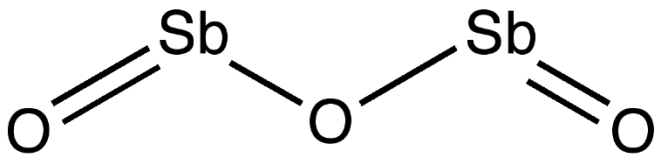
Human Cancer Studies



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January 24, 2018

Human Cancer Studies and Antimony Trioxide

Outline

- **Lung cancer –** occupational smelter worker cohorts
  - Background
  - Utility of lung cancer studies
  - Assessment of findings
- **Stomach cancer –** occupational cohort and case-control studies
  - Background
  - Utility of stomach cancer studies
  - Assessment of findings
- **Preliminary level of evidence conclusion**

Background

- **Lung cancer mortality is an adequate measure of lung cancer incidence**
  - Low survival: 18.1% survival five years after diagnosis[1]

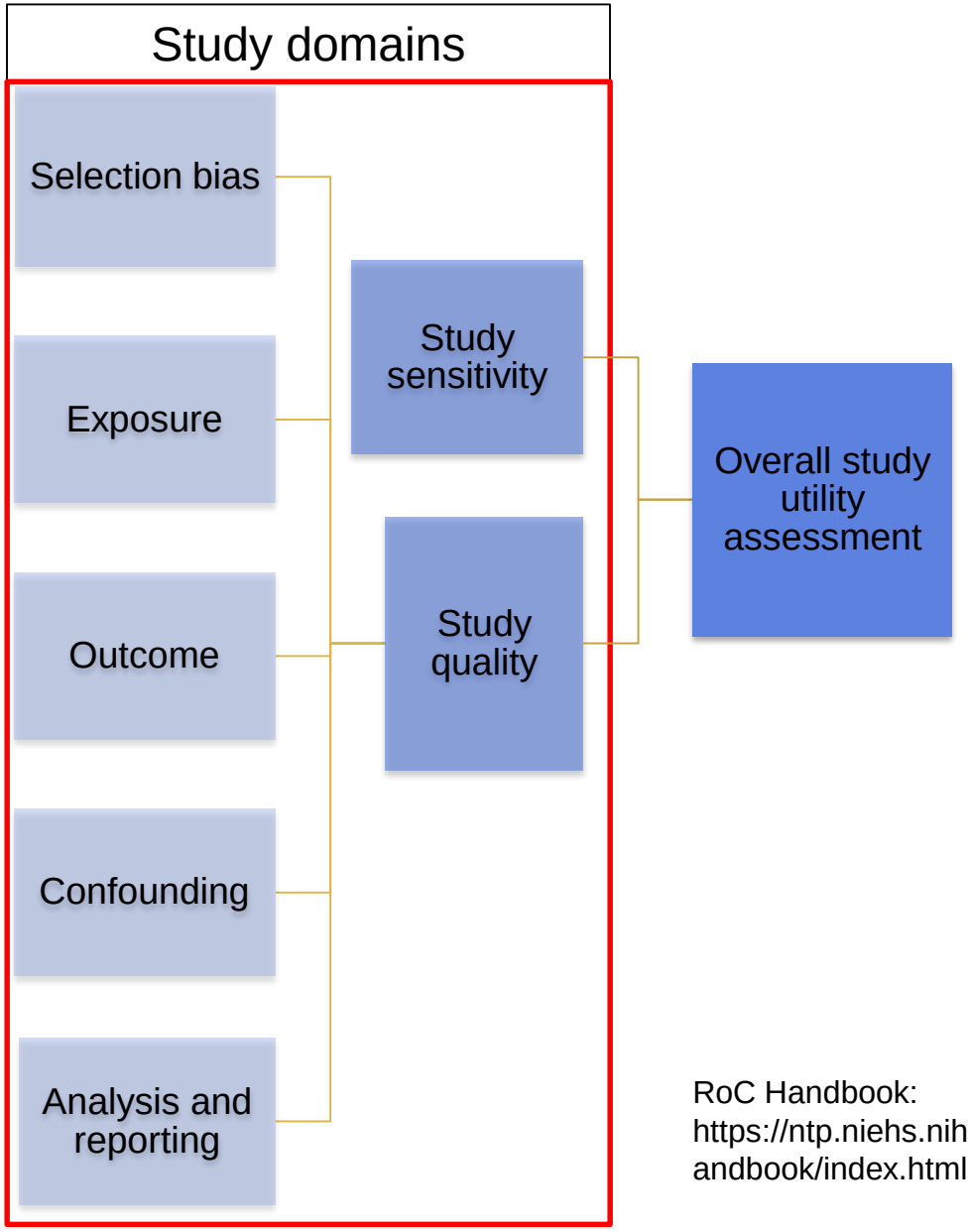
- **Potential confounders among lung cancer risk factors**
  - Occupational: arsenic, lead, polycyclic aromatic hydrocarbons (PAHs), asbestos
  - Non-occupational: current and past smoking

