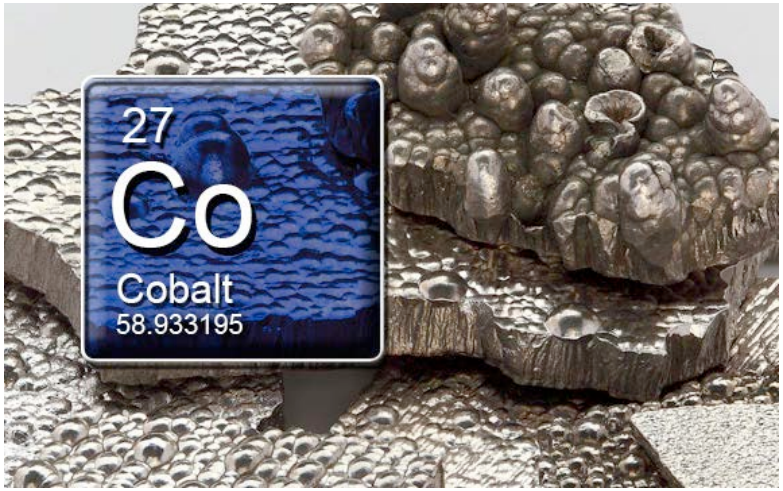
Human Cancer Studies



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Outline

Lung cancer - Cohort and nested case-control studies

- Background
- Methods of assessing study utility
- Utility of lung cancer studies
- Assessment of findings

Esophageal cancer - Case control studies

- Background
- Utility of esophageal cancer studies
- Assessment of findings

Other cancers and cobalt

Preliminary level of evidence conclusion

Background

Mortality is an adequate measure of incidence in lung cancer mortality studies

- **Low survival: 17.4% 5-year survival rate***
- **U.S. Rate (per 100,000)*** **Men** **Women**

Incidence	70.1	50.2
Mortality	59.8	37.8

Relevant confounders among lung cancer risk factors

- Occupational: **asbestos, chromium, nickel, arsenic**, soot, tar or radon.
- Non-occupational: **current and past smoking,** secondhand smoke, family hx, breast or chest radiation therapy, home radon exposure, air pollution, and HIV infection.

*http://seer.cancer.gov/statfacts/html/lungb.html 2007-2011

Background

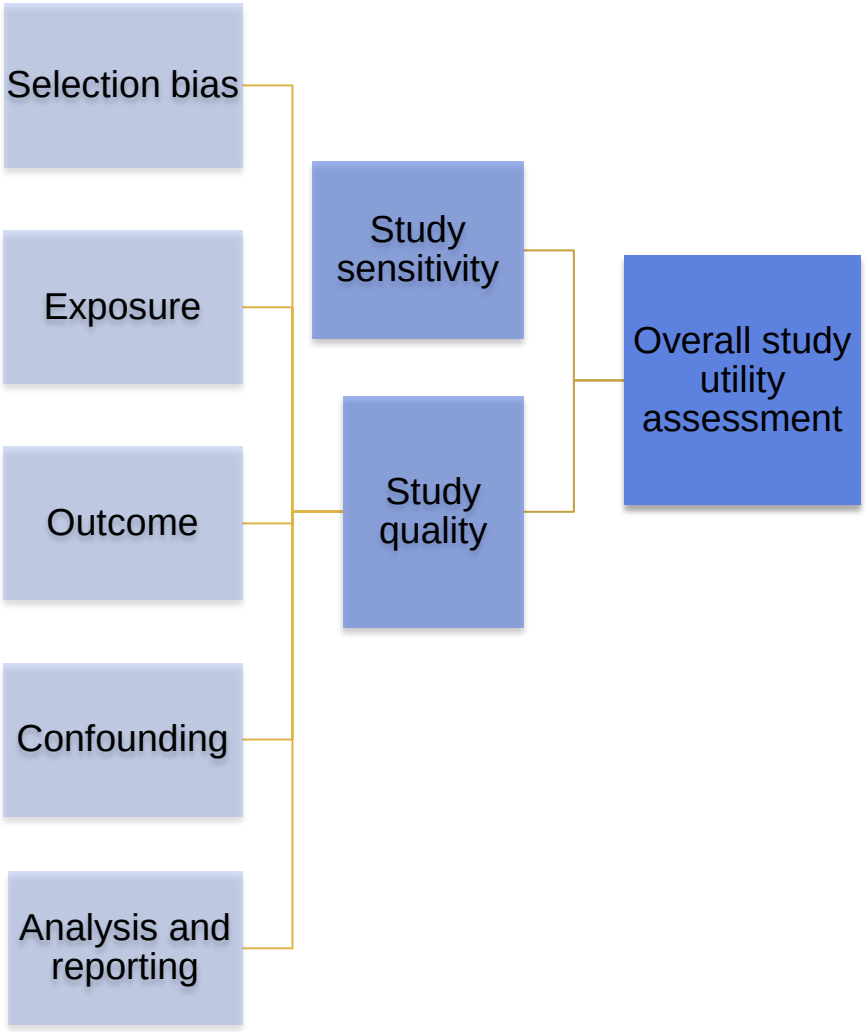
Cohort and nested case-control studies	Study design	Exposure assessment
French electrochemical workers		
Mur *et al*. 1987	Historical cohort mortality study of **cobalt production workers**; medical records used for outcome assessment; and nested case-control analysis	Company records - exclusive employment in each of 4 work groups, one being cobalt production
Moulin *et al*. 1993	Re-analysis with 8 additional years of follow up; death certificates used for outcome assessment	
French hard metal workers		
Moulin *et al.* 1998	Historical cohort mortality study of all **10 French hard metal factories**; and nested case-control analysis	Semi-quantitative job exposure matrix (JEM) classified workers as ever exposed to “other” cobalt, not including tungsten carbide
Wild *et al.* 2000	Historical cohort mortality study of **largest French hard metal factory**	

