



Use of Toxicity Data in Cancer Risk Assessment

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Standard Components of Cancer Risk Assessment Used by Environmental Agencies

Risk Assessment Step	Outcome
1. Hazard Identification	Level of Evidence for Carcinogenicity
2. Dose Response Assessment	Cancer risk versus exposure
3. Exposure Assessment	Human exposure estimates
4. Risk Characterization	Estimates of cancer risk for those exposed

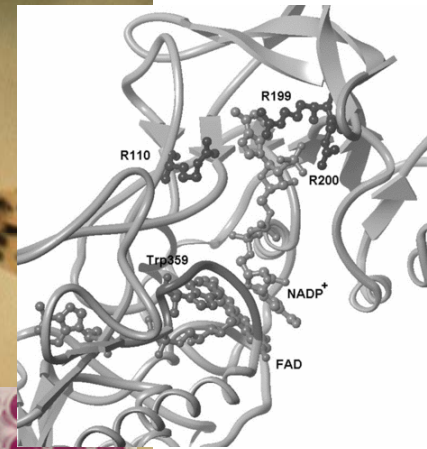
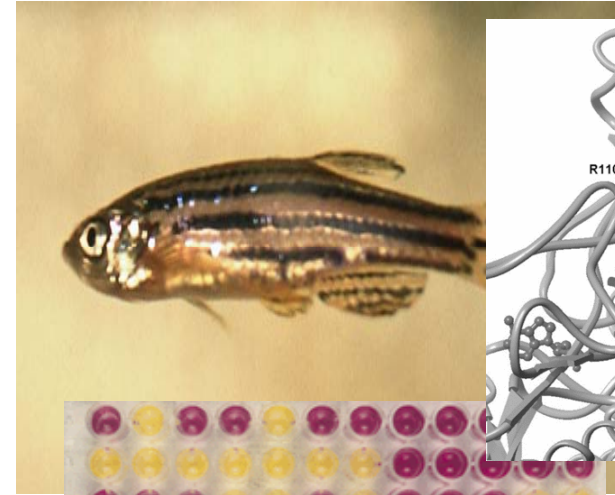
Cancer Hazard Identification Evidence Labels

- Environmental Protection Agency:
 - “suggestive of carcinogenic potential”
 - “likely human carcinogen”
 - “carcinogenic to humans”
- National Toxicology Program:
 - “known human carcinogen”
 - “reasonably anticipated to be carcinogenic to humans”
- International Agency for Research on Cancer:
 - “possibly carcinogenic to humans”
 - “probably carcinogenic to humans”
 - “carcinogenic to humans”
- California’s Proposition 65:
 - “known to the state to cause cancer”

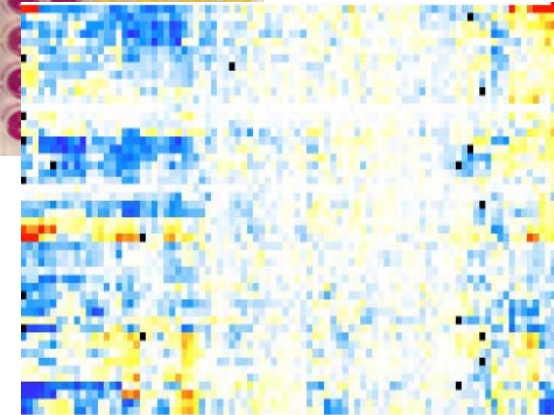
Biological systems for hazard and dose response assessment



Animal
(mammalian)
“in vivo”



Human “in vivo”



“Other Relevant Data”

