

# Opening Remarks: Knowledge and Uncertainty “Captured” (or at least “chased” ?) - & Module A

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Thursday, October 12, 2006

**NS3 Symposium**

**Monterey, CA**

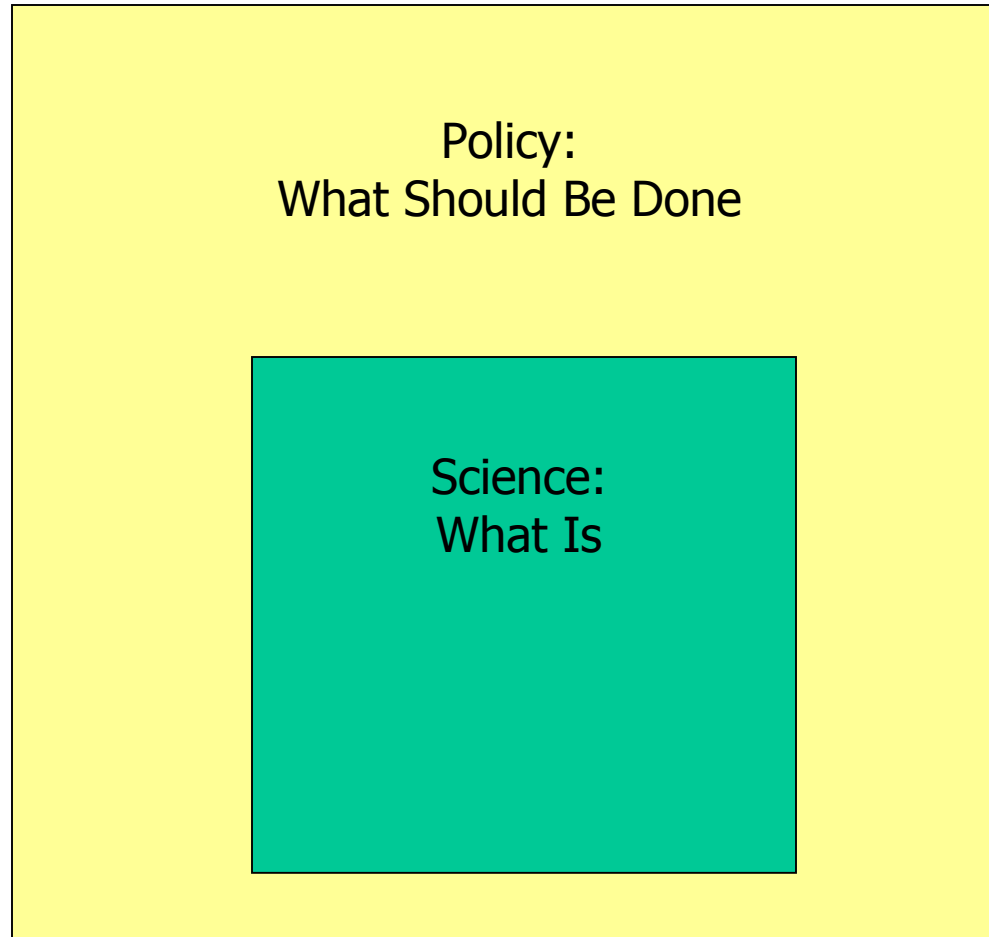
## *Suggested Schedule Change*

- Warner's introduction: very short (15 min)
- Josh Cohen: 8:15 to 9 AM
- Module A: 9 AM to 10 AM
- **Break: 10 AM- 10:30 AM**
- Module B: 10:30 – 11:30; start C prior to **12:00 noon – 1 PM lunch**

