Carcinogenicity of PSLT Particles: Epidemiology as a Risk Assessment 'Reality Check'

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Poorly Soluble Low Toxicity Particles: Presentation Outline

1. Do poorly soluble low toxicity particles (PSLTs) cause lung cancer?
2. Occupational exposure to PSLTs is common and may be substantial
3. Hazard, Exposure, Risk Assessment – and Epidemiology
4. Epidemiological studies of workers highly exposed to PSLTs: A ‘reality check’?
5. The Balancing Act:
   - Biological plausibility
   - Quality based study evaluation
   - Human-relevant exposures
   - Evidence Integration

1 Do poorly soluble low toxicity particles (PSLTs) cause lung cancer?

What are Poorly Soluble Low Toxicity (PSLT) Particles?

- Poorly Soluble, Low Toxicity particles (PSLTs) have been inconsistently characterized
  - Generally are chemically inert
  - Lack of known specific toxicity
  - Macrophage clearance from lungs is quicker than their dissolution (ETETOC 2013)
- Particle size (<200 nm), dimensions (aspect ratio >3:1), surface chemistry / surface-reactivity* and dose can affect toxicity

*Freshly fractionated crystalline silica exhibits surface-related cytotoxicity that diminishes with time

SOURCE: https://www.ecetoc.org/report2/introduction/definition-of-poorly-soluble-particles-of-low-toxicity/

Examples I: Evidence of Carcinogenic Potential (Hazard)

> **Carbon Black**

– IARC Classification Group 2B – “possibly carcinogenic to humans” (minority supported 2A – “probable”)

– Sufficient evidence in animals

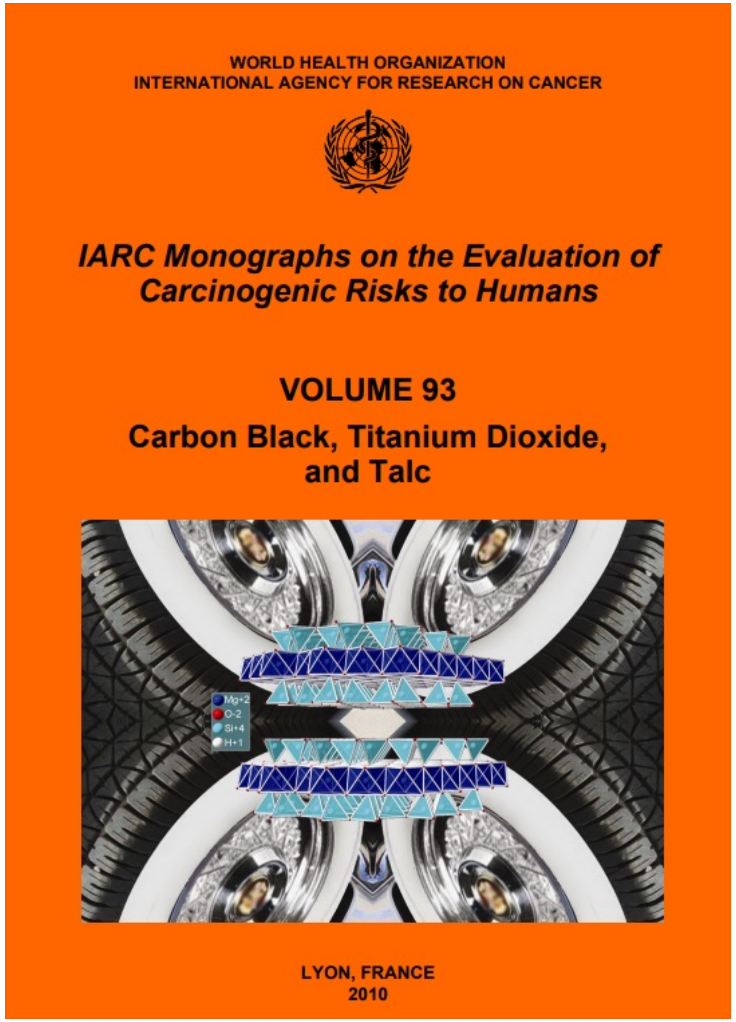
– Inadequate evidence in humans

> **Talc (via inhalation)**

– IARC Classification of Group 3 – “unclassifiable”

