

Test Data and Carcinogenesis

- a) Carcinogenic in test animal?
- b) Carcinogenic in humans?
- c) Dose-response
- d) Policy decisions

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1986 EPA Classifications

- Group A: Human carcinogen (sufficient human data available)
- Group B: Probable human carcinogen
 - B1: Limited human data
 - B2: Insufficient human data, but animal data sufficient
- Group C: Possible human carcinogen (animal data available, but limited and/or equivocal)
- Group D: Insufficient data to classify
- Group E: Data sufficient to conclude not carcinogenic to humans

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Inferring Human Carcinogenicity from Animal Data

- Conservative: Without evidence that tumors observed are specific to test animal, assume human carcinogenicity from carcinogenicity in any animal.
- Empirical and theoretical support
- More research needed
- “Science policy decision”

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1996 Draft EPA Guideline “Weight of Evidence” Descriptors

1. Known/Likely
 - Known: Based on epidemiological or epidemiological plus experimental evidence demonstrating causality
 - As if known: Based on epidemiological data showing plausible causal connection plus strong experimental evidence
 - Likely: Tumors produced by modes of action relevant to human carcinogenicity
2. Cannot Be Determined: Includes suggestive evidence, conflicting data, inadequate data, no data
3. Not Likely: Adequate evidence of lack of human carcinogenicity

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1999 EPA Draft Guidelines

“Weight of Evidence”

Descriptors

- Carcinogenic to Humans: Convincing epidemiological evidence of causality, or other strong evidence
- Likely to be Carcinogenic to Humans: Data demonstrate potential for human carcinogenicity
- Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential
- Data Are Inadequate for an Assessment of Human Carcinogenic Potential
- Not Likely to be Carcinogenic to Humans

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Extrapolations: Rats to Humans

- Metabolism. Default: Delivered dose is related to applied dose by a power of body weight.
- Dose averaging (Different lifespans; sporadic vs cumulative dose) Default: lifetime average daily dose
- High to low dose

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Extrapolation Beyond the Range of Data

- Current EPA default: Linearized Multistage Model (More later)
- 1996/1999 EAP draft default:
 - Point of Departure (LED₁₀ default)
 - Straight line from POD to origin
 - Considered generally conservative of public health, including sensitive subpopulations
 - Other methods if evidence supports

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LED₁₀ (Lower Estimated Dose(?) Associated with 10% Extra Risk)

- Fit curve in range of data
- Construct 95% confidence bands
- LED₁₀ is where “lower” confidence band gives 10% extra risk adjusted for background
- Used in non-cancer risk assessment
- 10% level at or just below limit of sensitivity for detecting statistically significant tumor increase in most studies

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