Low Dose Linearity
and implications
for Regulation

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by

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LINEARITY
AT LOW DOSES
IS USUAL!!

Walking blindfold across Michigan Avenue is safe: (Risk (R) = 0)

IF THERE ARE NO CARS!

The risk (R) increases roughly in proportion to the number of cars.
I will argue that:----

- Low dose linearity is common in societal risks
- Contrast Acute and Chronic Effects
- Cancers caused by pollution
  - look like other cancers
  - 30% of people get cancer

These are enough to set LINEARITY as the DEFAULT
Characteristics

- One dose or dose accumulated in a short time KILLS
- 1/10 the dose repeated 10 times DOES NOT KILL
CHRONIC EFFECTS
including CANCER

Characteristics

A dose just sub-acute can give effects if repeated.

Usually not all people affected - dose response is flatter
Typically an accumulated Chronic Dose = Acute $LD_{50}$
gives CANCER to 10% of the population.

E.g. $LD_{50}$ for radiation is about 350 Rems.
At 350 Rems about 10% of exposed get cancer.

(more or less depending on rate of exposure)
Development of a Model

PROPOSITION:

ANY ESTIMATE OF RISK implies A MODEL

(simplest: next year will be like last year)
Early Optimism Based on Poisons

There is a threshold below which nothing happens

_______BUT:_____

J.G. Crowther 1924

For radiation cancers:

Probability of Ionizing a Cell
Linear with Dose
Repair Mechanisms

- Thousands of **CELLS** are **MODIFIED** each **SECOND**
- NOT ALL LEAD to **CANCER**

**THEREFORE:**

**REPAIR OR REJECTION MECHANISMS MUST EXIST**
Repair Mechanisms

BUT

Does the Mechanism Reject/Repair:

ALL DAMAGED CELLS UP TO XXXX?

(implying a threshold)

OR 99.999% of CELLS INDEPENDENT OF DOSE

WE DON’T KNOW
SINCE 1970

ATTEMPTS to
REDUCE RISKS TO
ONE IN A MILLION PER LIFE

__________________________

THIS LEADS TO A BATTLE
THE BATTLE

LINEAR
Physicists
Academics
Environmentalists

THRESHOLD
Industry
Biologists
Toxicologists

REGULATORS IN THE MIDDLE
CHEMICAL INDUSTRY SPENT

- MILLIONS OF DOLLARS

  to prove that

- ORGAN DOSE/APPLIED DOSE
  ----> 0

- as

- APPLIED DOSE
  ----> 0
**Figure 8.** DNA adducts of aflatoxin in cells of the liver (158) 1 hr after administration of varying doses of aflatoxin.
Figure 9. DNA adducts of benz[a]pyrene in cells of the stomach (56) 18 hr after administration of varying doses of aflatoxin. $10^{-8}$ g/mouse corresponds to a dose of 30 mg/kg.
DNA adducts are (nearly) linear with applied dose over 5 orders of magnitude!

(FOR SOME SITES AND CANCERS)

[AN ADDUCT DOES NOT LEAD TO CANCER
BUT DOES PROVE THAT THE CHEMICAL REACHED THE CELL]

(e.g. Zeise, Crouch and Wilson
Env. Health Perspect. 73: 259 (1987)
GENERAL MODELS

ARMITAGE & DOLL, 1954/7

\[
dN/N = p_1 p_2 \ldots p_{k-1} p_k
= a_1 t a_2 t \ldots a_{k-1} t a_k (dt)
\]

CANCER RATE = \( 1/N \frac{dN}{dt} \)
\[
A t^{k-1}
\]
\[
\ln \text{Rate} = \ln A + k-1 \ln t
\]
ARMITAGE & DOLL explained

AGE DISTRIBUTION OF CANCERS

LATENCY

SYNERGISM AT HIGH DOSES
IS THE FORMULA:

\[ b_1 t \to b_1 t + a f(d) \]

SO THAT

\[
\frac{1}{Rate} \frac{d(\text{rate})}{dd} = \frac{a}{b_1 t} / \frac{df(d)}{dd}
\]

\[ dd = 0 \]

OR:

\[ b_1 t \to a f(d + d0) \]

SO THAT:

\[
\frac{1}{rate} \frac{d(\text{rate})}{dd} = \frac{a}{b_1 t} / \frac{df(d)}{dd}
\]

\[ d = d0 \]
Figure 1. Typical nonlinear, "threshold", dose-response relationship ($R = Ad^3$).
Figure 2. Threshold dose-response relationship ($R = Ad^2$) with axes shifted to $R_0$ and $d_0$. Note that $\delta R_0$ is proportional to $\delta d_0$. 
CANCER RATE is ANCHORED at HIGH DOSES so that the slope of dose-response (RISK) may be greater than the simple line to zero
Figure 3. Comparison of slope derived from incremental response model, $\beta_{inc}$, and that derived by extrapolation from high-dose laboratory data, $\beta_d$. Note that often $\beta_{inc} < \beta_d$. 
The POLLUTANT