– Limited evidence in animals (one positive study)

– Inadequate evidence in humans (limited for perineal)



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Examples II: Evidence of Carcinogenic Potential (Hazard)

> **Taconite (elongate mineral particles – EMPs)**
  - Not classified by IARC
  - "Taconite workers may have an increased risk for certain cancers. Lifestyle and work-related factors may play a role in elevated morbidity." University of Minnesota series of studies *

> **Crystalline Silica Dust (Quartz or Cristobalite)**
  - IARC Classification of Group 1 (carcinogenic to humans)
  - Sufficient evidence in animals
  - Sufficient evidence in humans
  - Technically not a PSLT

*SOURCE: Allen EM, Alexander BH, MacLehose RF, Nelson HH, Ramachandran G, Mandel JH. Cancer incidence among Minnesota taconite mining industry workers. Ann Epidemiol. 2015 Nov;25(11):811-5.

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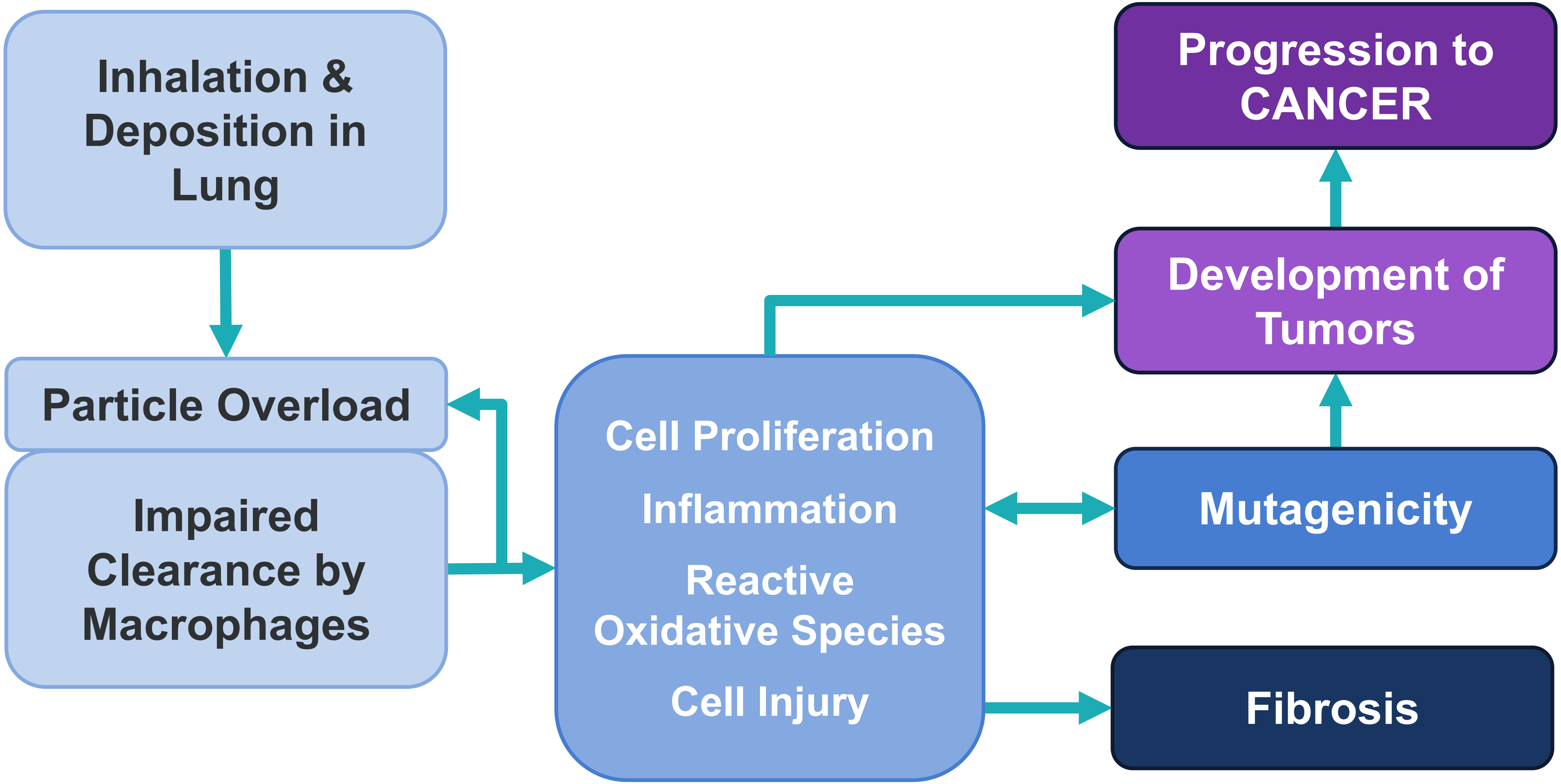
A Proposed Mechanism of Action in Rat Models