Background

Cohort and nested case-control studies	Study design	Exposure assessment
Other cohorts		
Tüchsen *et al.* 1996	Incidence cohort study of **Danish porcelain painters** in two factories	Company records of workers ever employed in underglazing or cobalt-free departments
Moulin *et al*. 2000	Historical cohort mortality study of **French stainless and alloyed steel workers**; and nested case-control analysis	Semi-quantitative JEM
Grimsrud *et al.* 2005	Incidence cohort of **Norwegian nickel refinery workers** in one refinery	Breathing zone personal samples for cobalt and nickel incorporated into semi-quantitative JEM; quantitative cumulative exposure

Human Study Utility

Bias and sensitivity domains



Domain level judgments

Low/minimal concern

Some concern

Major concern

Critical concern

No information

Human Study Utility

Study utility based on evaluation of bias and sensitivity

Bias	Sensitivity	Study Utility
Low/minimal concerns	High or moderate	
Low/minimal or some concerns	High or moderate	
Some or major concerns about several domains	Varies	
Major concerns about several domains	Varies	
Critical concerns about any domain	Varies	

Utility of Lung Cancer Studies

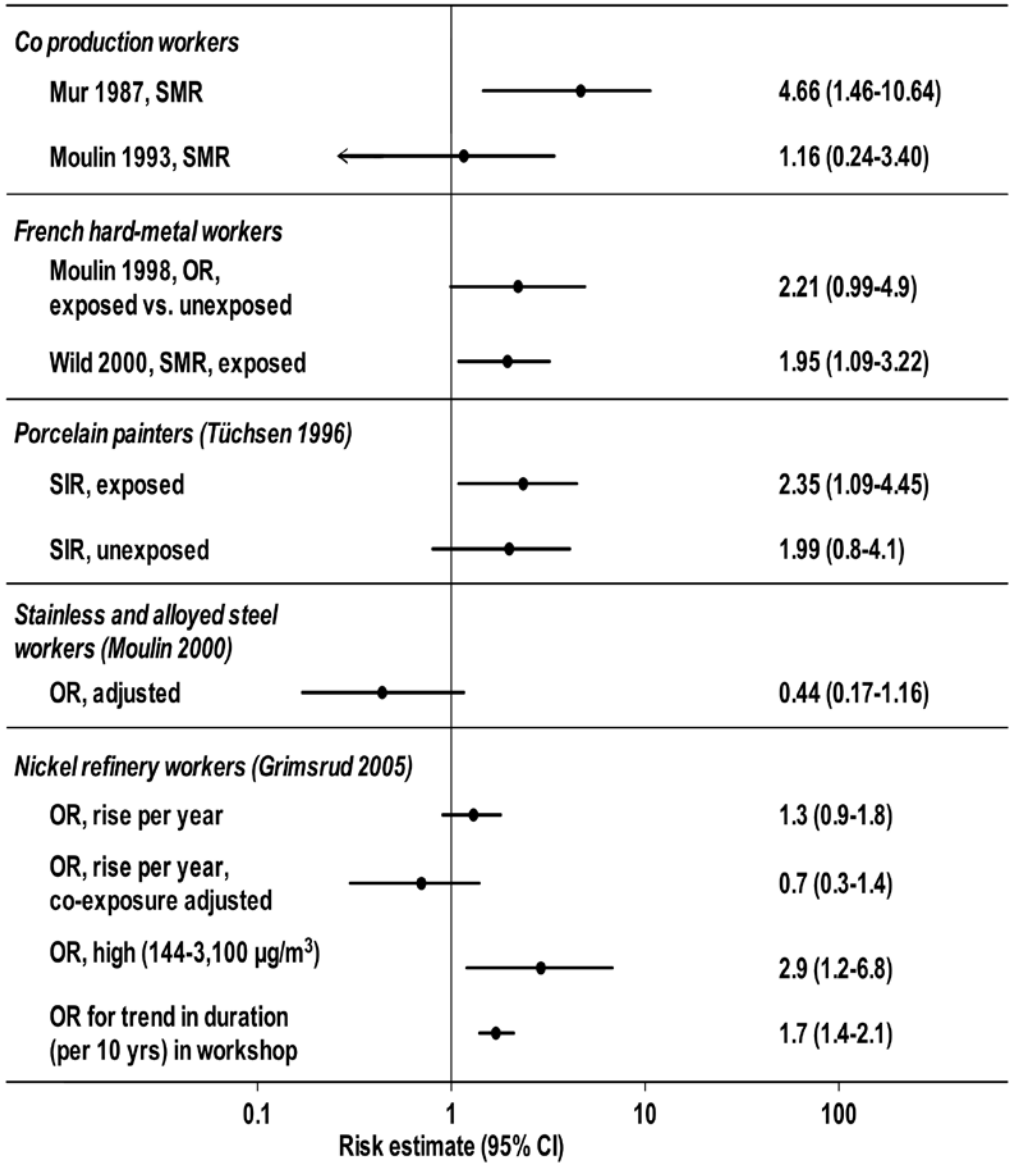
Rank	Study
High	–
Moderate	Grimsrud *et al*. 2005
Moderate/low	Tüchsen *et al.* 1996
	Moulin *et al.* 1998
	Wild *et al.* 2000
	Moulin *et al.* 2000
Low	Moulin *et al.* 1993
	Mur *et al.* 1987

No study had a "high" utility ranking. With one exception, all were of moderate/low or low quality