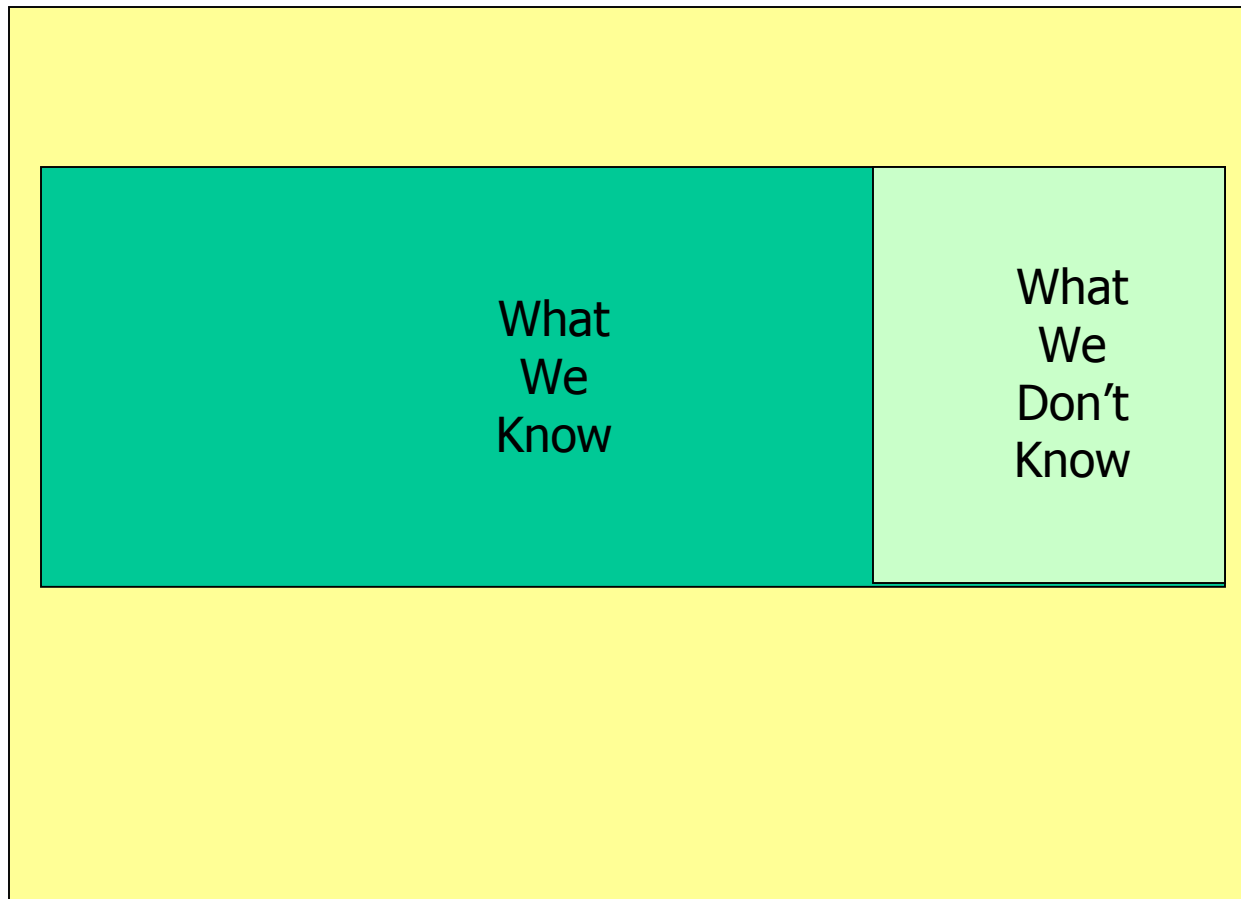
# *Scientific Charge*

1. Knowledge and uncertainty:
  - What scientific statements can be made with a high degree of confidence?
  - What scientific statements cannot be made with a high degree of confidence?
2. Of those scientific statements that cannot be made with a high degree of confidence, which are quintessential uncertainties for human cancer risk assessment?
3. Considering quintessential scientific uncertainties:
  - What specific research projects could be undertaken promptly and cost-effectively that would resolve them?
  - How should results from such studies be interpreted?
4. What constitutes best scientific judgment about quintessential scientific uncertainties that cannot be addressed by science promptly and cost-effectively?

