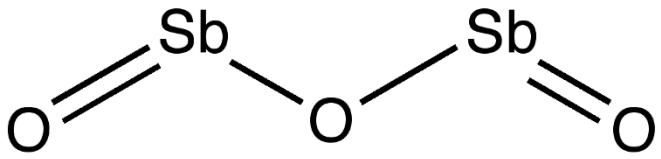
Cancer Studies in Experimental Animals



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National Institute of Environmental Health Sciences

January 24, 2018

One of the RoC listing criteria for *reasonably anticipated to be a human carcinogen*

- **Sufficient evidence of carcinogenicity from studies in experimental animals**
  - **Increased incidence of malignant and/or**

a combination of malignant and benign tumors

(1) in multiple species

or at multiple tissues sites

(2) by multiple routes of exposure, or

(3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset

Questions

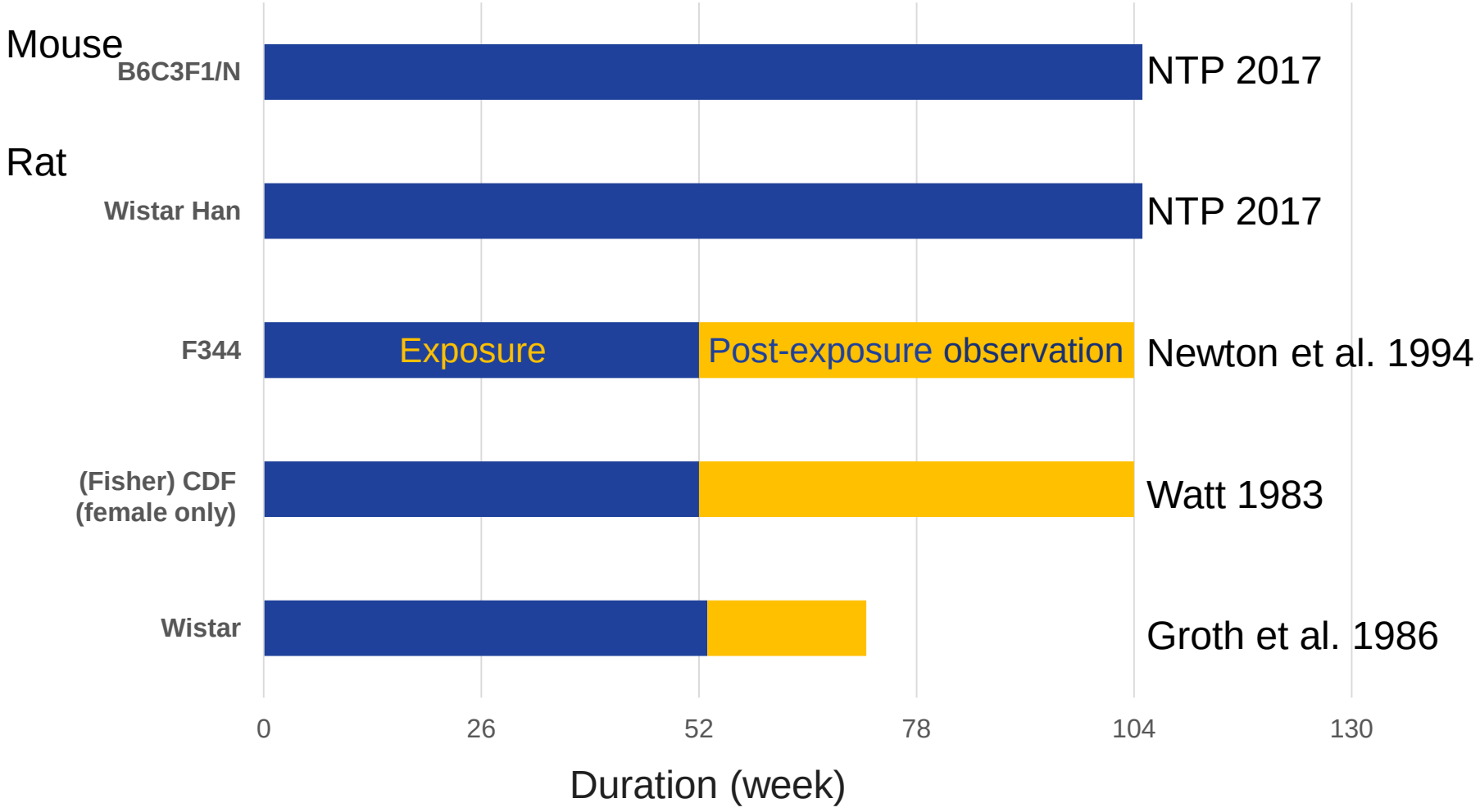
- **What is the level of evidence (sufficient or inadequate) for the carcinogenicity of antimony trioxide in animal studies?**
- **What are the methodological strengths and limitations of the studies?**
- **At what tissue sites were tumors observed?**
- **What role does lung overload play in causing any observed rat lung tumors?**

