Experience with Transgenic Models in the NTP Bioassay

NTP Workshop

Genetically Modified Rodent Models for Cancer Hazard Identification: Selecting Substances for Study and Interpreting and Communicating Results

February 21, 2003

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History of Use of Transgenic Models for Cancer Studies at the NIEHS

- Tennant et al.
  - MMTV driven v-Ha-ras, c-myc, c-neu mammary tumor models of Leder (1993)
  - v-Ha-ras Tg.AC (ζ- globin promoter) skin tumor model of Leder (1993 -)
- French et al.
  - p53 +/- knock out mouse of Donehower (1997 -)
- Maronpot et al.
  - Tg rasH2 (c-Ha-ras expression) developed by Katsuki (2000 -)
  - TRAMP (Pb-tag) prostate cancer model
- Rao et al.
  - MMTV driven v-Ha-ras, c-myc, c-neu mammary models (prevention)
- Mahler et al.
  - PIM1 lymphoma model

History of Use of Transgenic Models for Cancer Studies in the National Toxicology Program

- Eastin et al.
  - v-Ha-ras Tg.AC and p53+/- studies of genotoxic and non genotoxic human and rodent carcinogens and non carcinogens Tox Path 26:461-473 (1998)
  - ILSI/HESI ACT collaboration Tg.AC, Tox Path 29 (Suppl.) 2001
- Dunnick et al.
  - p53 +/- (1997 -) phenolphthalein, methylphenidate
    other models- APC, p16/p19 +/-
  - **French et al**. p53 +/- (1997 -) phenolphthalein molecular analysis
- Spalding et al.
  - p53+/-, and Tg.AC prospective studies on nine bioassay chemicals
    Tox Sci. 53:213-223, 2000

Reviews

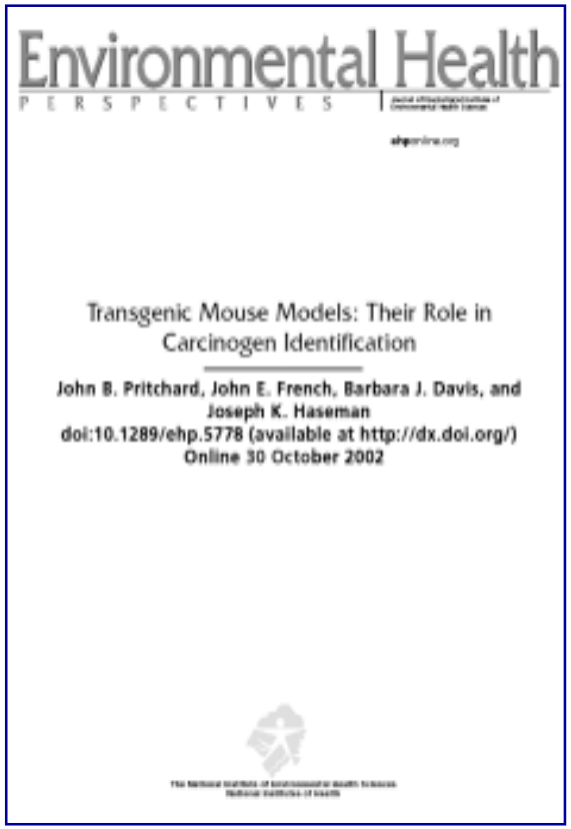
- NTP Board of Scientific Counselors, Feb. 1998
  - Conditional acceptance
    - p53+/- accepted, Tg.AC questioned
    - Noted lack of dose response information
    - Lack of understanding of “misses”
- Urged development of specific tumor site models and continued effort on these and other models for general carcinogen screens