[1] SEER Program, 2007-2013: https://seer.cancer.gov/statfacts/html/lungb.html

Overview of selected studies

Occupational cohort study	Study design	Exposure assessment	Likely antimony species
Antimony smelter workers			
Jones 1994, United Kingdom	Historical mortality cohort [SMR]	Company records	Antimony trioxide, other antimony oxides, antimony sulfides
Schnorr *et al.* 1995, United States	Historical mortality cohort [SMR]	Company records	Antimony trioxide, other antimony oxides, antimony sulfides
Tin smelter workers			
Jones *et al.* 2007, United Kingdom	Modeled cumulative inhalation and lung cancer mortality	Area and personal air sampling, job-exposure matrix	Antimony trioxide

Study Quality and Utility Assessment



Domain level judgments

Low/minimal concern (+++)

Some concern (++)

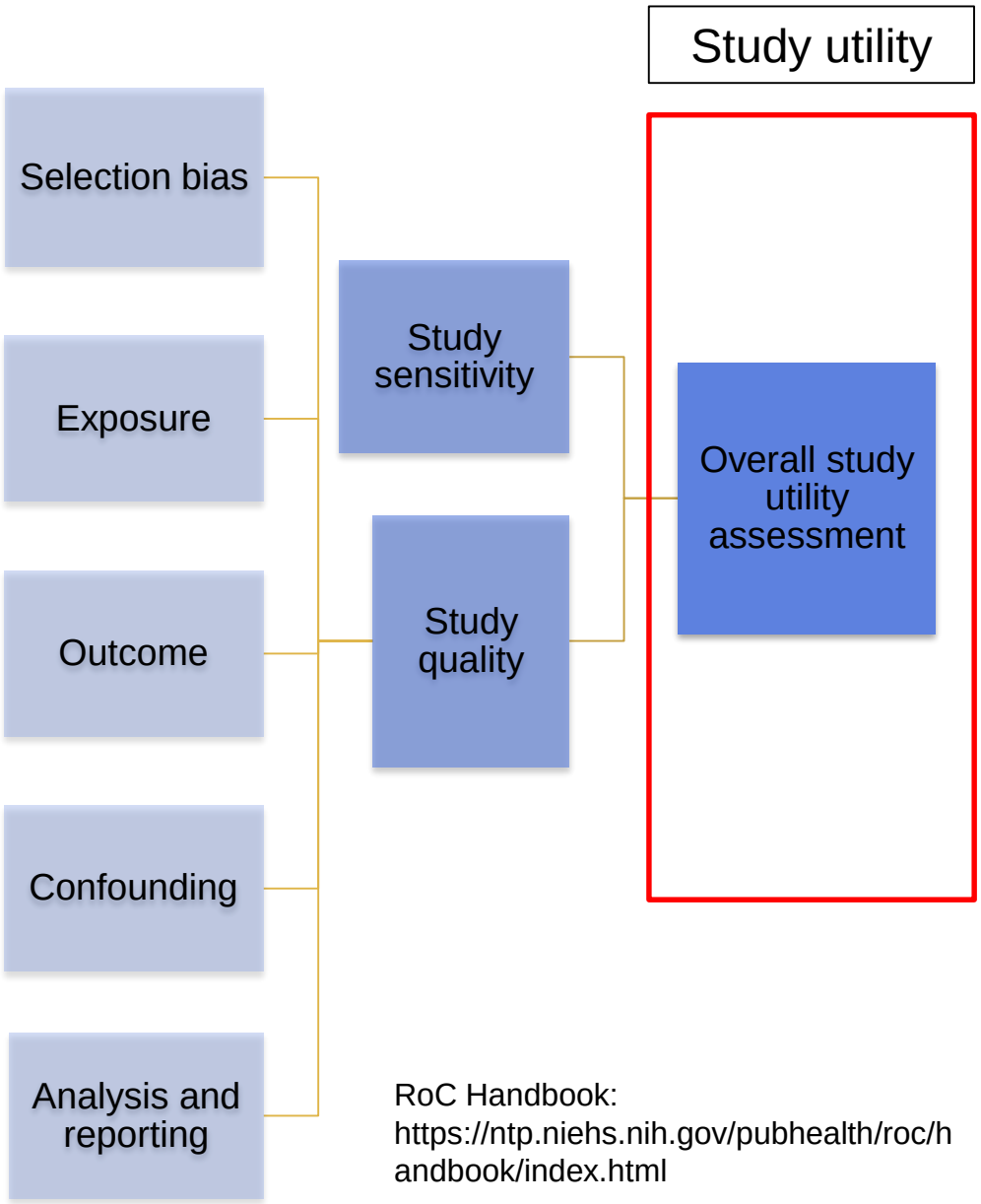
Major concern (+)