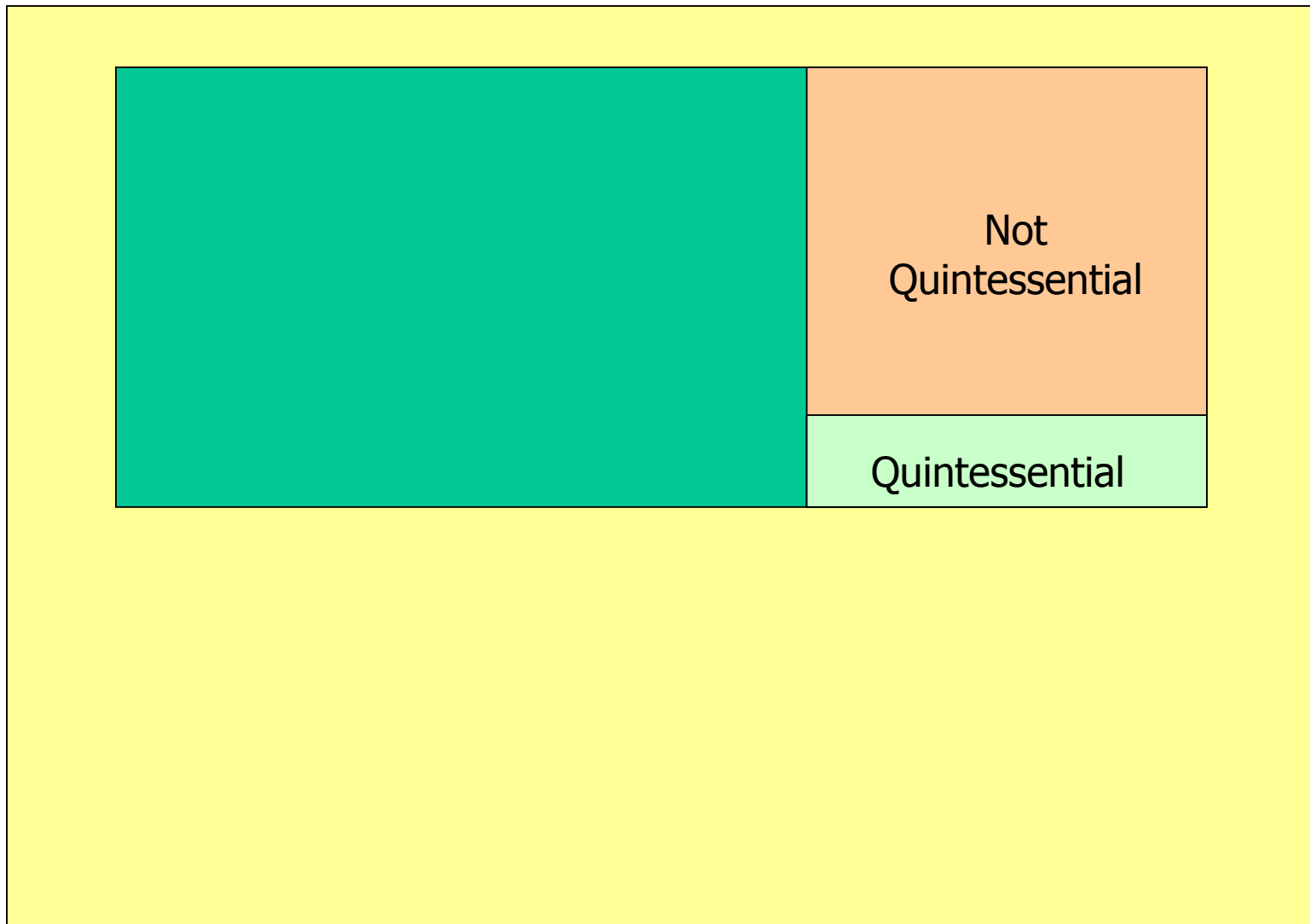
# Scientific Charge



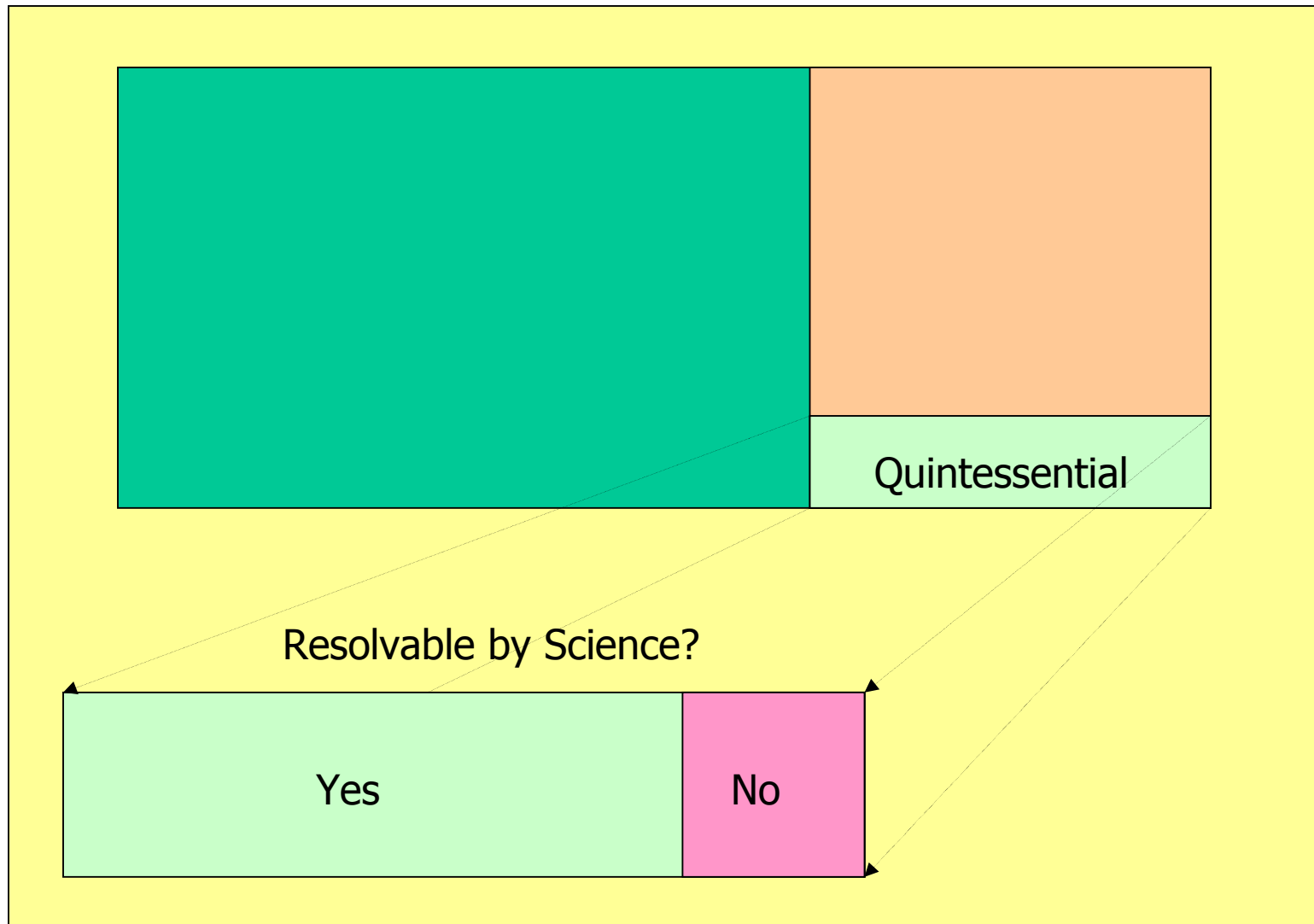
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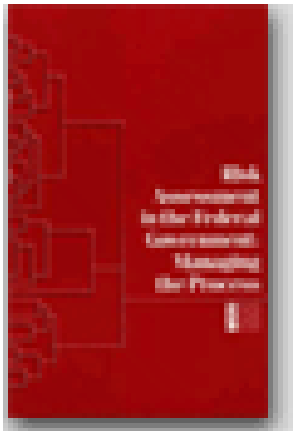
## *Program for Today and to Completion*

