Applying to Naphthalene Lessons from the NAS Review of the Dioxin Reassessment

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Purpose of Talk

- I know little about Naphthalene, so I have no position on its qualitative carcinogenicity designation or its quantitative risk
- I did serve on the National Academy committee that recently completed its review of EPA's dioxin risk assessment
  - How might I react to what I have seen in EPA's draft reassessment of naphthalene's carcinogenicity?
- Note – What I say about the NAS dioxin report should not be interpreted as representing that report
  - The report itself is the authority

Overview

1. EPA's qualitative designation of naphthalene as a "likely human carcinogen"

2. EPA's use of a linear dose-response

3. EPA's quantification of the cancer slope factor

Part 1:
EPA's Qualitative Designation of Carcinogenicity

- NAS findings for dioxin
  - EPA did not explain how the available data satisfied the Agency's definition of "human carcinogen"
  - EPA should not expend substantial effort on the qualitative designation
    - Scientific evidence lies on a continuum
    - Not clear how designation makes a difference
    - Designation cannot be objectively evaluated (e.g., what is "convincing" evidence?)

EPA's Qualitative Designation of Naphthalene as a Likely Human Carcinogen

- EPA's draft IRIS summary states that naphthalene is likely to be carcinogenic because of its association with
  - Nasal tumors in rats (Abdo, 2001; NTP, 2000)
  - Alveolar/bronchiolar adenomas or carcinomas in female mice (NTP, 1992)
  - Number of tumors in A/J mice (Adkins, 1986)

Observations

- It would be useful if EPA identified the criteria it is using to place naphthalene into the "likely" category, although it appears the Agency is using the following (from the 2005 guidelines):
  - "an agent that has tested positive in animal experiments in more than one species, sex, strain, site, OR exposure route, with or without evidence of carcinogenicity in humans;" (p. 2-55) (emphasis added).

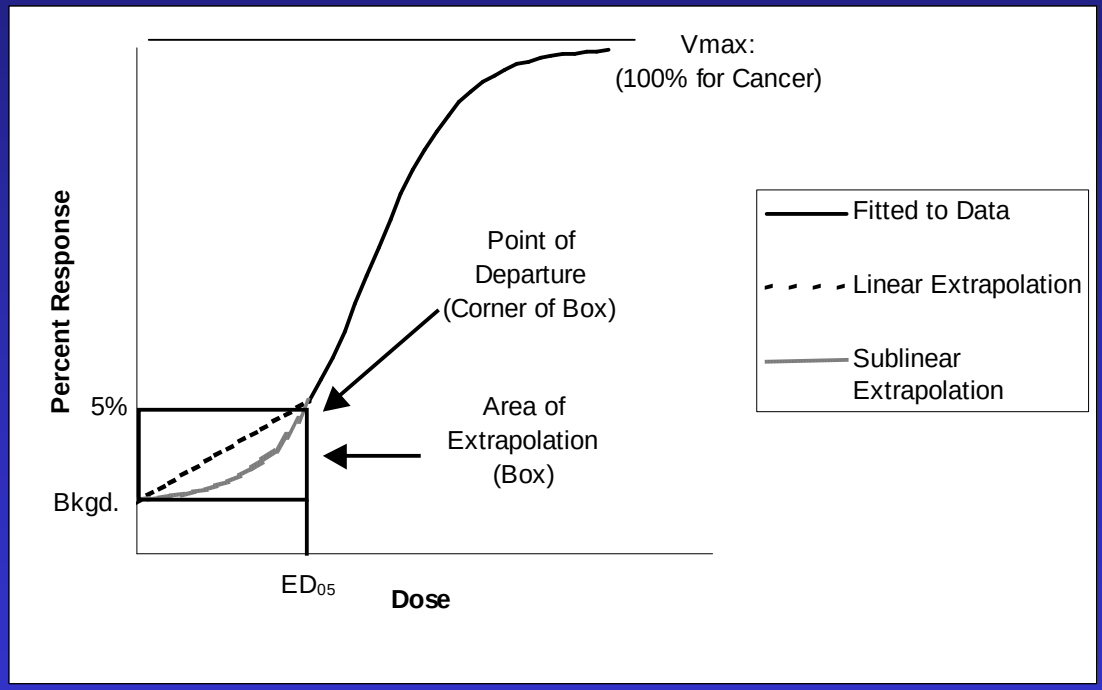
Observations (Continued)

- For some reason, the NTP (1992) and Adkins (1986) data were sufficient only for a Group C designation in 1998 (“possible human carcinogen”).
  - What was it about the earlier data that was insufficient to move naphthalene above Group C?
  - How do the new data fill that gap?

Observations (Continued)

- Is specification of the qualitative designation a scientifically meaningful exercise?
  - "Although the term 'likely' can have a probabilistic connotation in other contexts, its use as a weight of evidence descriptor does not correspond to a quantifiable probability of whether the chemical is carcinogenic" (p. 2-53).
  - "Adequate evidence consistent with this descriptor covers a broad spectrum… The examples below are meant to represent the broad range of data combinations that are covered by this descriptor; they are illustrative and provide neither a checklist nor a limitation for the data that might support use of this descriptor" (p. 2-55).