Adapted from IARC Vol. 93 (2010), p. 167, Figure 4.2 (Carbon Black)

Animal Evidence of Carcinogenicity of PSLT Particles (Hazard)

- Several chronic inhalation studies of PSLT (e.g. carbon black, TiO_2, and talc) demonstrated lung cancer, but only at "lung particle overload" doses in rats
- Mechanism of Action (MOA): Chronic lung inflammation
  - MOA could to be relevant to humans. . .
  - But same effects not observed in other animal species
- Many epidemiological studies fail to demonstrate associations between PSLT particles and risk of lung cancer

How do we address interspecies (including rat to human) extrapolation?

2 Occupational exposure to PSLTs is common and may be substantial

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PSLT Particle Exposure in the Workplace

- Exposure to ‘dusts’ in the workplace – especially ‘nuisance dusts’ remains common
- Exposure to PSLT particles occurs across many industrial sectors:
  - Mineral mining, milling, preparation
  - Welding, asphalt and other fume/dusts
  - Manufacturing of textiles, glassware, roofing, pulp and paper products, etc.
  - Nanomaterial manufacturing and use (e.g., gold, copper, titanium dioxide)
- PSLT particle exposures may impact millions of workers globally

SOURCE: https://golchaminerals.com/pure-white-talc-at-dagota-ug-face/

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PSLT particle exposure assessment is critical to risk evaluation

> Sampling/monitoring instrumentation for PSLTs has improved – but is not perfect
  - Current debate regarding PSLT mass fraction, surface area and diameter characteristics
  - Lack of standard sampling methods for nanoparticles
  - Direct reading instruments (DRIs) allow for sensitivity, but lack specificity

> Establishing OELs for PSLTs – and especially nanoparticles – must consider feasibility

> Uncertainties in measurement need to be described, reduced

> Valid exposure assessment is the Achilles' Heel of epidemiology!

> **Epidemiological studies can reflect real-world exposures, but poor characterization will affect quantitative risk estimates**

3 Hazard, Exposure, Risk Assessment – and Epidemiology

Human Health Risk Assessment

- **Human Health Risk Assessment** quantifies the effects of a **hazard** by unit of **exposure**
- For some PSLT particles, hazard classification based only on animal evidence
  - Associated with overloading rat lungs
  - Leads to chronic inflammation → cell proliferation → oxidative stress
- Occupational exposures to PSLTs are common and can be measured/estimated
- Risk assessment, therefore, is possible

- Cancer risk assessment, however
  - Classically employs linear no-threshold (LNT) models
  - Unit risk applies to all non-zero exposures
- Risk assessment results sometimes conflict with epidemiological evidence

US CDC: Epidemiology is the Preferred Basis if Risk Evaluation

> "Epidemiology is often described as the basic science of public health, and for good reason:
  - **quantitative discipline** that relies on a working knowledge of probability, statistics, and sound research methods. .
  - a **method of causal reasoning** based on developing and testing hypotheses grounded in such scientific fields as biology, behavioral sciences, physics, and ergonomics to explain health-related behaviors, states, and events. . .
  - an **integral component of public health**, providing the foundation for directing practical and appropriate public health action. . ." (CDC)

