The Case For Both Individual And Population Toxicity Thresholds

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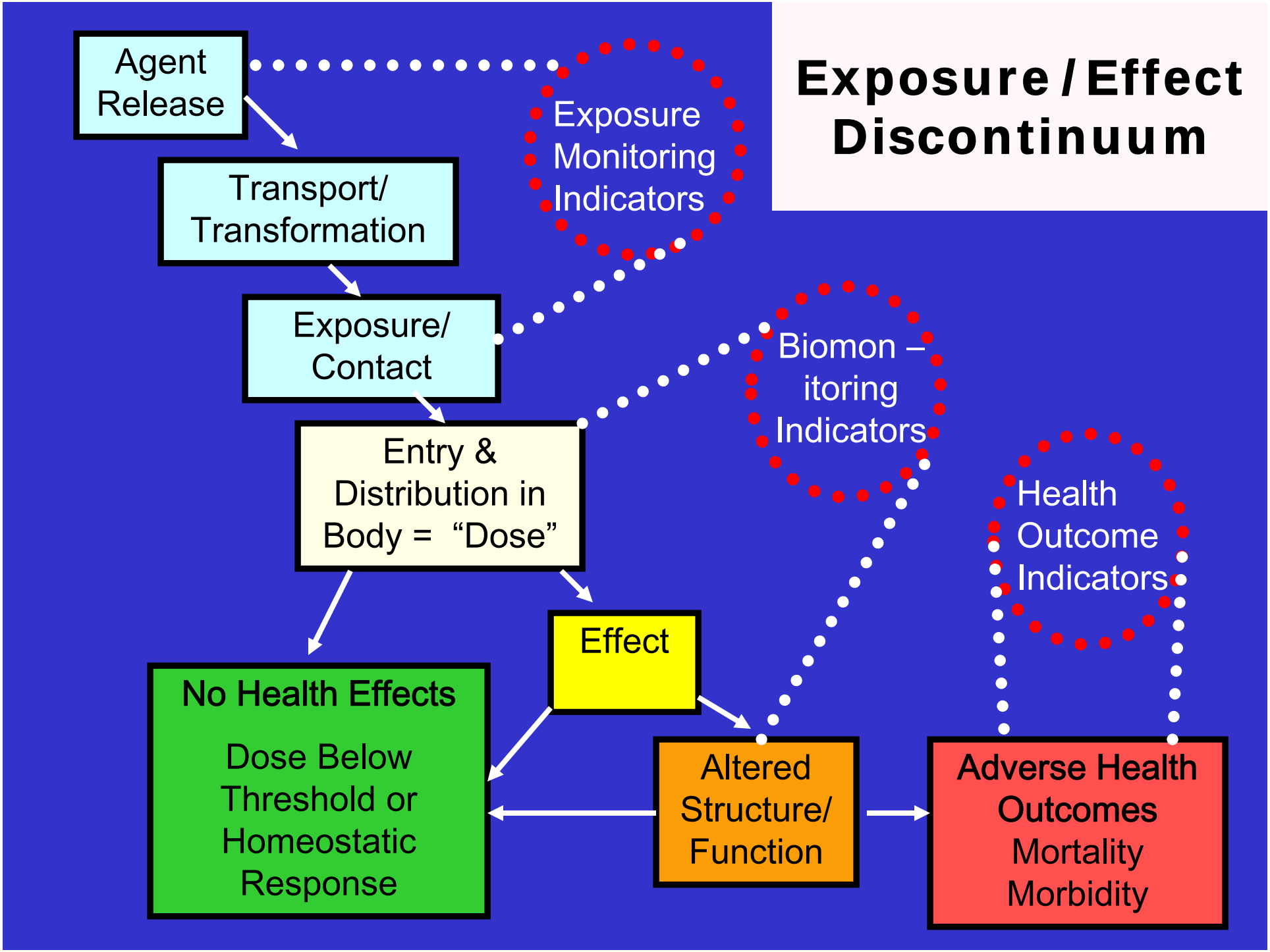
Thresholds?

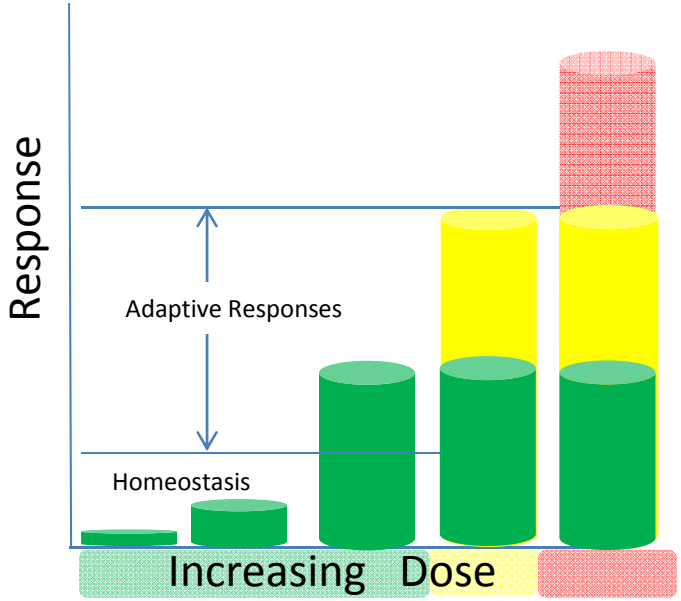
The practical difficulty in establishing a “no-effect” level for a particular compound using a manageable number of experimental animals and the more complex problem of extrapolating a safe level for humans must not be permitted to obscure the fact that thresholds do exist.”

