IRIS Assessment Plan for Vanadium Pentoxide Inhalation

Matthew D. Stout, Ph.D., DABT
Toxicologist
Office of Program Operations
Division of the National Toxicology Program
National Institute of Environmental Health Sciences

Question 2

- Interpretation and potential use of data on noncancer respiratory responses in NTP’s chronic inhalation study (2002)

NTP Chronic Study of Vanadium Pentoxide

- Designed based on review of data from short term NTP studies
- Conducted in accordance with NTP Specifications for the Conduct of Toxicology and Carcinogenesis Studies and Federal Good Laboratory Practice Regulations
- Male and female F344/N rats and B6C3F1 mice exposed to aerosolized particles via whole body inhalation, 6 hr/day, 5 day/week for up to 2 years, at exposure concentrations of:
  - Rats: 0, 0.5, 1 or 2 mg/m^3
  - Mice: 0, 1, 2 or 4 mg/m^3

https://ntp.niehs.nih.gov/go/tr507abs

In-life effects observed during chronic studies

Rats

- Survival: Similar between control and exposed groups (male and female)
- Body weights: Exposed groups within 10% of control group
- No exposure related clinical observations

Mice

- Survival: Significantly less than controls at the highest exposure concentration in male mice; similar to controls in female mice
- Body weights: Lower than controls in an exposure-concentration responsive manner; more apparent in female mice
- Clinical observations: thin, abnormal breathing at higher exposure concentrations

Noncancer respiratory responses

- Exposure to vanadium pentoxide caused a spectrum of nonneoplastic lesions in the respiratory tract (nose, larynx, and lung) in rats and mice
- Lung lesions included:
  - Alveolar and bronchiolar epithelium hyperplasia, Inflammation, fibrosis, and alveolar histiocytosis of the lung in male and female rats and mice
  - An unusual squamous metaplasia of the lung in male and female rats
- Hyperplasia of the bronchial lymph node occurred in female mice
- Many of the increases in incidence and/or severity were exposure concentration-responsive
- Patterns generally similar between sexes in each species

Bronchiolization

- Hyperplasia of the alveolar and bronchiolar epithelium in both rats and mice
- Effects consistent with bronchiolar epithelium proliferation and migration into alveoli (bronchiolization)
  - A metaplastic change
  - Unclear if associated with carcinogenicity
- Squamous metaplasia in rats – relatively rare but observed in a limited number of other NTP inhalation studies

Question 3

- Interpretation and potential use of data on tumor responses in rodents in NTP’s chronic inhalation study (2002)

NTP Levels of evidence for carcinogenic activity

- Clear evidence of carcinogenic activity
  - Dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy
- Some evidence of carcinogenic activity
  - Chemical-related increased incidence of neoplasms in which the strength of the response is less than that required for clear evidence
- Equivocal evidence of carcinogenic activity
  - Marginal increase of neoplasms that may be chemical related
- No evidence of carcinogenic activity
- Inadequate study

Alveolar/bronchiolar adenoma or carcinoma in rats and mice

	Control	Low conc	Mid Conc	High Conc
Male rats	4	10	6	9
Female rats	0	3	1	1
Male mice	22	42***	43***	43***
Female mice	1	32***	35***	32***

N=48-50/group
***p<0.001

Level of evidence for carcinogenic activity in rats

Male rats

- Under the conditions of this 2-year inhalation study, there was ***some evidence of carcinogenic activity*** of vanadium pentoxide, based on the occurrence of alveolar/bronchiolar neoplasms
  - No significant increases
  - 0.5 and 2.0 mg/m^3 responses at or above historical controls
  - Carcinomas only in exposed groups
  - Relatively rare in unexposed male rats

Female rats

- Under the conditions of this 2-year inhalation study, there was ***equivocal evidence of carcinogenic activity*** of vanadium pentoxide, based on the occurrence of alveolar/bronchiolar neoplasms
  - No significant increases
  - 0.5 mg/m^3 response similar to historical controls
  - One carcinoma in the 2 mg/m^3 group
  - Relatively rare in unexposed female rats
  - Highest occurrence in the low exposure concentration group

