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Lung Cancer and Exposures in Ontario Hard Rock Mines

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Executive Summary

Ontario hard rock miners have been exposed to four major carcinogens: respirable crystalline silica (RCS), diesel exhaust (DE), radon or radon decay products (RDP)[a] and arsenic for many decades. The following is a summary of the findings from published scientific literature on the association between exposure to these carcinogens and the risk of lung cancer among miners and in particular among Ontario uranium or gold miners. A number of relevant studies have been published in the last 10-15 years.

RCS

- There is compelling evidence that Ontario hard rock miners exposed to RCS are at much greater risk of lung cancer than many other occupations also exposed to RCS.
- Several studies have found statistically significant increased risk of lung cancer at concentrations of RCS substantially below the current Ontario Ministry of Labour, Immigration, Training & Skills Development (MLITSD) occupational exposure limit (OEL) of 0.1 mg/m^3.
- There is consistent evidence for an increasing risk of lung cancer with increasing cumulative exposure to RCS. Recent studies (Liu et al 2017, Lai et al 2018, Ge et al 2020a) have observed statistically increased risk at much lower cumulative exposures to RCS (i.e., ≤ 0.4 mg/m^3 – years) than in earlier studies (Steenland et al 2001, Sogl et al 2012, Liu et al 2013, Kachuri et al 2014).
- A large 2020 pooled analysis of European and Canadian case-control studies with detailed RCS exposure and smoking histories observed a statistically significant increased risk of lung cancer for those who ever had exposure to RCS, those with the lowest exposure duration (1-9 years) and those in the lowest cumulative exposure category (<0.4 mg/m^3-years) (Ge et al 2020a). The median of the lowest cumulative exposure category; 0.22 mg/m^3-years, would be equivalent to just over 2 years of exposure to the current Ontario Ministry of Labour, Training and Skills Development (MLITSD) Occupational Exposure Limit (OEL) for RCS of 0.1 mg/m^3 (0.22 mg/m^3-years ÷ 0.1 mg/m^3 = 2.2 years) or about 9 years of exposure to the proposed lower OEL of 0.025 mg/m^3 (0.22 mg/m^3-years ÷ 0.025 mg/m^3 = 8.8 years). There was no evidence of a threshold and there was a statistically significant ($p<0.1$ for trend) increased risk of lung cancer with increasing cumulative exposure to RCS.
- An important finding from this study was the statistically significant increased risk of lung cancer among non-smokers exposed to RCS and the statistically significant exposure-response trend for lung cancer risk with increasing cumulative RCS exposure. Non-smokers with a cumulative RCS exposure of ≥ 2.4 mg/m^3-years had a 40% statistically significant increased risk of lung cancer; OR=1.4; 95% CI 1.03-1.86).

[a] *The term "radon" as used in this document is meant to include radon decay products (RDP)*

- A supermultiplicative[b] effect between smoking and occupational RCS exposure for overall lung cancer risk was found in the 2020 pooled case-control study that was similar to the finding in a 2013 study that observed a greater than additive and closer to multiplicative interaction between cumulative RCS exposure and smoking.
- Many studies have shown that the increased risk of lung cancer from exposure to RCS remains statistically significant after adjusting for smoking and that smoking alone does not explain the increased lung cancer mortality.
- Recent studies with good quality exposure information have shown that exposure to RCS causes lung cancer among RCS-exposed workers who do not have silicosis, and that this risk increases with increasing cumulative exposure to RCS (Liu et al 2013, Ge et al 2020a). RCS is a direct-acting lung carcinogen and silicosis is not a necessary intermediate step between RCS exposure and lung cancer.

DE

- Underground production and maintenance miners are among the occupations with the highest exposure to DE [mean DE concentrations measured as respirable elemental carbon (REC) of 135 ug/m^3 and 141 ug/m^3 respectively (range 53 ug/m^3 to 637 ug/m^3)] (Pronk et al 2009, IARC 2013).
- Analysis of the exposure-response relationship in recent studies found that statistically significant increased risk of lung cancer was associated with DE exposures well below the current MLITSD OEL for DE of 310 ug/m^3 measured as REC (Vermeulen et al 2014).
- A large 2020 pooled analysis of European and Canadian case-control studies with detailed DE exposure and smoking histories observed an elevated lung cancer risk for those who ever had occupational exposure to DE (Ge et al 2020b). Increasing trends in lung cancer risk were associated with increases in both exposure duration and cumulative exposure (p for trend <0.01). Statistically significant increased risk was also observed in all ranges of duration and cumulative exposure to DE. Notably, this included the lowest categories of exposure duration (1-9 years) and cumulative exposure (>0 to 22 µg/m^3-years) with a median exposure of 11 µg/m^3-years. An exposure threshold for DE related lung cancer was not observed within the cumulative exposure ranges that were investigated.
- An important finding from the 2020 pooled case-control study was the positive exposure-response trend that was observed among never smokers who were exposed to DE (test for trend p value =0.03) and the statistically significant increased risk of lung cancer for those never smokers in the highest cumulative DE exposure category of > 178 µg/m^3-years
- This study also observed a superadditive[c] effect between smoking and occupational exposure to DE for increased risk of lung cancer

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[b] Supermultipicative interaction represents a scenario in which the risk ratios of lung cancer for those exposed to RCS and smoking were higher than the product of the cancer risk ratios from RCS exposure and smoking alone.

[c] Superadditive interaction represents a scenario in which the risk ratios of lung cancer for those exposed to DE (REC) and smoking were higher than the sum and less than the product of the cancer risk ratios from DE (REC) exposure and smoking alone.

- Using the data from a 2014 published study on the exposure-response relationship between DE exposure and lung cancer mortality, OHCOW has developed a DE Lung Cancer Relative Risk Calculator which estimates that a miner with 20 years of exposure to 50 ug/m^3 of REC, which is the low end of the reported exposures for underground miners, would have a greater than 2-fold increased risk of lung cancer. Conversely, only 7.5 years of exposure to the current Ontario MLITSD occupational exposure limit (OEL) of 310 ug/m^3 for underground mines would result in a similar increased risk of lung cancer.
- A 2018 study, the first to quantify the burden of lung cancer attributable to occupational DE exposure in Canada estimated that based on 2011 lung cancer statistics, 2.4%; 95% CI 1.6%-6.6% of lung cancers in Canada were attributable to occupational exposure to DE (Kim et al 2018). This study also observed that half the of estimated burden was among those exposed at low levels of DE (range of >0 to <10 ug/m^3 with a mean exposure of 5 ug/m^3). Underground mining was an occupation with the highest burden of lung cancer attributable to DE exposure.

Radon

- Ontario uranium miners and to a lesser extent, gold miners have been exposed to radon from the mid-1950s until the last Ontario uranium mine closed in 1996.
- All Ontario Uranium Mining Cohort studies and updates from 1974 to 2015 have found statistically significant increased lung cancer mortality (Muller et al 1974, Ham, 1976, Muller et al 1983, Muller et al 1989, Kusiak et al 1993, OCRC, 2015).
- The 2015 update of the Ontario Uranium Miners Cohort study showed a positive exposure-response relationship between cumulative radon exposure and lung cancer incidence and mortality without evidence of a threshold (OCRC 2015). There was a statistically significant nearly 2-fold increase in lung cancer incidence (RR=1.92; 95% CI 1.45-2.54) at cumulative exposures from > 50 working-level months (WLM) to 100 WLM. The statistically significant lung cancer mortality risk increased from 1.41; 95% CI 1.03-1.94 for cumulative radon exposures of >20 to 30 WLM to a greater than 2-fold increased risk at cumulative exposures > 100 WLM (RR=2.33; 95% CI 1.73-3.14). For comparison the current MLITSD OEL for radon in underground mines is 1 WLM per year.
- An important finding of this study was the statistically significant increase in lung cancer mortality observed at very low doses (>0 to 1 WLM) for miners exposed after 1970 (RR=1.43; 95% CI 1.05-1.95). This finding indicates that the lung cancer mortality risk among miners exposed during the lowest exposure period (after 1970) was similar to the risk for the full cohort (RR= 1.34; 95% CI 1.27-1.42).
- The finding of a strong linear exposure-response relationship between radon and risk of lung cancer from the recent update of the Ontario Uranium Miners Cohort is consistent with the BEIR linear no-threshold model (Rage et al 2018, BEIR VI 1999). These findings are also consistent

with those reported recent updates of large cohorts of French and German uranium miners exposed to low levels of radon (Rage et al 2018, Kreuzer et al 2018).

- A 2019 analysis of a joint cohort of Czech, French and Canadian uranium miners found a statistically significant monotonic increase in the relative risk of lung cancer mortality with increasing cumulative radon exposure from 20 to 100 WLM (Lane et al 2019). The finding of a statistically significant increased lung cancer mortality with cumulative radon exposures > 20 WLM is consistent with the results of the OCRC 2015 update of the Ontario uranium mining cohort.
- Many epidemiological studies over the past 30 years have observed a greater than additive but less than multiplicative interactive effect of radon and cigarette smoke on risk for lung cancer (BEIR VI 1999 Lane et al 2010, Hunter et al 2013, Bijwaard et al 2011, Leuraud et al 2011, Tomasek 2013).
- A 2018 update of a large German cohort of nearly 60,000 uranium miners found that adjusting for smoking had little effect on the risk estimates for lung cancer (Kreuzer et al. 2018). Similarly, a 2019 analysis of a joint cohort of Czech, French and Canadian uranium miners found that the statistically significant linear relationship between radon exposure and lung cancer mortality persisted after controlling for smoking (Lane et al 2019).
- Radon and RCS pose individual risks of lung cancer for miners; however, there is increasing evidence that miners exposed to a combination of RCS and radon may have an even greater risk of developing lung cancer. A study of German uranium miners suggested that the combined effect of radiation exposure and smoking was likely more additive than multiplicative (Sogl et al 2012).
- The combined effect of radiation and DE exposure is somewhat uncertain and was first addressed in two recent studies that suggest DE exposure may account for a larger proportion of the lung cancer risk among uranium miners than radon (Cao et al 2017, Chang et al 2018).

Arsenic

- A 1991 study of Ontario gold miners found that in gold miners who did not mine uranium, mortality from lung cancer was associated with exposure to radon in gold mines and to arsenic before 1946 but not with exposure to arsenic after 1946 (Kusiak et al 1991). Analysis of the joint effect of exposure to radon and arsenic showed that each exposure acted independently so that the risk to a gold miner exposed to both radon and arsenic is the sum of the risk from each exposure.
- The 1993 update of the Ontario Uranium Cohort found that the combined effect of exposure to radon and arsenic for uranium miners who also mined gold, was more complicated than for gold miners who never mined uranium (Kusiak et al 1993). This study concluded that the amount of exposure to radon seemed to determine the size of the increase in mortality from lung cancer caused by exposure to arsenic. The study also concluded that Ontario uranium miners who also

worked in gold mines have a greater risk of lung cancer than those miners who only worked in uranium mines. This may be partly due to arsenic exposure in Ontario gold mines.

Conclusion

When taken together, the published scientific literature to date provides compelling evidence that Ontario hard rock miners are at increased risk of lung cancer from occupational exposure to RCS, DE, radon and arsenic. These exposures pose an individual risk for lung cancer and there is epidemiological evidence that the risk from combined exposure to these carcinogens is greater than the risk from exposure to the individual carcinogens (i.e., additive or multiplicative effects).

Although the WSIB has policies on lung cancer and uranium mining (Policy 23-02-03) and lung cancer and gold mining (Policy 16-02-07), the epidemiological evidence used to support these policies are now more than 20 years out of date. More recent findings from the scientific literature indicate a need for modification of these policies to be consistent with the new analyses of the risk of lung cancer among hard rock miners.

Introduction

This summary considers the epidemiological evidence for the risk of lung cancer among Ontario miners as a result of exposure to four major carcinogens: respirable crystalline silica (RCS), diesel exhaust (DE), radon and arsenic exposure (as a modifying factor for lung cancer risk from radon exposure). Ontario miners have been exposed to these four cancer-causing agents for many decades and a considerable amount of research has been undertaken, particularly within the last 10 to 20 years, on the carcinogenic effects of these exposures. Ontario miners have also been exposed to other carcinogens such as asbestos (a contaminant in hard rock ore, used in brakes of underground mining equipment, insulation around pipes) and polycyclic aromatic hydrocarbons (PAHs) from oils used to lubricate equipment such as drills and blasting agents (nitrosamines and PAHs). However, these exposures were not considered in this summary.

Literature searches for relevant scientific and medical articles published up to July 1, 2022 were carried out on the PubMed database using combinations of search terms including: lung cancer, mining, Ontario, uranium mining, gold mining, silica, radiation, radon, arsenic, diesel exhaust emissions. Additional information was also accessed from readily available sources such as the Occupational Cancer Research Centre (OCRC), CARcinogen EXposure (CAREX) Canada, Canadian Cancer Society, International Agency for Research on Cancer (IARC).

Lung Cancer

Occurrence

Canadian Cancer Statistics 2017, reported that lung cancer was the third most commonly diagnosed cancer among Ontario men (5,300 new cases) after prostate and colorectal cancer and it was the second most commonly diagnosed cancer among Ontario women (5,300 new cases) after breast cancer. It is also estimated that lung cancer was the leading cause of cancer death among Ontario men (3,700 deaths) and women (3,400 deaths) in 2017.

The incidence and mortality rates of lung cancer generally increase between 45 and 54 years of age. Lung cancer is relatively rare in individuals younger than age 40. Rates continue to rise progressively with increasing age until 75 years of age. In the 75 to 84 years category, the rates begin to decline and substantially decrease in the >85 years category.

Classification

Lung cancer includes cancers of the lung, bronchus or trachea. There are two main types of lung cancer: non-small cell lung cancer (NSCLC), the more common type of lung cancer that grows more slowly and makes up about 75-80% of all lung cancer cases, and small cell lung cancer (previously called oat cell cancer) (SCLC) that grows and metastasizes more quickly than NSCLC. NSCLC, which can also metastasize, has historically been divided into four types: adenocarcinoma, squamous cell carcinoma,

bronchoalveolar cell carcinoma, and large-cell carcinoma. Adenocarcinoma and squamous cell carcinoma are the most frequently occurring cell types. The 2015 World Health Organization Classification of Lung Tumors classified SCLC, large cell neuroendocrine carcinoma, and carcinoid tumors as neuroendocrine tumors. All lung cancers are grouped by the International Classification of Diseases (ICD) under ICD-9 code 162 or the more recent ICD-10 classification of C33-34.