Rozman, Doull and Hayes in Handbook of Pesticide Toxicology


Exposure / Effect Discontinuum
Agent Release
Transport/ Transformation
Exposure/ Contact
Entry & Distribution in Body = "Dose"
Effect
No Health Effects
Dose Below Threshold or Homeostatic Response
Altered Structure/ Function
Adverse Health Outcomes
Mortality
Morbidity
Exposure Monitoring Indicators
Biomon – itoring Indicators
Health Outcome Indicators

Toxicity Pathway
"Exposure- Effect Discontinuum"

Response is Dependent on Dose: Not All Exposures Will Produce Adverse Effects



Higher Dose Leads to Altered Organ Structure / Function → Adverse Health Outcome

Higher Dose Leads to Altered Organ Structure / Function → No Adverse Outcomes

Higher Dose Leads to Altered Physiology: Adaptive Response → No Adverse Outcomes

Higher Dose Elicits Homeostatic Response → No Adverse Outcome

Chemical Properties → Protein binding, DNA Binding, Receptor Binding → Gene Expression, Protein Production, Altered Signaling → Dose Below Threshold → No Adverse Outcomes

Toxicant → Interaction with macromolecules → Cellular Responses → Effects → Organism Responses

Toxicity Pathway →

Exposure – Effect Discontinuum: Illustrated in Graphic from NRC "Toxicity Testing in the 21st Century" 2007

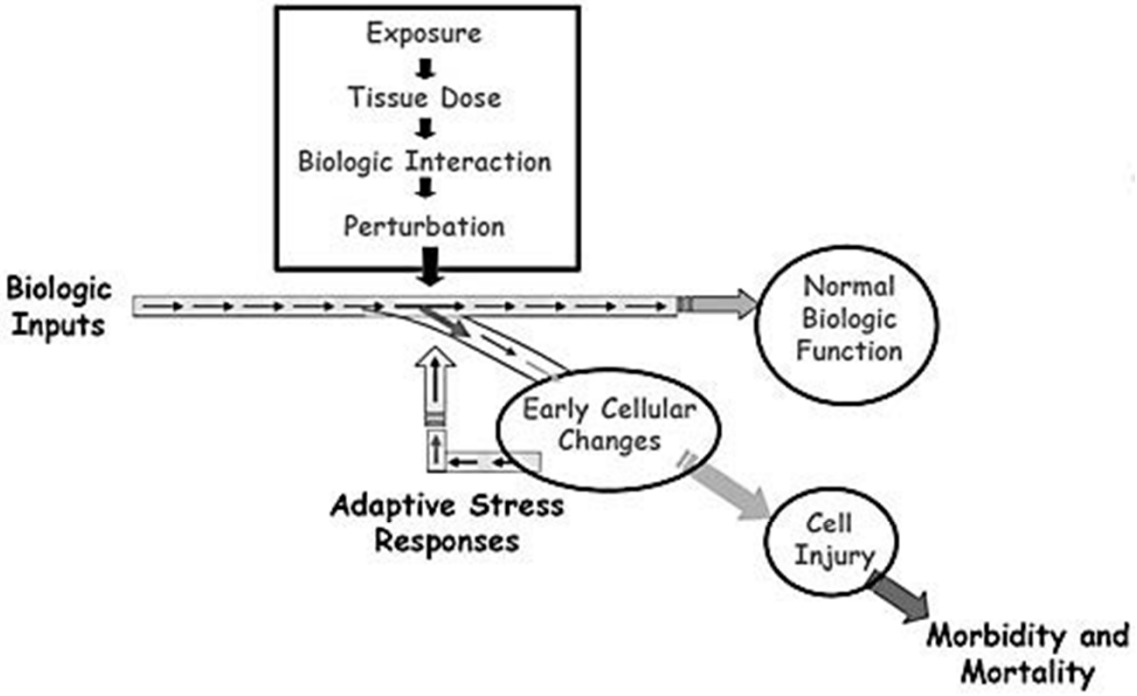


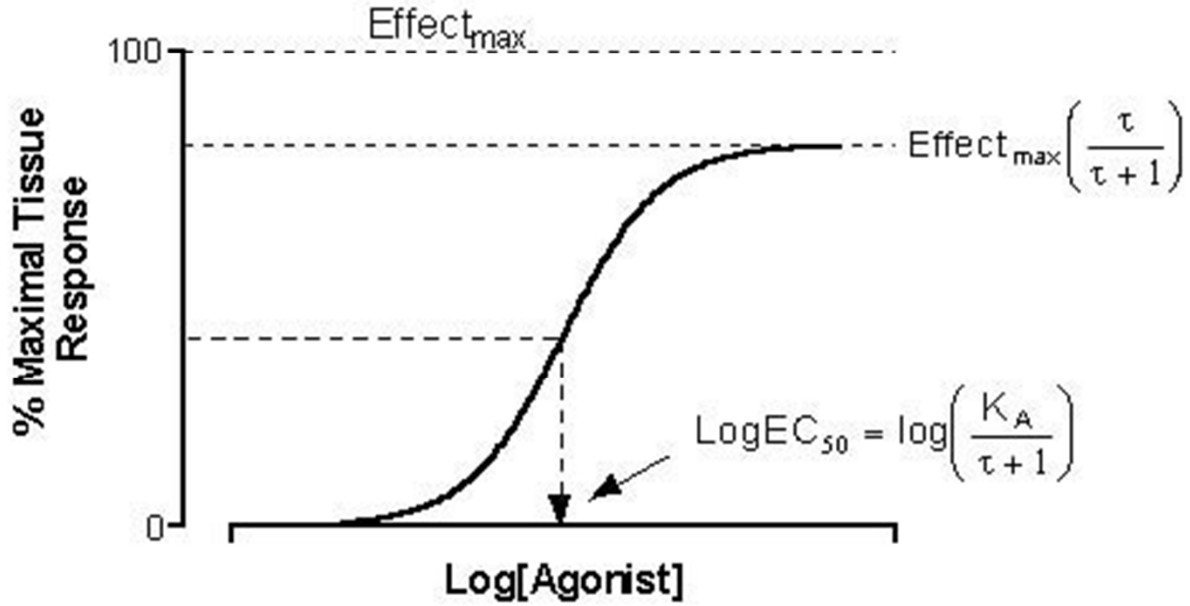
FIGURE 2-2 Biologic responses viewed as results of an intersection of exposure and biologic function. The intersection leads to perturbation of biologic pathways. When perturbations are sufficiently large or when the host is unable to adapt because of underlying nutritional, genetic, disease, or life-stage status, biologic function is compromised, and this leads to toxicity and disease. Source: Adapted from Andersen et al. 2005. Reprinted with permission; copyright 2005, *Trends in Biotechnology*.