Current NIEHS/NTP Statistics

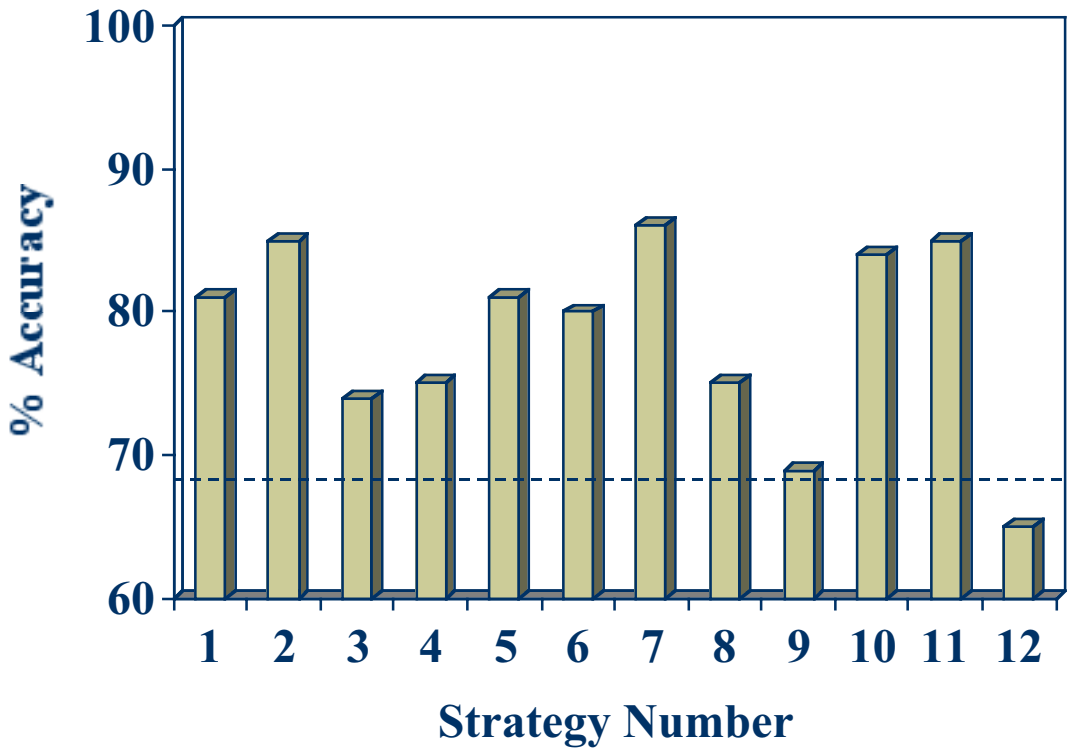
- In house and contracted studies with genetically modified mice -
  - About 100 studies with cancer models
  - Tg.AC, p53+/-, p16/p19 +/-, TRAMP, MMTV/neu, PIM1, rasH2, MMTV/ras, MMTV/myc, APC
  - Prevention of site specific cancer- 18 studies, 17 chemicals or mixtures- TRAMP, MMTV/neu
  - Retrospective studies, model development- 55 studies, 30 chemicals-Tg.AC, p53+/-, p16/p19+/-, rasH2, APC, MMTV/ras, MMTV/myc
  - Prospective studies- 27 studies, 15 chemicals

Transgenic Mouse Models

- Pritchard et al. evaluation
  - **Concordance of selected model results with IARC and ROC carcinogen lists**
  - **Design and analysis issues**



Transgenic Model Performance



% Accuracy = Positive findings for IARC/ROC Known/ Suspected Carcinogens plus Negative for IARC/ROC Non-Listings