Non-Occupational Risk Factors

The Canadian Cancer Society Lung Cancer Risk Factors describes the major non-occupational risk factors for lung cancer.

Cigarette Smoking

Cigarette smoking is the most well-established risk factor for the development of lung cancer, with the large majority (80% to 90%) of lung cancers attributable to cigarette smoking. In 2004, IARC concluded that many studies typically showed a 10-fold or greater increase in risk of lung cancer among smokers as compared with those who never smoked (IARC 2004). The most important factor that affects lung cancer risk is the duration and intensity of regular smoking. For those who smoke 20 cigarettes/day, the risk of lung cancer increases by 3-fold after 20 years of smoking, 11-fold after 30 years, 13-fold after 40 years, and 40-fold after 50 years of smoking. The risk of lung cancer also increases with the number of cigarettes smoked per day; heavy smokers (>20 cigarettes/day) have higher risks than moderate smokers (10-20 cigarettes/day).

Smoking cessation results in a significant reduction in the relative risk of lung cancer. However, former smokers still have significantly higher risks than non-smokers, but substantially lower risks than those who continue smoking. Ex-smokers who stopped smoking at 30 years of age avoid more than 90% of the risk attributable to smoking compared to continuing smokers. However, when these ex-smokers reach age 75, their estimated excess risk of lung cancer is still approximately 4-fold higher than non-smokers.

Environmental Tobacco Smoke (ETS)[d]

Secondhand smoke or ETS is classified in the 2006 U.S. Surgeon General's Report and the 2004 IARC Monograph 83 as a confirmed human carcinogen. Several meta-analyses included in these reports have shown that there is a statistically significant and consistent increase in lung cancer risk in spouses of smokers and in never-smokers exposed to environmental tobacco smoke at the workplace.

[d] *Environmental Tobacco Smoke (ETS) is smoke that comes from the burning of a tobacco product and smoke that is exhaled by smokers. Inhaling environmental tobacco smoke is called involuntary or passive smoking, also called ETS and secondhand smoke.*

Family History

Researchers have found that genetics seem to play a role in some families with a strong history of lung cancer. The International Lung Cancer Consortium (ILCCO) was established in 2004, with the goal of sharing compatible data from lung cancer epidemiology studies to achieve greater power than from single studies alone. As of 2012, 57 international lung cancer studies were included in ILCCO.

Cote et al 2012 published the results of the ILCCO pooled analysis of family history of lung cancer and increased risk for disease, using data from 24 case-control studies in the ILCCO. To date, this is the largest pooled analysis incorporating a traditional case-control analysis and using data from individual family members to examine lung cancer risk adjusted for gender and smoking status of each relative. Individuals with family history in a first-degree relative[e] were found to be at an approximately 50% increased risk of lung cancer compared to those without a family history; and this association remained regardless of gender, race/ethnicity, histological type and adjustment for other known lung cancer risk factors.

Specifically, the odds ratio (OR) for first-degree relative with lung cancer was 1.51; 95% confidence interval (CI) 1.39-1.63, adjusting for smoking and other potential confounders. The association was strongest for those with a family history in a sibling, after adjustment; OR=1.82; 95% CI 1.62-2.05. Never smokers with positive familial history of lung cancer showed a lower association; OR=1.25; 95% CI 1.03, 1.52. The risk was slightly stronger for those with an affected sibling; OR=1.44; 95% CI 1.07-1.93.

Chronic Obstructive Pulmonary Disease (COPD)

The Science Committee of the Global Initiative for Obstructive Lung Disease (GOLD) concluded in its 2018 Report (GOLD 2018), that “There is ample evidence of an association between COPD and lung cancer”, with the evidence being stronger for emphysema than for airflow limitation alone and strongest for those with both. Age and smoking positively affected lung cancer risk.

In 2006, Sin et al reported on the findings from a scientific literature review and roundtable meetings of experts on the effect of the presence of one or more additional conditions on COPD mortality. With regard to lung cancer and COPD, the authors concluded that COPD is an independent risk factor for lung cancer, with a two to five-fold increase in lung cancer incidence in smokers with chronic bronchitis or emphysema compared to smokers without COPD. They also found that COPD is associated with a greater risk for lung cancer incidence than restrictive lung disease (e.g., idiopathic pulmonary fibrosis or sarcoidosis), and more severe COPD is associated with greater risk of lung cancer than mild COPD.

A 2011 study by Raviv et al examined the pathophysiologic mechanisms that may explain the association between COPD and lung cancer. Among these is chronic inflammation, with damage to airway epithelial

[e] *First-degree relatives share about half of their genes with the person such as a parents, siblings or children. A second degree relative of a person is an uncle, aunt, nephew, niece, grandparent, grandchild or half- sibling.*

cells and more rapid cellular turnover and propagation of DNA errors, and interaction with cigarette smoke and other inhaled lung carcinogens in a manner that increases the likelihood of malignant transformation of cells lining the airways. The impaired mucociliary clearance[f] associated with chronic airflow obstruction and inflammation enhances exposure of the airway epithelium to inhaled noxious and carcinogenic substances. Although all lung cancer cell types have been associated with COPD, greater risk has been shown for squamous cell carcinoma which arises in the airways. An additional factor may be genetic predisposition shared by lung cancer and COPD. Among the genes that has been implicated is α-1-antitrypsin[g].

Respirable Crystalline Silica (RCS)

Occupational Exposure to RCS and Lung Cancer

The association between occupational exposure to RCS and silicosis has been well established for many decades. The possible carcinogenicity of RCS began to be more intensively studied in the 1980s after increased rates of lung cancer were observed among Ontario miners in a 1982 mortality study by Finkelstein et al, a Scandinavian study of occupations exposed to RCS by Westerholm in 1980, and literature reviews by Goldsmith et al in 1982 and 1986.

The 1997 IARC Monograph 68 classified RCS as carcinogenic in humans (Group 1) based on the limited studies available at that time (IARC 1997). Much of the evidence for this classification was provided from studies of highly exposed workers within specific industries showing that lung cancer risk tended to increase with increasing cumulative exposure to RCS (Checkoway et al in 1993 and 1996), increasing duration of exposure (Merlo et al 1991, Partanen 1994, Costello et al 1988, 1995, Dong et al 1995) and increases in peak intensity of exposure (Burgess et al 1997, Cherry et al 1997, McDonald et al 1997).

In its 2012 IARC Monograph 100C, IARC reaffirmed the Group 1 classification of RCS based on the strong evidence from a pooled analysis by Steenland et al 2001 and 7 meta-analyses published between 1995 and 2009 (Smith et al 1995, Steenland et al 1997, Tsuda et al 1997, Kurihara et al 2004, Lacasse et al 2005, Peluccchi et al 2006, Erren et al 2008).

The 2001 pooled analysis by Steenland et al of 10 cohort studies, with quantitative RCS exposure data published between 1988 and 2000, reported a statistically significant 20% overall increased risk of lung cancer based on nearly 1,000 lung cancer deaths; SMR = 1.2; 95% CI 1.1-1.3. Additional relevant studies have been published since the IARC 2009 Monograph 100c. Poinen-Rughooputh et al 2016 is

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[f] Mucociliary clearance refers to the mechanism by which foreign particles are trapped and removed from the respiratory system. Mucus and the underlying respiratory mucous membrane contain mucus-producing cells and cilia (hairlike structures) also known as the mucociliary escalator, that cover the inside of the bronchi, bronchioles, and nose. The rapid back and forth movements of the cilia push the mucus and anything in it, such as inhaled particles or microorganisms up and out into the throat, where they can either get swallowed or removed through the mouth by the cough reflex.

[g] Alpha1 antitrypsin deficiency is a disorder that causes the alpha-1 antitrypsin (AAT) protein to be reduced or missing from the blood. This protein is necessary for healthy lungs and the body uses it to protect the lungs from damage. If a person has low or no levels of AAT their lungs may be damaged.

the most recent and largest meta-analysis to date. This meta-analysis included 85 cohort and case-control studies published up to April 29, 2016.

Table 1 summarizes the range of risk estimates from the meta-analyses considered by IARC and the 2016 meta-analysis (IARC 2012b, Poinen-Rughooputh et al 2016). These results confirm a consistent, statistically significant increased risk of lung cancer incidence and mortality across study types: cohort and case-control. When analysed by type of industry, the 2016 meta-analysis (discussed above) found that miners had the highest risk of lung cancer based on 18 studies (pooled SMR = 1.48; 95% CI 1.18–1.86).

Table 1 Risk Estimates for Exposure to RCS and Lung Cancer Reported in Meta-Analyses published up to 2016*	
Risk Estimates from 7 meta-analyses considered by IARC in 2009	
Cohort studies	**1.25 (1.20-1.40) to 1.29 (1.20-1.40)**
Case Control Studies	**1.41 (1.18-1.70) to 1.42 (1.22-1.65)**
Risk Estimates from Poinen-Rughooputh et al 2016 meta-analysis	
Cohort studies (SMR) mortality	**1.55 (1.38-1.75) [63 studies]**
Cohort studies (SIR) incidence	**1.68 (1.45-1.96) [19 studies]**
Case-Control (OR) mortality	**1.82 (1.25-2.66) [5 studies]**
Case-Control (OR) incidence	**1.34 (1.24-1.46) [9 studies]**

** SMR = standardized mortality ratio, SIR = standardized incidence ratio, OR = odds ratio*
statistically significant risk estimates in bold
adapted from information in IARC Monograph 100c 2012 & Poinen-Rughooputh et al 2016

Taeger et al 2015 reported the findings from another large pooled case-control analysis that used data from the IARC SYNERGY database (http://synergy.iarc.fr). Smoking- adjusted risks for lung cancer incidence among coal miners, ore miners and quarrymen were estimated from over 14,000 lung cancer cases. A strength of the SYNERGY database is detailed information on smoking and occupational history that allows for adjustment for smoking and exposure to lung carcinogens from other at-risk jobs. After adjusting for smoking and work in other at- risk occupations, those who ever worked as an ore miner had a greater than 2-fold statistically significant increased risk of lung cancer [OR=2.34 (1.36-4.03)].

Exposure Response

Several studies and meta-analyses have shown consistent evidence for an increased risk of lung cancer associated with cumulative exposure to RCS. The following is a summary of these studies.

Steenland et al 2001 This pooled analysis of 5 mining and 5 non-mining studies demonstrated a clear exposure-response between cumulative RCS exposure and increased risk of lung cancer (Table 2). The findings were similar for the mining and non-mining subgroups and they remained unchanged when the analysis omitted studies with suspected other confounders (radon, arsenic, PAHs). There was a 30% statistically significantly increased risk of lung cancer associated with a cumulative RCS exposure of about 2.0 mg/m^3-years. The lung cancer risk rose to 50% and appeared to level off at cumulative

exposures greater than 12.8 mg/m^3-years (median cumulative exposure for this category was 28.0 mg/m^3-years). This analysis represented the largest existing body of data, available at that time, for determining an exposure-response relationship for silica and lung cancer. Three of the mining cohorts (Chen et al 1992, Steenland et al 1995, deKlerk et al 1998) reported statistically significant risk estimates ranging from 1.2 to 2.1 and two of these were gold mines in the USA (Steenland et al 1995) and Australia (deKlerk et al 1998).

Table 2 Cumulative Exposure to RCS and Lung Cancer Mortality from a Pooled Analysis of 10 cohort studies (5 mining & 5 non-mining)	
Cumulative Silica Exposure (mg/m^3-years)	**Risk of Lung Cancer (95% CI)**
<0.4	1.0
0.4-2.0	1.0 (0.8-1.3)
2.0-5.4	**1.3 (1.0-1.6)**
5.4-12.8	**1.5 (1.2-1.8)**
>12.8	**1.5 (1.2-1.9)**

statistically significant risk estimates in bold
adapted from information in Steenland et al 2001
median RCS exposures ranged from 0.05 mg/m^3 to 0.59 mg/m^3

Sogl et al 2012 This 2012 German study of a large cohort of nearly 60,000 uranium miners also observed a positive trend between cumulative RCS exposure and risk of death from lung cancer. The unadjusted risk estimates showed a statistically significant increased risk of lung cancer mortality for cumulative RCS exposures greater than 2.0 mg/m^3-years. After adjusting for exposure to radon, arsenic and other potential effect modifiers (age at median exposure, time since median exposure, radon exposure rate), the positive trend remained; however, a statistically significant increased risk was observed only in the two highest exposure categories (cumulative RCS exposures > 20 mg/m^3-years). These results are summarized in Table 3.

Table 3 Risk of Death from Lung Cancer by Cumulative RCS Exposure		
Cumulative RCS exposure (mg/m^3-years)	**Relative Risk (95% confidence intervals) [number of cases] unadjusted**	**Relative Risk (95% confidence intervals) [number of cases] adjusted for radon, arsenic and effect modifiers**
0-0.5	1.00 (reference) [137]	1.00 (reference) [137]
0.5-2.0	1.2 (0.89-1.35) [238]	0.95 (0.77-1.12) [238]
2-5	**1.26 (1.00-1.51) [356]**	0.96 (0.78-1.13) [356]
5-10	**1.38 (1.10-1.66) [430]**	0.86 (0.67-1.04) [430]
10-20	**2.45 (1.98-2.92) [936]**	1.14 (0.87-1.40) [936]
20-30	**3.76 (3.02-4.49) [664]**	**1.51 (1.08-1.94) [664]**
30-56	**4.71 (3.62-5.80) [189]**	**2.02 (1.28-2.75) [189]**

statistically significant risk estimates in bold *adapted from information in Sogl et al 2012*

Liu et al 2013 A large Chinese cohort study of 34,000 tungsten miners, iron miners, and pottery workers had high quality information on occupational exposures to potential carcinogens, silicosis status and smoking history. As shown in Table 4, a positive exposure-response trend (p for trend = 0.001) was observed for risk of lung cancer with increasing cumulative RCS exposures. A greater than 50% statistically significant increased risk was observed for cumulative exposures of RCS ranging from 1.12 to 2.91 mg/m^3 - years. The risk increased to 70% in the highest cumulative RCS exposure category (≥.6.22 mg/m^3 - years). This study also estimated that the excess lifetime risk of lung cancer for workers exposed to an exposure limit[h] of 0.1 mg/m^3 for a typical working career of 45 years, was 0.51% (or 51 excess deaths per 10,000 workers). This is much higher than the 0.1% (or 1 excess death per 1,000 workers over a working lifetime) which is the acceptable risk suggested by the US Occupational Safety and Health Administration (OSHA) and other health and safety agencies.