- Small numbers of workers exposed to "cobalt alone"
- Most studies had limited exposure assessment, potential bias, and low sensitivity to detect associations
- Half the studies did not evaluate exposure-response relationships
- Problems with potential confounding and the inability to control for co-exposures in most studies

Assessment of Lung Cancer Findings

Increased risks, alternative explanations can't be excluded



Different methods of outcome ascertainment; FU dropped 1 exposed case

"Cobalt alone" (w/o tungsten carbide) not controlled for other carcinogenic co-exposures

Risk is elevated in both exposed and unexposed workers

Exposure misclassification; negative findings for known lung carcinogens.

Adjusting for co-exposures changes OR from + to – (continuous)

Controlling for other carcinogenic co-exposures yields no estimate (categorical)

Elevated risks in workshop with high cobalt levels, and a significant trend

Background

Incidence is measured in esophageal cancer studies

- **Low survival: 17.5% 5-year survival rate***
- **U.S. Rate (per 100,000)***

	Men	Women
Incidence	7.7	1.8
Mortality	7.5	1.6

Relevant confounders among esophageal cancer risk factors

- Occupational: rubber production industry, tetrachloroethylene exposure, and dry cleaning.
- Non-occupational: x- and gamma-radiation, **alcohol,** betel quid, **tobacco smoking,** smokeless tobacco, drinking hot Mate, pickled vegetables, red and processed meats, and high temperature drinks.