Outline

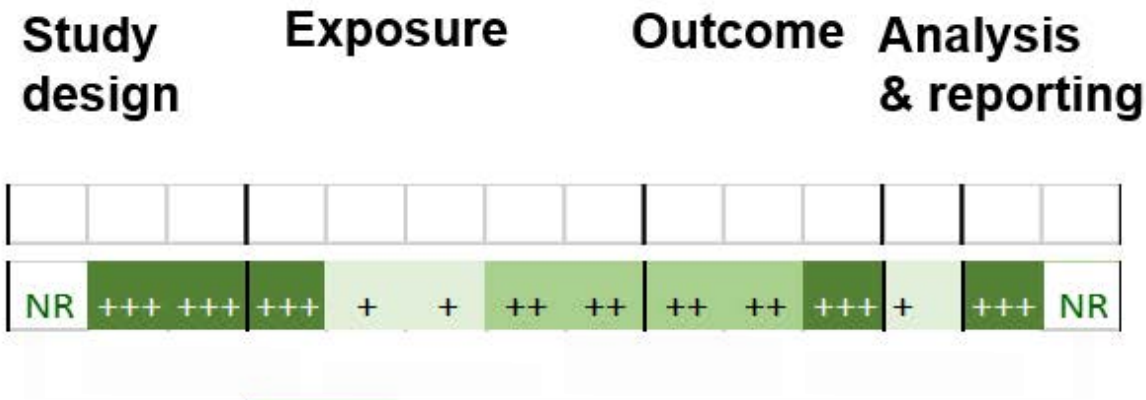
- **Studies included**
- **Study quality assessment**
- **Findings**

- **Questions to reviewers**

Five inhalation studies meet inclusion criteria



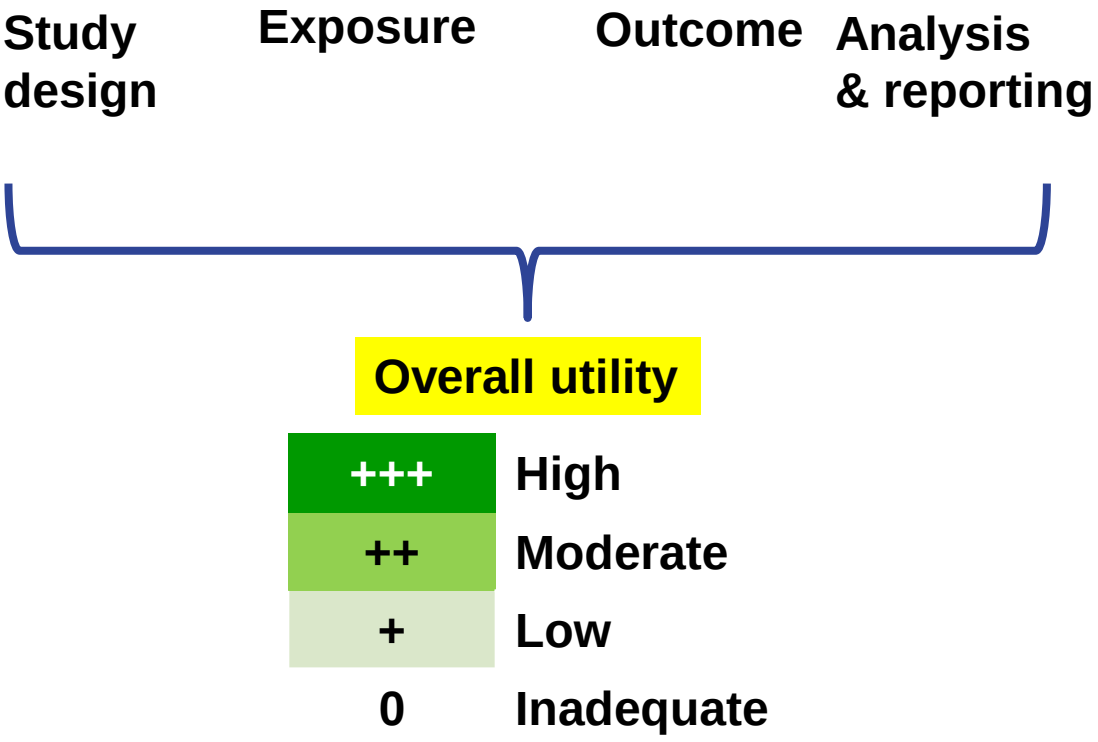
Study qualities (potential bias and sensitivity) were assessed consistently using standard questions



