NTP
National Toxicology Program

# Maximum Tolerated Dose (MTD): Concepts and Background
## (Minimally Toxic Dose)

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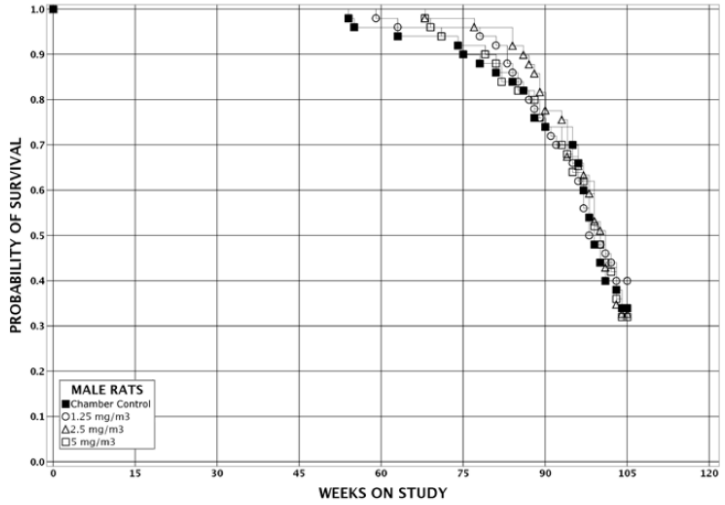
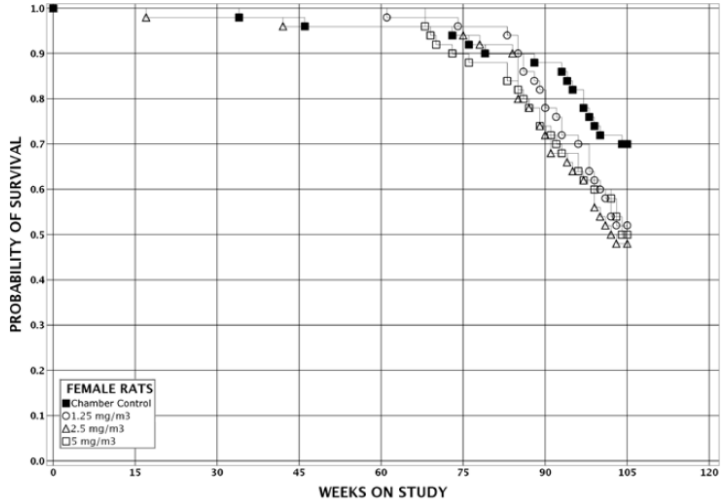
# Generating Data for Human Health Protection

- Animal studies are conducted to provide data for human health risk assessment
  - Exposures too high results in overt toxicity and a compromised study
  - Exposures too low results in a lack of useful information
- Power to detect an effect influenced by number of animals within a group
- Group size and dose selection greatly impacts findings, interpretation, and modeling of the response