Epidemiological evidence demonstrates the human health risks of PSLTs under the "natural" circumstances of use and exposure, i.e., "human-relevant exposure"

SOURCE: US CDC https://www.cdc.gov/csels/dsepd/ss1978/lesson1/section1.html

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Epidemiology and Human Health Risk Assessment for PLSTs

- Quantitative risk assessment ***can*** be based on epidemiological study results, however:
  - Exposure must be quantified
  - Risk quantitatively estimated by exposure level(s)

Key questions:

- What if epidemiological studies are lacking?
- What if epidemiological studies demonstrate no increased risk?
- Many risk assessments are based on animal data only (with interspecies extrapolation)
- Does the risk assessment accurately address risk at human-relevant exposures?

Epidemiology's Weaknesses

- Many occupational cohort studies of PSLTs lack robust exposure assessment
- Workplaces with PSLTs exposures often have other hazardous exposures
- PSLT heavy exposure may produce non-cancer effects including lung epithelial cell injury and fibrosis (with or without lung cancer)
- Systematic reviews and meta-analyses may not consider individual study quality

Nevertheless, there are many good occupational epidemiological studies of workers heavily exposed to PSLT particles. . .

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4 Epidemiological studies of workers highly exposed to PSLTs:

A ‘reality check’?

Epidemiological Study of PSLT Particles: US Carbon Black Workers

- Cohort mortality study of 6,634 US Carbon Black workers from 18 facilities
- Job Exposure Matrix created using over 8,000 time-weighted average measurements
- Vital status traced for 98.5% of the full cohort
- Lung cancer mortality analyzed by various exposure indicators

US Carbon Black Workers Study: SMRs by Exposure Surrogates

Exposure Surrogate	Full Cohort: 6634 Carbon Black Workers		
	Observed	Expected	SMR (95% CI)
Length of employment, yrs			
1–4	63	74.9	0.84 (0.65–1.08)
5–9	28	35.3	0.79 (0.53–1.15)
10–19	32	40.6	0.79 (0.54–1.11)
≥20	61	87.0	0.70 (0.54–0.90)
Time since first exposure, yrs			
<10	4	6.3	0.63 (0.17–1.62)
10–19	6	20.1	0.30 (0.11–0.65)
20–29	34	45.5	0.75 (0.52–1.04)
≥30	140	165.9	0.84 (0.71–1.00)
Time since cessation of exposure, yrs			
0 to <1	10	33.8	0.30 (0.14–0.54)
1–4	21	18.1	1.16 (0.72–1.78)
5–14	37	50.4	0.73 (0.52–1.01)
≥15	116	135.7	0.85 (0.71–1.02)

SOURCE: Dell LD, et al. Cohort Study of Carbon Black Exposure and Risk of Malignant and Nonmalignant Respiratory Disease Mortality in the US Carbon Black Industry. J Occup Environ Med. 2015 Sep; 57(9):984-97.

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Epidemiology Studies of PSLT Particles – Talc Miners and Millers

- 5 cohorts conducted in multiple locations (4,178 workers in 5 countries)
- High historical exposures to talc
  - Large excess of non-malignant respiratory disease (primarily silicosis) mortality
  - No excess of mesothelioma demonstrated (1 mesothelioma death)
  - No excess of lung cancer demonstrated (166 lung cancer deaths)
- Italian cohort study (Ciocan et al. 2021) update just published
  - 1184 miners and 565 millers employed 1946–1995 and followed 1946–2020
  - No asbestos has been detected

Lung cancer results in cosmetic talc miners and millers

Study	Period, Location	Cohort Size	Lung Cancers	Lung Cancer SMR (95% CI)
Fordyce et al. (2019)	1940-2012 (Vermont)	427	32	1.44 (0.98-2.03)
Wild et al. (2002)	1945-1996 (France)	1070	21	1.23 (0.76-1.89)
Wild et al. (2002)	1973-1995 (Austria)	542	7	1.06 (0.43-2.19)
Ciocan et al. (2021)	1946-2020 (Italy)	1749	85	1.02 (0.82-1.27)
Wergeland et al. (2017)	1953-2011 (Norway)	390	21	1.17 (0.73-1.79)
TOTAL	**60+ years**	**4,178**	**166**	**1.13 (0.97-1.31)**

SOURCE: Adapted from Boffetta P, Mundt KA, Thompson WJ. The epidemiologic evidence for elongate mineral particle (EMP)-related human cancer risk. Toxicol Appl Pharmacol. 2018 Dec 15;361:100-106.