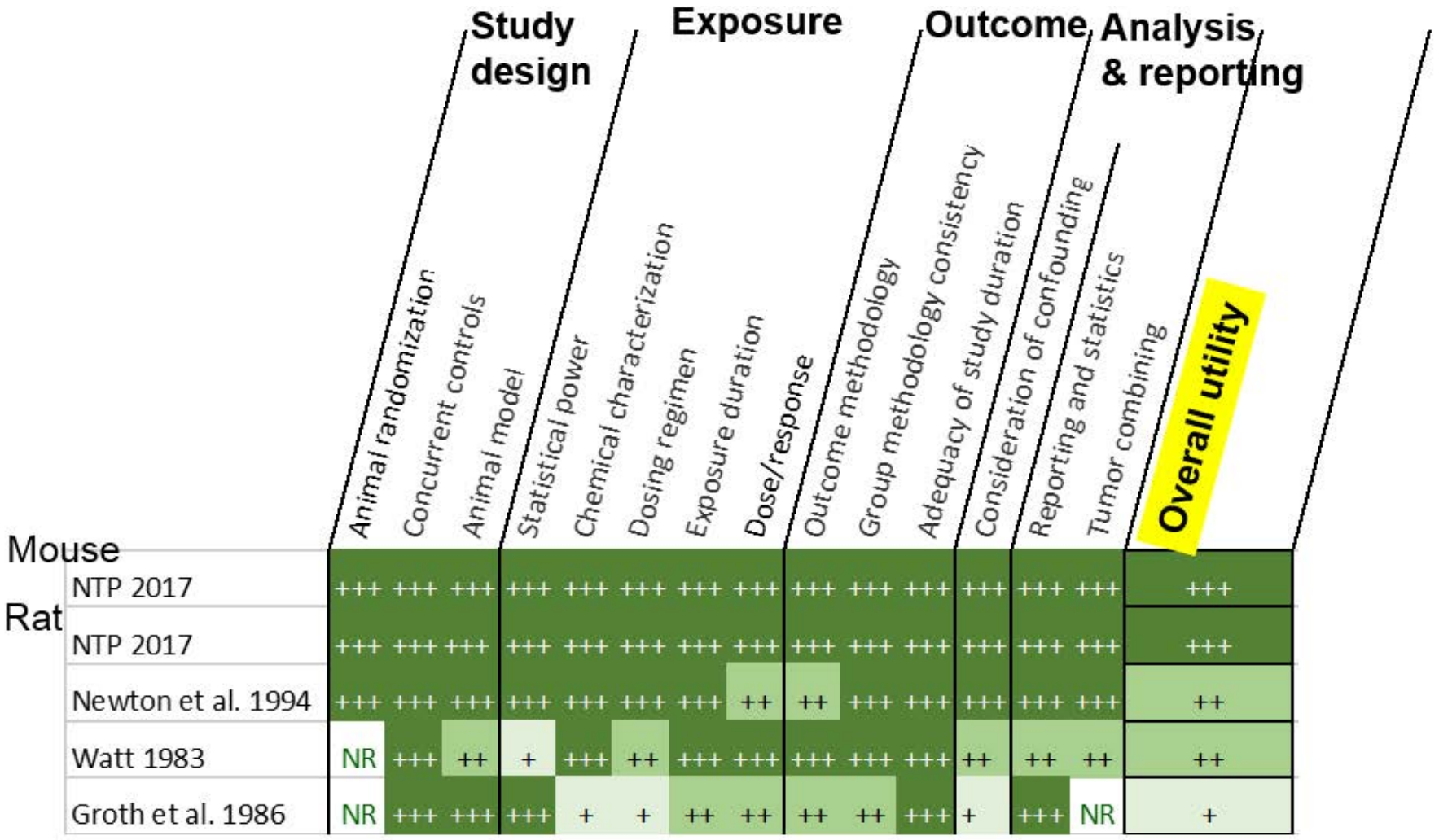
For questions, see Handbook for Preparing RoC Monograph