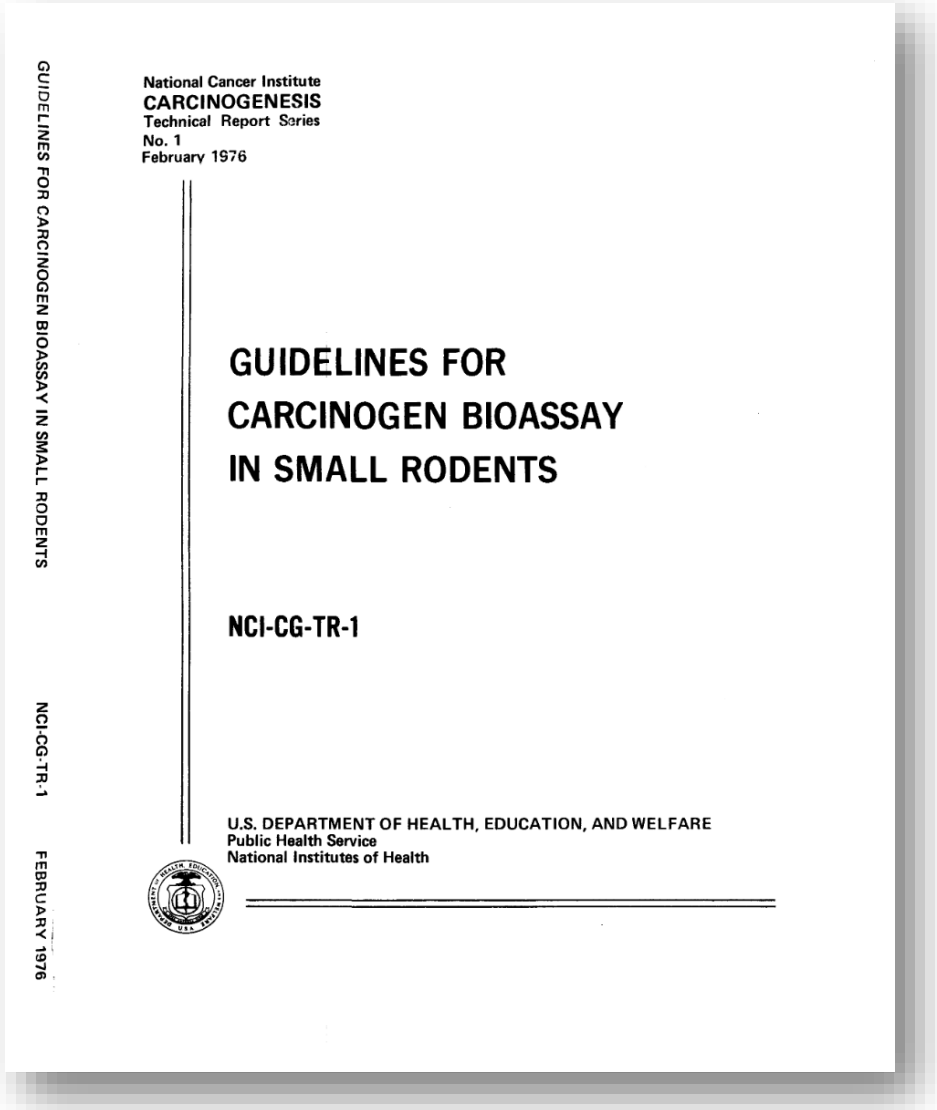


# History of the Maximum Tolerated Dose (MTD)

- Development and acceptance of the rodent cancer bioassay lead to the development of a Maximum Tolerated Dose (MTD) (or Minimum Tolerated Dose)

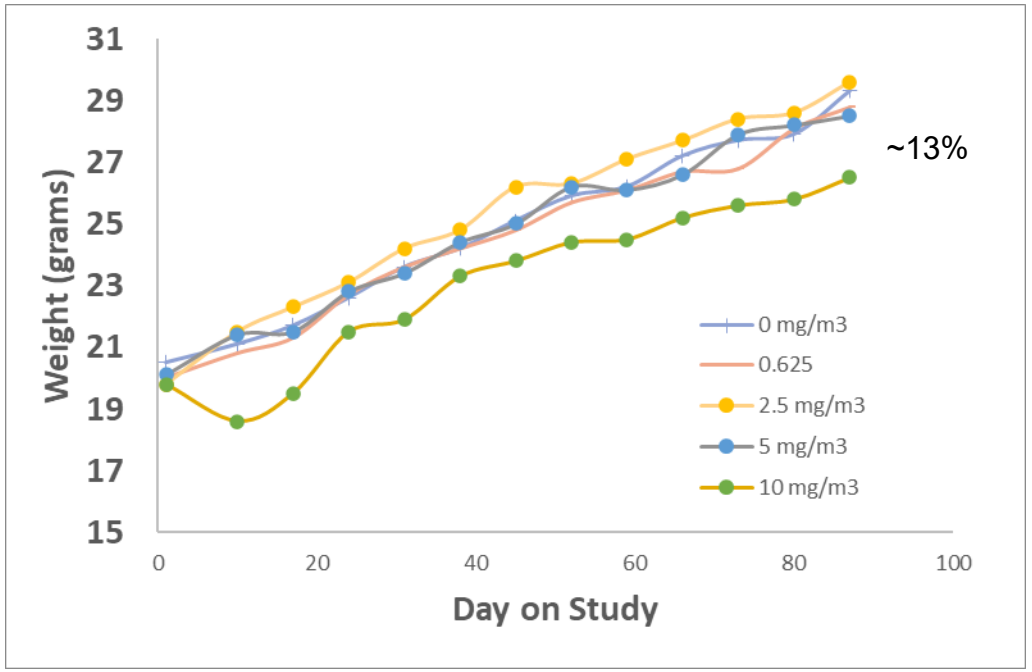
- National Cancer Institute publication "Guidelines for Carcinogen Bioassay in Small Rodents" by Sontag, Page, Saffiotti provided first standardized MTD:
  - "The MTD is defined as the highest dose of the test agent during the chronic study that can be predicted not to alter the animals' longevity from effects other than carcinogenicity"