Ciocan et al. (2021) – Update of Val Chisone talc miners and millers

Table 3

Standardized mortality ratio for selected causes stratified by duration of employment.

Cause of deaths	Duration of employment					
	<15 years		15–24 years		25+ years	
	Obs	SMR (95 % CI)	Obs	SMR (95 % CI)	Obs	SMR (95 % CI)
All causes	430	1.27 (1.15–1.40)	331	1.21 (1.08–1.35)	413	1.15 (1.05–1.27)
All cancers	116	1.06 (0.88–1.28)	72	0.91 (0.71–1.15)	116	1.01 (0.83–1.21)
Oral & pharyngeal cancer	15	4.44 (2.48–7.32)	6	2.42 (0.89–5.27)	13	3.76 (2.00–6.44)
Esophageal cancer	8	3.14 (1.35–6.18)	4	2.04 (0.55–5.21)	2	0.72 (0.09–2.59)
Lung cancer	31	1.03 (0.70–1.46)	18	0.87 (0.52–1.38)	36	1.12 (0.78–1.55)
Ischemic heart disease	41	0.89 (0.64–1.21)	28	0.69 (0.46–1.00)	36	0.69 (0.48–0.96)
Cerebrovascular disease	25	0.77 (0.50–1.14)	15	0.47 (0.26–0.78)	34	0.84 (0.58–1.17)
Non-neoplastic respiratory diseases	42	1.79 (1.29–2.42)	47	2.19 (1.61–2.91)	63	2.29 (1.76–2.92)
Pneumoconiosis	11	4.19 (2.09–7.50)	16	8.78 (5.02–14.3)	42	15.1 (10.9–20.4)
Liver cirrhosis	22	1.75 (1.10–2.65)	28	2.70 (1.79–3.90)	18	1.37 (0.81–2.17)

SOURCE: Ciocan C, et al. Mortality in the cohort of talc miners and millers from Val Chisone, Northern Italy: 74 years of follow-up. Environ Res 2021; 203:111865.

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Epidemiology Studies of PSLT Particles – Taconite

- Iron ore - hematite and taconite - mined in Minnesota (US) since the 1890s
- Taconite elongate mineral particles (EMPs) of concern for carcinogenicity
- Cancer surveillance indicated increased lung cancer and mesothelioma in taconite workers

- Six publications on taconite miners identified (including cohort expansion and updates)
- Statistically significantly increased SMR for lung cancer among taconite miners reported in one study (Allen et al. 2014)
- Case-control evaluation identified no association with Taconite EMP exposure indicators (Allen et al. 2015b)

Source: Dell LD et al. Integration of Evidence on Community Cancer Risks from Elongate Mineral Particles in Silver Bay, Minnesota. Risk Anal. 2021 Sep;41(9):1674-1692.

Lung cancer results for taconite workers

Study	Period	Cohort Size	Lung Cancers	Lung Cancer SMR or OR (95% CI)
Higgins et al. (1983)	1952-1976	5,751	15	0.84 (0.47-1.38)
Cooper et al. (1988, 1992)	1959-1988	3,444	62	0.87 (0.52-0.86)
Allen et al. (2014)	1960-2010	31,067	949	1.16 (1.09-1.24)
Allen et al. (2015a)	1988-2010	40,720	973	1.1 (1.0-1.3)
Allen et al. (2015b)	1960-2010	N/A	1,706	Hematite only 0.81 (0.67-0.98) 0.13 to <0.45 EMP/cm^3-yrs 1.0 (0.79-1.25) 0.45 to <2.35 EMP/cm^3-yrs 0.98 (0.77-1.24) $\geq$2.35 EMP/cm^3-yrs 0.82 (0.57-1.19)

SOURCE: Dell LD, Gallagher AE, Yost LJ, Mundt KA. Integration of Evidence on Community Cancer Risks from Elongate Mineral Particles in Silver Bay, Minnesota. Risk Anal. 2021 Sep;41(9):1674-1692.