Study qualities were assessed consistently

Each study was given one level of overall utility in assessing carcinogenicity



All studies have some level of utility



Mice Had Increased Incidences of

Lung tumors

Benign	Alveolar/bronchiolar adenoma (F)
Malignant	Alveolar/bronchiolar carcinoma (M and F)
Combined	Alveolar/bronchiolar adenoma or carcinoma (F)

Skin tumors

Benign	Fibrous histiocytoma (M)
Combined	Fibrous histiocytoma or fibrosarcoma (M)

Lymphoma

Malignant	Lymphoma (F)

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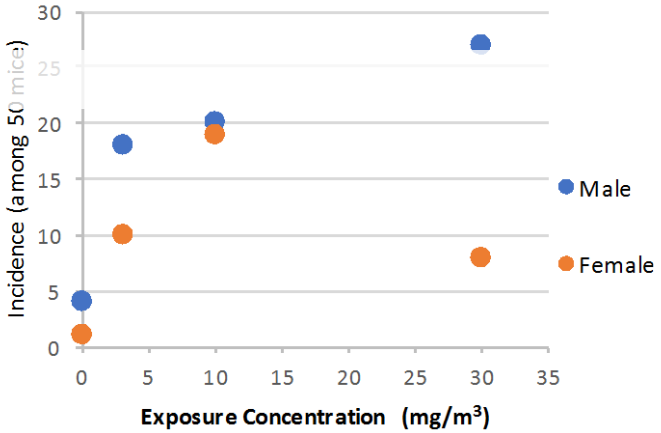
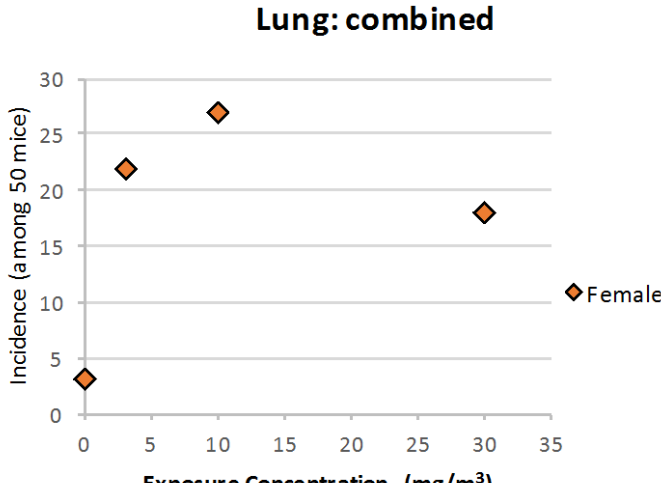