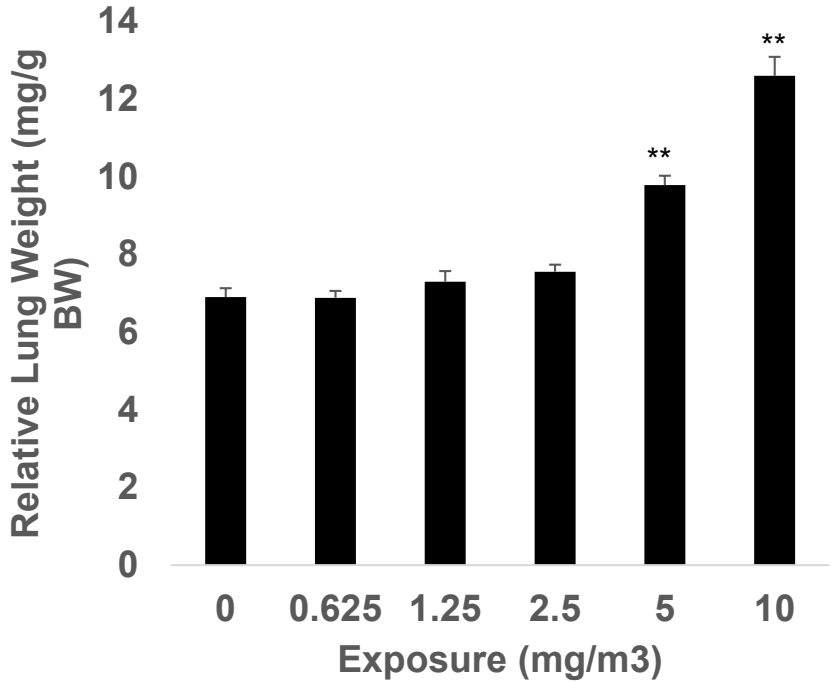


# Maximum Tolerated Dose

- An *estimation* of dose that results in a response considered to be challenging, but does not yield overt toxicity
  - These data are usually generated from a shorter-term study (e.g. 90-day rodent study)
- No exact criteria: can vary depending on study design and endpoints evaluated. A MTD requires justification and could be based on:
  - Reduced weight compared to controls at the end of a 90-day subchronic study (>10%)
  - Overt adverse pathology
  - Maternal parameters if including multigenerational exposure
- Absence of findings in shorter term studies can lead to use of a limit dose, e.g. 1000 mg/kg/day, in the definitive study (default MTD)