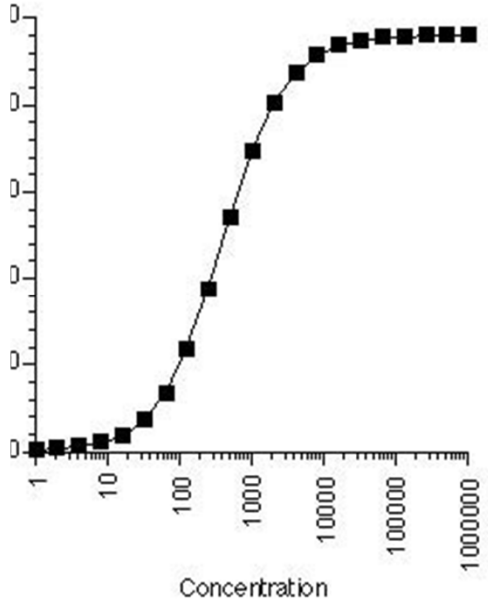
Thresholds in Biological Interactions

- Law of Mass
- Hill Equation

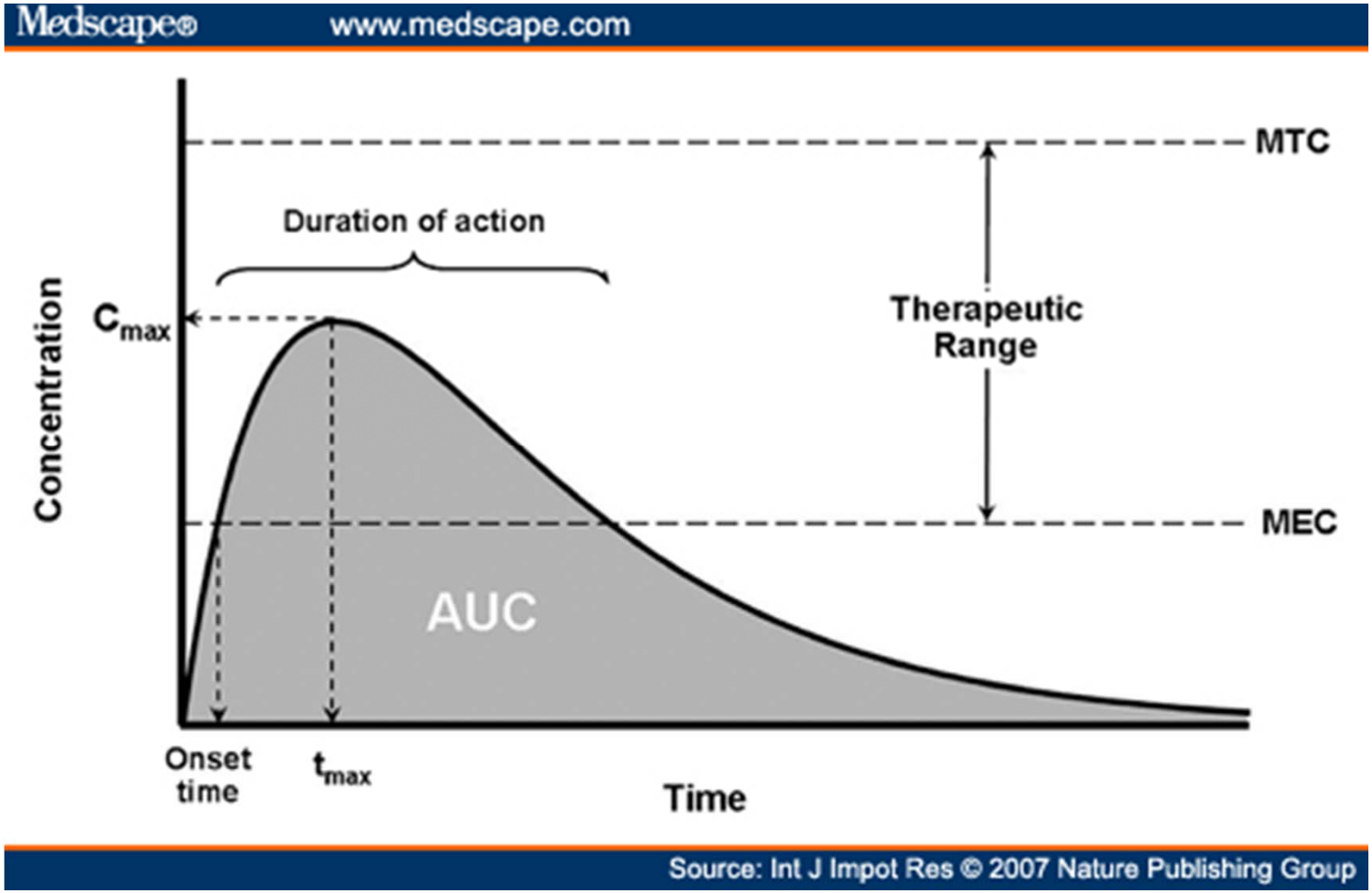
$$R + L \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} RL$$

$$\text{Effect} = \frac{E_{Max} \bullet C^{\gamma}}{EC_{50\%}^{\gamma} + C^{\gamma}}$$