Table 4 Cumulative Exposure to RCS and Risk of Lung Cancer Mortality*	
Cumulative RCS Dust Exposure (mg/m^3-years)	**Risk of Lung Cancer (OR) (95% confidence intervals) [number of cases]**
0.01 to < 1.12	1.26 (0.98-1.60) [128]
1.12 to <2.91	**1.54 (1.16-2.05) [84]**
2.91 to <6.22	**1.68 (1.26-2.24) [96]**
≥ 6.22	**1.70 (1.23-2.34) [75]**

** 25-year lag (exposures within 25 years of diagnosis not included) and adjusted for sex, facility, year of birth and smoking history, statistically significant risk estimates in bold, [n] = number of cases statistically significant risk estimates in bold*
p for trend = 0.001
adapted from information in Liu et al 2013

Kachuri et al 2014 This Canadian population-based case-control study assessed the risk of lung cancer associated with different durations of exposure at different concentrations of RCS, and by cumulative exposure to RCS. Data for this analysis came from the lung cancer case-control component of the Canadian National Enhanced Cancer Surveillance System (NECSS), a collaborative effort between Health Canada and the cancer registries in provinces.

An important finding in this study was the exposure-response relationship between duration of exposure to RCS and lung cancer (Table 5). Statistically significant risk of lung cancer was found for durations of 10 to < 30 years and > 30 years after adjusting for cigarette smoking and exposure to other carcinogens. Duration of exposure alone may not be sufficient to assess the risk of lung cancer due to variability in exposure intensity across jobs and over time. To overcome this limitation, this study also assessed duration at three levels of exposure (low, medium, high)[i]. Long term exposure (≥ 30 years) to RCS at low concentrations was associated with a statistically significant increased lung cancer risk even after

[h] *The current Ontario Ministry of Labour exposure limit for RCS is 0.1 mg/m^3*
[i] *The study stated that "Concentration was assessed on a relative scale with respect to established benchmarks. Nonexposed was defined as exposure up to background levels found in the general environment." However, the cut points (i.e., values of mg/m^3) were not provided for low, medium and high exposures.*

adjusting for smoking and exposure to other lung carcinogens (OR=1.63; 95% CI 1.19-2.23). Due to low numbers, statistically significant associations with duration of exposure at medium or high levels were not observed.

Table 5 Risk of Lung Cancer and Duration of Exposure to RCS	
Exposure Metric	**Risk of Lung Cancer Adjusted Odds Ratio* (95% confidence interval) [number of cases]**
Total Duration of Exposure	
< 10 years	0.94 (0.73-1.20) [187]
10-30 years	1.19 (0.92-1.55) [201]
≥ 30 years	**1.67 (1.21-2.24) [190]**
	p for trend = 0.002
Duration of Exposure at medium or high concentrations	
< 5 years	0.74 (0.44-1.25) [33]
5 to <15	1.20 (0.73-1.99) [45]
≥ 15	1.44 (0.85-2.45) [51]
Duration of Exposure at low concentrations	
< 10 years	0.93 (0.71-1.12) [167]
10 to <30	1.04 (0.79-1.37) [164]
≥ 30	**1.63 (1.19-2.23) [160]**

** adjusted for age, province of residence, cigarette smoking (pack years), environmental tobacco smoke (ETS), exposure to diesel and gasoline emissions and asbestos*
statistically significant risk estimates in bold;
adapted from information in Kachuri et al 2014

This study also included an analysis of the cumulative exposure that incorporated duration of employment, frequency of RCS exposure and exposure concentration. Cases were divided into thirds (tertiles) of cumulative exposure to RCS. The increasing lung cancer risk observed with increasing cumulative RCS exposure remained significant after adjusting for cigarette smoking and exposure to other possible lung carcinogens (p for trend = 0.004). The cases in the highest tertile of cumulative exposure had a nearly 2-fold statistically significantly increased risk (Table 6).

Table 6 Cumulative Occupational Exposure to RCS and Risk of Lung Cancer		
Cumulative RCS Exposure [number of cases]	**Risk of Lung Cancer OR unadjusted (95% confidence intervals)**	**Risk of Lung Cancer OR adjusted* (95% confidence intervals)**
Lowest tertile [163]	1.04 (0.80-1.34)	1.01 (0.77-1.31)
Middle tertile [168]	1.02 (0.79-1.31)	0.97 (0.75-1.27)
Highest tertile [214]	**1.91 (1.47-2.49)**	**1.81 (1.34-2.42)**
p value for trend	**<0.0001**	**0.004**

** adjusted for age, province of residence, cigarette smoking (pack years), environmental tobacco smoke (ETS), exposure to diesel and gasoline emissions and asbestos*
statistically significant risk estimates in bold
adapted from information in Kachuri et al 2014

The finding of increased risk of lung cancer with increasing cumulative exposure to RCS is consistent with other population-based studies of occupational RCS exposure in Canada (Vida et al 2010) and Europe (Bruske-Hohlfeld et al 2000, Cassidy et al 2007, Preller et al 2010) and the Steenland et al 2001 pooled analysis.

Liu et al 2017 Another analysis of the large cohort of nearly 45,000 Chinese workers from 20 metal mines and 9 pottery factories used in the Liu et al 2013 study was analyzed to specifically examine the association between low levels of RCS and risk of mortality including lung cancer. Lifetime highest RCS exposure intensity was used to classify the workers into three exposure groups: those with highest lifetime mean RCS exposure of ≤ 0.35 mg/m^3, ≤ 0.10 mg/m^3 and ≤ 0.05 mg/m^3 that corresponded to widely used occupational exposure limits[j]. As noted earlier, this cohort had high quality information on occupational exposures to potential carcinogens, silicosis status and smoking history. Hazard ratios for lung cancer mortality risk associated with RCS, after adjusting for smoking history, for the three exposure categories are summarized in Table 7. A statistically significant increased risk of lung cancer was observed for cumulative RCS ranging from 0.48 mg/m^3-years to > 1.94 mg/m^3-years.

The authors noted that in comparison with the results in their previous study (Liu et al 2013), low level RCS exposure was associated with a similar overall increased risk of lung cancer (exposed vs unexposed; 43%, 41% and 45% for the ≤ 0.05 mg/m^3, ≤ 0.10 mg/m^3 and ≤ 0.35 mg/m^3 exposure levels, respectively, vs. 44% for any level of RCS exposure in the Liu et al 2013 study).

[j] The Permissible Exposure Limit (PEL) for RCS in China varies from 0.07 mg/m^3 to 0.35 mg/m^3 depending on the amount of silica in the dust; current Ontario Ministry of Labour TWAEV for RCS = 0.1 mg/m^3; Occupational Safety and Health Administration (OSHA) in the US lowered its PEL for RCS to 0.05 mg/m^3 in 2016.

Table 7 Hazard Ratios (HR) for Lung Cancer Mortality at Different Lifetime Highest Cumulative RCS Exposures*			
Quartile of Cumulative RCS Exposure (mg/m^3-years) for Workers with Lifetime Highest RCS Exposure ≤ 0.05 mg/m^3			
0.01-0.26	**0.27-0.47**	**0.48-0.67**	**>0.67**
HR (95% CI) [# of deaths]			
1.47 (0.88-2.47) [16]	1.36 (0.77-2.39) [14]	**1.58 (1.00-2.50) [22]**	1.29 (0.76-2.19) [16]
Quartile of Cumulative RCS Exposure (mg/m^3-years) for Workers with Lifetime Highest RCS Exposure ≤ 0.10 mg/m^3			
0.01-0.34	**0.35-0.59**	**0.60-0.86**	**>0.86**
HR (95% CI) [# of deaths]			
1.53 (1.07-2.20) [36]	1.30 (0.89-1.90) [32]	**1.64 (1.16-2.30) [42]**	1.20 (0.83-1.74) [34]
Quartile of Cumulative RCS Exposure (mg/m^3-years) for Workers with Lifetime Highest RCS Exposure ≤ 0.35 mg/m^3			
0.01-0.56	**0.57-1.04**	**1.05-1.94**	**>1.94**
HR (95% CI) [# of deaths]			
1.43 (1.10-1.86) [77]	**1.29 (1.00-1.68) [78]**	**1.75 (1.37-2.24) [94]**	**1.76 (1.32-2.36) [70]**

**source – adapted from Tables 3, 4, 5 in Liu et al 2017*

Lai et al 2018 This study reported findings for a sub-cohort of 7,665 iron miners that were part of the larger study by Liu et al 2013. This study extended the follow-up from the original 2013 study for this cohort by 10 years to 2012. RCS exposure was divided into four levels; unexposed, low (≤ 0.49 mg/m^3 years), medium (0.49 to 0.84 mg/m^3 years) and high (≥ 0.84 mg/m^3 years)[k]. Based on a total of 262 lung cancer deaths, this study confirmed a statistically significant increased risk of lung cancer for all categories of cumulative RCS exposure (Table 8). This study also found that each 1 mg/m^3 - year of increase in cumulative RCS exposure was associated with a statistically significant 19% increase in risk of death from lung cancer [HR = 1.19 (1.05 – 1.35)].

Table 8 Cumulative Exposure to RCS and Risk of Lung Cancer Mortality for a Sub-cohort of Iron Miners	
Cumulative RCS Dust Exposure (mg/m^3-years)	**Risk of Lung Cancer; Hazard Ratio (95% confidence intervals)**
Low < 0.49	**1.67 (1.13-4.47)**
Medium 0.49 to 0.84	**1.67 (1.19-2.32)**
High > 0.84	**1.68 (1.22-2.330)**

*based on the distribution of cumulative RCS exposure, cases were divided equally into unexposed, low, medium and high exposure groups; **p-value for trend =0.001*
statistically significant risk estimates in bold
source: adapted from information in Lai et al 2018

k For comparison, these cumulative exposure categories would equate to < 5 years, 5 to 8 years and > 8 years of exposure to the current MOL OEL of 0.1 mg/m

Poinen-Rughooputh et al 2016 This recent meta-analysis, discussed earlier, was based on studies with well characterized RCS exposure data. A positive exposure-response relationship was observed between cumulative RCS exposure and risk of lung cancer in a subgroup of 19 cohort mortality studies and is summarized in Table 9. There was a statistically significant increased risk in the low RCS exposure category [1.19 (1.02-1.39)]. However, the risk estimates for the second, third and fourth quartile were not statistically significant (p>0.05) and the authors suggested that this was likely due to the high level of heterogeneity among the studies

Table 9 Cumulative Exposure to RCS and Risk of Lung Cancer Mortality*	
Cumulative RCS Exposure (mg/m^3-years)	**SMR (95% CI) [number of studies]**
0 to ≤ 0.83	**1.19 (1.02-1.39) [5]**
0.83 to ≤ 3.9	1.27 (0.89-1.82) [5]
3.9 to ≤ 8.35	1.33 (0.94-1.87) [4]
> 8.35	1.36 (0.87-2.13) [5]

** based on a subgroup analysis of 19 cohort mortality (SMR) studies*
statistically significant risk estimates in bold
source: adapted from Table 2 in Poinen-Rughooputh et al 2016

Ge et al 2020a A clearer understanding of the exposure-response relationship between RCS exposure and lung cancer is provided by this 2020 pooled analysis of 14 case-control studies from Europe and Canada. The objectives of this analysis were to address the knowledge gaps in lung cancer risk associated with low levels of occupational RCS exposure and the joint effects of smoking and RCS exposure on lung cancer risks. The study included 16,901 cases and 20,965 control subjects for which detailed smoking and occupational exposure histories were available. A quantitative job-exposure matrix was used to estimate RCS exposure by occupation, time period, and geographical location. Quantitative RCS estimates were derived for each job title, region and year using 23,640 historical personal RCS measurements. As RCS sampling data before 1960 was sparse, RCS concentrations before 1960 were assumed to be the same as those in 1960.

Statistically significant increased risk of lung cancer was observed for RCS exposed workers compared to nonexposed workers across three occupational exposure indices including,

Ever exposed OR=1.30; 95% CI 1.23-1.38
Longest duration (>29 years) OR=1.48; 95% CI 1.34-1.63
Highest cumulative exposure (>2.4 mg/m^3-years) OR=1.45; 95% CI 1.31-1.60

An important observation of this study was the statistically significant increased risk of lung cancer for those workers in the lowest exposure duration (1-9 years) OR= 1.22; 95% CI 1.12-1.31 and those in the lowest cumulative exposure category (<0.4 mg/m^3-years) OR=1.15; 95% CI 1.04-1.27 (median cumulative exposure 0.22 mg/m^3-years). The median of the lowest cumulative exposure category would be equivalent to just over 2 years of exposure to the current Ontario RCS OEL of 0.1 mg/m^3 (0.22 mg/m^3-

years ÷ 0.1 mg/m^3 = 2.2 years) or about 9 years of exposure to the proposed lower OEL of 0.025 mg/m^3 (0.22 mg/m^3-years ÷ 0.025 mg/m^3 = 8.8 years).

There was no evidence of a threshold and there was a statistically significant (p<0.1 for trend) increased risk with increasing cumulative exposure to RCS. Table 10 summarises the lung cancer odds ratio associated with various indices of occupational RCS exposure.