# Female Mice: Cobalt 13-week Inhalation Exposure (TR-581)

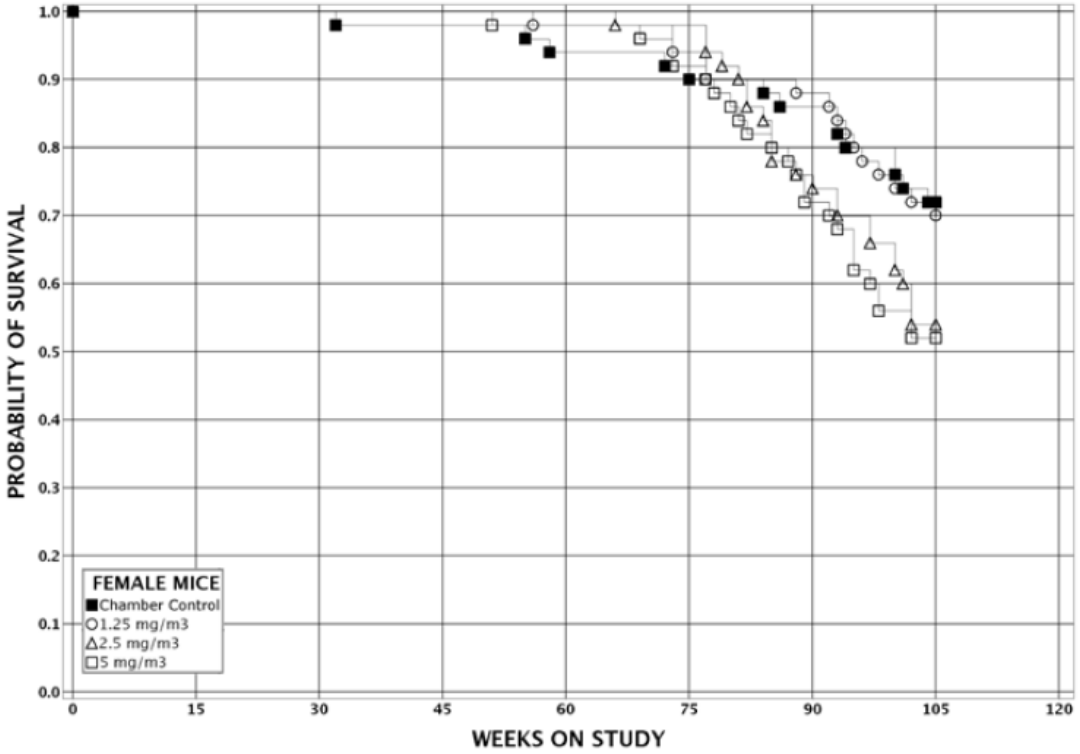



Body weight and lung weight difference at 10 mg/m$^3$
Moderate severity of lesions in nose and lung at 10 mg/m$^3$

**5 mg/m$^3$ selected as MTD for two year bioassay**

# Female Mice: Cobalt 2 year Inhalation Exposure (TR-581)




| Alveolar/Bronchiolar Neoplasms | Control | 1.25 mg/m$^3$ | 2.5 mg/m$^3$ | 5 mg/m$^3$ |
|---|---|---|---|---|
| Adenomas | 3/49 | 9/50 | 8/50 | 10/50 |
| Carcinomas | 5/49 | 25/50 | 38/50 | 43/50 |
| Adenoma or Carcinoma | 8/49 | 30/50 | 41/50 | 45/50 |