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Epidemiology Studies of PSLT Particles – Silica and Lung Cancer

- Shahbazi et al. (2021) meta-analysis of 19 studies
- Reported “a **positive and significant increasing dose-response trend** between silica exposure and the risk of developing lung cancer”

Silica Exposure	Lung Cancer Meta-RR
< 0.50 mg/m^3	1.14 (95% CI: 1.05-1.23; I^2 = 79%
0.50-0.99 mg/m^3	1.34 (95% CI: 1.05-1.71; I^2 = 45%)
1.00-1.99 mg/m^3	1.14 (95% CI: 1.00-1.30; I^2 = 70%)
2.00-2.99 mg/m^3	1.47 (95% CI: 1.05-2.06; I^2 = 57%)
3.00-3.99 mg/m^3	1.44 (95% CI: 0.99-2.11; I^2 = 58%)
≥ 4.00 mg/m^3	1.64 (95% CI: 1.20-2.24; I^2 = 88%)

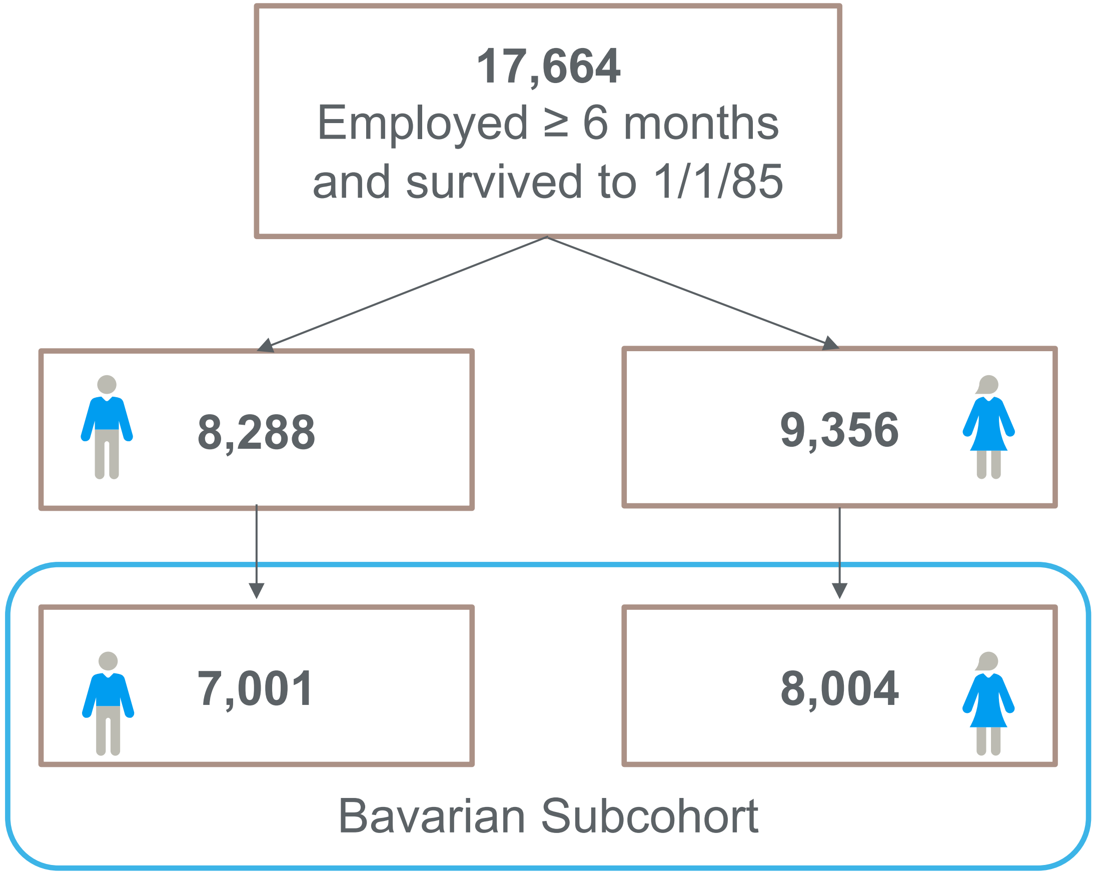
- Only 6 studies had a high NOS score, but all 19 were included in the meta-analysis

