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Pancreatic Cancer and Exposures in Ontario Mines

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Executive Summary

The information gathered in this literature search on pancreatic cancer (PC) and exposures in Ontario mines was used to complement and update work previously performed in 2017 [1]. A literature search was completed on National Center for Biotechnology Information (NCBI), Google Scholar and EBSCO host up to August 2018 using Boolean search techniques "pancreatic" AND "cancer" AND "mining" / "miner" / "mine" / "asbestos" / "solvents"/ "arsenic" / "ionizing radiation" / "radon" / "dust" / "diesel" / "diesel exhaust" / "aluminum" / "silica" as well as "pancreatic cancer" AND "occupational exposure" AND "meta-analysis" / "review".

A 2017 Canadian Cancer Society (CCS) report [1] identified the following non-occupational lifestyle risk factors for PC:

- smoking
- excess body weight
- dietary factors
- alcohol consumption

In this review a statistically significant association is defined as:

- a relative risk (RR) or equivalent with the lower limit of the 95% confidence interval being greater than (>) 1
- meta-relative risk (MRR) or equivalent with the lower limit of the 95% confidence interval being greater than 1; shortened as: MRR + C.I.>1)

A non-statistically significant excess risk is defined as:

- RR, MRR or equivalent > 1 but the lower limit of the 95% C.I. <1)

Compounds of interest with a possible association between occupational exposure and increased risk of PC include:

- nickel and nickel compounds*
- cadmium*
- thorium*
- aliphatic and alicyclic hydrocarbons
- chromium and its compounds
- polycyclic aromatic hydrocarbons (PAHs)

- silica
- asbestos
- iron and iron compounds
- metalworking fluids

(* indicates a statistically significant association in previous studies)

Occupations identified as having non-statistically significant excess risk include:

- metal working/plating/degreasing
- chemical workers/chemists
- machine and engine mechanics
- thorium processing
- auto mechanics
- rubber workers
- wood workers
- electrical workers.

The International Agency for Research on Cancer (IARC) [2] lists only three non-lifestyle factors with limited evidence for PC in humans: thorium 232 and its decay products, X-radiation and gamma radiation.

Based on work by Boffeta [26] and the IARC 105 review [27], diesel exhaust emissions are not a causal factor.

Carta et al. [28], in a study of aluminum smelter workers, found increased SMRs of 2.4 (95% CI: 1.1-5.2) and 5.0 (95% CI 2.1-12.1) for all workers and anode workers respectively and suggested PAHs rather than aluminum as the agent of concern [28]. Additional data for PAHs are presented by Ojajärvi (2000) [9], while Kaupiinen et al. (2003) [29] found increased SMRs in bitumen workers and construction workers.

A paper by Ojajärvi et al. [9] linked occupational exposure to silica and an increased risk of PC. Carver and Gallichio (2018) in a review of heavy metals suggested a link between PC and low-level arsenic exposure [31].

A recent review by Park (2018) [33] of metal working fluid exposures concluded that, even at low exposures (0.1 mg/m^3), there was an increased risk of PC and other cancers.

There is no evidence of thorium exposure in mining and association with pancreatic cancer. A significant association was found for lung cancer by Chen et al. who reported a lung cancer

SMR of 6.13 (95% CI: 4.41 – 8.52) for dust-exposed miners; the dust also had a 10% silica content [40].

A clinic-based self-report study by Antwi (2015) [41] found an OR > 1.2 for regular exposure to asbestos, benzene or chlorinated hydrocarbons while Manthrop (2017) [42] found a suggestive positive association with soot (odds ratio (OR): 3.4; 95% CI: 1.3-8.6).