$p < 0.001$

Survival generally unaffected until late in the study as neoplasms increase

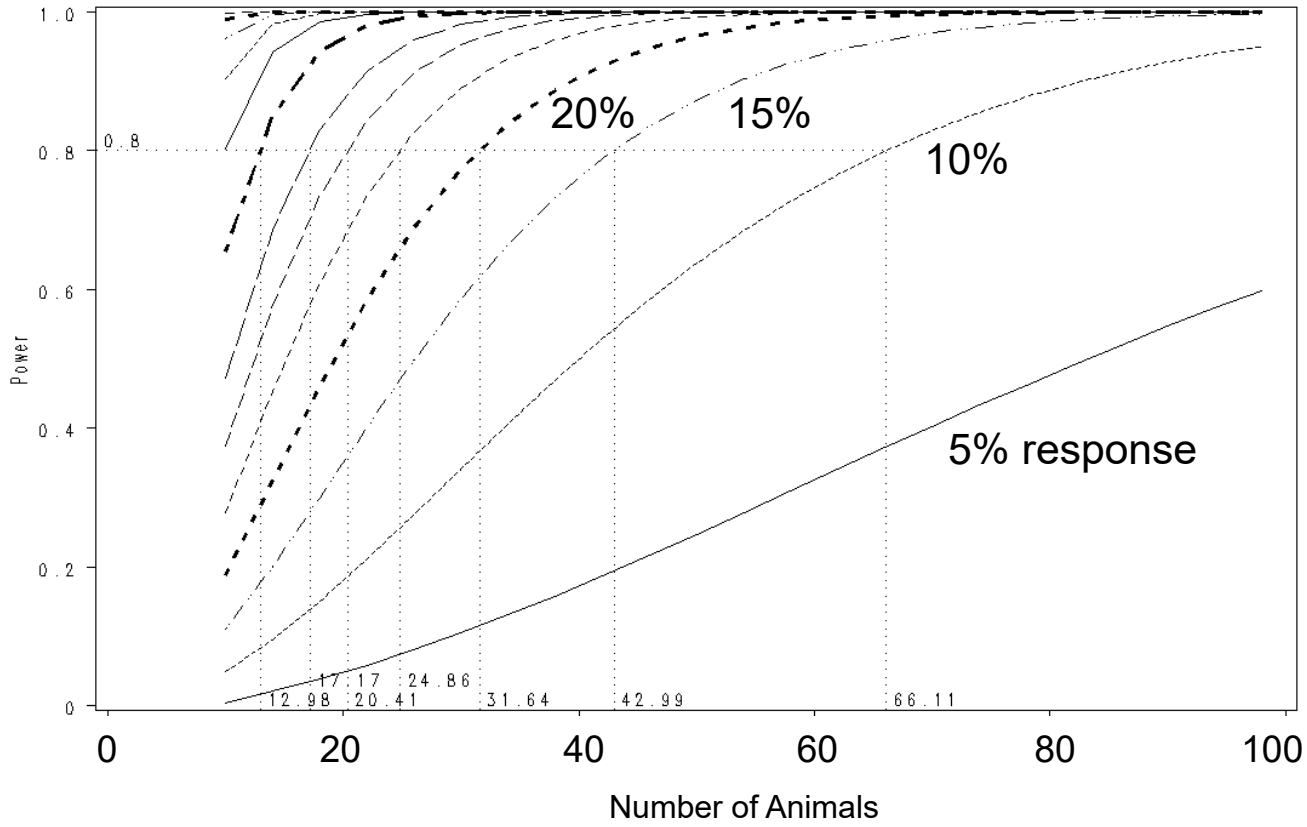
# Dose Selection Factors

- NTP studies evaluating 79 chemicals: 1984-94
  - 21% Unacceptable rate of body weight gain
  - 12% Mortality or clinical signs associated with pharmacology
  - 4% Toxicokinetics
  - 12% No evidence and used practical limits doses (e.g. 5% feed)
  - 18% Site of application toxicity
  - 34% Systemic organ toxicity

Bucher 2000

# Maximum Tolerated Dose Advantages

- Using the MTD increases probability of finding an effect
  - Number of animals used in studies (e.g. n = 50/group) has a limited power in detecting an effect.
  - Lower exposure levels generally require a higher number of animals used to detect an effect.
  - Higher exposure levels increase magnitude of effect increasing probability of detection.




Power curves for 0.1% control rate (rare)

# Maximum Tolerated Dose Advantages

- Increases probability of finding an effect with animal models of unknown sensitivity
  - Animal model systems have variability in responses across tissues (sites of toxicity)
  - Higher exposure will increase probability of response in low sensitive site

**Table 1. Underlying tumor incidence in the high dose group that can be detected with 50%, 70% and 90% power by using Fisher's exact test with 50 animals per group.**

| Spontaneous tumor rate, % | Underlying tumor incidence, % | | | | | |
|---|---|---|---|---|---|---|
| | $p < 0.05$ test | | | $p < 0.01$ test | | |
| | 50% | 70% | 90% | 50% | 70% | 90% |
| 0.1 | 9.5[a] | 11.8 | 15.8 | 13.5 | 16.2 | 20.5 |
| 1.0 | 11.0 | 13.8 | 18.4 | 15.1 | 18.2 | 23.4 |
| 3.0 | 14.0 | 17.4 | 22.9 | 18.9 | 22.8 | 29.0 |
| 5.0 | 17.0 | 20.8 | 27.0 | 22.5 | 26.8 | 33.3 |
| 10.0 | 24.2 | 28.8 | 35.7 | 30.2 | 34.9 | 41.9 |
| 20.0 | 36.8 | 41.7 | 49.0 | 43.2 | 48.4 | 56.0 |
| 30.0 | 48.1 | 53.6 | 61.1 | 54.8 | 59.9 | 67.0 |

[a]Tumor incidence; for example, if the spontaneous tumor rate is 0.1%, a one-sided Fisher's exact test comparing control and high dose groups of 50 animals each would have a 50% chance of detecting an underlying tumor incidence of 9.5% in the high dose group. Exact power calculations for Fisher's exact test were obtained by the method described by Haseman (*53*).

Haseman 1984

# Maximum Tolerated Dose Advantages

- The MTD aids in interpretation of findings: removing high-dose findings from studies may decrease certainty of mid- and lower-dose findings
  - Haseman and Lockhart 1994: 50 of 195 NCI/NTP studies had elevated, but not statistically significant increased incidences at lower doses suggesting carcinogenic process present
  - Removing MTD exposure would likely reduce certainty in the response and response modeling

# Summary

- The goal of animal studies is to provide data for human health protection, which dose selection influences the outcome.

- The use of the Maximum Tolerated Dose is considered a pragmatic way to evaluate potential chemical toxicity under conditions of limited animal groups, unknown animal model sensitivity, and uncertainty in dose response interpretation.

- Endpoints evaluated for ascertaining MTD have increased over time and often include histopathology, ADME, clinical observations, clinical pathology.

# Questions

# References


- Bucher, JR. Doses in Rodent Cancer Studies: Sorting Fact from Fiction.  Drug Metabolism Reviews. 2000 32(2).
- Haseman, JK. Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies.  Environmental Health Perspectives. 1984 vol. 58.
- Haseman, JK and Lockhart, A. The Relationship between Use of the MTD and Study Sensitivity for Detecting Rodent Carcinogenicity. Fundamental and Applied Toxicology. 1994 vol. 22.