Part 2:
Quantitative Risk Assessment
Dose Response Linearity



EPA Treated the Dioxin Dose-Response Relationship as Linear (1)

- "Science policy" argument
  - "The linear default is selected on the basis of the agent's mode of action when the linear model cannot be rejected and there is insufficient evidence to support an assumption of nonlinearity" (EPA Dioxin Reassessment, p. 5-15)

EPA Treated the Dioxin Dose-Response Relationship as Linear (2)

- Extrapolation below POD is limited
  - "… because ED_{01} estimates require little extrapolation from the range of observation and current body burdens are within a factor of 10 of ED_{01} estimates, use of a linear model is both consistent with the data and unlikely to require more than an order of magnitude extrapolation…" (EPA Dioxin Reassessment, p. 6-9)

NAS Committee Reaction (1)

- There is sufficient evidence to reject the default linearity assumption
  - TCDD is not genotoxic
  - TCDD effects are receptor-mediated
  - Animal liver tumors were secondary to hepatic toxicity
  - Bioassay data suggest nonlinearity (Hill coefficient > 1)

NAS Committee Reaction (2)

- Using the ED_{01} as the point of departure is not justified
  - Data are insufficient to nail down its value with sufficient certainty
  - Extrapolation is therefore greater than EPA suggests

NAS Committee Reaction (3)

- In the risk assessment, "science policy" should not be used to favor one scientific hypothesis over another:
  - "To the extent that EPA favors using default assumptions for regulating dioxin as though it were a linear carcinogen, such a conclusion should be supported by scientific evidence… Alternatively, the decision to use the linear dose-response relationship could be made as part of risk management…" (p. 100).

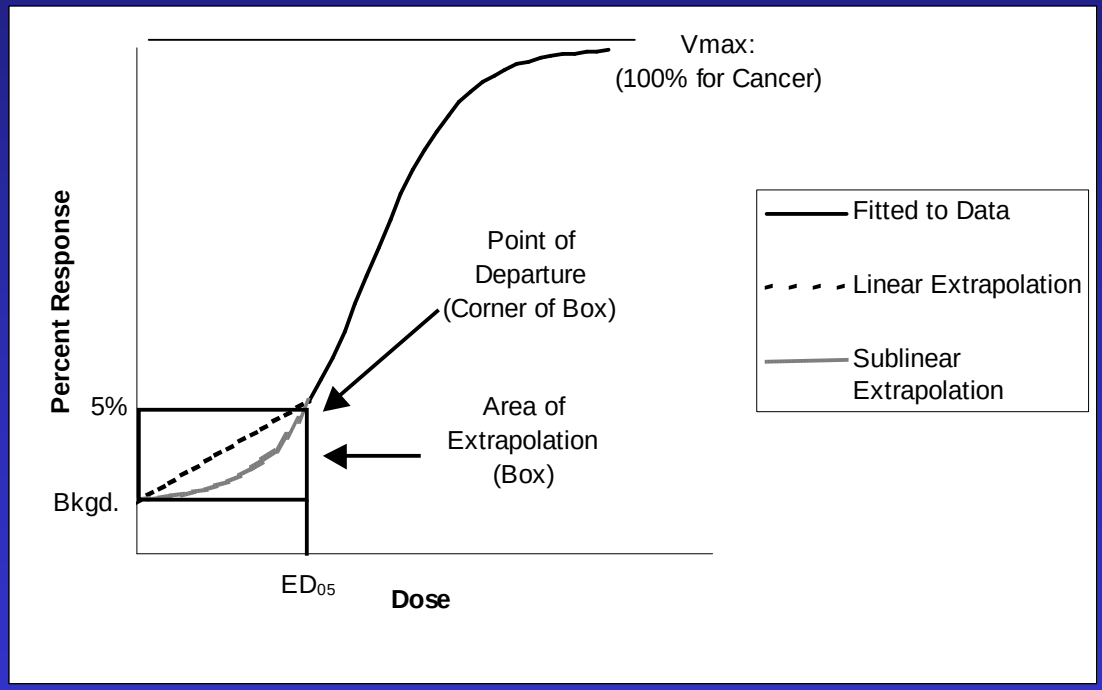
Linearity in the Case of Naphthalene

- Naphthalene is negative in most genotoxicity tests
- EPA relied on "science policy"
  - "According to the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999), a linear mode of extrapolation to low doses was selected (i.e., linear extrapolation to the origin from the point of departure) because mode of action data are incomplete and inadequate to invoke a nonlinear low-dose extrapolation" (p. 68 in the 2004 Tox Review).

Linearity in the Case of Naphthalene (Continued)

- Whether the dose-response is linear is important
  - Occupational exposures are 3 to 4 orders of magnitude below those tested in bioassays to date (Green and Crouch, 2004, p. 1,6).