Mice Lung Tumors

Antimony trioxide concentration	3 mg/m^3	10 mg/m^3	30 mg/m^3
Pulmonary overload	No	Yes	Yes
Preneoplastic	F, M	F, M	F, M
Benign	F	F	F
Malignant	F, M	F, M	F, M
Combined	F	F	F

- Overload –
  - may be from poorly soluble, low intrinsic toxicity particles
- Overload alone does not lead to lung tumors in mice
- Tumors increased at 3 mg/m^3 (i.e., below overload threshold)
- Genotoxicity seen in lung (increased DNA damage) and in blood (increased micronucleus)

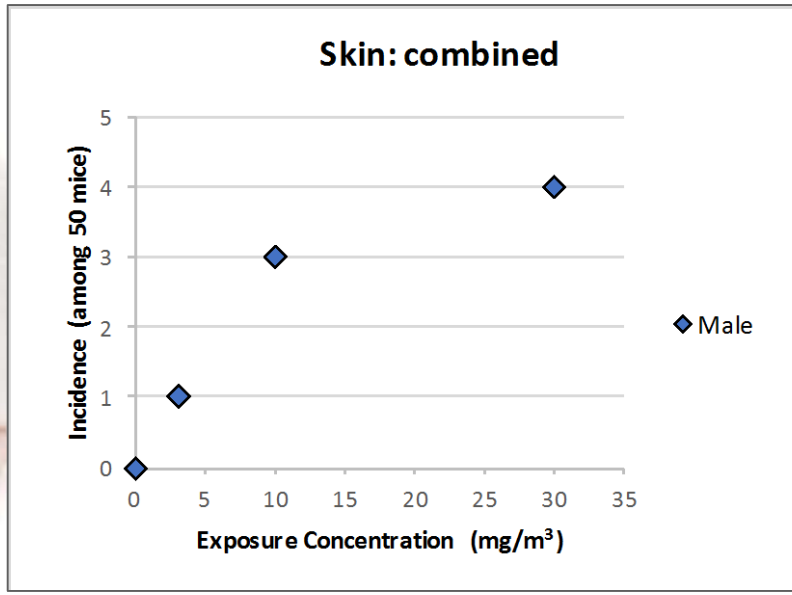
→ Antimony trioxide has some intrinsic toxicity

Mice Had Increased Incidences of

Skin tumors

Benign Fibrous histiocytoma (M)

Combined Fibrous histiocytoma or fibrosarcoma (M)



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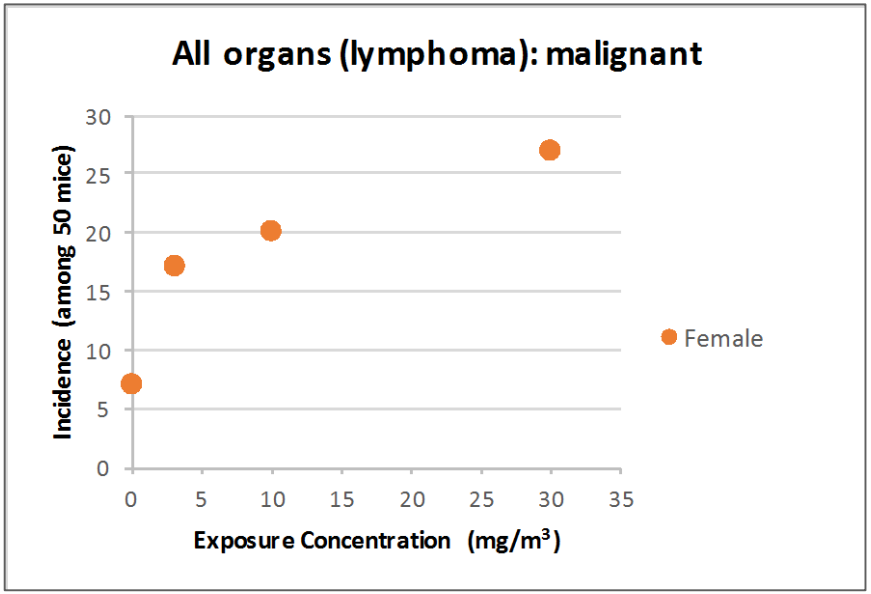

