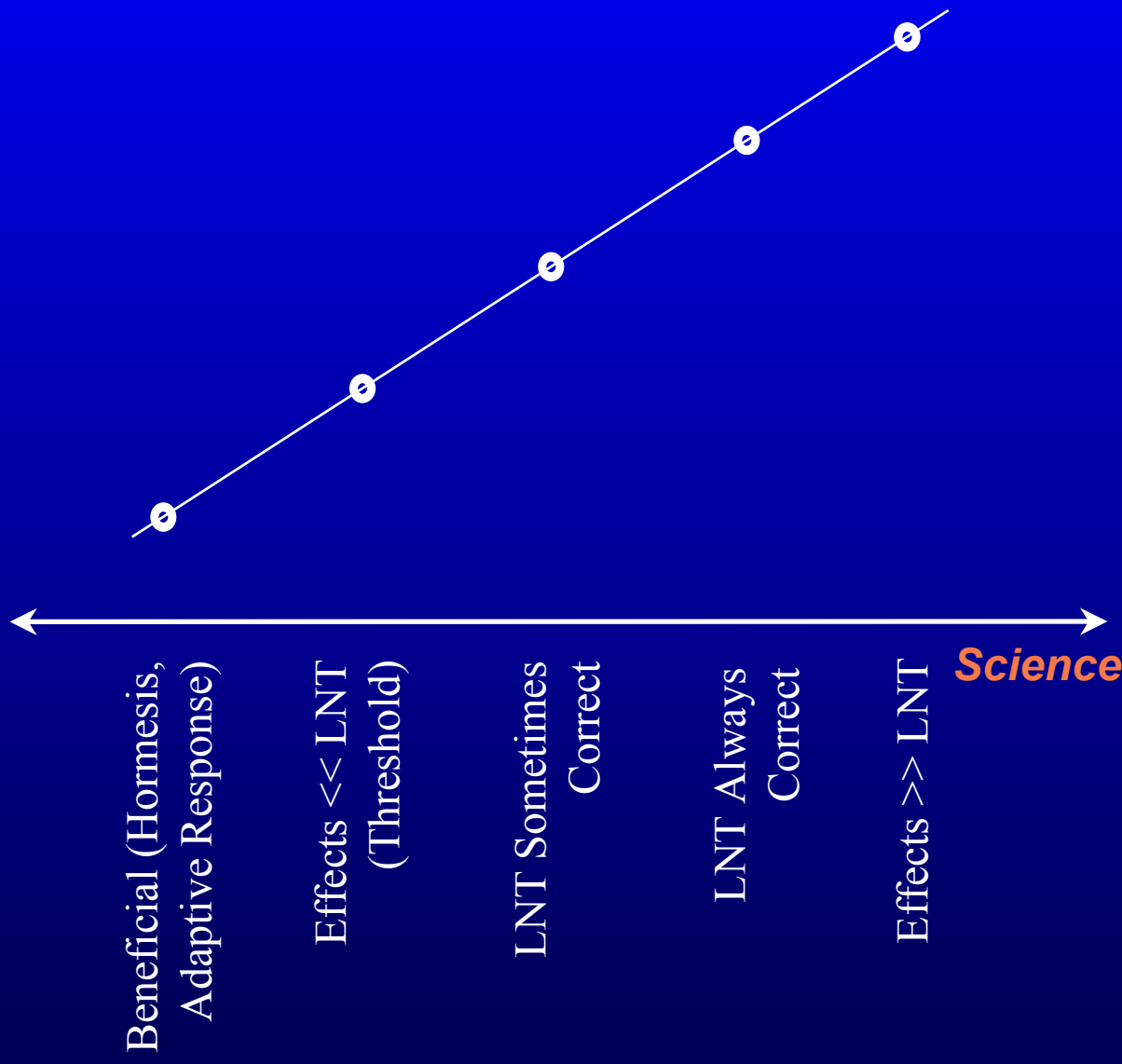
Uses of Risk Assessments: Stephen L. Brown's "3 P's"

- prevention (protection)
  - standards
  - uncertainty
  - conservatism
- prediction
  - prospective or retrospective individual risks
- priority-setting
  - risk ranking

A *Linear* Relationship?

In the Absence of Knowledge at Low Doses, LNT-based Policy is…





Beliefs About Effects of Low Doses of Radiation

Conclusions

- Evidence must be *weighed*
- All models are wrong but some are useful
- Scientifically, LNT is simplistic and
  - wrong for some cancers
  - right for some cancers
  - probably right for heritable ill-health
- LNT is ok for risk management with ALARA and *de minimis*
- LNT is wrong for individual risk predictions