Part 3:
Quantitative Risk Assessment
EPA's quantification of the cancer slope factor



EPA's Estimation of the Cancer Slope Factor for TCDD is Based on Results from Three Occupational Cohort Studies

- EPA's cancer slope factor for dioxin is based on data from three epidemiology studies
  - Becher et al. (1998) – 1,189 workers exposed to TCDD during the production of phenoxy herbicides
  - Steenland et al (2001) – 3,538 chemical factory workers exposed to TCDD
  - Ott and Zober (1996) – 253 workers exposed to TCDD in the days, months, and years following a 1953 chemical plant accident in 1953

NAS Committee Reaction: Four Sources of Uncertainty EPA Did Not Fully Account for Quantitatively

1. Full range of parameter values reflecting statistical imprecision
2. Use of other points of departure (not just the ED_{01}/LED_{01})
3. Use of alternative dose-response functional forms
4. Uncertainty introduced by estimation of historical exposures

Uncertainty not Quantitatively Addressed in the Naphthalene Assessment (1)

- Statistical imprecision
  - EPA reported the central estimate and the upper 95% confidence interval value
  - EPA could have also reported the lower 95% confidence interval value

Uncertainty not Quantitatively Addressed in the Naphthalene Assessment (2)

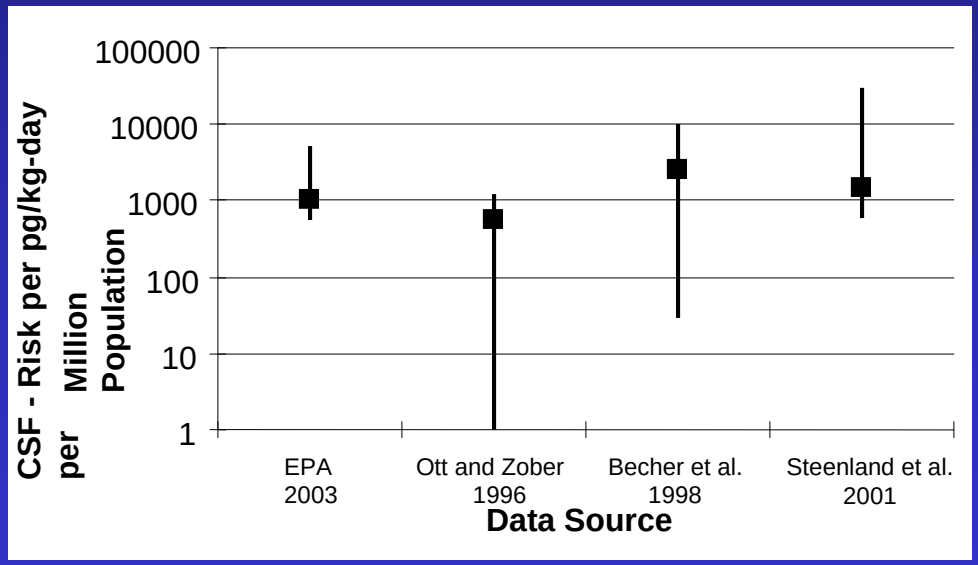
- Data sets used
  - EPA omitted female rat data
    - "In the absence of more specific biological reasoning for selection of a particular risk, the highest risk … was selected as the point of departure
    - EPA could have considered the full range of values implied by both data sets
  - EPA did not evaluate the consistency of its risk estimate with human population data
    - Even if human data are insufficient to compute risk, they can be used to bound risk

Uncertainty not Quantitatively Addressed in the Naphthalene Assessment (3)

- Extrapolation from rats to humans
  - EPA assumes that the nasal tumors in rodents will occur in humans
    - How plausible is this hypothesis?
  - EPA assumes that "Category 1" gas assumptions are appropriate for quantitatively extrapolating risk to humans
    - The Agency did not rule out the applicability of "Category 3" gas assumptions

Why Should Uncertainty Be Fully and Quantitatively Characterized?

- Failure to do so results in a false sense of precision
  - Example from the dioxin analysis



Note – This figure reflects only statistical uncertainty of the dose response parameters (issue #1)

Conclusions (1)
Qualitative Carcinogen Classification

- EPA should evaluate the usefulness of these classifications

- If they are used, EPA should clearly explain what criteria it uses to classify compounds

Conclusions (2)
Extrapolation Below the Point of Departure

- EPA should provide a scientific basis for using low dose linearity

- In the absence of overwhelming evidence of linearity, EPA's risk assessment should include estimates based on both linear and non-linear assumptions

Conclusions (3)
Point of Departure / Cancer Slope Factor Estimation

- "… the [dioxin] Reassessment qualitatively addressed many sources of uncertainty but … failed quantitatively to sufficiently address uncertainty and variability that resulted from the numerous decisions EPA made in deriving point estimates…" (NAS Committee, p. 136).

- "EPA should identify the sources of uncertainty and quantitatively characterize their impact…" (NAS Committee, p. 136)