MISTEC: Methods for Intermittent and/or Short-Term Exposure to Carcinogens

Rory Conolly, ScD
Co-Chair, MISTEC Subcommittee
(US Environmental Protection Agency, National Health and Environmental Effects Research Laboratory)

May 13, 2010
HESI Annual Meeting

Outline

- MISTEC
  - Mission, membership, sponsorship
- Cancer risk assessment
  - Default continuous, lifetime exposure
  - Need methodology for discontinuous, less-than-lifetime exposures
- Framework developed by MISTEC
  - Use threshold of toxicological concern (TTC) when data-poor.

MISTEC

To develop a framework for estimating potential human cancer risk from intermittent and/or short-term exposures

MISTEC Subcommittee Participation

LEADERSHIP

Susan P. Felter, PhD
(Procter & Gamble Company)

Rory B. Conolly, ScD, DABT
(US EPA National Health and Environmental Effects Research Laboratory)

INDUSTRY

Eli Lilly and Company
ExxonMobil Biomedical Sciences
Johnson & Johnson Pharma.
Procter & Gamble Company
Unilever

PUBLIC

Imperial College London
Michigan State University
National Institute for Public Health and the Environment (RIVM)
New York Medical College
NIEHS
University of Arizona
US Environmental Protection Agency (NCCT, NHEERL, Office of Water)
US Food and Drug Administration (CDER, CFSAN)
World Health Organization

Workshop
December 1 – 3, 2009

- “Workshop to Develop a Framework for Estimating Potential Human Cancer Risk from Intermittent and/or Short-Term Exposures”
- Washington, DC
- 50 invited attendees
- Manuscript in preparation

Workshop Sponsors

Eli Lilly and Company

ExxonMobil Biomedical Sciences, Inc.

Georgia Pacific LLC

ILSI Europe

ILSI North America Task Force on Food and Chemical Safety

Johnson & Johnson Pharmaceuticals

NIH National Institute of Environmental Health Sciences

The Procter & Gamble Company

SOT Food Safety Specialty Section

SOT Regulatory and Safety Evaluation Specialty Section

SOT Risk Assessment Specialty Section

Unilever

US EPA National Center for Computational Toxicology

US EPA National Health and Environmental Effects Research Lab.

US FDA Center for Food Safety and Applied Nutrition

Less-than-lifetime exposures

- Short-term
  - Accidental release (air, water)
  - Contaminant introduced into the food supply for short period
  - Contaminant in a pharmaceutical used for a short duration
  - Off-gassing from materials/paints/adhesives/ solvents/etc. used in building construction
- Intermittent
  - Consumer products (low level contaminants)
  - Agricultural chemicals used seasonally

Historical Perspectives in Quantitative Cancer Risk Assessment (CRA)

- 1958: Delaney Clause (US FDA)
- 1961: Federal government initiated testing program for carcinogenicity (NCI, then NTP)
- 1970s and 1980s: Quantitative CRA is born
- 1980s-2000s: Carcinogen risk assessment guidelines published by various agencies, *all focused on an assumption of ~daily, lifetime exposure.*
- **2010s: New ways to consider less-than-lifetime exposures?**

Lifetime of continuous exposure

- Traditional approaches to quantitative cancer risk assessment assume a lifetime of continuous exposure.
- Actual exposures used in bioassays are adjusted to calculate equivalent continuous exposure:
  - If dose to animals in bioassay is 1 mg/kg, dosed 5 times per week, then equivalent 7 day/wk exposure is 1 x 5/7 = 0.7 mg/kg
  - Assumes the biology is linear
    - (!) this is a large assumption
    - Haber's rule

Haber's rule

- C x T = *k*
  - A lifetime of exposure or one day
- Assumes that pharmacokinetic and pharmacodynamic processes are all linear with dose.
  - Many examples of nonlinear PK and PD
    - Vinyl chloride, chloroform, drugs, etc.

US EPA (2005): Less than lifetime

- For less-than-lifetime human exposure scenarios…the lifetime average daily exposure or dose has often been used… associated with a linearly proportional reduction of the lifetime risk, regardless of when exposures occur. ***Such averaging may be problematic in some situations.***

How do we define these situations??

Is guidance really needed??

The Cranberry Scare of 1959

- On November 9, 1959, Secretary Flemming (HEW) announced, 17 days before the Thanksgiving holiday, that some of the 1959 crop of cranberries contained traces of aminotriazole (Amitrol), which had been shown to cause thyroid cancer in rats.

The Cranberry Scare of 1959

- 99% of the crop had not been contaminated.
- Caused cranberry growers to cease using amitrole as a herbicide, as demanded by the farmers' largest consumer, the Ocean Spray company.

The Cranberry Scare of 1959

If only MISTEC had been around!!

Is guidance really needed??

- Cranberries, 1959
  - Amitrol
- Crystalline silica in cat litter, 1980
- Apples, 1986
  - Alar

Is guidance really needed??

- Much has been learned about mechanisms linking exposure with effect
  - Nonlinearities
    - Haber's rule a special case, not general
- Extensive database
  - Empirical guidance

How can we approach this problem?

- The lack of guidance does not mean that decisions do not have to be made!
- What it does mean is that there will be no consistency in how decisions are made.
- We need to remain flexible, and open to revising methods as more information becomes available.
- So – what do we know, and how can we use the information available today to develop flexible guidelines?