G = Genotoxic Chemicals

N = Nongenotoxic Chemicals

1 = Trp53+/-

2 = Trp53+/- G only

3 = Tg.AC

4 = RasH2

5 = p53-G/Ras-N

6 = p53-G/Ras-All

7 = p53-G/Tg.CA-N

8 = p53-G/TgAC-All

9 = Rodent Bioassay

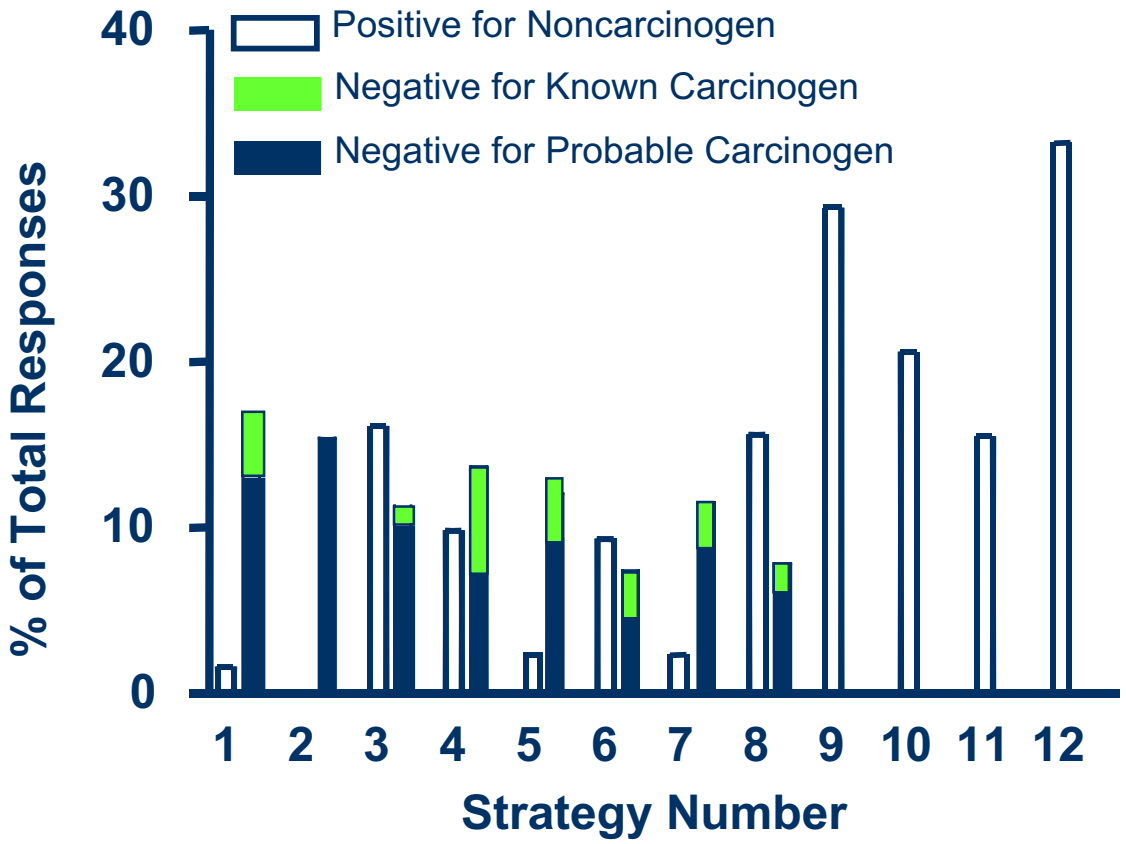
10 = Rat Bioassay Plus Tg.AC-N or Trp53-G

11 = Rat Bioassay Plus RasH2-N or Trp53-G

12 = Rat Bioassay Plus Genotoxicity

NTP National Toxicology Program

Is There a Pattern in the Missed Calls?



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BSC Tech Report Subcommittee Review

- NTP Board of Scientific Counselors Technical Reports Subcommittee, Sept. 2002
  - Review of Tg.AC studies of Pentaerythritol triacrylate and Trimethylolpropane triacrylate
    - Breakout group 2 - example 9
    - *NTP proposed "clear evidence of carcinogenic activity"*
  - In your opinion, is there sufficient scientific evidence using this model to evaluate the potential carcinogenicity of each compound? If not what steps should the NTP take next?
- Subcommittee rejected proposed conclusion
- Suggested that more appropriate, model specific descriptive language be developed

BSC Review Sept. 2002 Questions

- Does the Board have recommendations regarding the issues to consider 1) in choosing a transgenic animal for mechanistic research and 2) in validating its use for screening?

- Under what conditions would the Board feel a positive result in a single or in multiple transgenic models sufficiently reflects a reasonable concern for carcinogenicity in humans? What additional research is needed to “validate” that the conditions suggested by the Board are scientifically sound?