Table 10 Lung Cancer Odds Ratios Associated with Various Indices of Occupational RCS Exposure*

Occupational RCS Exposure	Odds Ratio[1] (95% Confidence Interval) [no. of cases]
Never	1.0 (referent)
Ever exposed	**1.30 (1.23-1.38) [4,923]**
Duration (years)	
1-9	**1.22 (1.12-1.31) [2,035]**
10-19	**1.20 (1.08-1.34) [926]**
20-29	**1.45 (1.26-1.66) [635]**
>29	**1.48 (1.34-1.63) [1,327]**
Test for trend; p value excluding never exposed	**<0.01**
Cumulative Exposure (mg/m^3-years)	
>0-0.39	**1.15 (1.04-1.27) [1,113]**
0.4-1.09	**1.33 (1.21-1.47) [1,221]**
1.1-2.39	**1.29 (1.17-1.42) [1,231]**
≥2.4	**1.45 (1.31-1.60) [1,358]**
Test for trend; p value excluding never exposed	**<0.01**
Time since last exposure[2] (years)	
< 5	**1.43 (1.18-1.73) [934]**
5-9	**1.43 (1.15-1.77) [462]**
10-19	**1.36 (1.13-1.63) [679]**
20-29	**1.26 (1.08-1.47) [617]**
30-39	1.09 (0.99-1.20) [1,300]
Test for trend; p value excluding never exposed	**0.10**

** adapted from Table 2 in Ge et al 2020a*

[1] Odds ratios adjusted for study, age group, sex, smoking (pack-years, time since quitting smoking) and exposure to other occupational carcinogens

[2] Odds ratio in "time since last exposure" is additionally adjusted for duration (continuous) of RCS exposure. Trend test limited to exposed subjects

This study corroborates the meta-analysis of 19 studies by Poinen-Rughooputh et al 2016 (discussed above) that calculated a statistically significant pooled risk estimate of 1.19; 95% CI 1.01-1.39, for workers with a mean cumulative RCS exposure of 0.42 mg/m^3-years.

Lung Cancer and Silicosis

Silicosis is scarring of the lung parenchyma[l] (fibrosis) resulting from inhalation of RCS; silicosis is an indicator of high occupational exposure to RCS. It was earlier thought that silicosis was a necessary precursor to the development of lung cancer. However, recent epidemiological evidence shows that silicosis is not a necessary precursor or intermediate step for the development of lung cancer and it appears that RCS can cause lung cancer directly.

A 2008 meta-analysis by Erren et al was the most thorough attempt at that time to address the issue of whether exposure to RCS is associated with lung cancer risk in individuals without silicosis. This meta-analysis identified 11 studies (9 cohort and 2 case-control studies) published between 1966 and January 2007 that reported lung cancer in workers exposed to RCS but who did not have silicosis. The authors used substantially different and more sophisticated analytical methods than those used in previous meta-analyses (Kurihara et al 2004, Lacasse et al 2005, Peluccchi et al 2006). Six of the eleven studies included in the 2008 meta-analysis by Erren et al, reported an excess risk of lung cancer for workers exposed to RCS but who did not have silicosis and three of the risk estimates were statistically significant. The summary risk estimate (SRE) based on all 11 studies combined and 9 cohort studies combined showed a 20% significantly increased risk of lung cancer among non-silicotics (Table 11). However, there was considerable heterogeneity (differences between the studies) that made it difficult to provide a conclusive answer to the question of whether non-silicotics exposed to RCS are at a greater risk of lung cancer.

Table 11 Meta-Analysis of non-silicotics exposed to RCS and risk of lung cancer

Type of Study	Number of Studies	Summary Risk Estimate SRE (95% CI)	Homogeneity P-value
All studies combined	**11**	**1.2 (1.0-1.3)**	**[0.07] ***
Cohort studies	**9**	**1.2 (1.0-1.4)**	**[0.07] ***
Case-control studies	**2**	1.0 (0.7-1.5)	0.26
Smoking adjusted	**3**	1.0 (0.8-1.3)	0.49
Not smoking adjusted	**8**	**1.2 (1.0-1.4)**	**[0.05] ***

** square brackets indicate substantial heterogeneity between the studies (i.e., P<0.10) contributing to the SRE*

adapted from Erren et al 2008

IARC Monograph 100c (IARC 2012b) reviewed 6 meta-analyses that summarized the results of studies of lung cancer among workers with silicosis (Smith et al 1995, Steenland et al 1997, Tsuda et al 1997, Kurihara et al 2004, Peluccchi et al 2006, Erren et al 2008). The risk estimates ranged from 1.70 to 3.27 and all were statistically significant regardless of the type of study (cohort, case-control, all studies combined) or whether the studies controlled for smoking.

[l] *lung parenchyma is the portion of the lung involved in gas transfer - the alveoli, alveolar ducts and respiratory bronchioles.*

The Liu et al 2013 study of tungsten miners, iron miners and pottery workers in China added significantly to the literature on the risk of lung cancer among non-silicotics exposed to RCS. This study was large enough to analyze the risk of lung cancer for workers with and without silicosis and had high quality information on occupational exposures to RCS and other potential lung carcinogens (e.g., radon), silicosis status and smoking history. At cumulative RCS exposures > 1.12 mg/m^3-years, workers without silicosis had a similar statistically significant increased risk of lung cancer as that observed for all workers (with silicosis and without silicosis combined), which demonstrated that silicosis was not a requirement for lung cancer (Table 12). Both groups of workers in the highest exposure category (≥ 6.22 mg/m^3-years) had a 70% increased risk of lung cancer. In this study the mean cumulative RCS exposure was 7.1 mg/m^3 - years for silicotics and 3.1 mg/m^3 - years for non-silicotics, which supports the well-established observation that silicosis is a marker for high RCS exposure.

Table 12 Cumulative Exposure to RCS and Risk of Lung Cancer Death among RCS-Exposed Workers without Silicosis compared to all RCS Exposed Workers*

Cumulative RCS Exposure (mg/m^3-years)	Risk of Lung Cancer Death (95% confidence intervals) [number of cases]	
	Workers without silicosis	All workers
0.01 to < 1.12	1.12 (0.86-1.46) [102]	1.26 (0.98-1.60) [128]
1.12 to <2.91	**1.41 (1.03-1.93) [63]**	**1.54 (1.16-2.05) [84]**
2.91 to <6.22	**1.58 (1.14-2.19) [65]**	**1.68 (1.26-2.24) [96]**
≥ 6.22	**1.70 (1.15-2.52) [41]**	**1.70 (1.23-2.34) [75]**

** 25-year lag (exposures within 25 years of diagnosis not included) and adjusted for sex, facility, year of birth and smoking history, statistically significant risk estimates in bold, [n] = number of cases statistically significant risk estimates in bold; adapted from information in Liu et al 2013*

The 2016 meta-analysis by Poinen-Rughooputh et al had sufficient data from 34 studies to calculate separate risk estimates for silicotics and non-silicotics. By comparison, the previous systematic meta-analysis by Erren et al in 2008 only included 11 studies. The updated meta-analysis found that workers exposed to RCS and who had silicosis had a greater than 2-fold statistically significant increased risk of lung cancer, a finding consistent with other studies included in IARC Monograph 100C and the Smith et al 1995 study. A subgroup analysis of 4 cohort mortality studies showed a statistically significant increased risk of death from lung cancer for workers exposed to RCS but who did not have silicosis [SMR = 1.78 (1.07-2.96)] (Table 11). This was a considerably higher risk estimate than the SRE of 1.2 reported by Erren et al 2008.

Table 13 summarises the pooled risk estimates for the cohort and case-control studies included in the 2009 IARC and the 2016 Poinen-Rughooputh meta-analyses.

Table 13 Risk Estimates for Exposure to RCS and Lung Cancer in Silicotics and Non-silicotics Reported in Meta-Analyses published up to 2016*		
Worker Status	**RCS exposed with silicosis**	**RCS exposed without silicosis**
Risk Estimates from 7 meta-analyses considered by IARC in 2009**		
Cohort studies	**1.69 (1.32-2.16) to 2.78 (2.41-3.22)**	1.19 (0.87-1.57) **to 1.20 (1.10-1.30)**
Case Control Studies	**1.70 (1.15-2.52) to 3.27 (1.32-8.20)**	0.97 (0.68-1.38) **to** 1.00 (0.70-1.30)
Risk Estimates from meta-analysis by Poinen-Rughooputh et al in 2016		
Cohort studies; mortality (SMR)	**2.32 (1.91-2.81) [24 studies]**	**1.78 (1.07-2.96) [4 studies]**
Cohort studies; incidence (SIR)	**2.49 (1.87-3.33) [4 studies]**	1.18 (0.86-1.62) **[2 studies]**
Case-Control; mortality (OR)	**2.56 (1.84-3.57) [3 studies]**	**NA**
Case-Control; incidence (OR)	**NA**	**NA**

** adapted from information in IARC Monograph 100C and Poinen-Rughooputh et al 2016*
*** Smith et al 1995, Steenland et al 1997, Tsuda et al 1997, Kurihara et al 2004, Lacasse et al 2005, Peluccchi et al 2006, Erren et al 2008*
statistically significant risk estimates in bold
SMR = standardized mortality ratio, SIR = standardized incidence ratio, OR = odds ratio

Ge et al 2020a found that the risk for lung cancer was similar for those workers with silicosis as it was for those without silicosis (Table 14). This supports the findings from the Erren et al 2008 and the 2016 Poinen-Rughooputh meta-analyses discussed above and supports the evidence for a direct association between RCS exposure and lung cancer without requiring silicosis as an intermediate step.

Table 14 Lung Cancer Odds Ratios Associated with Cumulative Occupational RCS Exposure in Workers without Silicosis*	
Cumulative RCS Exposure (mg/m^3-years)	**Odds Ratio; OR[1] (95% CI) [number of cases]**
never	1.0 (referent) [6,091]
>0-0.39	**1.22 (1.07-1.40) [665]**
0.4-1.09	**1.50 (1.31-1.71) [720]**
1.1-2.39	**1.48 (1.30-1.69) [757]**
≥2.4	**1.42 (1.25-1.63) [740]**
p value for trend excluding never exposed <0.01	

** adapted from Table 3 in Ge et al 2020a*

[1] Odds ratios adjusted for study, age group, sex, smoking (pack-years, time since quitting smoking) and exposure to other occupational carcinogens

Cigarette Smoking and the Risk of Lung Cancer from Exposure to RCS

The effect of cigarette smoking and exposure to other occupational carcinogens on the risk of lung cancer can be analyzed in two different ways: examining the effect of the carcinogen of interest by taking into account the contribution of cigarette smoking as a confounder in multivariate analysis[m], and by examining the combined effect of smoking and the carcinogen of interest.

Confounding Effect of Cigarette Smoking or Other Lung Carcinogens

The 2012 IARC Monograph 100E confirmed cigarette smoking as the major cause of lung cancer and that it can magnify the effects of other lung carcinogens (IARC 2012c). When a population is exposed to a lung carcinogen in addition to smoking, both contribute to the risk of lung cancer. The contribution of smoking to the risk of lung cancer from exposure to another lung carcinogen is an example of confounding that must be taken into account to avoid biasing the observed results. When the confounding effect of cigarette smoking is taken into account, the resulting adjusted risk estimate is a better indication of the true effect of the carcinogen of interest. As noted throughout this summary, some studies of RCS and lung cancer have taken smoking into account and adjusted the risk estimates for lung cancer accordingly. Fewer studies have taken smoking into account due to the difficulty in obtaining accurate smoking histories.

The 2016 Poinen-Rughooputh et al meta-analysis compared the pooled risk estimate of smoking-adjusted standardized mortality ratio (SMR) cohort studies with that of the unadjusted studies. The pooled risk estimate for the two studies that adjusted for smoking found that lung cancer risk was slightly greater and remained statistically significant compared to the studies that did not adjust for smoking.

A similar result was found by grouping the SMR studies into those with exposure to other lung carcinogens[n] and those without exposure to other lung carcinogens. The pooled risk estimate decreased very slightly but remained statistically significant after controlling for exposure to other potential lung carcinogens. Therefore, it may be concluded that despite potential exposure to other lung carcinogens, the significant relationship between RCS exposure and lung cancer remained intact.

Table 15 summarizes these findings from the 2016 Poinen-Rughooputh et al meta-analysis.

IARC observed that many of the meta-analyses (Smith et al 1995, Tsuda et al 1997, Kurihara et al 2004, Lacasse et al 2005, Lacasse et al 2009, Erren et al 2008) included in their 2012 Monograph on RCS reported an elevated risk of lung cancer from exposure to RCS after adjusting for smoking.

In 2016, the Occupational Safety and Health Administration (OSHA) in the USA also considered the issue of a confounding effect from smoking in their Final Rule on Occupational Exposure to Respirable Crystalline RCS (OSHA 2016). OSHA concluded that, based on their independent review of the available

[m] *Multivariate analysis is a set of statistical techniques used for analysis of data that contain more than one variable*
[n] *other lung carcinogens were radon, arsenic, asbestos, diesel exhaust, polycyclic aromatic hydrocarbons (PAHs), talc, cadmium, amphiboles*

studies, it was unlikely that smoking explained the observed positive exposure-response trends for RCS and lung cancer.

Table 15 Effect of Cigarette Smoking or Exposure to other Occupational Carcinogens on the Risk of Lung Cancer from RCS Exposure	
Potential Confounders	**Summary Risk Estimate SMR (95% confidence interval)**
Cigarette Smoking	
Not adjusted	**1.55 (1.37-1.75) [61 studies]**
Adjusted	**1.83 (1.51-2.22) [2 studies]**
Occupational carcinogens[1]	
Not Adjusted	**1.35 (1.17-1.57) [30 studies]**
Adjusted	**1.32 (1.14-1.54) [13 studies]**

[1]occupational carcinogens included: radon, arsenic, asbestos, diesel exhaust, polycyclic aromatic hydrocarbons (PAHs), talc, cadmium, amphiboles

statistically significant risk estimates in bold

adapted from Table 2 in Poinen-Rughooputh et al 2016

Combined Effect of Cigarette Smoking and RCS Exposure

Few studies have assessed the combined effect of cigarette smoking and RCS exposure on the risk of lung cancer. Analysis of the interactive effects of exposure to multiple carcinogens that affect the same organ or tissue requires a large enough number of lung cancer cases to allow for a stratified analysis[o] and detailed occupational exposure and smoking histories. The population-based case-control study by Kachuri et al 2014 in eight Canadian provinces met these requirements and was able to investigate the effect of cigarette smoking on the risk of lung cancer from occupational exposure to RCS. This was also the first study to date to adjust for lifetime exposure to environmental tobacco smoke (ETS)[p] at work and at home.