- **Today:** summary discussion by each module: what have we learned, what is quintessential, possible research paths forward to improve knowledge & reduce uncertainty

# *Program for Today and to Completion*

- **Today:** summary discussion by each module: what have we learned, what is quintessential, possible research paths forward to improve knowledge & reduce uncertainty
- **Next 30 days:** written material in to facilitator and planning committee
- **Soon thereafter:** submit set of papers for publication: Introduction and summary, paper for each module

# The Red Book (or “Mis-Read” Book), 1983



National Research Council,  
***Risk Assessment in  
the Federal Government:  
Managing the Process***, 1983

See also: ***Science and Judgment in Risk  
Assessment***, 1994

(both available at [www.nap.edu](http://www.nap.edu) )

20<sup>th</sup> Anniversary Special Issue: ***Human and  
Ecological Risk Assessment (HERA)***, Vol. 9,  
No. 5, August 2003. See W. North paper,  
other papers, editors' comments

# Risk Assessment: “Figure 1”

Our focus

Mix of policy, science

Policy



Source: National Research Council, *Risk Assessment in the Federal Government: Managing the Process* (“Red Book”), 1983, page 21

# Risk Assessment: a Bridge between Research and Decision Makers

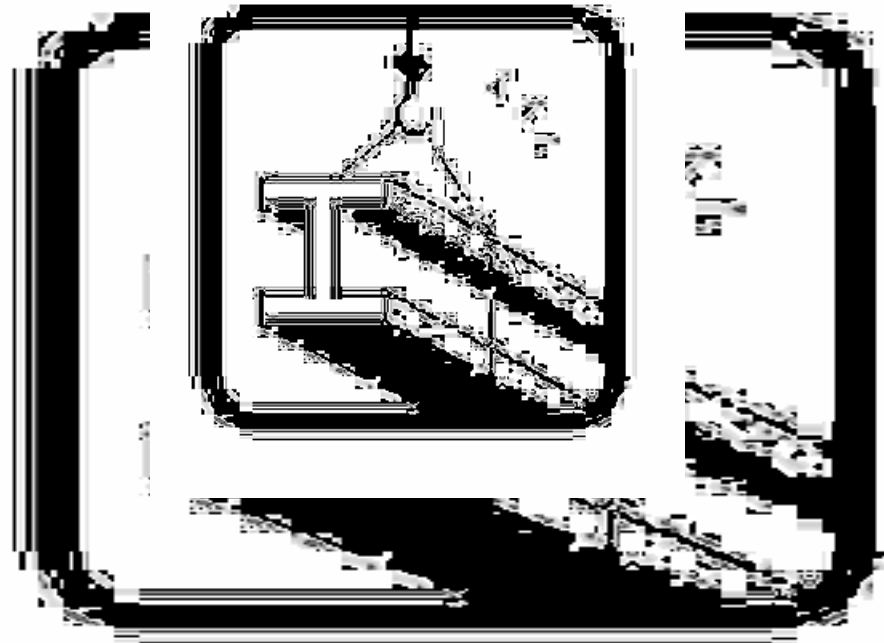
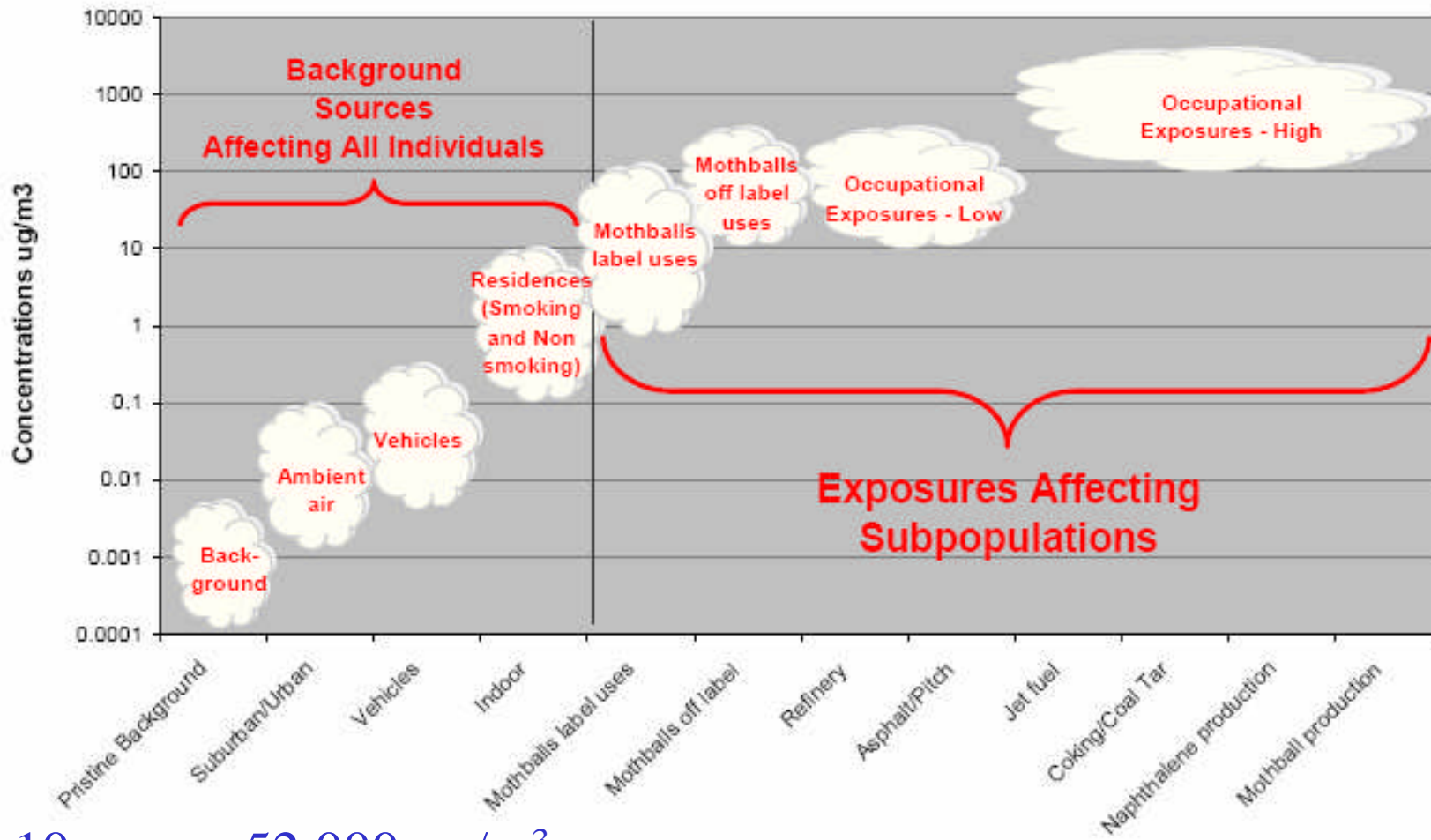


Figure 1. General Ranges of Naphthalene Air Concentrations in Different Populations



10 ppm = 52,000  $\mu\text{g}/\text{m}^3$

Source: Paul Price