Critical concern (0)

No information

RoC Handbook: https://ntp.niehs.nih.gov/pubhealth/roc/handbook/index.html

Study Quality and Utility Assessment



Domain level judgments

Low/minimal concern (+++)

Some concern (++)

Major concern (+)

Critical concern (0)

No information

Overall study utility level

High utility (+++)

Moderate utility (++)

Low utility (+)

Inadequate utility (0)

RoC Handbook:
https://ntp.niehs.nih.gov/pubhealth/roc/handbook/index.html

Quality and Utility of Lung Cancer Studies

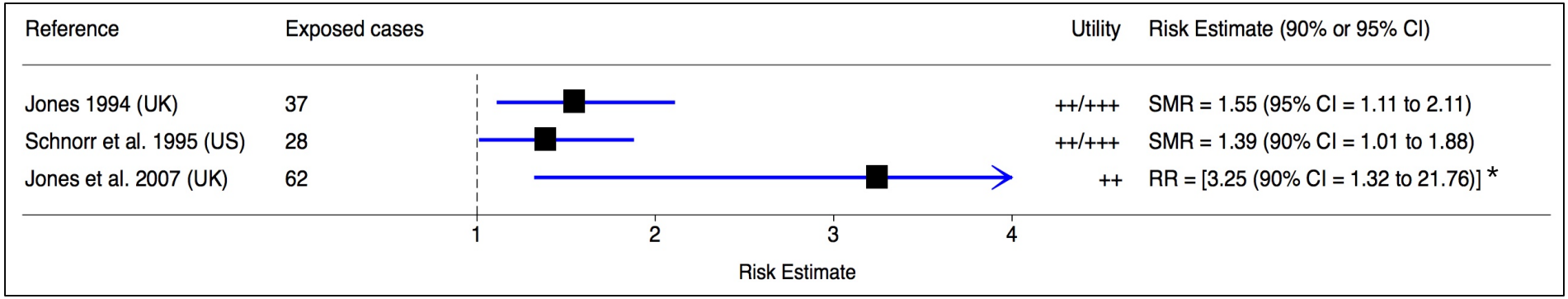
Studies were “high/moderate” or “moderate” utility

Study type, citation	Consideration for potential bias						Quality	Utility
	Selection	Exposure	Outcome	Confound-ing	Analysis	Selective reporting	Sensitivity	Integration
Antimony smelter workers								
Jones 1994	++	+++/++	+++	+	+++	+++	++	+++/++
Schnorr *et al.* 1995	++	++	+++	+++	++	+++	++	+++/++
Tin smelter workers								
Jones *et al.* 2007	++	++	+++	++	++	+++	+	++

- Antimony smelter studies had high/moderate utility, and tin smelter study had moderate utility to inform a cancer hazard evaluation.
- Most studies had some or major concerns of selection bias, exposure misclassification, and study sensitivity.
- Most studies had some or major concerns of confounding by occupational co-exposures and smoking.