Level of evidence for carcinogenic activity in mice

Male mice

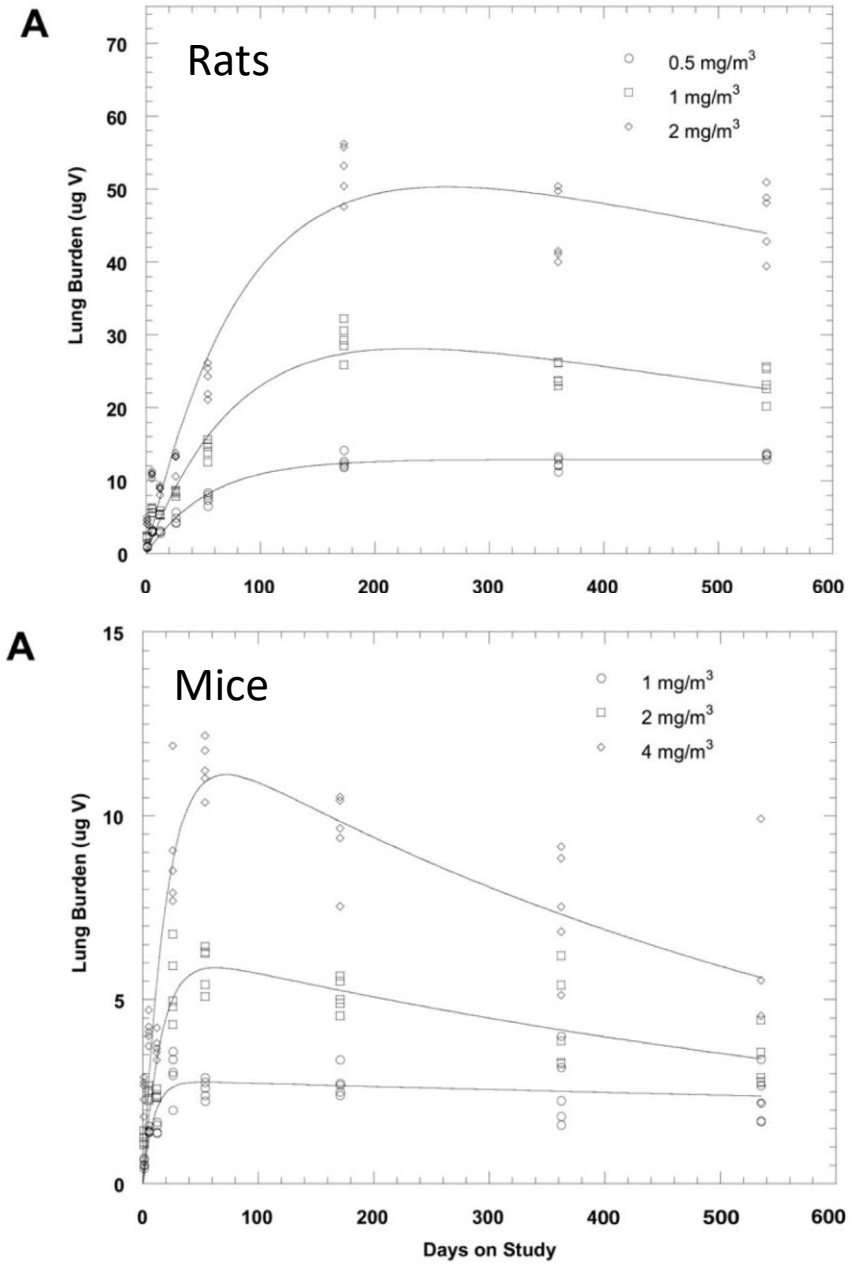
- Under the conditions of this 2-year inhalation study, there was ***clear evidence of carcinogenic activity*** of vanadium pentoxide, based on increased incidences of alveolar/bronchiolar neoplasms
  - Response exceeded historical controls and significant in all concentration groups
  - Multiplicity

Female mice

- Under the conditions of this 2-year inhalation study, there was ***clear evidence of carcinogenic activity*** of vanadium pentoxide, based on increased incidences of alveolar/bronchiolar neoplasms
  - Response exceeded historical controls and significant in all concentration groups
  - Multiplicity

Lung burden

- Increases proportional to exposure concentration
- Steady state → decrease in deposition with increasing exposure concentration
  - Potentially due to changes in lung function
- Mice remove vanadium from lung faster than rats
- Longer lung clearance half times relative to short term studies
- Dose to lung higher in rats, but mice received several fold higher dose to lung per unit body weight
  - May help explain flat exposure-response for neoplasms in mice but does not explain differences between rats and mice



Question 4

- Cancer mode of action for alveolar/bronchiolar neoplasms induced by vanadium pentoxide inhalation

Mode of action considerations

- Vanadium can alter alveolar macrophage integrity and function, likely resulting in impaired clearance
- Vanadium pentoxide appears to be slightly soluble in the lung
  - As such, may be cytotoxic
- Molecular pathology
  - Alterations in K-*ras* in carcinomas in exposed groups with loss of heterozygosity, with no clear exposure concentration-response
- Cascade of events initiated by accumulation of protein tyrosines
- Induction of cytokines, macrophage inflammatory proteins, mediators of pulmonary fibrogenesis and other proliferative and inflammatory responses in the lung