IS PRESUMED TO ACT TO INCREASE PROBABILITY AT ONE STAGE

(OTHER STAGES CAUSED by NATURAL BACKGROUND)
CRITICAL ISSUES FOR LINEARITY

• The POLLUTANT ACTS
  • in the same way as
  • WHATEVER ELSE INFLUENCES THE
  • CANCER RATE

• CANCERS CAUSED BY
  • THE POLLUTANT
• ARE INDISTINGUISHABLE FROM OTHER CANCERS
NOTHING SAID ABOVE SAYS WHETHER THE SLOPE IS

+ POSITIVE

OR

— NEGATIVE
THE POLLUTANT gives CANCER AT HIGH DOSES

So: DEFAULT SLOPE is POSITIVE

BUT...

IF ANTICANCER EFFECTS CAN BE DEFINITIVELY SHOWN AT LOWER DOSE DEFAULT SLOPE SWITCH TO NEGATIVE
Fig. 1 Skin cancer prevalence rates as a function of arsenic concentration in drinking water for all literature. The line represents a best fit to all data using the MSTAGE program with a threshold of 103 ppb \( y = 3.23 \times 10^{-5} \) \( \text{D} \) 
\( - 3.33 \times 10^{-3} \) for \( \text{D} > 103; \)
\( P \) value = 0.80. The square symbols illustrate the data from Tseng [12]; the triangles all other data (see Table 2).
Fig. 2 Multistage model of overall skin cancer prevalence as a function of arsenic dose rate in the study by Tseng and coworkers [12]. — best fit, —— 95% limit on q1.
Fig. 3 Multistage model of male skin cancer mortality as a function of arsenic dose rate in the study by Wu and co-workers [15]. --- best fit, ---- 95% limit on q1.
Arsenic risk

• Skin lesions are unique
• There seems to be a threshold at 50 -150 ppb

• (Data from Taiwan and also from Inner Mongolia)
• BUT
• Internal cancers may be different
Dose-response vs. arsenic level

total cancer mortality (males)

best fit:
q0 = 1.177e-3
q1 = 5.629e-6
q2 = 0.0
q3 = 0.0

95% limit on q1:
q0 = 1.060e-3
q1 < 6.129e-6
q2 = 0.0
q3 = 0.0

--- best fit
----- 95% limit on q1
Figure 8: Bladder Cancer Relative Risk Estimates by Arsenic Drinking Water Concentration—All Studies Combined

$R^2 = 0.4968$
Figure 5: Lung Cancer Relative Risk Estimates by Arsenic Drinking Water Concentration-Results for females combined

\[ y = 0.0076x + 1 \]
\[ R^2 = 0.7084 \]
Figure 12. Age standardized incidence of lung cancer in coke oven workers versus cumulative exposure to coal tar pitch volatiles (87). $^a$Significantly nonlinear ($p < 0.01$). $^b$Coal tar pitch volatiles.
Arsenic risk

• For internal cancers
• At 500 ppb Measured Risk
  • (Chile) is 10%
    • If linear,
      • risk is one in a million
      • at 5 parts per trillion!!
    • “background” is about
      • 2 parts per billion
Figure 7.1
Estimated Adjusted Mortality Rate-Ratios from the Six-Cities Study Plotted against Non-Inhalable Particles (TSP-IP), the Coarse Fraction of Inhalable Particles (IP-FP), Fine Particles (PM$_{2.5}$), and Sulfate Particles

Units are $\mu g/m^3$. 
Figure 9.3
Lung Function Estimates for Children in 22 U.S. and Canadian Communities

FIGURE 9.1
Schematic of Lung Function vs. Age Showing Loss of Life Expectancy (LOLE)

Lung Function

Threshold of Adequate Lung Function

Age (Years)
RISK
due to
LIFETIME
exposure to
AIR POLLUTION
is
3 to 5% in the USA!
It is not only mutagens that show linearity

Linearity may be usual

Consider Non-carcinogens and carcinogens

SIMILARLY!!!!
MY CONCLUSION
(REPEAT OF 20 YEARS AGO)

IT IS NOT POSSIBLE TO REGULATE A ONE IN A MILLION LIFETIME RISK CONSISTENTLY

• ATTEMPTS TO DO SO
  • ARE
  • ARBITRARY
  • and
• CAPRICIOUS
Legislators still want < 1 in a million!

Where does this leave regulators???

IN THE MIDDLE
(as usual)

BUT

keep telling the legislatures

the facts of life!