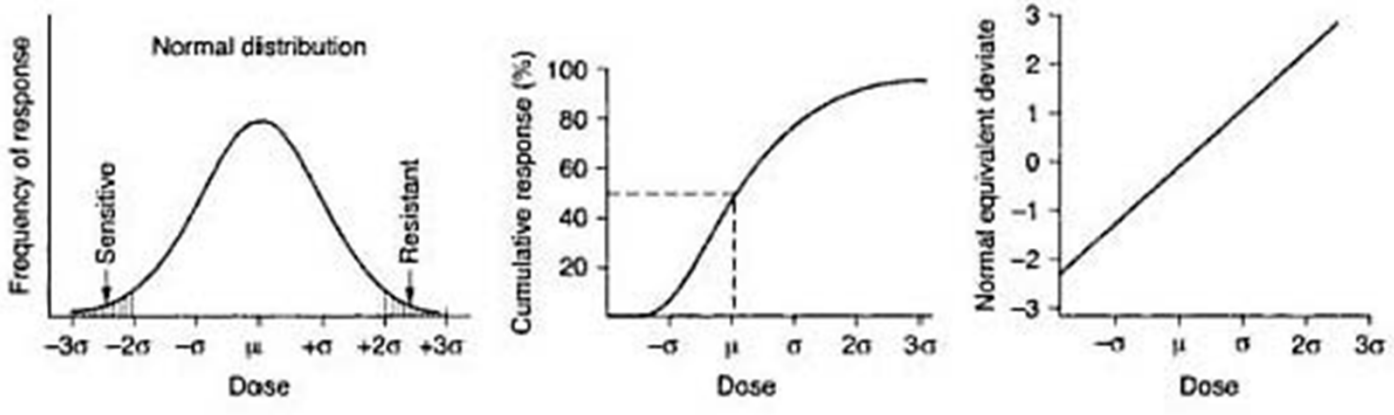


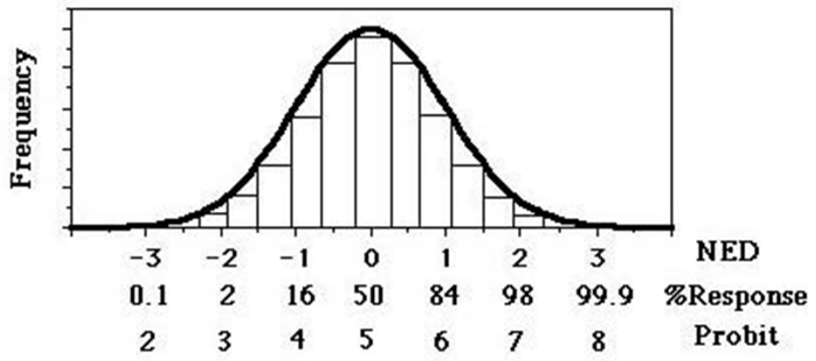
Thresholds in Biological Responses



Population Response

- Quantal dose response: variability in the population is addressed





NRC Silver Book

Science and Decisions: Advancing Risk Assessment
http://www.nap.edu/catalog/12209.html

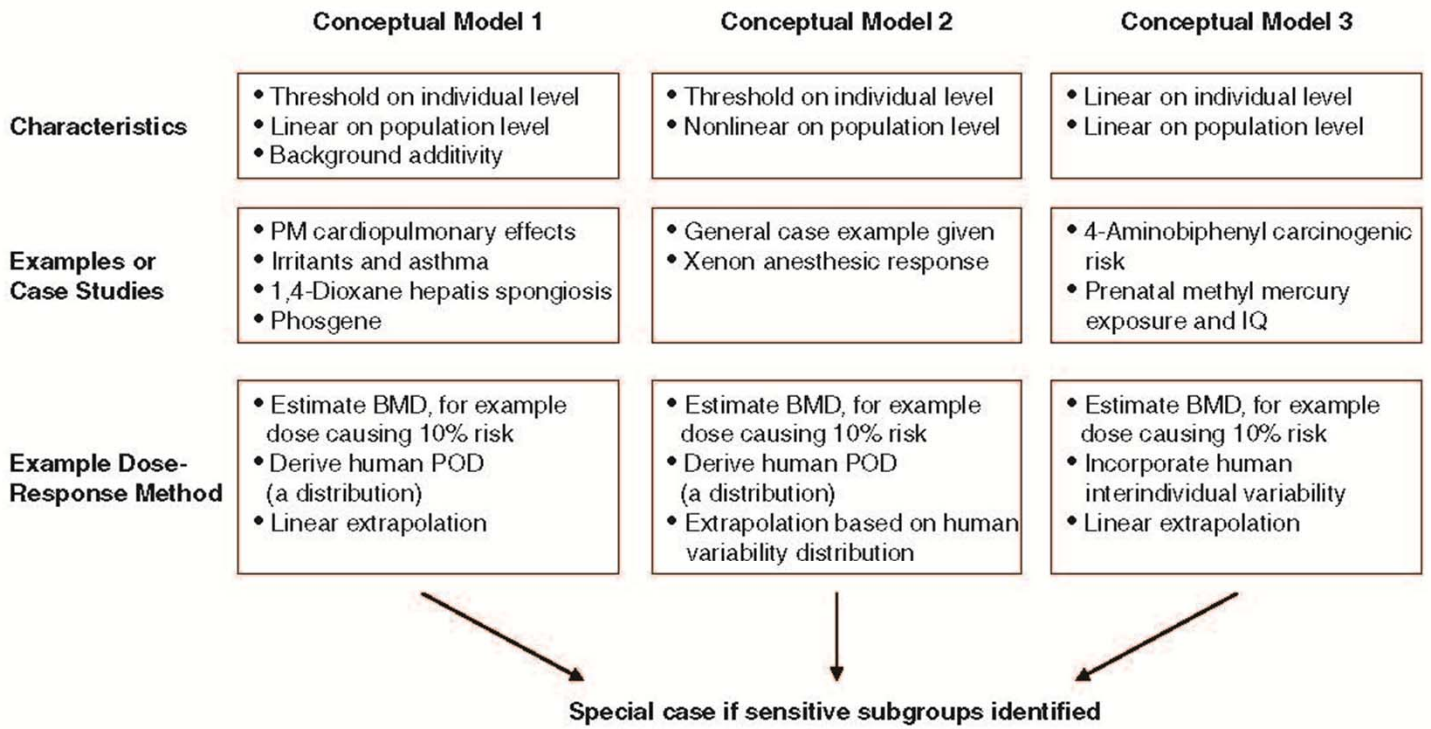


FIGURE 5-12 Three example conceptual models lead to different descriptions of dose-response relationships at individual or population levels. These are illustrated in the case studies. For each conceptual model, there may be a sensitive subgroup that should be addressed with separate dose-response analysis.

What is the hypothesis?