## *QUOTE: National Research Council 1994 and EPA 2005 Guidelines for Carcinogen Risk Assessment*

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NRC [1994] recommended that where the Agency “reports estimates of risks to decisions-makers [sic] and the public, it should present **not only point estimates of risk, but also sources and magnitudes of uncertainty associated with these estimates.**”

- EPA *Guidelines for Carcinogen Risk Assessment*, page 1-3, citing the final recommendation from the Executive Summary of *Science and Judgment in Risk Assessment*, National Research Council, 1994



*QUOTE: Next Sentence in the EPA 2005  
Guidelines for Carcinogen Risk Assessment*

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NRC [1994] recommended that where the Agency “reports estimates of risks to decisions-makers [sic] and the public, it should present **not only point estimates of risk**, but also sources and magnitudes of uncertainty associated with these estimates.” **Thus, the identified uncertainties serve as a feedback loop to the research community and decisionmakers, specifying areas and types of information that would be particularly useful.**

- EPA *Guidelines for Carcinogen Risk Assessment*, page 1-3



## *Yet Another **Quote** from the EPA 2005 Guidelines for Carcinogen Risk Assessment*

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When there are alternative procedures having significant biological support, the Agency **encourages assessments to be performed using these alternative procedures**, if feasible, in order to shed light on the uncertainties in the assessment, recognizing that the Agency **may decide to give greater weight to one set of procedures than another** in a specific assessment or management decision.