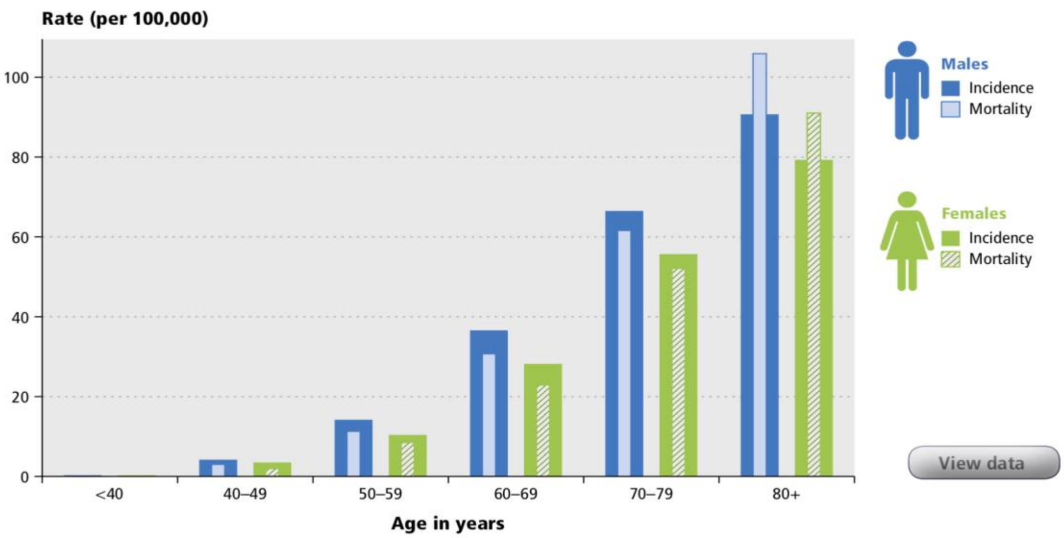
Data related to mining or miners and pancreatic cancer are sparse. Studies with more detailed exposure data are needed in order to make comparison to the compounds or occupations listed above.

Introduction

Pancreatic cancer (PC) is a disease that for the most part progresses rapidly with a poor prognosis. According to a 2017 Canadian Cancer Society (CCS) report, PC is the 12th most common cancer diagnosed in Canada but is the 4th-ranked leading cause of cancer death [1].

Figure 1 illustrates the incidence rates (2011-2013) and mortality rates (2010-2012) for PC by age among Canadian men and women. Men have consistently higher incidence and mortality rates than women.

Figure 1 Age-standardized pancreatic cancer incidence (2011–2013) and mortality (2010–2012) rates, by age group, Canada (source: Canadian Cancer Society 2017 report [1])



Note: Rates are based on three years of pooled data from 2011–2013 for incidence and 2010–2012 for mortality. Rates are age-standardized to the 2011 Canadian population. Actual incidence data were available to 2013 for all provinces and territories except Quebec, for which data were available to 2010 and projected thereafter. Actual mortality data were available to 2012. For further details, see *Appendix II: Data sources and methods*.

Analysis by: Surveillance and Epidemiology Division, CCDP, Public Health Agency of Canada
Data sources: Canadian Cancer Registry, National Cancer Incidence Reporting System and Canadian Vital Statistics Death databases at Statistics Canada

Figure 2 summarises the population attributable risk of modifiable lifestyle factors that account for just less than 40 % of all PCs. Occupation and/or exposure to chemicals are not addressed in the CCS publication.

Figure 2 Population-attributable risk of modifiable risk factors for pancreatic cancer (source: Canadian Cancer Society 2017 report [1])