The combined effect of smoking and occupational exposure to RCS was investigated using a stratified analysis in which the risk (OR) was estimated for the duration of RCS exposure across three categories of cigarette smoking: low < 10, moderate 10 to < 40 and high ≥ 40 pack years. The reference category consisted of participants with <10 cigarette pack-years who were not exposed to RCS. The stratified analysis of the interaction between duration of RCS exposure and different pack-year smoking histories is summarized in Table 16.

[o] stratified analysis is the analysis of sub-groups within the entire study population

[p] Environmental Tobacco Smoke (ETS) is smoke that comes from the burning of a tobacco product and smoke that is exhaled by smokers. Inhaling environmental tobacco smoke is called involuntary or passive smoking, also called ETS and secondhand smoke.

Table 16 Interaction between Cigarette Smoking and RCS Exposure		
Cigarette smoking (pack-years)	**Duration of RCS Exposure[1] (years)**	**Odds Ratio[2,3,4] OR (95% confidence interval) [number of cases]**
< 10	unexposed	1.00 [76]
	< 10	0.99 (0.47-2.08) [9]
	10 to < 30	0.71 (0.31-1.61) [7]
	≥ 30	0.63 (0.26-1.52) [6]
10 to < 40	**unexposed**	**6.30 (4.78-8.31) [469]**
	< 10	**5.66 (3.84-8.34) [82]**
	10 to < 30	**7.98 (5.33-11.95) [88]**
	≥ 30	**10.42 (6.77-16.06) [89]**
≥ 40	**unexposed**	**18.82 (13.93-25.43) [493]**
	< 10	**21.15 (13.09-34.16) [90]**
	10 to < 30	**21.83 (13.57-35.10) [95]**
	≥ 30	**42.53 (23.54-76.83) [87]**
Synergy Index (S)[5] 2.38 (1.35-4.21)		
Multiplicative Index (V)[6] 3.59 (1.51-8.49)		

[1] exposures were restricted to estimates with reliability > possible; estimates with low reliability were classified as unexposed

[2] adjusted for age, province of residence, cigarette pack years, exposure to ETS, cumulative exposures to diesel or gasoline emissions and exposure to asbestos (yes/no)

[3] statistically significant risk estimates in bold

[4] the risk estimates for < 10 pack-year category is based on very small numbers of cases (< 10) compared to other categories

[5] synergy index (S) >1 indicates the effect is multiplicative: S=1 indicates the interactive effect is more consistent with an additive model

[6] multiplicative index (V) =1 indicates a multiplicative interaction; V < 1 indicates an interaction that is less than multiplicative; V > 1 indicates an interaction that is more than multiplicative

adapted from Table 4 in Kachuri et al 2014

Compared to those with <10 pack-years of smoking and who were not exposed to RCS, those who were exposed to RCS for ≥ 30 years and had ≥ 40 pack-years of smoking had the highest risk of lung cancer [OR = 42.53 (23.54–76.83)]. The odds ratios for those cases with a smoking history of < 10 pack-years are less reliable than those for the moderate and heavy smoking category because they are based on small numbers of cases (< 10).

The lung cancer risk for the moderate smoking group (10 to < 40 pack-years) had a greater than 5 -fold increased risk after less than 10 years of RCS exposure. The risk increased to greater than 10-fold after 30 or more years of RCS exposure. In the heavy smoking group (> 40 pack-years) the risk of lung cancer also doubled from greater than 20-fold after less than 10 years of RCS exposure to greater than 40-fold after 30 or more years of RCS exposure.

These large increases in risk estimates with increasing duration of RCS exposure and intensity of smoking suggested that there was a greater than additive interaction between RCS and cigarette smoke.

The authors calculated synergistic and multiplicative indices[q] based on these results and concluded that the interaction between duration of RCS exposure and cigarette smoking was at least multiplicative, but the possibility of super multiplicative effects could not be excluded.

This study also examined the odds of lung cancer for different durations of RCS exposure within each smoking category (Table 17). Compared with the unexposed category, smokers with 10 to <40 pack-years of smoking and ≥ 30 years of RCS exposure had significantly higher odds of developing lung cancer [OR = 1.65 (1.14–2.40)]. The same was true among heavy smokers (≥ 40 pack-years) [OR for ≥ 30 years of RCS exposure = 2.26 (1.30–3.94)].

For clarification it should be noted that in order to calculate the risk estimates across the smoking categories, the authors of the study assigned an odds ratio of 1.0 to each of the unexposed RCS categories for the moderate (10 to < 40 pack-years) and heavy (> 40 pack-year) smoking categories. For example, in Table 15 the OR for 10 to < 40 pack-year smokers that had no exposure to RCS was 6.30; however, for comparison purposes an OR of 1.0 was assigned for this category as shown in Table 15. The resulting odds ratios for different durations of RCS exposure were calculated by dividing the OR for the unexposed cases (OR= 6.30) into the odds ratios listed in Table 16. For example, the resulting OR of 1.65 for those with ≥ 30 years of RCS exposure and 10 to < 40 pack-years of smoking was calculated by dividing 10.42 by 6.30 = 1.65.

Table 17 Adjusted Risk Estimates of Lung Cancer for duration of Exposure to RCS across Cigarette Pack-Year Smoking Categories*

	Cigarette smoking (pack years)		
Duration of RCS Exposure[1] (years)	**< 10**	**10 to < 40**	**> 40**
	Odds Ratio (OR)[2]		
Unexposed	1.00 [76]	1.00 [469]	1.00 [493]
< 10	0.99 (0.47-2.08) [9]	0.90 (0.65-1.24) [82]	1.12 (0.73-1.73) [90]
10 to < 30	0.71 (0.31-1.61) [7]	1.27 (0.90-1.78) [88]	1.16 (0.76-1.78) [95]
≥ 30	0.63 (0.26-1.52) [6]	**1.65 (1.14-2.40) [89]**	**2.26 (1.30-3.94) [87]**

** adapted from Table 5 in Kachuri et al 2014*

[1] exposures were restricted to estimates with reliability > possible; estimates with low reliability were classified as unexposed

[2] adjusted for age, province of residence, cigarette pack years, exposure to ETS, cumulative exposures to diesel or gasoline emissions and exposure to asbestos

statistically significant risk estimates in bold

Kachuri et al concluded that the two sets of results summarized in Tables 16 and 17 supported the likelihood that the interaction between a duration of more than 30 years of occupational exposure to RCS and smoking is multiplicative. The results of this study are consistent with those of a 1991 mortality study by Hnizdo et al of South African gold miners and two case- control studies (Vida et al 2010, Cassidy et al

[q] the synergy (S) and multiplicativity (V) indices were modeled after similar analyses of the joint effects of asbestos exposure and smoking on lung cancer risk by Villeneuve et al 2012 and Frost et al 2011.

2007) that also found the combined effect of RCS exposure and smoking to be more consistent with a multiplicative model. The authors of this paper also provided the following cautionary statement: "However, caution should be exercised when inferring the existence of a biological interaction on the basis of an observed statistical interaction, especially because of the complex nature of RCS-induced carcinogenesis."

The Ge et al (2020a) study overcame the main limitation of earlier studies by having a large enough number of cases exposed to RCS (4,923) that allowed for stratification and interaction analysis for different risk factors. Detailed lifetime occupational and smoking histories were available for all subjects. Stratified analysis showed that regardless of smoking status, increasing RCS exposure was associated with increasing risk of lung cancer (Table 18). Risks of lung cancer for different RCS exposure groups were similar for former and current smokers, with ORs of 1.47; CI 1.27-1.70 and 1.29; CI 1.20-1.62 for the highest exposed group respectively.

For never smokers, the odds ratios for all RCS cumulative exposure categories were > 1, with the highest exposed category (≥2.4 mg/m^3-years) having a statistically significant OR of 1.40; 95% CI 1.03-1.86. This finding is comparable to that in the Liu et al 2013 study in which never smokers with cumulative RCS exposure > 1.12 mg/m^3-years had a lung cancer hazard ratio of 1.60; 95% CI 1.01-2.55. The Ge et al study was the first to report an exposure-response association between cumulative RCS exposure and lung cancer among never smokers.

Table 18 Lung Cancer Risks Associated with Cumulative Occupational RCS Exposure by Smoking Status*

Cumulative Exposure (mg/m^3-years)	Never Smokers	Former Smokers	Current Smokers
	OR[1] (95% CI) [number of cases]	**OR[2] (95% CI) [number of cases]**	**OR[3] (95% CI) [number of cases]**
None	**1.0 (referent) [1,121]**	**1.0 (referent) [3,696]**	**1.0 (referent) [7,161]**
>0-0.39	1.17 (0.85-1.57) [60]	1.07 (0.92-1.25) [366]	**1.19 (1.03-1.39) [687]**
0.4-1.09	1.07 (0.78-1.43) [59]	**1.37 (1.18-1.59) [433]**	**1.33 (1.15-1.550 [729]**
1.1-2.39	1.02 (0.75-1.36) [60]	**1.35 (1.16-1.570 [441]**	**1.29 (1.11-1.50) [730]**
≥2.4	**1.40 (1.03-1.86) [69]**	**1.47 (1.27-1.70) [496]**	**1.39 (1.20-1.62) [793]**
test for trend, p value	**<0.01**	**<0.01**	**<0.01**
p value excluding never exposed	**0.02**	**<0.01**	**0.07**

** adapted from Table 5 in Ge et al 2020a*

[1] Odds ratios adjusted for study, age group, sex and exposure to other occupational carcinogens

[2] Odds ratios adjusted for study, age group, sex, smoking (pack-years, time since quitting smoking) and exposure to other occupational carcinogens, pack-years, and time since quitting smoking

[3] Odds ratios adjusted for study, age group, sex, exposure to other occupational carcinogens and pack-years

statistically significant risk estimates in bold

The Ge et al (2020a) study also observed a supermultiplicative[r] effect between smoking and occupational RCS exposure for overall cancer; relative excess risk due to interaction (RERI) = 2.34; 95% CI 1.85-2.83 (Table 19). This is similar to the observation of a greater than multiplicative effect in the 2014 Canadian case-control study by Kachuri et al (Table 16 above), and also to the finding in the Liu et al 2013 study that observed a greater than additive and closer to multiplicative interaction between cumulative RCS exposure and smoking; RERI = 1.27; 95% CI 0.75-2.25.

Table 19 Interactions between Occupational RCS Exposure and Smoking for all Lung Cancers*

Exposure Status	Odds Ratio; OR1 (95% CI) [number of cases]
Never smoker & never RCS	**1.0 (referent) [1,121]**
Never smoker & ever RCS	**1.02 (0.87-1.19) [248]**
Ever smoker& never RCS	**6.37 (5.91-6.87) [10,857]**
Ever smoker & ever RCS	**8.72 (8.00-9.52) [4,675]**
p value multiplicative interaction1	**<0.01**
RERI (Relative Excess Risk due to Interaction)1	**2.34 (1.85-2.83)**

**adapted from Table 6 in Ge et al 2020a*

[1] interaction on the multiplicative scale is present when p < 0.05

statistically significant risk estimates in bold

Diesel Exhaust

Diesel engines are used in a variety of industries to power vehicles (e.g., trucks, forklifts, buses, railroad engines) and a wide range of heavy-duty equipment (e.g., mining equipment, earth movers, other construction equipment). The use of diesel-powered vehicles for ore haulage underground in Ontario gold mines began in the 1960s (Kabir et al 1993).

Diesel exhaust is a complex mixture of gases and particulates generated by the combustion of diesel fuel (IARC 2013, NTP 2006, CAREX 2019). The composition of DE depends on the type of diesel fuel, the type and age of the engine, tuning and maintenance, workload, and the exhaust treatment system. The gas compounds can include water vapour, carbon dioxide, carbon monoxide, nitrogen oxides, and volatile organic compounds, such as benzene and formaldehyde. The particulates consist of elemental and organic carbon, ash, sulfate, and metals. Polycyclic aromatic hydrocarbons (PAHs) and nitroarenes are present in the gas phase and are also adsorbed onto the surface of the elemental carbon particles. Almost all the particulates in DE are respirable (<10 micrometers in diameter), with the majority having diameters of less than 1.0 micrometers. The particulates can occur individually or can “clump” together into clusters called agglomerates.

[r] Supermultipicative interaction represents a scenario in which the risk ratios (OR) of lung cancer for those exposed to RCS and smoking was higher than the product of the cancer risk ratios from RCS exposure and smoking alone.

Elemental carbon (EC), also referred to as respirable elemental carbon (REC), has been chosen by researchers as a surrogate or representative indicator of DE exposure since the early 1990s when it was found that most of the carcinogenic and mutagenic properties of DE were associated with the carbon particles (IARC Vol 105).

The three most widely studied occupations at risk of lung cancer associated with DE exposure are:

1. *Underground miners*
2. *Railroad workers*
3. *Transportation workers (e.g., truck drivers, bus and subway drivers)*

Table 20 summarizes some representative occupational exposures to DE from air sampling done between 1990 and 2007 (IARC 2013, Pronk et al 2009).

The current MLITSD mining regulations (MOL Reg 854) require that the time-weighted average exposure value (TWAEV) for DE in underground mines must not exceed 0.4 mg/m^3 or 400 ug/m^3 measured as total carbon (TC), or that the elemental carbon (EC) multiplied by 1.3 is not more than 0.4 mg/m^3, therefore, the equivalent TWAEV for EC is 310 ug/m^3.