Assessment of Lung Cancer Findings

Increased risk of lung cancer mortality, but unmeasured confounding may complicate results



- Small number of studies (n=3) examined antimony-exposed lung cancer deaths.
- Two antimony smelter cohort studies used ever-exposure to antimony and conducted an external analysis.
- Concurrent exposure to other metals during smelting process and high prevalence of smoking among workers may confound the results.

* NTP calculated estimate based on Jones *et al.* (2007), Table 3 (weighted Sb exposure, β =1.18, p-trend: 0.013)

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  - Utility of stomach cancer studies
  - Assessment of findings
- **Preliminary level of evidence conclusion**

Background

- **Stomach cancer mortality is an adequate measure of stomach cancer incidence**
  - Low survival five years after diagnosis[1]
- **Potential confounders among stomach cancer risk factors**
  - Occupational: lead, asbestos
  - Non-occupational: current and past smoking

[1] SEER Program, 2007-2013: https://seer.cancer.gov/statfacts/html/stomach.html

Overview of selected studies

Study	Study design	Exposure assessment	Likely antimony species
Jones 1994, United Kingdom	Historical mortality cohort; local and national mortality data	Company records	Antimony trioxide, other antimony oxides, antimony sulfides
Schnorr *et al.* 1995, United States	Historical mortality cohort; state and national mortality data	Company records	Antimony trioxide, other antimony oxides, antimony sulfides
Wingren and Axelson 1993, Sweden	Case-control study, art-glass producing area	Occupation on death records and regional use patterns	Antimony trioxide

Quality and Utility of Stomach Cancer Studies

Two “high/moderate” and one “low” utility studies

Study type, citation	Consideration for potential bias						Quality	Utility
	Selection	Exposure	Outcome	Confound-ing	Analysis	Selective reporting	Sensitivity	Integration
Antimony smelter workers (cohort studies)								
Jones 1994	++	+++/++	+++	+	+++	+++	++	+++/++
Schnorr *et al.* 1995	++	++	+++	+++	++	+++	++	+++/++
Case-control study of art glass producing area in Sweden								
Wingren and Axelson 1993	+++	+	++	+	++	++	+	+

- Antimony smelter studies had high/moderate utility, and case-control had low study utility.
- For case control study, major concerns for potential exposure misclassification, confounding bias from occupational co-exposures, and major concerns for study sensitivity.

Utility of Stomach Cancer Studies

Inconsistent associations across studies

Study	Exposed cases	Exposure level	Risk estimate
Jones 1994 (UK)	2	Ever exposure	SMR: 0.42 (0.05–1.51)
Schnorr *et al.* 1995 (US)	10	Ever exposure	SMR: 1.49 (0.71–2.74)
Wingren and Axelson 1993 (Sweden)	NR	Low antimony use	OR: 1.60 (0.90–2.60)
		High antimony use	OR: 0.80 (0.30–2.00)

- Limited by small number of studies (n=3) and small number of exposed cases.
- Although two studies found positive associations with stomach cancer, there were inconsistent findings within and across studies.
- Likely unmeasured confounding from smoking and occupational lead.

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Summary – Human Cancer Studies

NTP preliminary conclusion:

"The data available from studies in humans are **inadequate** to evaluate the relationship between human cancer and exposure specifically to antimony trioxide or other antimony compounds."

- Limited by:
  - Number of studies with small sample sizes for stomach and lung cancers.
  - Potential confounding due to smoking and occupational co-exposures.

Human Cancer Studies on Antimony Trioxide

Questions?

Human Cancer Studies

- Comment on whether the scientific information from the cancer studies in humans for antimony trioxide is clear, technically correct, and objectively presented.
  - Identify any information that should be added or deleted.
- Comment on whether the approach (described in the Protocol) and assessment of the utility of the human cancer studies (risk of bias and sensitivity to detect an effect) for informing the cancer evaluation (Appendix C, Sections 4.2) is systematic, transparent, objective, and clearly presented.
- Provide any scientific criticisms of NTP's cancer assessment of the epidemiologic studies of exposure to antimony trioxide, including how the findings from the individual studies were interpreted and the evidence across studies was synthesized.