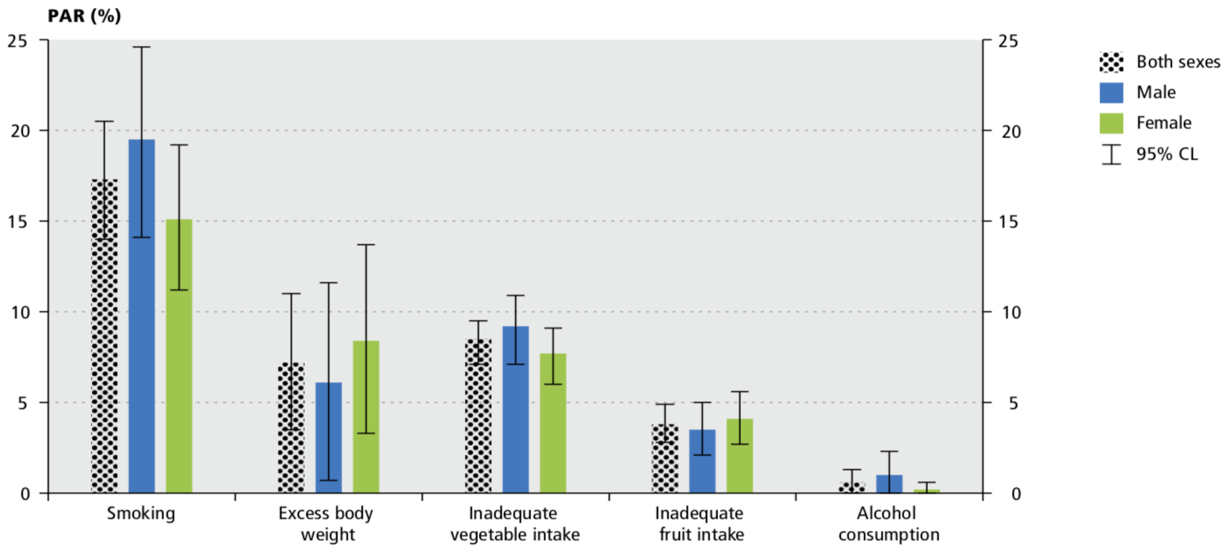
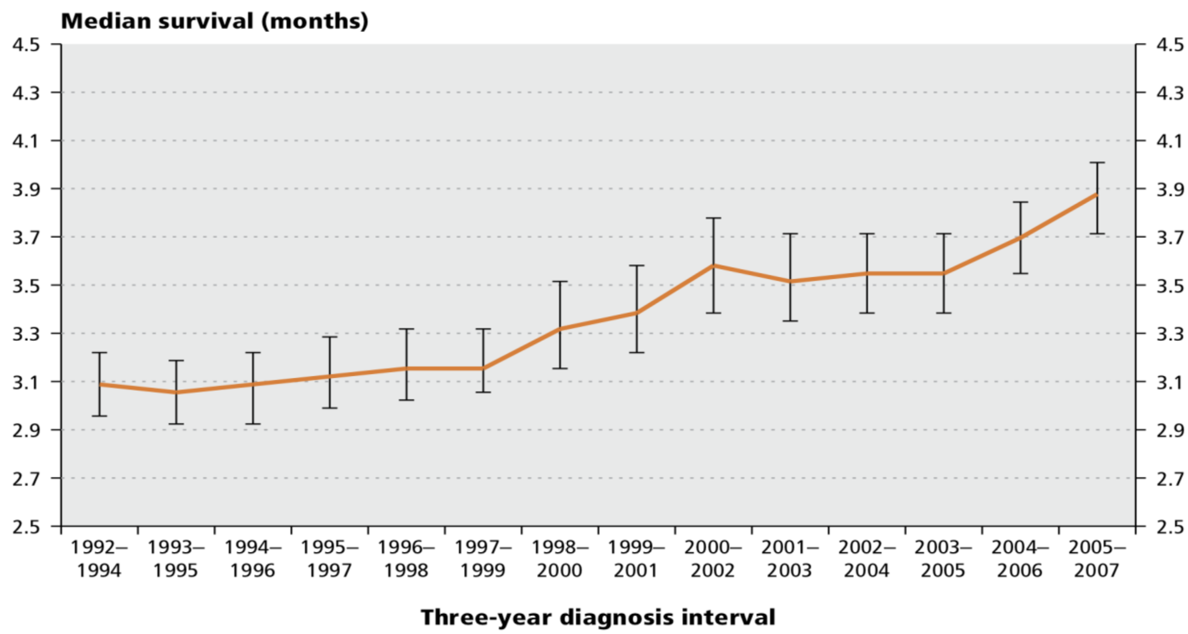


Figure 3 Pancreatic cancer median survival times*, ages 15–99, Canada (excluding Quebec†), 1992–1994 to 2005–2007 [1]



Analysis by: Health Statistics Division, Statistics Canada
Data source: Canadian Cancer Registry database at Statistics Canada

* Survival times were measured from the date of diagnosis to the date of death from any cause. Survival times were sorted by duration; the midpoint of these times is referred to as the median survival time. As such, median survival is viewed as the length of time after diagnosis at which approximately half of individuals diagnosed with pancreatic cancer have died and half continue to survive. Rolling three-year periods were used to reduce variability in individual estimates. Error bars refer to 95% confidence intervals.

† Data from Quebec were excluded, in part, because the method for ascertaining the date of cancer diagnosis differs from the method used by other provinces and territories, and because of issues in correctly ascertaining the vital status of cases.

Figure 3 shows the median PC survival times for ages 15 to 99 in the period 1992 to 2007. Cases of PC are almost always diagnosed at an advanced stage, and with few treatment options available, the resulting 5-year survival rates are among the lowest of any cancer. The 2017 CCS [1] report states "*… the median all-cause survival for pancreatic cancer cases diagnosed from 2005 to 2007 was 3.9 months, or just under 17 weeks …*"

Occupational Risk Factors

Occupation and/or exposure to chemicals are not addressed in the 2017 CCS report. Table 1 from IARC [2] summarises agents with sufficient or limited evidence for PC in humans. Only thorium, x-radiation and gamma radiation are agents that could be considered as occurring in an occupational environment.