Table 20 Occupational exposure to DE measured as elemental carbon (EC)[*]

Occupation/Job Title	**Elemental Carbon[s] (ug/m^3) (personal sampling)**	
	Range	**Average/Mean**
High Exposures > 50 ug/m^3		
tunnel construction	100 to 300	215
underground mining maintenance	**53 to 144**	**141**
underground mining production	**148 to 637**	**135**
Intermediate Exposures (≥ 10 ug/m^3 to 50 ug/m^3)		
dock workers (lift trucks)	4 to 122	43
diesel mechanics (trucks/buses)	4 to 39	29
railroad maintenance, mechanics	5 to 39	24
loading/unloading ships	6 to 49	11
above ground construction (heavy equipment operators)	4 to 13	10
Low Exposures (< 10 ug/m^3)		
vehicle testing, parking attendant, toll booth worker, transport terminal worker, traffic police officer	generally < 10	
unloading baggage from planes	generally < 10	
firefighters	non-detected to 40	generally < 10
mining- surface production	3.5 to 23	8
railroad train crews	4 to 20	8
truck drivers	1 to 22	2

[s] Elemental carbon (EC), also referred to as respirable elemental carbon (REC), was chosen by researchers as a surrogate or representative indicator of DE exposure since the early 1990s when it was found that most of the carcinogenic and mutagenic properties of DE were associated with the carbon particles [*] adapted from Tables 1 to 4 in Pronk et al 2009 [90] and IARC Monograph 105 [87] Tables 1.14 to 1.17.

There is considerable variation in DE exposures between different occupations or industries (IARC Monograph 105, Pronk et al 2009). Underground production or maintenance miners have the highest exposures to DE (≥ 50 ug/m^3), mainly because of the enclosed nature of the workplace and their proximity to the diesel vehicles and equipment. There can also be considerable variation in DE exposures within an occupation or industry. For example, underground miners are typically exposed to DE concentration 10 or more times greater than surface mine workers. There can also be differences in exposure within the same occupation due to variations in the diesel equipment or other exposure conditions. The variability in the concentrations of DE makes it difficult to assess the potential for health effects associated with these exposures.

The concentrations of DE in some workplaces have decreased in recent years largely because of stricter standards that required changes in diesel fuel composition (e.g., lower sulphur content) and more efficient exhaust treatment devices (e.g., filters or catalysts). The use of diesel-powered equipment and the resulting exposure to DE can be roughly divided into three periods:

1. *Traditional diesel exhaust (TDE) refers to the period before 1988 when diesel exhaust was essentially unregulated.*
2. *Transitional diesel exhaust refers to the period between about 1988 and 2006 when there were progressively more stringent emission requirements.*
3. *New technology diesel exhaust (NTDE) refers to the period after 2006 when the most recent diesel emission standards were adopted.*

The composition of NTDE is significantly different as it contains about 90% less particulates than TDE (IARC 2013, Pronk et al 2009, Hesterberg et al 2011). Since the carcinogenic properties of diesel exhaust appear to be associated with the particulates, it is thought that NTDE may be significantly less toxic than TDE. However, since the NTDE exposure period began in 2006/2007, there has been too short a time for epidemiological studies to observe the effect of exposures to lower concentrations of DE on long-latency diseases such as lung cancer. Present-day cases of DE-exposure-related lung cancer are most likely to be associated with workplace exposures to TDE era more than 20 years ago.

DE was previously evaluated by IARC (IARC 1989). At that time, DE was classified as *probably carcinogenic to humans (Group 2A)* on the basis of *limited evidence* from epidemiological studies in humans and *sufficient evidence* for carcinogenicity in experimental animals.

In 2013 IARC classified DE as carcinogenic to humans (Group 1) based on sufficient evidence that exposure is associated with an increased risk for lung cancer (IARC 2013). IARC concluded that the most informative evidence was from recent epidemiological studies of miners (Attfield et al 2012, Silverman et al 2012), railroad workers (Garshick et al 2004, Laden et al 2006), and trucking industry workers published up to 2012 (Steenland et al 1998, Garshick et al 2008, Garshick et al 2012) and a more-recently published pooled case-control study (Olsson et al 2011).

IARC found that the strongest evidence for an association between DE exposure and an increased risk of lung cancer was provided by two recent studies of a large cohort of US miners known as the Diesel Exhaust Mining Study (DEMS) (Attfield et al 2012, Silverman et al 2012). IARC gave greater weight to the DEMS nested case-control study, because it controlled for tobacco smoking. IARC concluded:

a. *The more informative epidemiological studies, many of which controlled for smoking, consistently showed a positive association between exposure to DE and an increased risk of lung cancer.*
b. *Most of the comparisons of exposed to unexposed groups indicated modest increases in risk and some analyses showed positive, statistically significant exposure-response trends.*
c. *Positive exposure-response trends were seen across different study designs and in several occupational settings.*
d. *It is improbable that the observed association between exposure to DE and the risk for lung cancer was caused by chance, bias or confounding.*

The DEMS included 198 lung cancer cases among over 12,000 workers from 8 US non-metal mines and was undertaken to specifically address some of the major shortcomings of earlier studies. Non-metal mines were chosen to reduce the likelihood of exposure to other lung carcinogens such as asbestos, RCS or radon. Detailed historical exposure to DE as respirable elemental carbon (REC) was estimated for the period from 1947-1967 (the period when diesel equipment was introduced in the mines) to 2007. The average REC concentration was 1.7 ug/m^3 for surface workers and 128.2 ug/m^3 for underground miners.

The DEMS included both a cohort analysis and a nested case-control study that adjusted for tobacco smoking. Both studies showed an increased risk of lung cancer with increasing exposure to DE as estimated by REC. The nested case-control study found statistically significant trends of increasing lung cancer risk with increasing average exposures of DE (ug/m^3), duration of exposure (years) and cumulative exposure (ug/m^3 –years). There was a statistically significant 2 to 3-fold increase in risk of lung cancer in the highest categories of cumulative exposure and average exposure. Table 21 summarises these findings.

Table 21 Lung Cancer Risk for Average, Cumulative and Duration of DE (REC) Exposure*	
Exposure Metric	
Average REC Intensity quartiles unlagged, µg/m3	**OR (95% CI) [cases]**
0 to < 1	1.0 (referent) [49]
1 to < 32	1.03 (0.50-2.09) [50]
32 to < 98	1.88 (0.76-4.66) [49]
≥ 98	2.40 (0.89-6.47) [50]
p for trend = 0.25	
Average REC Intensity Quartiles lagged 15 years, µg/m^3	**OR (95% CI) [cases]**
0 to < 1	1.0 (referent) [47]
1 to < 6	1.11 (0.59-2.07) [52]
6 to < 57	1.90 (0.90-3.99) [49]
≥ 57	**2.28 (1.07-4.87) [50]**
p for trend = 0.062	
Cumulative REC, quartiles unlagged, µg/m^3-years	**OR (95% CI) [cases]**
0 to < 19	1.0 (referent) [49]
19 to < 246	0.87 (0.48-1.59) [50]
246 to < 964	1.50 (0.67-3.36) [49]
≥ 964	1.75 (0.77-3.97) [50]
p for trend = 0.83	
Cumulative REC, quartiles lagged 15 years, µg/m^3-years	**OR (95% CI) [cases]**
0 to < 3	1.0 (referent) [49]
3 to < 72	0.74 (0.40-1.38) [50]
72 to < 536	1.54 (0.74-3.20) [49]
≥ 536	**2.84 (1.28-6.26) [50]**
p for trend = 0.001	
Duration of REC exposure, years	**OR (95% CI) [cases]**
Unexposed	1.0 (referent) [48]
0 to < 5	1.16 (0.53-2.55) [51]
5 to < 10	0.88 (0.38-2.03) [20]
10 to < 15	0.93 (0.39-2.21) [31]
≥ 15	2.09 (0.89-4.90)
P for trend = 0.43	

** adapted from Table 3 in Silverman et al 2012*

statistically significant risk estimates in bold

An important finding in the Silverman et al 2012 study was the increased risk of lung cancer with increased cumulative DE exposure among the 14 case subjects who never smoked. Never smokers with the highest cumulative DE exposure (≥ 304 μg/m^3- years) had a statistically significantly greater than 7-fold increased risk of lung cancer. This was the first study to observe increased lung cancer risk for never smokers exposed to DE. However, a limitation is that there were only a small number of cases who never smoked (n=7). The proportion of never smokers in this study (29%) was substantially lower than the 51% reported for the US population of men older than 18 years of age. The combined effect of DE exposure and intensity of cigarette smoking is shown in Table 22 below.

Table 22 Cumulative Respirable Elemental Carbon (REC) lagged 15 years OR[1] (95% CI), [number of cases] *

Smoking intensity (packs per day)	Tertile of cumulative REC exposure		
	0 to < 8 μg/m^3- years	**8 to < 304 μg/m^3- years**	**≥ 304 μg/m^3- years**
Never smoker	1.0 (referent) [3]	1.47 (0.29-7.50) [4]	**7.30 (1.46-36.57) [7]**
< 1	**6.25 (1.42-27.66) [10]**	**7.42 (1.62-34.00) [10]**	**16.35 (3.45-77.63) [15]**
1 to < 2	**10.16 (2.55-40.53) [29]**	**11.58 (2.87-46.71) [32]]**	**20.42 (4.52-92.36) [27]**
≥ 2	**26.79 (6.15-116.63) [19]**	**22.17 (4.84-101.65) [15]**	**17.38 (3.48-86.73) [10]**
unknown	4.13 (0.74-23.22) [4]	3.79 (0.64-22.41) [4]	**27.85 (5.03-154.31) [9]**

** adapted from Table 6 in Silverman et al 2012.*

[1] ORs adjusted for history of respiratory disease 5 or more years before date of death/reference date, history of other lung carcinogens for at least 10 years, and mine location (surface-only vs any underground work)

p value for interaction between smoking intensity and cumulative REC lagged 15 years = .086.

This study also observed attenuated lung cancer risk in miners who were heavy smokers and highly exposed to DE (i.e., a negative interaction between DE exposure and smoking). The authors proposed several possible mechanistic explanations to account for this including that at high levels of DE exposure polycyclic aromatic hydrocarbons (PAHs) and related compounds compete with the metabolic activation of PAHs in tobacco smoke leading to enzyme saturation.

A recent study by Ge et al (2020b) further assessed the risk of lung cancer from occupational exposure to DE and the interaction with smoking. A previous pooled case-control analysis on DE and lung cancer (Olsson et al 2011) was expanded by including three additional studies and a quantitative exposure assessment for DE exposure measured as REC. Subjects from 14 hospital and population-based lung cancer case-control studies in 13 European countries and Canada were pooled resulting in 37,866 subjects (16,901 cases; 20,965 controls). Although this study also analysed the lung cancer risk for females exposed to DE, only results for the male subjects will be discussed here in order to be consistent with other studies in this document.

Table 23 summarises the lung cancer odds ratios for categorical indices of DE exposure. Elevated lung cancer risk was observed for those with ever occupational exposure to DE (OR = 1.22; 95% CI 1.15-1.29). Increasing trends in lung cancer risk were associated with increases in both exposure duration and

cumulative exposure (p for trend <0.01). Statistically significant increased risk was also observed in all ranges of duration and cumulative exposure to DE. Notably, this included the lowest categories of exposure duration (1-9 years; OR = 1.07; 95% CI 1.00-1.16) and cumulative exposure (>0 to 22 µg/m^3-years; OR = 1.09; 95% CI 1.00-1.19) with a median exposure of 11 µg/m^3-years. An exposure threshold for DE related lung cancer was not observed within the cumulative exposure ranges that were investigated.

Table 23 Lung Cancer Odds Ratios (ORs)[1] Associated with Categorical Indices of Occupational Exposure to DE measured as REC*	
Occupational DE Exposure	**Odds Ratio; OR (95% CI) [no. of cases]**
Never	**1.0 (referent) [5,560]**
Ever	**1.22 (1.15-1.29) [8,045]**
Duration (years)	
1-9	**1.07 (1.00-1.16) [2,346]**
10-19	**1.23 (1.13-1.34) [1,774]**
20-29	**1.23 (1.12-1.35) [1,578]**
> 29	**1.39 (1.28-1.51) [2,347]**
Test for trend, p value/p value excluding never exposed	**< 0.01/<0.01**
Cumulative Exposure (µg/m^3-years)	
> 0 to 22	**1.09 (1.00-1.19) [1,684]**
23-70	**1.10 (1.02-1.20) [1,858]**
71-178	**1.24 (1.15-1.35) [2,113}**
> 178	**1.43 (1.32-1.54) [2,390]**
Test for trend, p value/p value excluding never exposed	**< 0.01/<0.01**

** adapted from Table 2 in GE et al 2020b.*

[1] ORs adjusted for study, age group, smoking pack-years [log (cigarette pack-years + 1)], time since quitting smoking and jobs with exposures to other lung carcinogens

statistically significant risk estimates in bold

To put these DE cumulative exposures into perspective, the current Ontario Ministry of Labour Training and Skills Development (MLITSD) occupational exposure limit for underground mines is 310 ug/m^3 measured as REC.

Analysis stratified by smoking status, found exposure-response associations between cumulative DE exposure and lung cancer regardless of smoking history (Table 24). Lung cancer risks were similar for men in the highest DE exposure group who were never smokers (OR = 1.41; 95% CI 1.04-1.88), former smokers (OR = 1.47; 95% CI 1.31-1.65) and current smokers (OR = 1.40; 95% CI 1.24-1.57).

An exposure-response trend was observed among never smokers who were exposed to DE (test for trend p value =0.03) and a statistically significant increased risk for those never smokers in the highest cumulative exposure category of > 178 µg/m^3-years (OR = 1.41; 95% CI 1.04-1.88). The Silverman et al (2012) study also reported a statistically significant risk among US miners exposed to > 304 µg/m^3-years

(OR = 7.30; 95% CI 1.46-36.57) (Table 21 above). The much higher risk in the US miners may be the result of higher cumulative exposure to DE or that the risk estimate was based on only 7 cases.