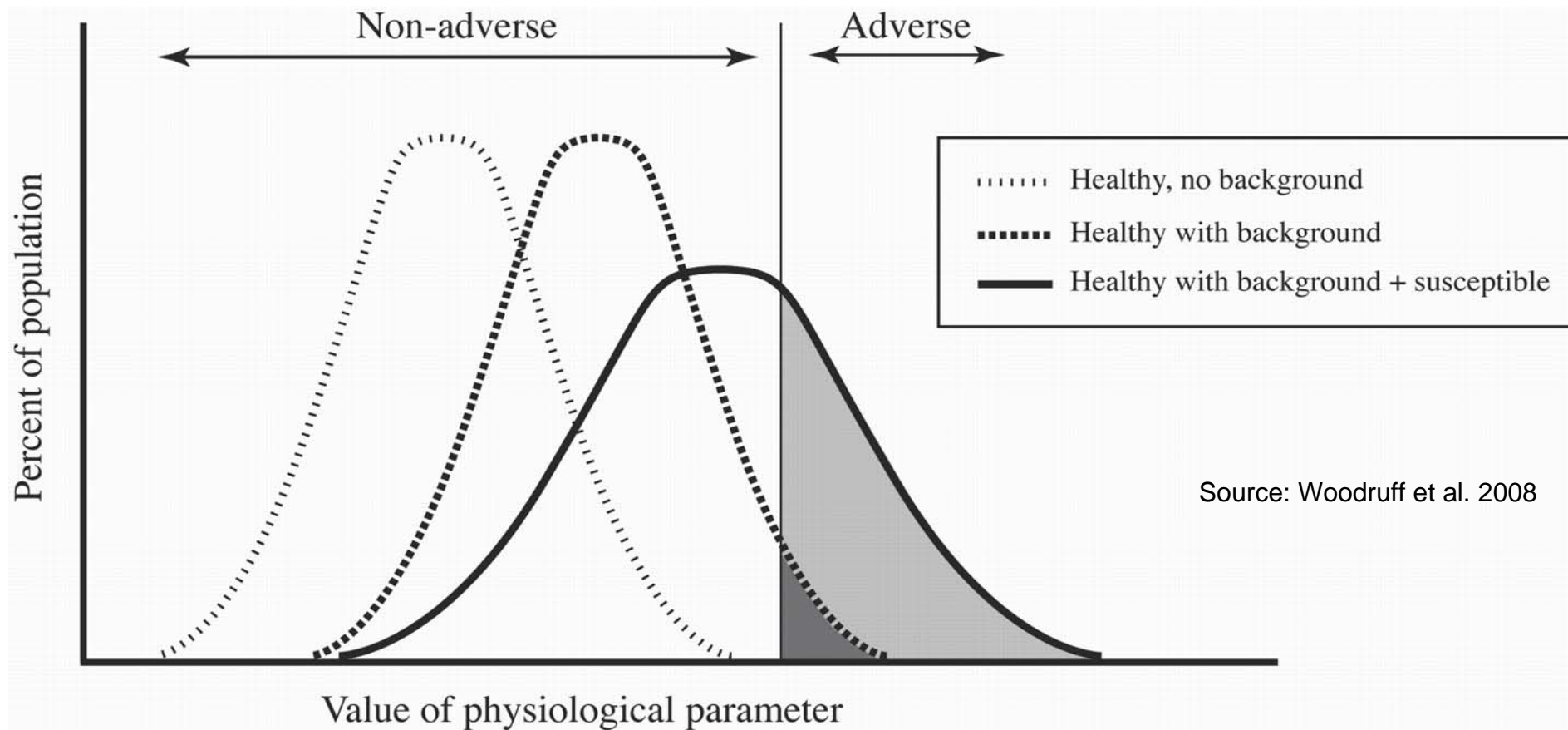
Evidence Maps to Cancer Classifications

Direct Human	Direct Animal	Mechanistic / Indirect	IARC	US EPA	NTP
Sufficient	-- --		Carcinogenic to humans (Group 1)	Carcinogenic to humans	Known to Be Human Carcinogen
Limited	Sufficient	Strong human mechanistic data			
		--			
Inadequate	Sufficient	Strong	Probably carcinogenic to humans (Group 2A)	Likely to be carcinogenic to humans	Reasonably Anticipated to Be Human Carcinogen
	Limited	Strong	Possibly carcinogenic to humans (Group 2B)		
	Sufficient	--			
Limited	Limited	--	Possibly carcinogenic to humans (Group 2B)	Inadequate Information to Assess	Reasonably Anticipated to Be Human Carcinogen
Inadequate	Inadequate	Strong & same class as other carcinogens			
		Strong/convincing			
Inadequate	Limited --		Not classifiable	Suggestive	Not classified