Table 1 List of IARC classifications for agents with sufficient or limited evidence for PC in humans (Volumes 1 to 125[a])

Cancer site	Carcinogenic agents with ***sufficient*** evidence in humans (IARC Class 1)	Agents with ***limited*** evidence in humans (IARC Class 2(A))
Digestive organs		
Pancreas	Tobacco, smokeless Tobacco smoking	Alcoholic beverages Red meat (consumption of) Thorium-232 and its decay products X-radiation, gamma-radiation

[a] This table does not include factors not covered in the *IARC Monographs*, notably genetic traits, reproductive status, and some nutritional factors.

Excerpt of pancreatic cancer only
Last update: 29 November 2019
https://monographs.iarc.fr/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf

The National Occupational Mortality Surveillance (NOMS) system maintained by the National Institute of Occupational Safety and Health NIOSH [3] list the following industries with statistically significant (i.e. the 95% CI does not include 100) proportional mortality ratios (PMRs) for PC:

- Chemical Mfg. (PMR:112; $p<0.01$)
- Machinery Mfg. (109; $p<0.01$)
- Food Mfg. (105; $p < 0.05$)
- Lumber and Wood Products Mfg. (88; $p < 0.05$)
- Stone, Clay, Glass Concrete Mfg. (91; $p < 0.05$)

- Computer & Electronic Product Mfg. (130; $p < 0.05$).

Mining as an occupation or industry was not identified by NIOSH.

Exposure and Occupation

The following table summarizes data from a review previously performed in 2017 and that may be applicable to some processes, occupations or tasks in the mining industry [4]. Exposures are divided into specific compounds or categories and grouped by studies with a statistically significant risk, non-statistically significant excess risk or with limited statistical analysis (suggestive association). (Table 3 presents selected MRRs and C.I. from Ojajärvi [9] as reference).

Table 2: Summary of Meta-Analyses; Critical or Systematic Reviews; Literature Reviews

Exposure (Compound, Group or Occupation)	Risk Estimates	Reference(s)
Studies showing significant association (RR or MRR or equivalent with the lower limit of the 95% C.I.>1)		
Cadmium	SMR	Schwartz [5]; Andreotti [6]
Chlorinated hydrocarbon compounds (CHC) or CHC solvents & related compounds (includes Trichlorethylene, & tetrachloroethylene)	MRR	Andreotti [6]; Ojajärvi [7-9]; Wartenberg [10]; Ward [11]; Lin [12]
Metal plating workers; metal degreasing; metal working	RR ; MRR	Ojajärvi [7 -8]; Dell [13]; Andreotti [6]; Gold [14]; Pietri [15]; Lin[12]; Berg [16]; Fraumeni [17]
Nickel and nickel compounds	MRR	Ojajärvi [7]
Thorium-232 and its decay products	IARC review	IARC [18]
X-radiation, gamma-radiation	IARC review	IARC [18]
Studies Reporting a Non-statistically Significant Excess Risk (RR/MRR >1) with the lower limit of the 95% CI <1; or SMR/SIR >100 with the lower limit of the 95% CI < 100)		
Aliphatic & alicyclic hydrocarbon compounds	MRR	Ojajärvi [7, 9]
Asbestos	SMR/SIR	Ojajärvi [9]; Pietri [15]
Chromium and chromium compounds	MRR	Ojajärvi [9]
Iron and iron compounds	MRR	Ojajärvi [9]
Machine and engine mechanics	MRR	Ojajärvi [7]
Metal working fluids/machining fluids/cutting oils	RR	Calvert [19]; Ward [11]; Pietri [15]
Polycyclic aromatic hydrocarbons (PAHs)	MRR, SMR, SIR	Ojajärvi [7, 9]; Andreotti [6]; Mastrangelo [20]; Pietri [15]; Kauppinen [27]
Silica dust	MRR	Ojajärvi [9]
Thorium processing plants	SMR	Conrath [21]

Studies with limited statistical analysis (weaker association)	
Exposure (Compound, Group or Occupation)	**Reference(s)**
Chemical workers/chemists	Weiderpass [22]; Gold [14]; Pietri [15]; Lin [12]; Berg [16]; Fraumeni [17]
Diesel engine exhaust	Ojajärvi [9]; Pietri [15]
Electrical and electronics technicians/workers	Minder [23]; Conrath [21]
Halogenated hydrocarbons	Gold [14];
Ionizing radiation	Andreotti [6]
Methylene chloride	Ojajärvi [8]; Dell [13]; Andreotti [6];
Nitrosamines	Andreotti [6]
Organic Solvents/solvents	Lynge [24]; Pietri [15]
Perchloroethylene (PCE)	Mundt [25]; Wartenberg [10]; Ward [11];
Petroleum (incomplete combustion)	Mundt [25]
Pulp and paper workers/timber workers	Weiderpass [22]; Conrath [21]
Rubber workers	Weiderpass [22];
Trichloroethylene	Ojajärvi [8];
Woodworkers	Weiderpass [22]

Table 3 takes the data from Ojajärvi (2000) [9] and provides the MRR and 95% C.I. for some of the various agents and occupations listed in Table 2 for reference.