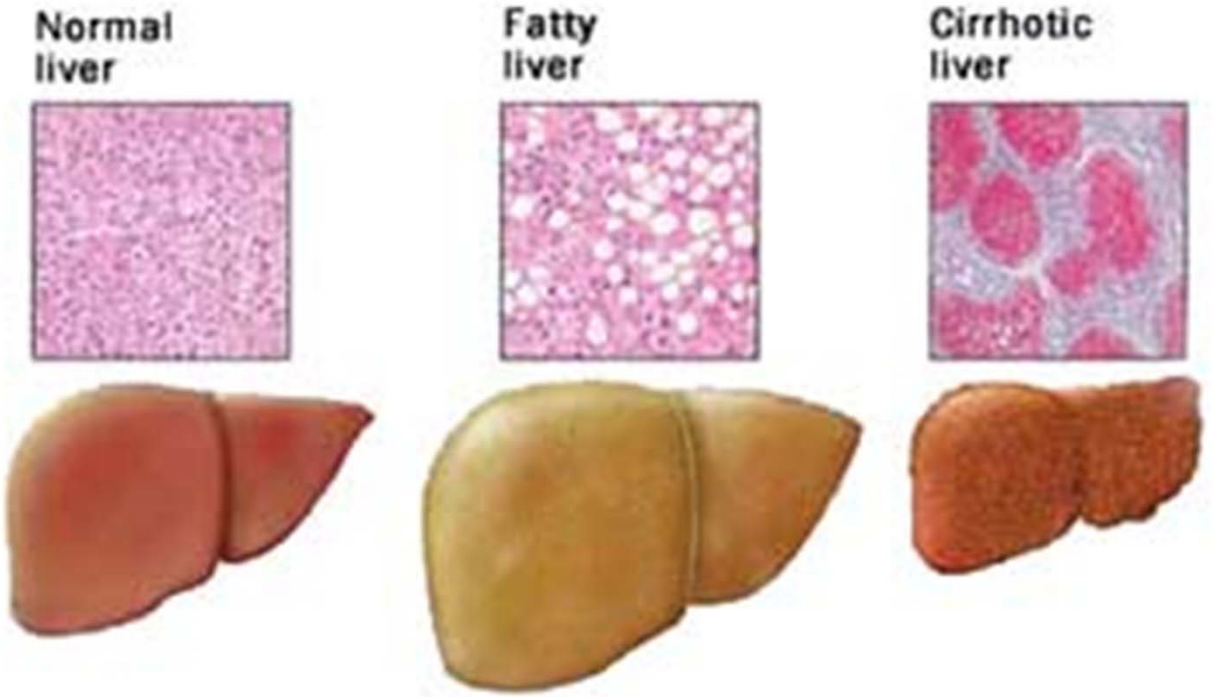
- Two components of Conceptual Model 1:
  - Threshold individual
    - There is a threshold dose at the individual level. No response will be observed at doses below the threshold.
  - Linear population
    - Due to variability in the population, even if there is a threshold at the individual level, there will be no apparent threshold at the population level

How to Evaluate this Hypothesis?

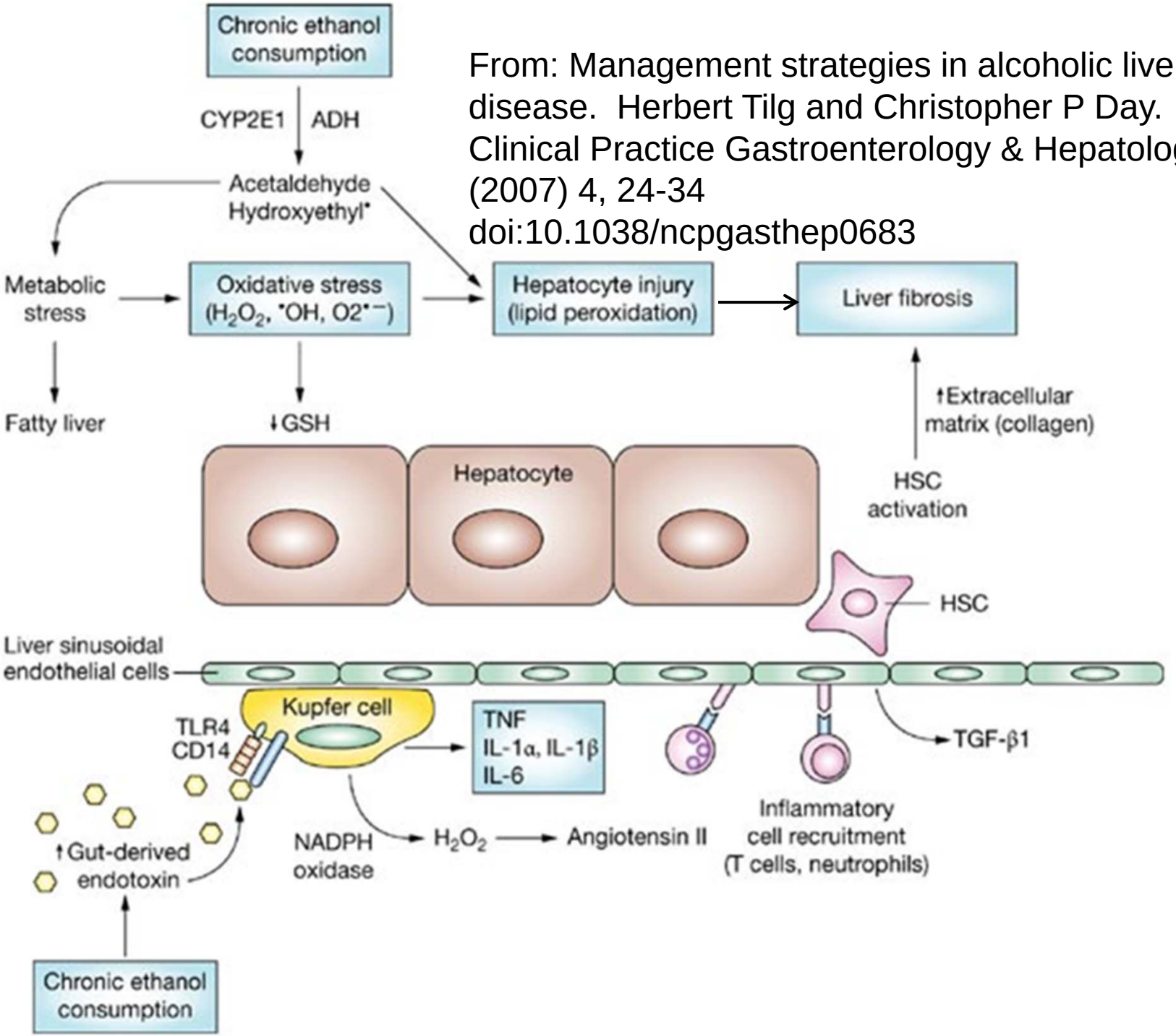
- Statistical evaluations will not provide the answers
  - Signal to noise within experimental data
  - Resolution between shallow linear, non-linear and zero slopes problematic
- MUST USE KNOWLEDGE OF BIOLOGICAL BASIS OF TOXICITY