Lymphoma

Malignant Lymphoma (F)

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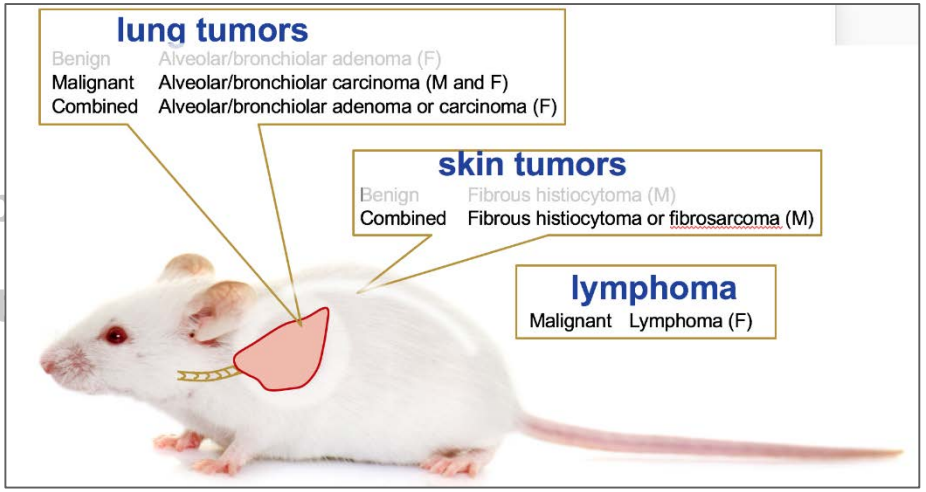

Rats Had Increased Incidences of

Lung tumors

Benign	Alveolar/bronchiolar adenoma (M* & F)	NTP 2017
Combined	Alveolar/bronchiolar adenoma or carcinoma (M*)	
Benign	Bronchiolar/alveolar adenoma (F)	Groth et al. 1986
Malignant	Squamous-cell carcinoma (F)	
Malignant	Scirrhous carcinoma (F)	
Malignant	Scirrhous carcinoma (F)	Watt 1983

Adrenal gland tumors

Benign	Pheochromocytoma (M & F)
Combined	Pheochromocytoma (F)

NTP 2017

Newton et al. 1994 reported no increase in tumors.

*M: carcinogenicity in male rats based on multiple factors (see following slides)

Rats had increased incidences of

Lung tumors

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Adrenal gland tumors

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*M: carcinogenicity in male rats based on multiple factors (see following slides)

Carcinogenicity in Male Rat Lung

Factors considered in NTP 2017 rat study

- **Incidences of alveolar/bronchiolar adenoma exceed current and historical controls**
- **Alveolar/bronchiolar carcinoma seen in 2/50 male rats at 10 mg/m^3**
  - **Rare tumor: 0/299 in NTP historical control, 2/731 at RCC, 1/1217 at Charles River (total: 3/2247, or 0.13%)**
- **Adenoma can progress to carcinoma**
- **Lung tumors in mice**
- **Some intrinsic toxicity of antimony trioxide: genotoxicity in mice**

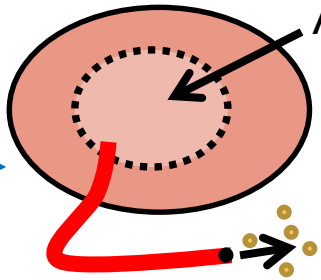
→**Antimony trioxide has lung carcinogenicity in rats, even though the increase in incidence was not statistically significant**