Table 3: MRR values for selected compounds

Significant association (MRR > 1 and 95% C.I. entirely >1		
Compound	**MRR**	**95% C.I.**
CHC solvents and related compounds	1.4	1.0 – 1.8
Nickel and nickel compounds	1.9	1.2 – 3.2
Non-Significant (MRR > 1 and 95% C.I. < 1		
aliphatic and alicyclic hydrocarbon solvents	1.3	0.8 – 2.8
chromium and chromium compounds	1.4	0.9 – 2.3
polycyclic aromatic hydrocarbons (PAHs)	1.5	0.9 – 2.5
silica dust	1.4	0.9 – 2.0
Excess risk (MRR ~ 1 and 95% C.I. < 1		
Compound	**MRR**	**95% C.I.**
arsenic	1.0	0.6 – 1.5
asbestos	1.1	0.9 – 1.5
cadmium and cadmium compounds	0.7	0.4 – 1.4
diesel engine exhaust	1.0	0.9 – 1.3
gasoline	1.0	0.8 – 1.2
iron and iron compounds	1.3	0.7 – 2.5
lead and lead compounds	1.1	0.8 – 1.5
oil mist	0.9	0.8 – 1.0
wood dust	1.1	0.9 – 2.5

Table 3: MRR values for selected compounds
Source: Ojajärvi, I. A.; et al. (2000) [9] MRR - meta-relative risk C.I. - confidence interval 95%

Recent Studies Relevant to Mining Exposures

The following is a summary of key studies or studies published in 2014 or later that are relevant to the Ontario mining industry.

Diesel Exhaust Emissions

Diesel exhaust emissions represent a significant exposure for miners ; however, Boffetta (2014) [26] concluded from his meta-analysis of data abstracted from 26 studies (2 prospective studies, 3 occupation/disease studies using a case-control methodology, 11 case-control studies, and 10 cohort studies) "… *The overall evidence from studies on occupational exposure to diesel exhaust and risk of pancreatic cancer leads to the conclusion of the absence of such association* …". IARC in Monograph 105 (2014) [27] also came to similar conclusions " *…(t)he meta-analyses found consistent elevated risk estimates for occupations associated with exposure to diesel exhaust and lung cancer and urinary bladder cancer, but not for pancreatic cancer, although fewer data were available for the latter…*".

PAHs

Carta et al. (2004) in a study of aluminum smelter workers found an overall SMR of 2.4; (95% CI 1.1-5.2) and for anode workers a SMR 5.0 (95% CI; 2.1-12.1) for pancreatic cancer [28]. Andreotti et al. (2012) [6] in a review of studies done over the period 1998 – 2010 that assessed the occupational risks factors for pancreatic cancer presents the data from Ojajärvi (2000) [9] and also references a study by Kaupiinen et al. (2003) [29]. Kaupiinen et al.in a cohort of 9,643 Finnish road paving workers found a SMR 2.39 (CI; 0.88 – 5.21) for bitumen workers and a SMR of 2.35 (CI; 1.08 - 4.47) for construction workers.

Silica

Kauppinen et al. (1995) lists an odds ratio OR = 2.0 (95% CI = 1.2-3.5) for inorganic dusts containing silica [30]. No additional insight into the silica risk is provided by studies conducted subsequent to Ojajärvi et al. (2000) [9]; Ojajärvi et al. state the MRR as 1.4 (95% CI; 0.9 – 2.0).

Ore Dust

Carver and Gallichio (2017) in *Cancer Causing Substances, Heavy Metals and Cancer* provide summary information for aluminum (Al), arsenic (As), beryllium (Be), cadmium (Cd), lead (Pb), mercury (Hg), nickel (Ni) and radium (Ra) [31]. A link to chronic low-level exposure to arsenic and pancreatic cancer is suggested while exposure to cadmium is thought to exert some influence on the inhibition of DNA repair and genomic instability. Lead (Pb) was elevated in individuals with PC [32].