Case Study: Ethanol-induced Cirrhosis in Humans

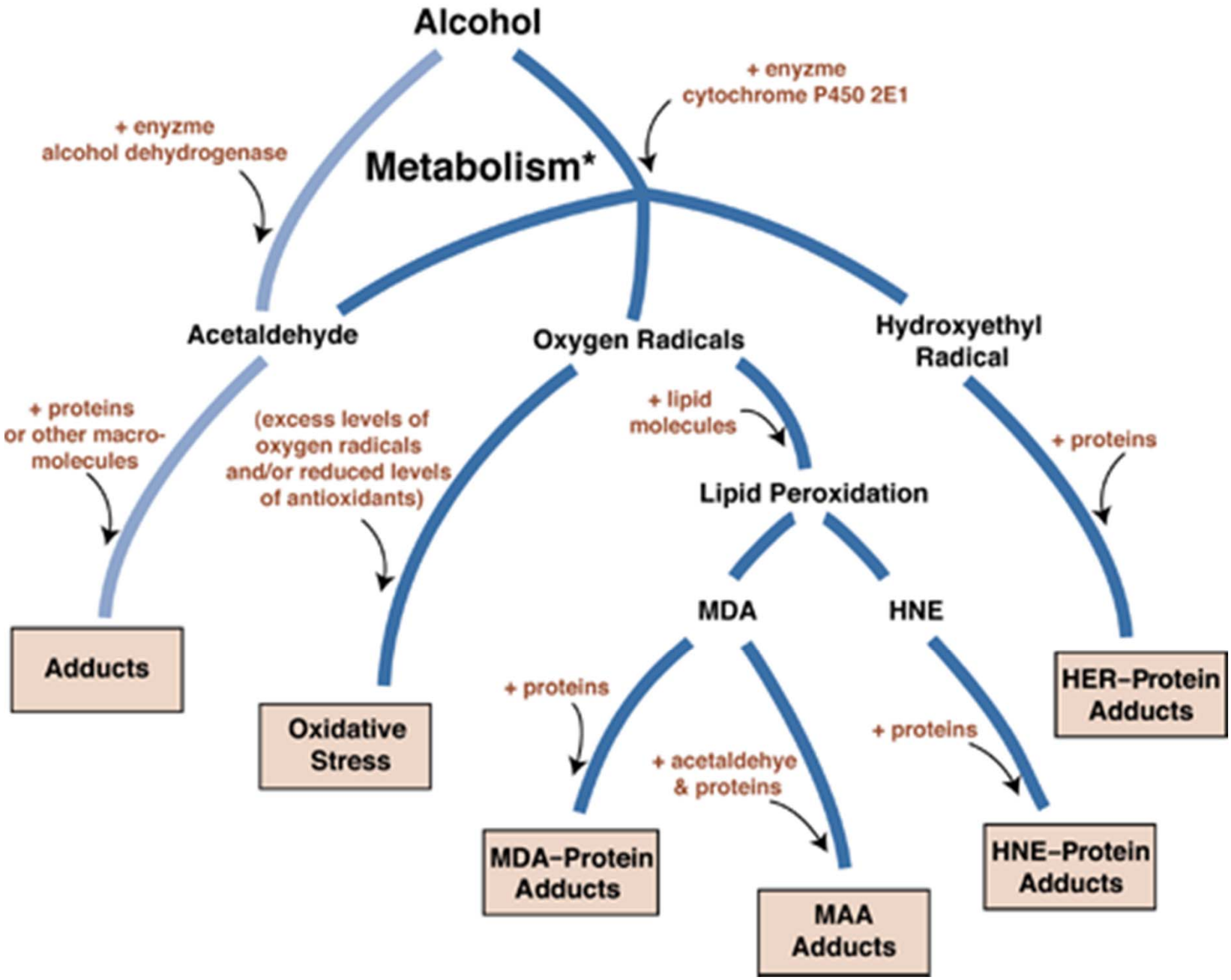
Rick Becker[1], Sean Hays[2]



Inflammation → Fibrosis → Cirrhosis



From: Management strategies in alcoholic liver disease. Herbert Tilg and Christopher P Day. Nature Clinical Practice Gastroenterology & Hepatology (2007) 4, 24-34
doi:10.1038/ncpgasthep0683


Alcohol
+ enyzme
cytochrome P450 2E1
+ enyzme
alcohol dehydrogenase
Metabolism*
Acetaldehyde
Oxygen Radicals
Hydroxyethyl
Radical
+ proteins
or other macro-
molecules
(excess levels of
oxygen radicals
and/or reduced levels
of antioxidants)
+ lipid
molecules
+ proteins
Lipid Peroxidation
Adducts
Oxidative
Stress
MDA
HNE
HER-Protein
Adducts
+ proteins
+ proteins
+ acetaldehye
& proteins
MDA-Protein
Adducts
MAA
Adducts
HNE-Protein
Adducts