- EPA *Guidelines for Carcinogen Risk Assessment*, page 1-8



*Another **Quote** from the EPA 2005 Guidelines for Carcinogen Risk Assessment, citing NRC 1994*

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The full extent of model uncertainty usually cannot be quantified; a partial characterization can be obtained by comparing the results of alternative models. Model uncertainty is expressed through comparison of separate analyses from each model, coupled with a **subjective probability statement**, where feasible and appropriate, **of the likelihood that each model might be correct.**

- EPA *Guidelines for Carcinogen Risk Assessment*, page 3-29



## *And Still Another **Quote** from the EPA 2005 Guidelines for Carcinogen Risk Assessment*

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With appropriate data and expert judgment, **formal approaches to probabilistic risk assessment** can be applied to **provide insight** into the overall extent and dominant sources of human variation and uncertainty. In doing this, it is important to note that **analyses that omit or underestimate some principal sources of variation or uncertainty** could provide a misleadingly narrow description of the true extent of variation or uncertainty and **give decisionmakers a false sense of confidence in estimates of risk.**

- *Guidelines for Carcinogen Risk Assessment*, page 3-31



# Module A: Naphthalene Animal Bioassays

- Speaker: Kamal M. Abdo, Ph.D.
- Panel:
  - Janet Benson (needs to leave early, also Mod C)
  - Alan Dahl (needs to leave early, also Mod C)
  - John Morris (also Mod C)
  - Roger Renne
  - Hanspeter Witschi
- Time: Until 10:00 AM break!!

## *Facilitator's Summary, Module A:*

### *What we know and don't know*

- Hazard Identification question affirmative: bioassay shows lung tumors in female mice and olfactory neuroblastomas in rats
- Bioassay at high doses producing extensive cytotoxicity; little information on what happens in whole animals at lower doses

# Conclusion

## Mouse Study of Naphthalene

### Carcinogenicity:

- ❖ **Males: Non-carcinogenic**
- ❖ **Females: Carcinogenic causing increased incidence of pulmonary alveolar/bronchiolar adenoma**

### Other Effects:

- ❖ **Increased incidence of nonneoplastic lesions of the nose and lung of mice of each sex.**

# Conclusion

## Rat Study of Naphthalene

### Carcinogenicity

- ❖ **Males: Carcinogenic – Increased incidence of Nasal Respiratory epithelium adenoma and Olfactory epithelium neuroblastoma**
- ❖ **Females: Carcinogenic - Increased incidence of Nasal Respiratory epithelium adenoma and Olfactory epithelium neuroblastoma**

### Other Effects:

- ❖ **Increased incidence of nonneoplastic nasal lesions of rats of each sex.**

## *Facilitator's Summary, Module A: Research Opportunities*

- Look for the dose break point -“no effect level” with mice, rats, monkeys (humans if possible) using most sensitive available methods for biomarkers/precursors of cytotoxicity and carcinogenicity

## *Facilitator's Summary, Module A: Research Opportunities*

- Look for the dose break point -“no effect level” with mice, rats, monkeys (humans if possible) using most sensitive available methods for biomarkers/precursors of cytotoxicity and carcinogenicity
- May want to repeat lifetime bioassay in mice and rats but first learn more via short-term testing
- Biological response is complex – may need to confirm hypotheses by testing in whole animals

## *Expansion by Panelists and Speaker*

- **Janet Benson** and **Alan Dahl** first – they have to leave, and they also should address Module C.
- Others on the Panel/Speaker
- Everybody still here

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- **All contributors: Please send in e-mail – written-out key ideas!**