*http://seer.cancer.gov/statfacts/html/lungb.html 2007-2011

Background

Population based case-control studies	Cases	Controls	Exposure assessment
W. Washington State, U.S.			
Rogers *et al.* 1993*	73	434	Single measurement of cobalt in toenail clippings collected at study enrollment
FINBAR Study, Ireland			
O'Rorke *et al.* 2012**	137	221	Single measurement of cobalt in toenail clippings collected at study enrollment

*Includes both squamous cell and adenocarcinomas
**Includes only adenocarcinomas

Utility of Esophageal Cancer Studies

Rank	Study
High	–
Moderate	–
Moderate/low	–
Low	Rogers *et al.* 1993
	O'Rorke *et al.* 2012

Both studies had low utility

- Both are well conducted population based case-control studies.
- Both used sound methodologies and included sufficient number of cases.
- Temporality not established as neither measured Co during relevant window of exposure.
- Uncertainty whether Co toenail levels reflected exposure to cobalt preceding cancer or resulted from changes due to tumor formation.

Assessment of Esophageal Cancer Findings

Risk of cancer with increasing levels of cobalt unclear

Study	Exposure category	Exposed cases	Risk estimate (95% CI)
W. Washington State, U.S.			
Rogers *et al.* 1993* *(µg/g)*	< 0.05 0.05−0.17 > 0.17	92* 127 66	1.0 2.4 (0.8−7.2) 9.0 (2.7−30.0)
FINBAR Study, Ireland			
O'Rorke *et al.* 2012** *(ppm)*	< 0.004 ≥ 0.004 and < 0.011 ≥ 0.011	34 39 52	1.0 1.13 (0.64−1.99) 1.54 (0.9−2.68) P_{trend} = 0.11

*Combined cases and controls

**Tertile cutpoints µg/g based on controls; reported in the publications as logarithmic transformations

Aerodigestive Cancers+ and Precancerous Conditions

Population	Endpoints	N	Levels	Results
Population based case-control studies				
W. Washington State, U.S.				
Rogers *et al.* 1996*	Larynx	114	< 0.05	1.0
		168	0.05−0.17	2.0 (1.0−3.8)
		62	> 0.17	1.0 (0.4−2.6)
	Oral cavity			
		135	< 0.05	1.0
		190	0.05−0.17	1.5 (0.9−2.6)
		92	> 0.17	1.9 (1.0−3.6)
Finbar study, Ireland				
O'Rorke *et al.* 2012	Barrett's esophagus	55	< 0.004**	1.0
		54	≥ 0.004 and < 0.011	1.08 (0.55−2.1)
		64	≥ 0.011	1.97 (1.01−3.85)
Cohort studies				
Cobalt production workers, France				
Mur *et al.* 1987	Buccal cavity, pharynx, larynx	2	-	3.36 (0.29−10.29)

+Aerodigestive cancers collectively include cancers of the oral cavity, esophagus, larynx, and pharynx.
*Rogers *et al.* reported only combined cases and controls.
**Tertile cutpoints µg/g based on controls; reported in the publications as logarithmic transformations.

Summary – Human Studies of Cancer and Cobalt*

- Most cohort studies of lung cancer reported approximately a doubling of the risk from exposure to various cobalt compounds; however, exposure to other known lung carcinogens and other limitations complicates interpretation of results.

- Increased risks of esophageal cancer were found in both of the population-based case-control studies; however, cobalt exposure was assessed in toenail samples after cancer diagnosis, which leads to uncertainty about whether cobalt levels in the toenails reflected exposure to cobalt preceding cancer or resulted from changes due to tumor formation.

Clarifications?

Reviewer Questions

1. Comment on whether the scientific information from the cancer studies in humans for cobalt and certain cobalt compounds is clear, technically correct, and objectively presented.

    - Identify any information that should be added or deleted.

2. Comment on whether the approach (described in the Protocol) and assessment of the utility of the human cancer studies (study quality and sensitivity) for informing the cancer evaluation (Appendix C, Sections 4.2.2 and 4.3.2) is systematic, transparent, objective, and clearly presented.

3. Provide any scientific criticisms of NTP's cancer assessment of the epidemiologic studies of exposure to cobalt and certain cobalt compounds, including how the findings from the individual studies were interpreted and the evidence across studies was synthesized.

NTP's Preliminary Level of Evidence Conclusion (Vote)

"The data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure to cobalt and certain cobalt compounds."

This conclusion is based on:

- While most lung cancer studies reported a doubling of the risk from cobalt*, exposure to other known lung carcinogens and other limitations complicates interpretation of results.

- Increased risks of esophageal cancer were found in both population-based case-control studies; however, cobalt levels were assessed in toenail samples after cancer diagnosis, leading to uncertainty regarding whether cobalt levels in the toenails reflected exposure to cobalt preceding cancer or resulted from changes due to tumor formation.