SOURCE: Shahbazi F, Morsali M, Poorolajal J. The effect of silica exposure on the risk of lung cancer: A dose-response meta-analysis. Cancer Epidemiol. 2021 Sep 22;75:1020-24

Shahbazi et al. (2021) meta-analysis excluded one large study!

Mundt KA et al. Respirable Crystalline Silica Exposure–Response Evaluation of Silicosis Morbidity and Lung Cancer Mortality in the German Porcelain Industry Cohort. JOEM 2011;53(3):282-9.

German Porcelain Workers Cohort



- About 100 plants (Western Germany)
- Participated in a medical surveillance and x-ray program for silicosis started in the early 1980’s
- Followed through 2005
- Bavarian Subcohort as focus group
- Identified 74 lung cancer deaths among men and 20 among women
- Update thorough 2020 underway!

Crystalline Silica and Lung Cancer: Exposure-Response

TABLE 2. Lung Cancer Hazards Ratios (HRs) and 95% Confidence Intervals (95% CI) by Categories of Cumulative Exposure (mg/m^3-years), Average Exposure (mg/m^3), Duration of Employment (years), and Smoking, Stratified by Sex and Controlling for Age and Smoking

	HR (95% CI)			
	n†	Male	*n*†	Female
Cumulative exposure				
≤0.5	19	Reference	1	Reference
>0.5–1.0	5	0.3 (0.1–0.9)	7	7.8 (1.0–63.2)
>1.0–1.5	5	0.4 (0.1–1.1)	3	4.2 (0.4–40.4)
>1.5–3.0	16	0.6 (0.3–1.2)	3	2.2 (0.2–21.8)
>3.0	29	0.5 (0.3–1.0)	6	3.2 (0.4–27.6)
≤3	45	Reference	14	Reference
>3–4	5	1.0 (0.4–2.4)	3	1.9 (0.5–6.6)
>4–5	3	0.7 (0.2–2.3)	1	0.7 (0.1–5.4)
>5–6	5	1.1 (0.5–2.9)	1	0.8 (0.1–6.1)
>6	16	0.8 (0.5–1.5)	1	0.4 (0.1–3.4)

SOURCE: Mundt KA et al. Respirable Crystalline Silica Exposure–Response Evaluation of Silicosis Morbidity and Lung Cancer Mortality in the German Porcelain Industry Cohort. JOEM 2011;53(3):282-9.