H E S I®

MISTEC PROPOSED FRAMEWORK

Framework options

1. Data-rich

2. Data-poor

H E S I®

1. Are there sufficient chemical-specific and/or (Q)SAR data from which to estimate human excess cancer risk assuming daily lifetime exposure?

Yes

2. Is there sufficient evidence for a nonlinear dose-response for the cancer endpoint?

Yes

3. Is the combination of low exposure dose and limited time for the exposure scenario in question such that, given all the available data, a negligible cancer risk is expected?[a]

Yes

No further cancer risk calculations needed

Data-rich

Data Poor: Threshold of Toxicological Concern (TTC)

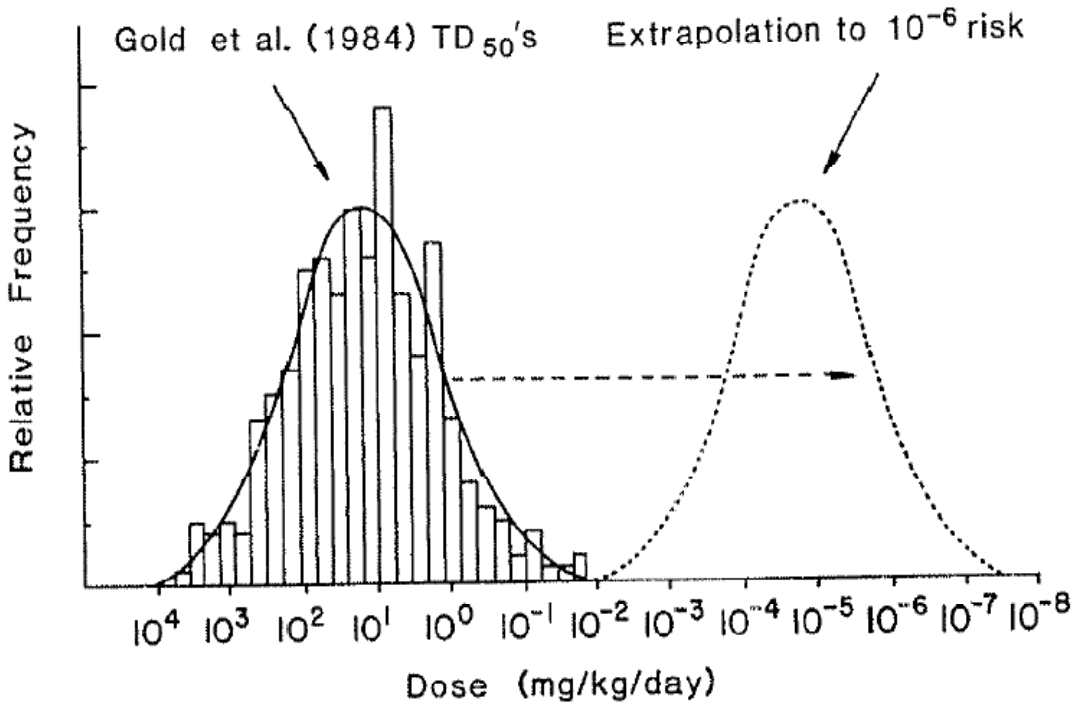
- TTC is a pragmatic risk assessment tool based on the principle of establishing a human exposure threshold for all chemicals, below which there is a very low probability of an appreciable risk to human health" (Kroes et al., 2004).
  - Relies on existing toxicological data on various chemical classes of substances to predict the toxicological potential of substances of undetermined toxicity.
  - Based on the concept that the chemical structure defines potential for toxicity and that structural features can be used to group substances into various categories of toxicological concern.

US FDA's Threshold of Regulation

[60 Fed. Reg. 36582-36596, July 17, 1995].

- The 1995 US FDA regulation specifies a limit for projected dietary exposure of **0.5 ppb**, translating into a daily exposure of **1.5 ug/day**.

- Based on analysis of 477 chemical carcinogens from the Gold et al. (1984) carcinogenic potency database.



Graph adapted from Munro et al., 1990.

H E S I®

1. Are there sufficient chemical-specific and/or (Q)SAR data from which to estimate human excess cancer risk assuming daily lifetime exposure?

Yes

No

2. Is there sufficient evidence for a nonlinear dose-response for the cancer endpoint?

Use appropriate TTC or other value from which to calculate an acceptable daily lifetime exposure.

Yes

No

3. Is the combination of low exposure dose and limited time for the exposure scenario in question such that, given all the available data, a negligible cancer risk is expected?

No

4. Is Haber's Rule (CxT) an appropriate way to estimate the cancer risk or acceptable exposure, with adjustments if necessary?

Yes

No

No further cancer risk calculations needed

Yes

Adjust using Haber's rule.

Case-by-case

Need for case studies

- Work to date has produced the framework and a manuscript (to be submitted ~ August 2010 to *Critical Reviews in Toxicology*).
- No opportunity as yet to rigorously test the framework.
  - Need to consider data-rich, data-poor and intermediate cases.

Acknowledgements

- Susan Felter (Procter and Gamble Company)
- Nancy Doerrer (HESI)
- Workshop Organizing Committee
- Workshop participants
- Sponsoring organizations

H E S I®

End