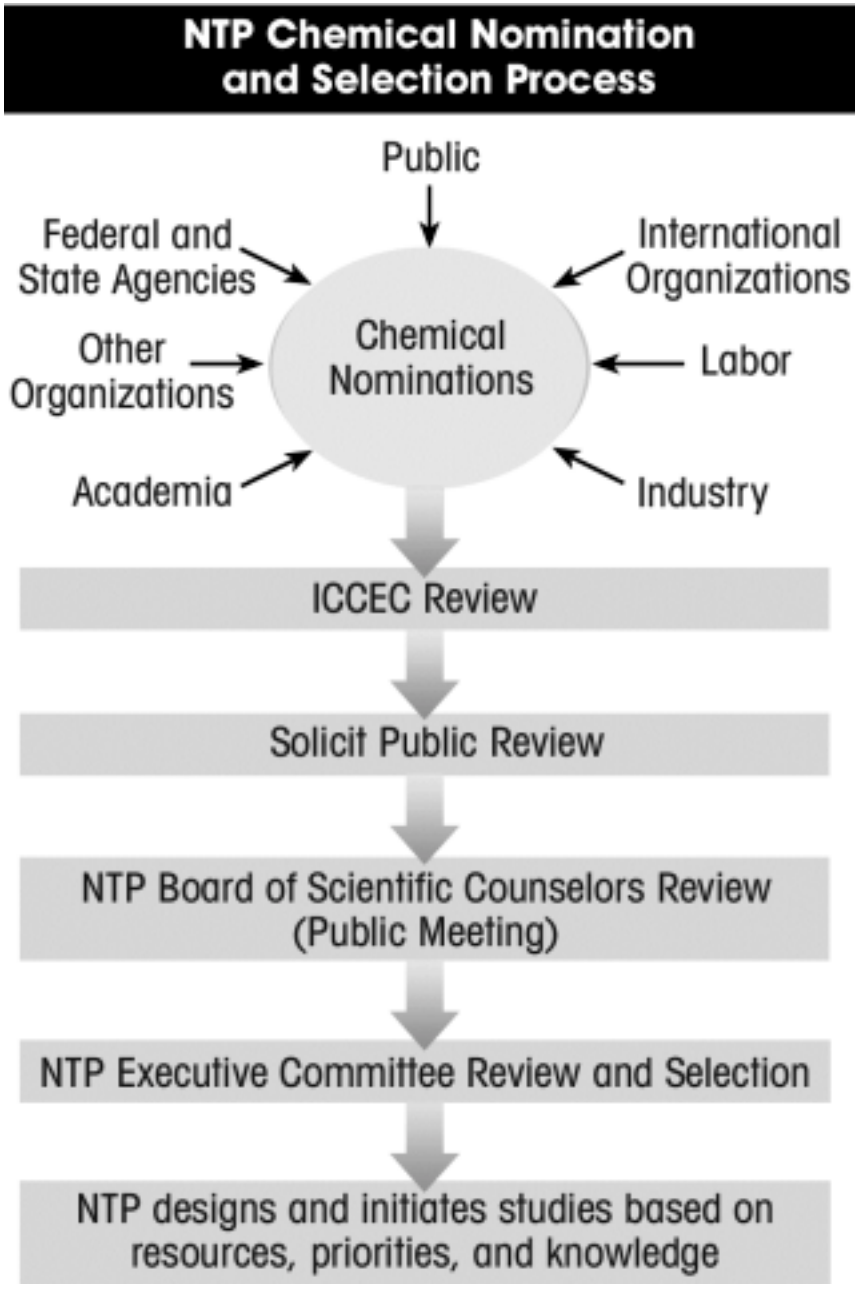
- Under what conditions would the Board feel a negative result in a single or in multiple transgenic models sufficiently reflects little or no concern for carcinogenicity in humans? What additional research is needed to “validate” that the conditions suggested by the Board are scientifically sound?

Questions for the Board (continued)

- Does the Board have suggestions concerning research the NTP can support to determine if positive findings in transgenic models can be used to predict risk (level of exposure versus probability of carcinogenic response) in human populations?

- To what degree would the Board suggest that we balance further research on the development of transgenic animals for understanding mechanisms with the validation of these animals as part of a carcinogenicity screening program?

NTP National Toxicology Program



Draft Revision to Nomination Review Process

- The NTP proposes that it would follow its current process and
  - at each level of review would specifically ask for input about whether studies in genetically modified animal models might provide data sufficient to address information needs concerning potential cancer hazards.
- The NTP would not ask for recommendations about specific models at any level of review.
  - Model selection would generally be left to the discretion of the NTP study scientists and study design team that are responsible for designing the research program for a specific substance.

NTP Workshop
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Remaining Agenda

and

Charge to the Breakout Groups

Agenda and Charge

- 10:00- 10:30 Break and split into workgroups
- Group 1: Marilyn Wind USCPSC (Chair)

  Solicit comment on a process for selection of appropriate nominated substances to undergo cancer hazard evaluation in genetically modified or "transgenic" models

- Farragut Room

Charge to Breakout 1

- Is the proposed process adequate to ensure that all stakeholders have a sufficient opportunity to provide comment on substances selected for study in genetically modified models?

- Address as many of the case studies as possible

Agenda and Charge

- 10:00- 10:30 Break and split into workgroups
- Group 2: Norman Drinkwater U. Wisconsin (Chair)

  Solicit comment on issues related to the proper interpretation of results from "transgenic" cancer models, the implications of these findings for public health decisions, and the most appropriate interpretive language to describe the results of such studies to the scientific/regulatory communities and the public
- Oasis Room

Charge to Breakout 2

- Does the scientific/regulatory community consider tumor findings in genetically modified mouse models as equivalent to tumor findings in traditional rodent cancer models? Is the answer the same for all commonly used models (Tg.AC, p53+/-, rasH2)?

- To what degree is the scientific/regulatory community confident that negative results in studies with genetically modified mouse models are equivalent to negative results in the traditional bioassay?

Address these questions after working through the 12 "case studies"

Agenda

- 12:00 to 1:00 Lunch (*on your own*)
- 1:00 Breakout groups continued
- 2:30 Break
- 3:15 Plenary Session Dr. Al Munson, NIOSH Chair
  - Breakout group reports
  - Open discussion
- 4:30 Adjourn