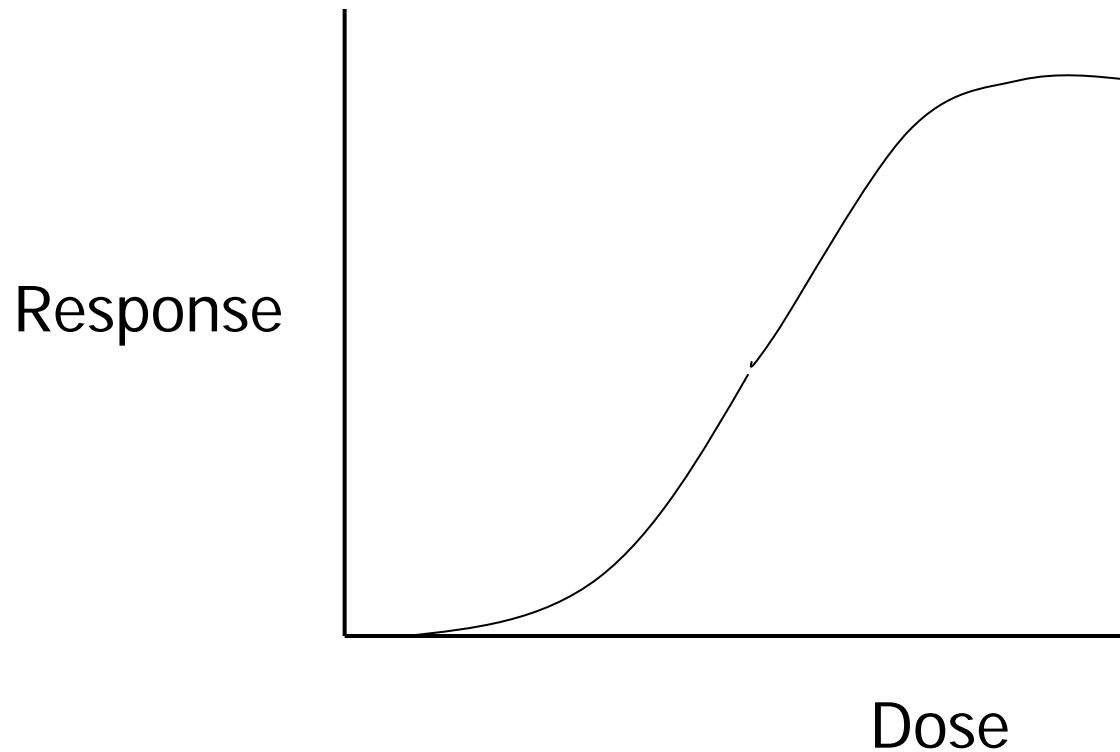
Need to Address Background and Vulnerability Impact on Risk

- Background
 - Biological
 - Exposure
- Vulnerability, e.g., from
 - Life stage
 - Genetics
 - Health disease status



Toxicity Testing Goal

- Dose Response Assessment



Deriving Dose Response Relationships

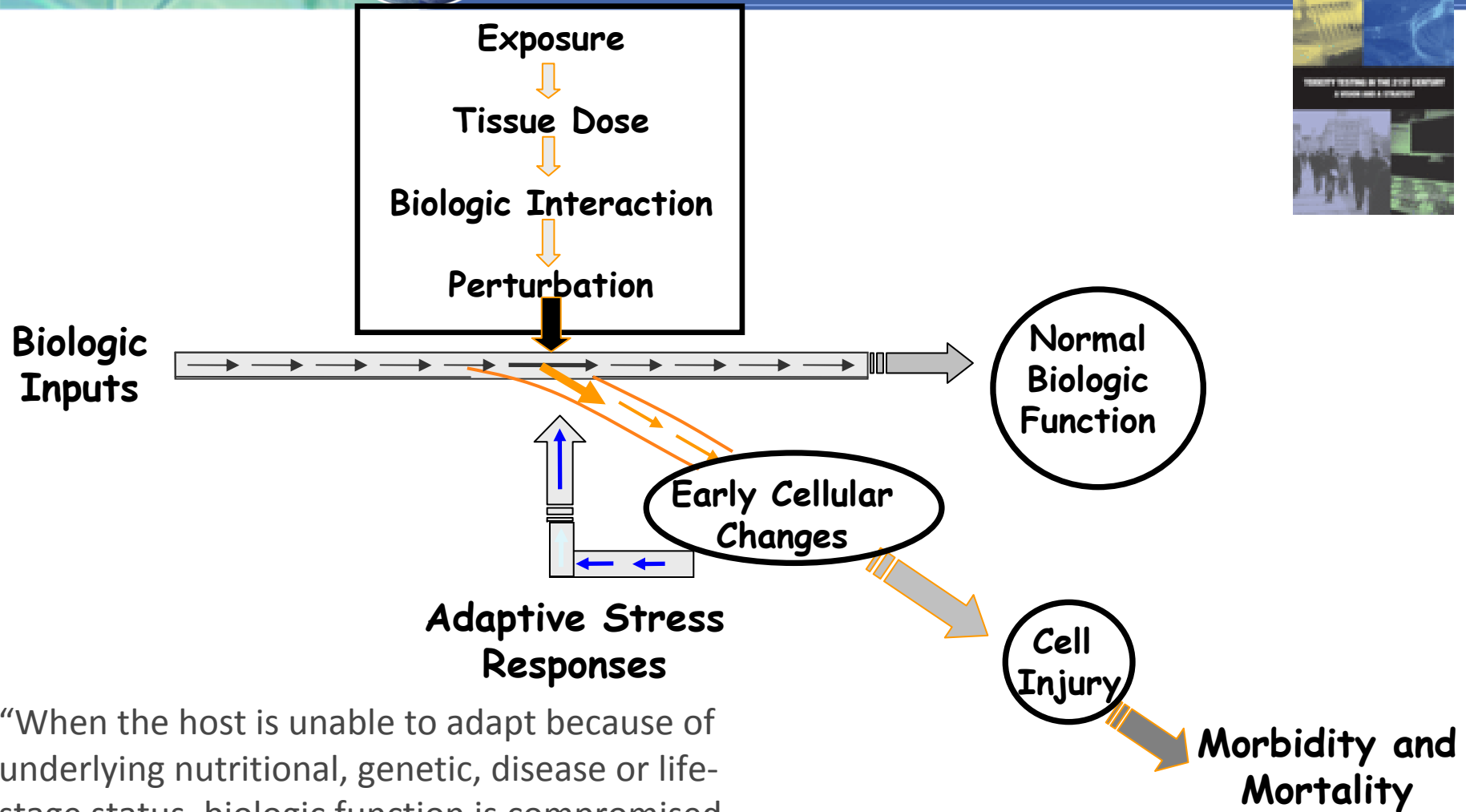
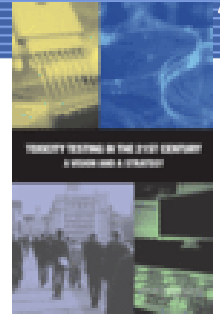
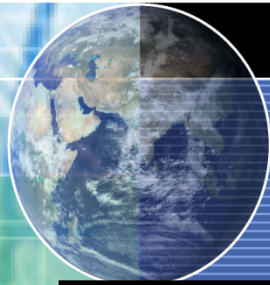
- Bioassay
 - Homogeneous animals
 - First exposed as adult animals
 - Controlled dose
 - Controlled environment
 - High Dose
- Worker populations
 - Exposed as adults
 - Relatively high dose
 - “Healthy workers”
 - Heterogeneous
 - Similar communities