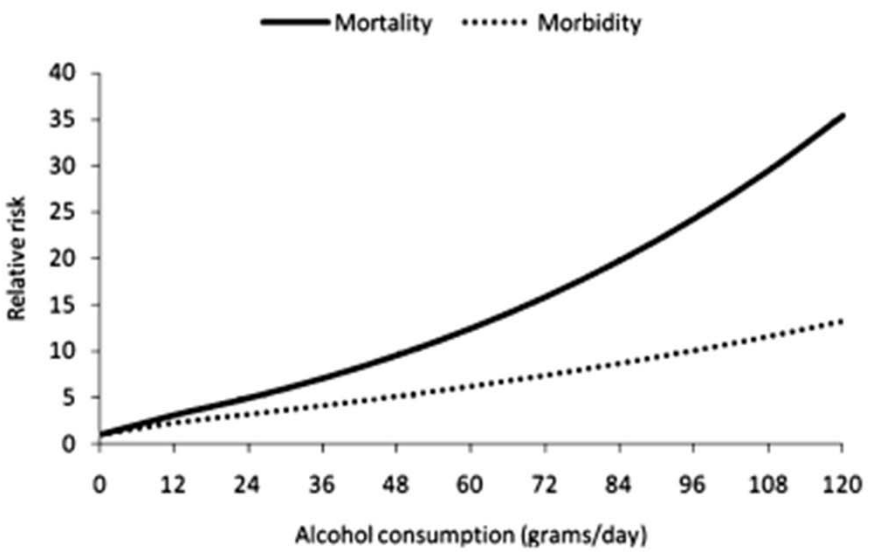
Methods : Mortality

- Benchmark dose (BMD) modeling of a meta-analysis of mortality relating to liver cirrhosis (Rehm et al., 2010)
  - BMD was conducted for data on males and females, separately.
  - A 1.5% excess risk was chosen as the benchmark response (BMR); Both BMD and BMDL (benchmark dose lower limit – 95% confidence limit) were calculated
  - BMDLs for males (25.7 g/day) and females (27.2 g/day)
  - Assume dose response relationship is linear
  - Calculate dose associated with a 1e-5 excess risk level (the level of response recommended in the NRC report)
  - Ethanol dose at 1e-5 excess risk of liver cirrhosis mortality in US population “predicted to be”0.018 g/day (0.3 mg/kg-day).

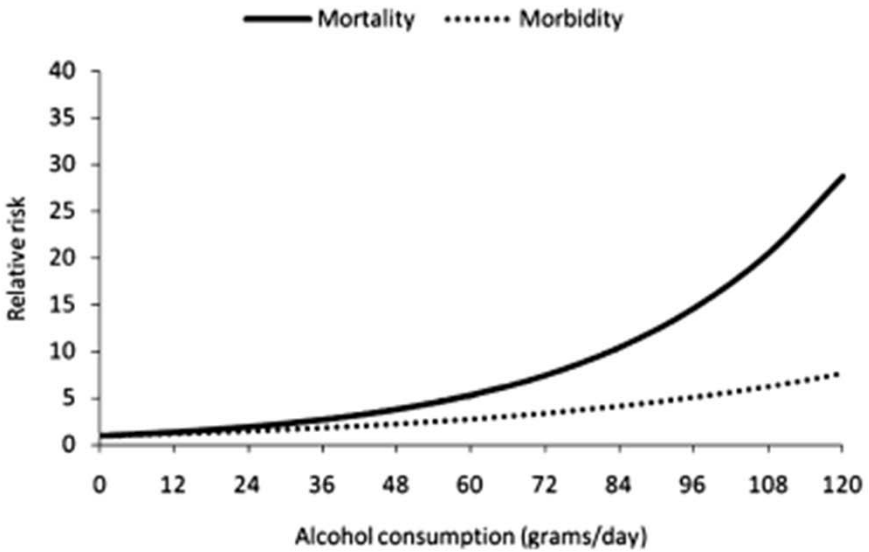
Methods : Morbidity

- Corrao et al. (1998) a meta-analysis = re-evaluated the dose-response information for each study and fit each to a log-linear model with relative risk (RR) as the response measure grams alcohol/day dose metric
- The slope (beta) and standard error about the slope were reported for each study included in the meta-analysis.
- Background incidence information so as to allow calculation of extra risk
  - Klatsky and Armstrong (1992) measured incidence of admissions to hospitals for liver cirrhosis that were alcohol related
  - Prevalence of liver cirrhosis in the US is approximately 400,000 (NIH, 1994)
  - Incidence of approximately 9000 cases/yr in the US or an incidence rate of 9000/305,000,000 (3e-5).
- Using the upper 95th percentile of the slope on the relation between RR and daily dose of alcohol (g/day) and assuming linear extrapolation of this dose response relationship, the dose of alcohol associated with a 1e-5 extra lifetime risk of liver cirrhosis is 0.11 g/day (1.6 mg/kg-day).

Women


Mortality
Morbidity
Relative risk
0
5
10
15
20
25
30
35
40
0
12
24
36
48
60
72
84
96
108
120
Alcohol consumption (grams/day)