→**Lung overload alone does not explain the lung tumors in rats**

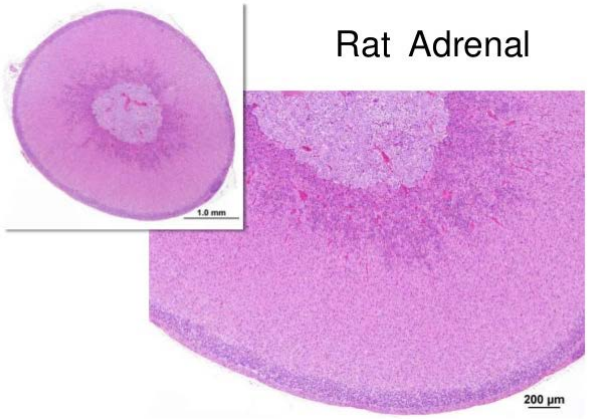
Pheochromocytoma of the Adrenal Medulla

Treatment (antimony trioxide) effect

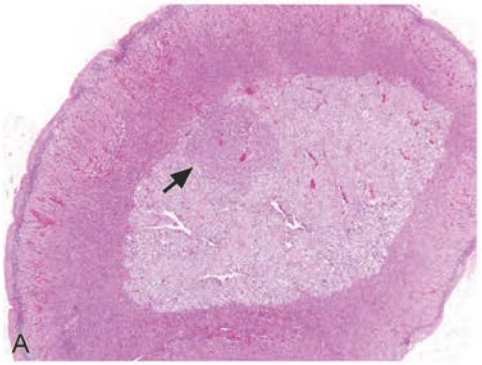
Hypoxia



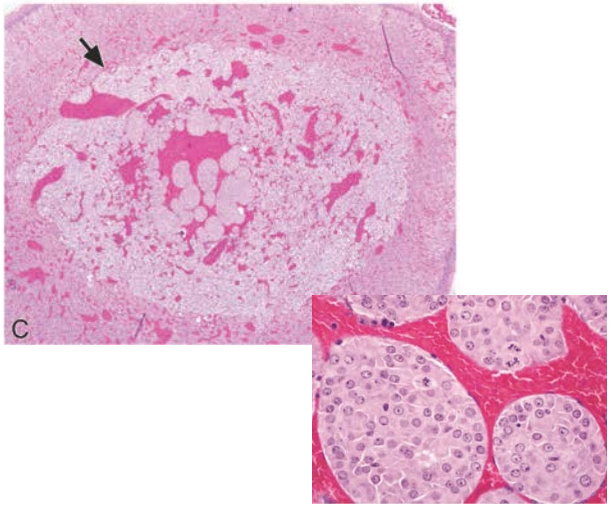
Catecholamines (epinephrine and norepinephine)



Normal



Hyperplasia



Pheochromocytoma

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Summary

Increased incidences in malignant tumors or combined tumors (benign or malignant) in two species at multiple tissue sites

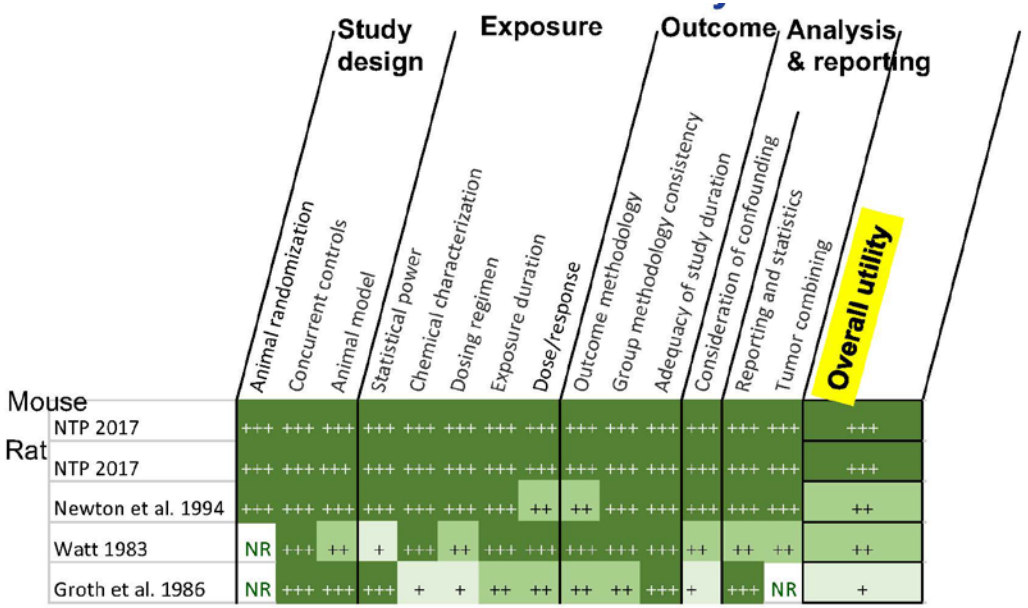
	Rat		Mouse	
Tissue sites	Malignant	Combined	Malignant	Combined
Lung	F	M	F, M	F
Adrenal gland	–	F	–	–
Skin	–	–	–	M
Whole body (lymphoma)	–	–	F	–