Metal working fluids (MWF)/mineral/lubricating oil

Park (2018) in a risk assessment of cancer outcomes related to MWF concluded that even at exposures of 0.1 mg/m^3 the potential for increased cancer risks including PC remained [33].

The Swedish Criteria Group for Occupational Standards (2017) [34] presented a review of studies related to MWF exposure in which they reported an elevated SMR for PC of 1.7 (95% CI 1.05-2.61) based on work by Eisen et al. [35] and Tolbert et al. (1992) [36]. Their conclusion recommends an exposure standard of 0.2 mg/m^3 as the cutting fluid inhalable fraction.

Thorium

Thorium is a naturally occurring, radioactive metal. Rocks in some underground mines may contain thorium in a more concentrated form than is found in soil samples, the latter being 6 parts per million [37].

Most epidemiological data for thorium deal with health effects following intravenous or intravascular injection of Thorotrast, a thorium-containing radiographic colloidal contrast medium suspension. Numerous studies confirm significant associations between Thorotrast treatment and risk of developing cancer, particularly liver cancer, leukemia, and cancers of the gall bladder. These studies have limited relevance to potential health effects from environmental and occupational exposures to thorium [39].

Health effects from inhalation of thorium have been assessed in a few occupational studies. Occupations with potentially high exposures to thorium include welders using thoriated tungsten welding electrodes during tungsten inert gas (TIG) welding. Firefighters may be exposed to elevated levels of thorium when inhaling smoke from forest fires [38,39]. Earlier studies of workers in a thorium processing facility suggested a possible increase in pancreatic cancers; however co-exposure to other toxic substances and lack of control for smoking limit interpretation. ATDSR noted in their summary that a follow-up study by Lui et al (1992) had found no increase in pancreatic cancer (SMR 1.47, 95% CI 0.70–2.71). [39]

Epidemiological studies of the association between thorium exposure and cancer in mining occupations have included workers at a thorium processing and gas mantle production plant and rare-earth iron mine in China [40] where workers had long-term exposure to thorium and silica dusts from the ore. Chen et al reported a lung cancer SMR of 6.13 (95% CI: 4.41 – 8.52) for dust-exposed miners; the dust also had a 10% silica content [40]. The study lacked control for silica and smoking as confounding factors.

Multiple causal factors
Antwi et al. (2015) in a clinic-based case-control study looked at self-reported exposure to several compounds and found statistically significant elevated odds ratios for pancreatic cancer for the following exposures: regular exposure to asbestos (OR 1.54, 95 % CI 1.23–1.92), benzene (OR 1.70, 95 % CI 1.23–2.35), and chlorinated hydrocarbons (OR 1.63, 95 % CI 1.32– 2.02) [41].

A 2017 thesis report by Manthrop (2017) on PC risks using data from the Montreal multisite cancer study concluded *"… suggestive positive associations were found for several agents including coal combustion products (OR 2.6, 95% CI [1.3-5.3]), soot (OR 3.4, 95% CI [1.3-8.6])* …" and commented on the paucity of more recent studies investigating pancreatic cancer [42].

Conclusions
This review presents recent study data and lists compounds with statistically significant risks or non-statistically significant excess risks associated with pancreatic cancer and can be seen to have applicability to the mining industry. Such exposures include nickel and nickel compounds, cadmium, thorium, aliphatic and alicyclic hydrocarbons, chromium and chromium compounds, PAHs, silica, asbestos, iron and iron compounds, and metalworking fluids. The use of chlorinated solvents presents a weaker association.

The occupation or industry of 'miner or mining' was not specifically mentioned in any of the studies reviewed or highlighted in this document. Some 'occupations' could possibly be transferred into a mine setting including metal working (welding, plate shop etc.), chemical workers/chemists (e.g. assay labs, production sampling and control), machine and engine mechanics (surface and underground), thorium processing (possible exposure based on mine type), auto mechanics (diesel engine mechanics) , rubber workers (e.g. rubberman), wood workers (e.g. tracks & shoring, treated timber), and electrical workers.

Studies of aluminum production workers do not appear to be relevant to the risk associated with prophylactic McIntyre aluminum powder exposure. The data suggest that compounds other than aluminum (e.g. PAHs) were the putative causal agent in aluminum production workers. In contrast to aluminum production workers with relatively low aluminum exposure, the aluminum exposures from the use of McIntyre powder were very high (35 mg/m^3) and occurred over a short duration (10 minutes).

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