Table 24 Lung Cancer Risks Associated with Cumulative Occupational DE Exposure by Smoking Status*			
Cumulative DE exposure (μm^3-years)	**OR (95% CI) [number of cases]**		
	Never Smokers[1]	**Former Smokers[2]**	**Current Smokers[3]**
Never	1.0 referent [256]	1.0 referent [1,868]	1.0 referent [3,436]
> 0 to 22	**1.40 (1.03-1.88) [66]**	1.11 (0.98-1.26) [624]	1.04 (0.92-1.18) [994]
23-70	0.94 (0.65-1.33) [41]	**1.23 (1.09-1.40) [656]**	1.01 (0.90-1.14) [1,161]
71-178	1.17 (0.85-1.60) [55]	**1.33 (1.18-1.50) [764]**	**1.15 (1.03-1.29) [1,294]**
> 178	**1.41 (1.04-1.88) [72]**	**1.47 (1.31-1.65) [875]**	**1.40 (1.24-1.57) [1,443]**
Test for trend, p value/ p value excluding never exposed	**0.03/**0.11	**< 0.01/**0.08	**< 0.01/0.05**

** adapted from Table 4 in GE et al 2020b.*

[1] ORs adjusted for study, age group, and occupations with exposure to other lung carcinogens

[2] ORs adjusted for study, age group, occupations with exposure to other lung carcinogens, smoking pack-years and time since quitting smoking

[3] ORs adjusted for study, age group, occupations with exposure to other lung carcinogens, smoking pack-years

statistically significant risk estimates in bold

The Ge et al (2020b) study also observed a superadditive[t] effect between smoking and occupational exposure to DE for overall lung cancer; relative excess risk due to interaction (RERI) = 2.49; 95% CI 1.92-3.07 (Table 25). A similar superadditive effect was seen in a Swedish study of dock workers (Emmelin et al 1993).

Table 25 Interactions between Occupational DE (REC) Exposure and Smoking for all Lung Cancers*	
Exposure Status	**Odds Ratio; OR[1] (95% CI) [number of cases]**
Never smoker & never DE(REC)	1.0 (referent) [256]
Never smoker & ever DE(REC)	1.24 (0.95-1.38) [234]
Ever smoker& never DE(REC)	**8.71 (7.62-10.0) [5,745]**
Ever smoker & ever DE(REC)	**11.4 (9.93-13.0) [6,269]**
p value multiplicative interaction[1]	0.18
RERI (Relative Excess Risk due to Interaction)[1]	**2.49 (1.92-3.07)**

**adapted from Table 5 in Ge et al 2020b*

[1] interaction on the multiplicative scale is present when p < 0.05

statistically significant risk estimates in bold

[t] Superadditive interaction represents a scenario in which the risk ratios (OR) of lung cancer for those exposed to DE (REC) and smoking was higher than the sum of the cancer risk ratios from DE (REC) exposure and smoking alone.

Lifetime Risk of Lung Cancer from DE Exposure

In 2014, a meta-analysis by Vermeulen et al of three occupational studies that were critical to the IARC evaluation was used to derive an overall exposure-response curve. These studies were: the DEMS case-control study (Attfield et al 2012, Silverman et al 2012) and two trucking industry studies (Steenland et al 1998, Garshick et al 2012). The exposure-response curve was used to estimate the risk of lung cancer for a lifetime (i.e., 45 years) of occupational exposure to average DE concentrations ranging from 1 to 25 ug/m^3 (measured as elemental carbon). Estimated numbers of excess lung cancer deaths for typical occupational exposures of 45 years ranged from 17 to 689 per 10,000 persons. It was estimated that a working lifetime (i.e., 45 years) of exposure to 10 µg EC/m^3 would result in 200 extra lung cancer deaths per 10,000. These rates of excess lung cancer deaths are much greater than the generally acceptable limits used in the United States and Europe which are generally set at 1 case of lung cancer per 1,000 exposed workers (or 10 cases per 10,000 workers).

Based on the Vermeulen et al exposure-response model, OHCOW has developed a Diesel Exposure Calculator that can be used to estimate the risk of lung cancer based on cumulative exposure to DE that can be accessed on the OHCOW website. For example, using the calculator it is estimated that an underground miner exposed for 18 years at the current MLITSD OEL of 310 ug/m^3 of REC would have a nearly 3-fold statistically significant increased risk of lung cancer; relative risk (RR) = 2.72; 95% CI 1.45-5.11. The MLITSD is currently reviewing proposed changes to lower the exposure limit for DE.

The Occupational Cancer Research Centre (OCRC) recommends adopting exposure limits of 20 µg/m^3 EC for the mining industry and 5 µg/m^3 EC for other workplaces, based on evidence of health effects at low levels and feasibility considerations (Vermeulen 2016, Silverman 2017) while continuing to work towards limits that reflect the current science (OCRC 2022).

These OELs are still much higher than the health-based limits from the Dutch Expert Committee on Occupational Safety (DECOS) limit of 1.00 µg/m^3 REC and the Finnish Institute of Occupational Health (FIOH) recommendation of 5 µg/m^3 REC that are often used as a reference for acceptable occupational OELs for DE.

The first study to quantify the burden of lung cancer attributable to occupational DE exposure in Canada estimated that based on 2011 lung cancer statistics, 2.4%; 95% CI 1.6%-6.6% of lung cancers in Canada were attributable to occupational exposure to DE (Kim et al 2018). This study also observed that half the estimated burden occurred among those exposed at low levels of DE (range of >0 to <10 ug/m^3 with a mean exposure of 5 ug/m^3. Underground mining was identified as an occupation with the highest burden of lung cancer attributable to DE exposure.

Ionizing Radiation (Radon)

Uranium production from Ontario mines began in 1954 with about 500 development miners and increased rapidly from 1957 to 1960 when there were about 10,000 uranium miners. After the demand for uranium oxide ore from Ontario mines suddenly decreased in the early 1960s, the number of uranium miners also decreased rapidly to about 1,000 by the mid-1960s (Ham 1976, Runnals 1981). There was a brief resurgence of uranium mining in the Elliot Lake region in the late 1970s because of power generation demands. However, by the 1990s only the Denison and Stanleigh uranium mines were in operation; and these mines ceased operation in 1992 and 1996, respectively.

Radon-222 is a radioactive gas released from the natural radioactive decay chain of uranium 238. Radon decays into a series of isotopes or radon decay products (RDP) through the emission of alpha particles. The half-life[u] of radon is 3.82 days. Lung cancer due to radon exposure is caused by the RDP which are suspended in air when radon gas is present, or when they attach to dust particles that are inhaled and deposited in the lungs (Bissett et al 2010, Canadian Nuclear Safety Commission 2011). Damage results when the inhaled RDP come into close proximity to lung tissue, particularly in the larger airways of the lung where these particles tend to settle out. Malignant change leading to cancer can occur if sufficient alpha radiation energy is released during a sensitive part of the lung cell life cycle, causing damage to cellular DNA.

Radon has been recognized as a hazard in mines for many years (ICRP 2010, IARC 2012a). The Committee on the Biological Effects of Ionizing Radiation (BEIR) that is part of the National Research Council (NRC) publishes periodic reports to advise the U.S. government on the relationship between exposure to ionizing radiation and human health. The BEIR Committee has published 7 reports to date and the most recent BEIR VII report addressed the health risks from exposure to low levels of ionizing radiation such as radon. The BEIR IV report published in 1988 informed the development of the WSIB Policy on Lung Cancer in Uranium Miners (BEIR IV).

In 2001, radon was classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1) because of the well-established link between radon exposure and lung cancer (IARC 2001) and the 2012 IARC review of Group 1 carcinogens reaffirmed this classification (IARC 2012a). Studies of uranium miners to date have demonstrated strong evidence for increased risk of lung cancer mortality compared to the general population, as well as strong exposure-response relationships between cumulative radon exposure and lung cancer mortality (Boice et al 2008, Lane et al 2010, Rage et al 2015, Schubauer-Berigan et al 2009, Tomasek et al 2012, Walsh et al 2015, Kusiak et al 1993).

The most relevant studies for this summary are those of Ontario uranium miners. Radon was also present in Ontario gold mines, but to a much lesser extent than in uranium mines. The 1993 Kusiak et al study reported that the average cumulative exposure to radon in gold mines was 2 working level months

[u] *Half-life means the time it takes for the amount of radioactivity to be reduced by half*

(WLM), with 99% of the cumulative exposures being less than 22 WLM. By comparison, the average cumulative exposure to radon in uranium mines was 30 WLM and 99% of the cumulative exposures were less than 255 WLM.

The Ontario Uranium Mining Cohort

The earliest evidence of increased risk of lung cancer in Ontario uranium miners was provided in a 1974 report (Muller et al 1974) that found a greater than 3-fold statistically significant increase in risk of lung cancer death among Ontario uranium miners [SMR = 3.13 (2.75-4.16)].

This finding resulted in the creation of the Ontario Uranium Miners Cohort to better understand the health effects associated with uranium mining. This cohort includes about 30,000 uranium miners and continues as one of the largest cohorts of uranium miners in the world with high quality exposure assessment. There have been several analyses and updates (Kusiak et al 1993, Ham 1976, Muller et al 1983, Muller et al 1989) of data collected from this cohort, with the most recent update published by OCRC (OCRC 2015).

Table 26 summarizes the risk estimates for lung cancer mortality reported in the Ontario Uranium Mining Cohort studies to date.

Table 26 Summary of Lung Cancer Mortality Reported in the Ontario Uranium Mining Cohort Studies

Study	Follow-up Period	Cohort size*	Lung Cancer SMR**	95% CI***
Muller et al 1974	1955-1973	8,649	3.13	2.75-4.16
Ham, 1976	1955-1974	~18,000	1.80	1.43-2.23
Muller et al 1983	1955-1977	15,984	1.81	1.50-2.14
Muller et al 1989	1955-1981	14,877	1.70	1.46-1.97
Kusiak et al 1993	1955-1986	21,346	2.25	1.91-2.64
OCRC, 2015	1954-2007	28,546	1.34	1.27-1.42

** Cohort sizes differ due to varying inclusion criteria and follow-up periods*
*** SMR = Standardized Mortality Ratio*
**** CI = Confidence Interval*

The OCRC 2015 update of the Ontario Uranium Mining cohort added 21 years of follow-up and examined lung cancer incidence as well as mortality (OCRC 2015, Navaranjan et al 2016). Presently, the Ontario Uranium Mining Cohort consists of 28,546 miners, with average age at entry of 28.8 years. Miners in the cohort had an average cumulative exposure to radon of 21.0 WLM (range 0 to 875.1) over an average of 5.3 years of total exposure (range 1 to 45 years). Based on these figures, the calculated average annual exposure to radon was 4 WLM (21 WLM ÷ 5.3 = 4.0 WLM/year). However, an individual miner's exposure to radon could vary widely as shown in the wide ranges of cumulative radon exposure and total years of exposure. For comparison, the current MLITSD OEL for radon exposure in mines and mining plants is 1.0 WLM/year (MLITSD Reg 854).

The overall lung cancer incidence over the period 1969 to 2005 for Ontario uranium miners, compared with the Canadian male population, was statistically significant; SIR = 1.30; 95% CI 1.23-1.37 [1291 cases]. Lung cancer mortality over the period 1954 to 2007 was also significantly increased compared to Canadian males SMR=1.34; 95% CI 1.27-1.42 [1230 deaths].

Exposure-Response

The BEIR VII report published in 2006 reaffirms the conclusions of the earlier BEIR reports IV and VI that, based on the available evidence from epidemiological studies and a comprehensive review of biological studies, a linear no-threshold model best describes the relationship between exposure to ionizing radiation and lung cancer. According to this model the risk of lung cancer increases as exposure to ionizing radiation (radon) increases. In addition, the BEIR committee has concluded that the risk would continue in a linear fashion at lower doses without a threshold, so that even the smallest radiation dose has the potential to increase the risk of lung cancer in humans. The linear Excess Relative Risk (ERR) model, based on 11 uranium mining cohorts, proposed by BEIR is as follows:

$$ERR_{radon} = \beta_{radon} \times w$$

where ERR_{radon} = Excess Relative Risk[v] of lung cancer from radon exposure,

β_{radon} = estimated cohort-specific exposure-response coefficient (ERR/WLM) and

w = cohort-specific cumulative radon exposure

The OCRC 2015 update of the Ontario Uranium Miners Cohort study showed a positive exposure-response relationship between cumulative radon exposure and lung cancer incidence. There was a 28%, close-to-significant, increase in lung cancer incidence (RR=1.28; 95% CI 0.96-1.70) at cumulative exposures of >30-50 WLM. There was a statistically significant nearly 2-fold increase in lung cancer incidence (RR=1.92; 95% CI 1.45-2.54) at cumulative exposures from > 50 WLM to 100 WLM and a greater than 2-fold increase in the highest cumulative exposure category of > 100 WLM.

A positive exposure-response relationship was also observed between cumulative exposure to radon and lung cancer mortality. The statistically significant lung cancer mortality risk increased from 1.41; 95% CI 1.03-1.94 for cumulative radon exposures of >20 to 30 WLM to a greater than 2-fold increased risk at cumulative exposures > 100 WLM (RR=2.33; 95% CI 1.73-3.14). A statistically significant increase in lung cancer mortality was also observed at very low doses (>0 to 1 WLM) for miners exposed after 1970 (RR=1.43; 95% CI 1.05-1.95). This finding indicates that the lung cancer mortality risk among miners exposed during the lowest exposure period (after 1970) was similar to the risk for the full cohort (RR= 1.34; 95% CI 1.27-1.42). Lung cancer incidence and mortality by cumulative exposure to radon among Ontario uranium miners are summarized in Table 27 below.

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[v] *Excess Relative Risk (ERR) corresponds to the percentage increase (or decrease if negative) of the health risk in one group compared to a reference group. Excess Relative Risk (ERR) = proportion of Relative Risk (RR) due solely to radiation exposure (ERR=RR-1)*
reference: National Cancer Institute https://radiationcalculators.cancer.gov/irep/model)

Table 27 Lung Cancer Incidence and Mortality by Cumulative Exposure to Radon Progeny in Working Level Months (WLM)* among Ontario Uranium Miners				
Lung Cancer Incidence			**Lung Cancer Mortality**	
Cumulative Exposure (WLM)**	**Mean Exposure (WLM)**	**Relative Risk (95% confidence limits) [number of cases]**	**Mean Exposure (WLM)**	**Relative Risk (95% confidence limits) [number of deaths]**
0	0	1 [70]	0	1 [60]
>0 to 1	0.35	1.10 (0.82-1.48) [119]	0.36	**1.43 (1.05-1.95) [125]**
>1 to 5	2.64	0.99 (0.75-1.32) [165]	2.66	1.22 (0.91-1.65) [162]
>5 to 10	7.22	0.86 (0.64-1.15) [124]	7.23	1.06 (0.77-1.44) [121]
>10-20	14.30	1.02 (0.77-1.34) [186]	14.30	1.24 (0.92-1.660[179]
>20-30	24.40	1.21 (0.90-1.62) [119]	24.40	**1.41 (1.03-1.94) [111]**
>30-50	38.60	1.28 (0.96-1.70) [150]	38.60	**1.56 (1.15-2.12) [145]**
>50-100	70.00	**1.47 (1.11-1.95) [174]**	69.90	**1.81 (1.35-2.45) [163]**
>100	163.50	**1.92 (1.45-2.54) [174]**	162.7	**2.33 (1.73-3.14) [165]**

** WLM = Working Level Months; a working level (WL) is defined as 1.3 x 10^3 MeV of potential alpha energy per litre of air and 1 WLM corresponds to exposure to 1 WL during 1 month; i.e., 170 working hours.*
*** Cumulative exposures lagged by 5 years*
statistically significant risk estimates in bold
adapted from Table 3 in OCRC 2015

After applying the linear Excess Relative Risk (ERR) model proposed by BEIR, the 2015 OCRC update estimated an ERR/WLM[w] (β_{radon}) of 0.0064 for lung cancer incidence and 0.0066 for lung cancer mortality (Figures 1 and 2).