Questions

- **What is the level of evidence (sufficient, limited, or inadequate) for the carcinogenicity of antimony trioxide in animal studies?**
  - **NTP proposes “sufficient” level of evidence (multiple species, multiple tissue sites)**

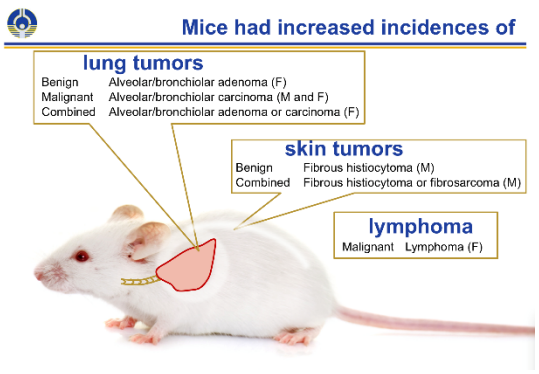
Questions

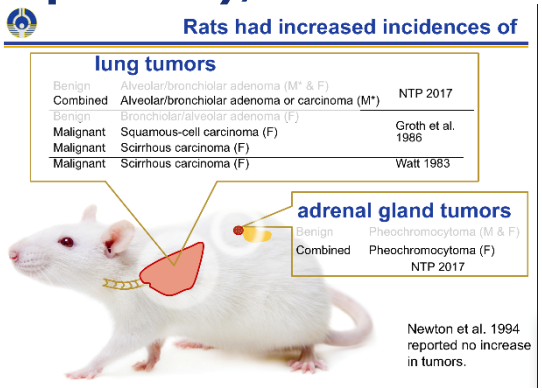
- **What is the level of evidence (sufficient, limited, or inadequate) for the carcinogenicity of antimony trioxide in animal studies?**
  - **Propose "sufficient"**
- **What are the methodological strengths and limitations of the studies?**



Questions

- **What is the level of evidence (sufficient, limited, or inadequate) for the carcinogenicity of antimony trioxide in animal studies?**
  - **Sufficient (multiple species, multiple tissue sites)**
- **What are the methodological strengths and limitations of the studies?**
- **At what tissue sites were tumors observed?**
  - **Lung, skin, whole body (lymphoma), and adrenal gland**





Questions

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  - **Sufficient (multiple species, multiple tissue sites)**
- **What are the methodological strengths and limitations of the studies?**
- **At what tissue sites were tumors observed?**
  - **Lung, adrenal gland, skin, and lymphoma (whole body)**
- **What role does lung overload play in causing observed rat lung tumors?**
  - **Lung tumors are not completely explained by overload (e.g., intrinsic toxicity)**

Cancer Studies in Experimental Animals

- **Comment on whether the scientific information from cancer studies in experimental animals for antimony trioxide is clear, technically correct, and objectively presented.**
  - **Identify any information that should be added or deleted.**
- **Comment on whether the approach and assessment of the utility of the animal carcinogenicity studies (study quality and sensitivity to detect an effect) for informing the cancer evaluation is systematic, transparent, objective, and clearly presented (Sections 5.2, Appendix D).**
- **Provide any scientific criticisms of NTP's cancer assessment of the experimental animal studies of exposure to antimony trioxide and how findings from the scientific evidence across studies were synthesized (Section 5.3).**