5 The Balancing Act:

Biological plausibility

Quality based study evaluation

Human relevant exposures

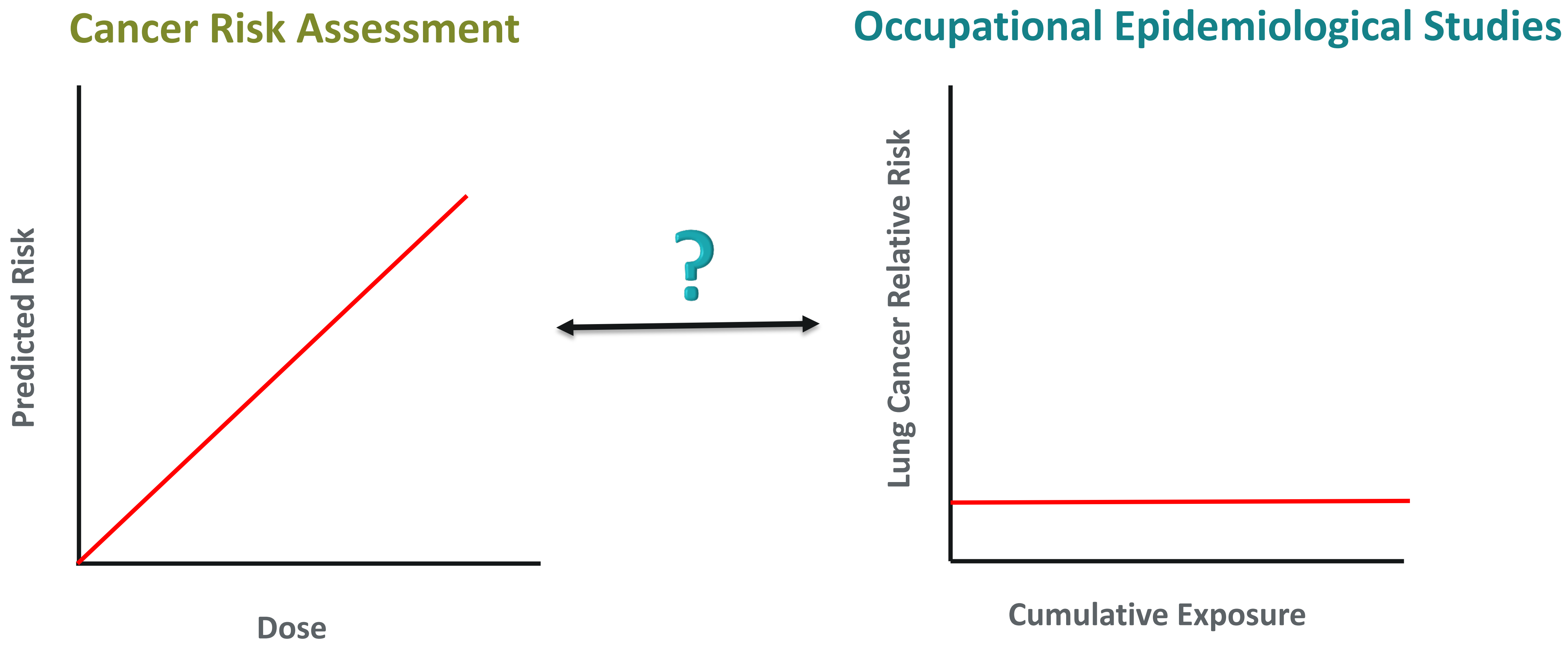
Evidence Integration

Epidemiology Studies – Risk Evaluation

- A causal relationship between PSLTs and lung cancer in humans must consider
  - Biological plausibility
  - Quality of exposure measurement / estimation in epidemiological studies
  - Risk estimates by specific level of exposure (exposure-response analyses)
  - Potential role of confounding causes (especially tobacco smoking and radon)

- The epidemiological evidence for PSLTs (e.g., carbon black, talc, taconite) and lung cancer:
  - Consistently does **not** demonstrate elevated risks related to exposure
  - Suggests no compelling exposure–response relationships
  - Though biologically plausible, does not support PSLTs as causing lung cancer at human-relevant exposures
  - Raises questions about relevance of rat studies with particle-overload exposure conditions

PSLTs and Disease Risk: Harmonizing the Evidence



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Where Evidence Conflicts, the Gap may be Larger

Risk Assessment

- Possibly based on very high doses
- Generally predicted risk
- Based on unit risk (UR, IUR), i.e., increased rate per unit of exposure
- Linear, no threshold (LNT) default assumption

Other limitations

- Species selection, incomplete MOA, etc.

Epidemiological Studies

- Possibly based on 'low' exposure
- Generally observed risk
- Based on observed risk compared with referent (assumed background) risk
- Exposure-response function not necessarily 'forced' into LNT

Other limitations

- Statistical power, study bias, confounding, etc.

Closing Comments

1. **Some** PSLTs **probably do** cause lung cancer (at least in rats)
2. PSLT exposure may be **poorly characterized** (e.g., nano); however, **epidemiological studies address real-world exposures**
3. Human Health Risk Evaluation is improved when evidence from toxicology, mechanistic studies and epidemiological studies is **integrated**
4. Epidemiological studies of workers highly exposed to PSLTs may provide **the 'reality check'** needed for science-based decision-making in regulatory, policy and litigation arenas.

Thank you