Men


Mortality
Morbidity
Relative risk
0
5
10
15
20
25
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35
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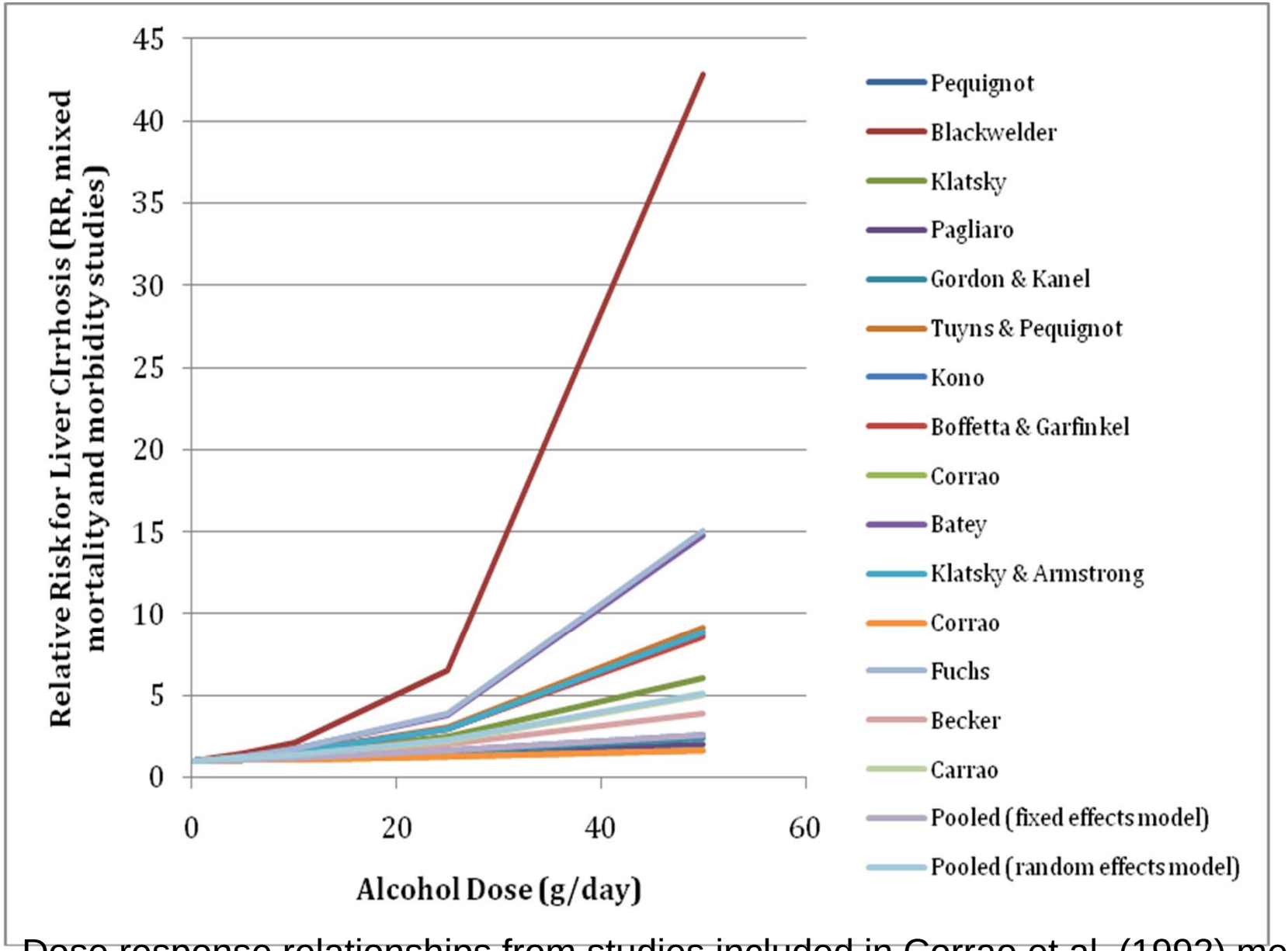
0
12
24
36
48
60
72
84
96
108
120
Alcohol consumption (grams/day)



Dose response relationships from studies included in Corrao et al. (1992) meta-analysis. Function of each dose response model was LN(RR)=beta * AI, where beta is the slope of the linear term and AI is the alcohol intake (g/day).

Dose-Response Model	
Study	Klatsky & Armstrong, 1992
beta	0.0358
SE	0.004
Background Incidence of Liver Cirrhosis	
Cases per 100,000 hospital visits	26
Hospital admissions/yr in US	34667000
Background incidence of cirrhosis cases/yr	9013
US population	305000000
Background Incidence rate	2.96E-05
Extra Risk	
Lifetime Rate	2.07E-03
Tolerable extra cases	1.00E-05
Target cases	2.08E-03
Target RR	1.004834
Dose @ Target RR (g/day)	0.11

Excess Risk: Consumption of Alcoholic Beverages

- Average alcoholic drink contains 10 to 13 grams of alcohol
- If the dose response is linear, then at an individual risk of 1e-5 risk for hepatic cirrhosis mortality & morbidity
- NRC recommended linear approach would indicate that the “average” person (with no traits that would make them more sensitive to ethanol metabolism or developing liver cirrhosis) could consume only a single beer once every 555 days (to protect against mortality) or 90 days (to protect against development of liver cirrhosis).

There are numerous sources of ethanol exposures in addition to the consumption of alcoholic beverages. These include exposures from fruits, breads, and other food products.

One exposure that may be very illustrative in helping to evaluate the question is exposure of children to quantifiable levels of ethanol in fruit juices.

For example, ethanol content in apple juice and grape juice may be “not more than 5 gr/kg juice,” and in orange juice “not more than 3 gr/kg juice.”

http://siweb.dss.go.th/standard/Fulltext/codex/CXS_048E.pdf
http://siweb.dss.go.th/standard/Fulltext/codex/CXS_082E.pdf
http://siweb.dss.go.th/standard/Fulltext/codex/CXS_045E.pdf

Excess Risk: Low Level Exposures via Consumption of Fruit Juice

- Typical doses of ethanol from fruit juices have been calculated to be approximately 0.35 grams/day per individual
- If the dose response is linear, then for hepatic cirrhosis mortality and morbidity, linear population response would:
  - "predict" approximately 3e-5 "risk" of developing alcoholic liver cirrhosis simply from consumption of fruit juices (0.35/0.11 grams/day).
  - For alcohol-induced mortality from hepatic cirrhosis, the linear extrapolation method would "predict" a 20e-5 "risk" of mortality from cirrhosis solely from consumption of fruit juices (0.35/0.018 grams/day)
- WHAT DOES THIS ANALYSIS INDICATE RE: THE HYPOTHESIS OF LOW DOSE LINEAR IN THE POPULATION?

Evaluating the Hypothesis

What is the evidence for a non-linear threshold response at molecular, cellular level?	What is the evidence for linear no threshold response at molecular cellular level?
What is the evidence for a non-linear threshold response at organ system level?	What is the evidence for linear no threshold response at organ system level?
What is the evidence for a non-linear threshold response at individual level?	What is the evidence for linear no threshold response at individual level?
What is the evidence for a non-linear threshold response at population level?	What is the evidence for linear no threshold response at population level?

Conclusions

- Can't address this issue with statistics alone
- Need to apply knowledge of processes of chemical interactions with biological systems
- Need to employ a systematic, structured evaluative process = KEDRF (ILSI)/Hypothesis-based WoE (Rhomberg)
- ARA "Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment"

http://www.allianceforrisk.org/ARA_Dose-Response.htm

ARA "Beyond Science and Decisions

Workshop Series Objectives

- To increase the efficiency, scientific credibility, and utility of chemical risk assessment, addressing particularly problem formulation and dose-response analysis based upon:
  - *the NAS Report on Science and Decisions, and*
  - *other relevant science-based initiatives, national & international*
- To develop a practical guidance for dose-response assessment techniques applicable to specific problem formulations for use by risk assessors/managers at a variety of levels (*e.g.*, states, regional managers, people in a variety of agencies, and in the private sector)
- To implement a multi-stakeholder approach to share information, ideas, and techniques in support of developing practical, problem-driven risk assessment guidance.

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