Extrapolation

- General Population
 - All ages
 - Male and female
 - Heterogeneous Pharmacokinetics
 - Heterogeneous Pharmacodynamics
 - Varied environments

Toxicity Testing in the 21st Century



“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.”

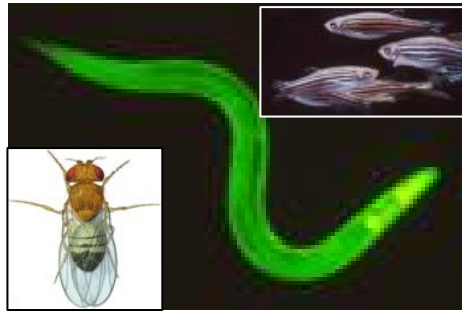
Toxicological Data



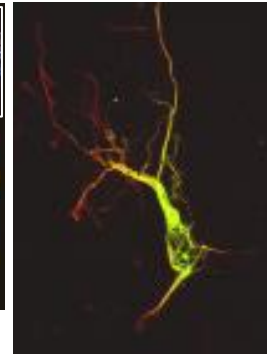
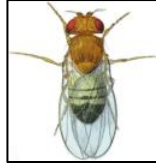
1-3/year



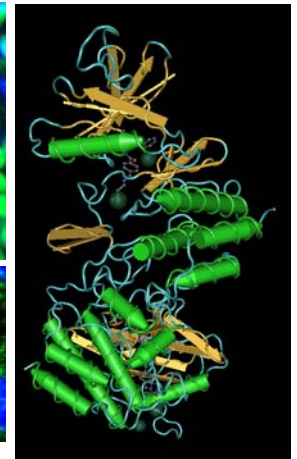
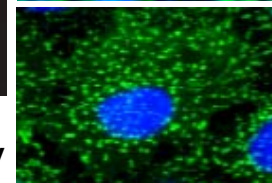
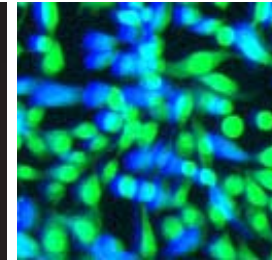
10's/year



100's/year



10,000's/day



100,000's/day

**High Throughput
Molecular mechanism**