As shown in Figures 1 and 2, the exposure-response coefficients ERR/WLM (β_{radon}) may be used to estimate the relative risk[x] for lung cancer incidence or mortality over the continuous range of radon exposures.

$RR = \beta_{radon} \times w + 1$

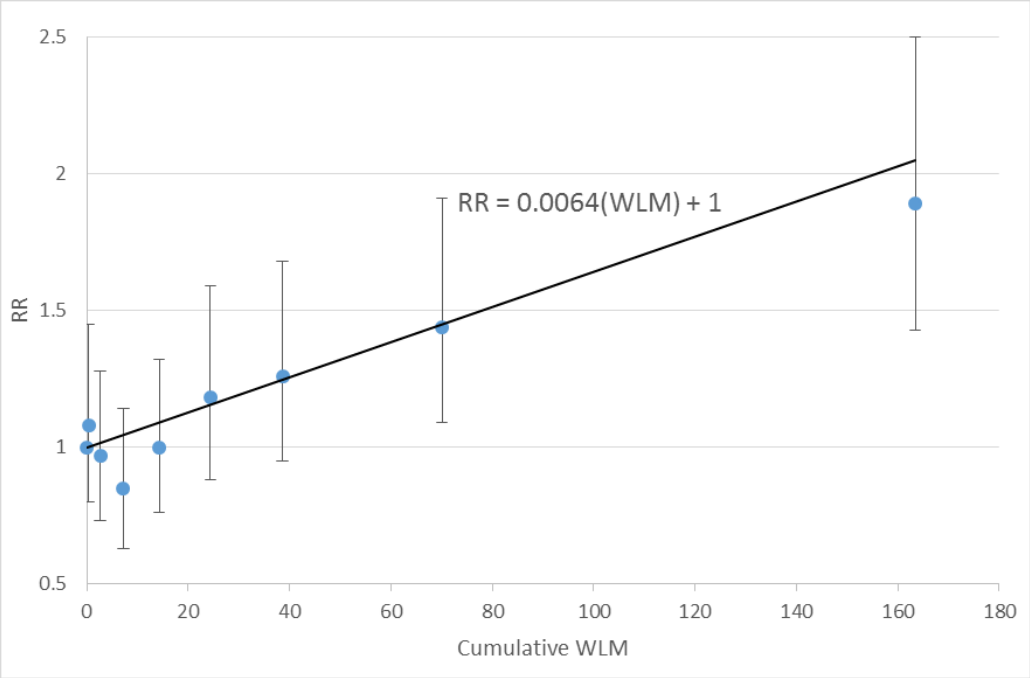
For lung cancer incidence, $RR = 0.0064 \times w + 1$

For lung cancer mortality, $RR = 0.0066 \times w + 1$

For example, for a cumulative radon exposure of 40 WLM[y], the relative risk (RR) for lung cancer incidence can be estimated as RR = 0.0064 x 40 WLM + 1 = 1.26; and the relative risk (RR) lung cancer mortality can be estimated as: RR = 0.0066 x 40 WLM + 1 = 1.26.
This means that a cumulative radon exposure of 40 WLM would increase the lifetime risk of lung cancer incidence and mortality by about 26%.

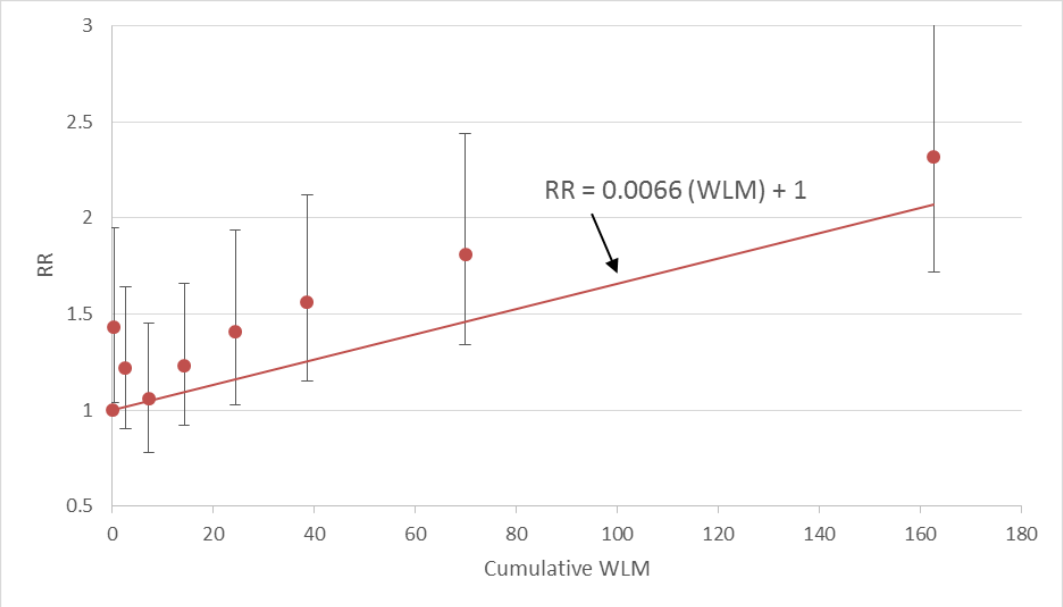
[w]Excess Relative Risk per Working Level Month (ERR/WLM) is also referred to as β_{radon} or the exposure response coefficient from which Relative Risk can be calculated: (RR = β_{radon} x cumulative radon exposure in WLM + 1)
[x]Relative Risk (RR) = ratio of the total risk from exposure divided by risk due to background alone
[y]a cumulative exposure of 40 WLM would be equivalent to a 40-year work history as a uranium miner exposed at the current MOL exposure limit of 1 WLM/year

Figure 1 Relative risk of lung cancer incidence by cumulative exposure to radon and excess relative risk per WLM (ERR/WLM), with a five-year lag[z] applied



excerpted from OCRC 2015

Figure 2 Relative risk of lung cancer mortality by cumulative exposure to radon and excess relative risk per WLM (ERR/WLM), with a five-year lag applied



excerpted from OCRC 2015

z Five-year lag = exposures prior to 5 years before diagnosis are not included; excerpted from OCRC 2015

The finding of a strong linear exposure-response relationship between radon and risk of lung cancer from the 2015 update of the Ontario Uranium Miners Cohort (Figures 1 and 2) is consistent with the BEIR linear no-threshold model. These findings are also consistent with those reported in recent updates of large cohorts of French (Rage et al 2018) and German (Kreuzer et al 2015, Kreuzer et al 2018) uranium miners exposed to low levels of radon.

The Rage et al 2018 study of an extended cohort of 5400 French uranium miners that were followed up from 1946 to 2007, had an average of 13.0 years of exposure to an average radon cumulative dose of 35.1 WLM. A statistically significant excess of lung cancer deaths was observed (SMR=1.32; 95% CI 1.14-1.51), and the ERR (β_{radon}) for lung cancer mortality was calculated as 0.73/100 WLM (0.0073/WLM).

The 2018 update of the German uranium mining cohort by Kreuzer et al added another 10 years of follow-up (up to 2013) to the earlier 2010 analysis by Walsh et al. When the simple, linear EER model was applied to the full cohort, miners with cumulative exposures of < 100 WLM, the ERR/WLM (β_{radon}) for lung cancer mortality was 0.006; 95% CI 0.008-0.028.

Table 28 shows that the risk estimates from the Ontario (Kusiak et al 1993, OCRC 2015), French (Rage et al 2018) and German (Kreuzer et al 2018) cohorts of uranium miners are similar to those reported in three earlier independent, large scale pooled analyses of uranium mining cohorts (BEIR IV 1988, Lubin et al 1994, UNSCEAR 2009,).

Table 28 Summary of Excess Relative Risk (ERR) for lung cancer mortality per working level months (WLM) from published analyses of mining studies

Reference	Number of cohorts	Number of miners	ERR per WLM
Lubin et al (1994)	**11**	**60,570**	**0.0049**
BEIR IV (1999)	**11**	**60,705**	**0.0059**
UNSCEAR (2009)	**9**	**125,627**	**0.0059**
Rage (2018) (France)	**1**	**5,400**	**0.0073**
Kreuzer (2018) (Germany)	**1**	**58,974**	**0.0060**
Kusiak (1993) (Ontario)	**1**	**21,346**	**0.0089**
OCRC (2015) (Ontario)	**1**	**28,546**	**0.0066**

The effects of low occupational exposures to radon and the factors that may confound and modify this risk are not well understood. A 2019 study assessed the risk of lung cancer mortality at low radon exposures (< 100 WLM) in a joint cohort analysis of Czech, French and Canadian[aa] uranium miners, employed in 1953 or later (Lane et al. 2019). The full cohorts of Czech, French and Canadian uranium miners were included among the 11 mining cohorts considered in the BEIR IV, VI and VII reports. For the purpose of this analysis, the cohorts were restricted to time periods after radiation protection measures were introduced, especially mechanical ventilation systems and when radon progeny measurements

[aa] *The Canadian cohort was taken from the full cohort of underground miners and mill workers near the town of Eldorado in Northern Saskatchewan known as the Beaverlodge cohort.*

were routinely made in work areas and/or of individuals, as part of regulatory requirements. These periods corresponded to lower radon exposures and lower radon exposure rates; 1953-1999 for the Czech cohort, 1956-1999 for the French cohort and 1965-1999 for the Canadian cohort.

The mean cumulative radon exposure was 45.1, 32.9 and 32.3 WLM for the Czech, French and Canadian cohorts respectively. The overall mean cumulative exposure for the joint cohort was 36.42 WLM and the excess relative risk per working level month (ERR/WLM) was 0.022 (95% CI 0.013-0.034) based on 408 lung cancer deaths. The relative risks of lung cancer mortality by categories of radon exposure for the joint cohort restricted to cumulative exposures <100WLM is summarized in Table 29.

Table 29 Relative risks of lung cancer mortality by categories of radon exposure for the joint cohort restricted to cumulative exposures <100WLM

Cumulative Radon Exposure (WLM)	Mean Cumulative exposure (WLM)	Relative Risk* (95% CI) [number of lung cancer deaths]
0.0	0.0	1.00 [32]
>0.0-2	1.5	0.83 (0.51-1.34) [39]
3-9	6.0	0.94 (0.60-1.50) [51]
10-19	14.6	1.41 (0.90-2.25) [48]
20-39	29.6	**1.62 (1.06-2.52) [63]**
40-59	49.5	**2.02 (1.31-3.18) [66]**
60-79	69.4	**2.39 (1.55-3.76) [64]**
80-100	88.7	**2.32 (1.45-3.76) [45]**

statistically significant risk estimates in bold

** p value for linear trend <0.001*

This analysis of the joint cohort of Czech, French and Canadian uranium miners found a statistically significant monotonic[bb] increase in the relative risk of lung cancer mortality with increasing cumulative radon exposure from 20 to 100 WLM. The finding of a statistically significant increased lung cancer mortality with cumulative radon exposures > 20 WLM is consistent with the results of the OCRC 2015 update of the Ontario uranium mining cohort. Although the mortality rates were higher than the 2015 OCRC study and the Rage et al 2018 update of the large French cohort, this may reflect the greater uncertainty in the radon exposure estimates of early studies or extrapolated radon exposure in those studies which may have resulted in underestimating the radon risk.

Sensitivity analyses found that the statistically significant linear relationship between radon exposure and lung cancer mortality persisted after controlling for tobacco smoking.

[bb] *Monotonic refers to a sequence of values that consistently increase and never decrease or consistently decrease and never increase in value.*

Modifying Factors

The 2015 OCRC update of the Ontario Uranium Miner Cohort Study also examined the effect of potentially modifying factors on the association between radon exposure and lung cancer incidence and mortality. In brief, lung cancer mortality from radon exposure was modified by attained age, time since first exposure, time since last exposure, age at first exposure and dose rate[cc]. Lung cancer incidence was modified by time since first exposure, time since last exposure and exposure rate[dd]. A detailed discussion of these factors is beyond the scope of this summary and the 2015 OCRC study and BEIR reports should be consulted for further information.

Other exposures that may affect lung cancer incidence and mortality among uranium miners are discussed below and include: cigarette smoking, respirable crystalline silica (RCS), diesel exhaust (DE), other types of mining (i.e., gold, nickel, copper) and arsenic exposure in gold mines.

Cigarette Smoking

Cigarette smoking is the major cause of lung cancer, and smoking status can modify the effect of other lung carcinogens such as radon. The interactive effect may be additive, in which case the effect of smoking appears to add to the effect of another lung carcinogen. The interactive effect may also be greater than additive (super-additive) or multiplicative.

Many epidemiological studies over the past 30 years have observed a greater than additive but less than multiplicative interactive effect of radon and cigarette smoke on risk for lung cancer (BEIR VI 1999, Lane et al 2010, Hunter et al 2013, Bijwaard et al 2011, Leuraud et al 2011, Tomasek 2013). A limitation of the Ontario Uranium Mining Cohort studies to date has been the lack of adequate information on the smoking status of the uranium miners. However, the Muller et al 1974, 1983, 1989 and Kusiak et al 1993 and 1991 studies of lung cancer among Ontario uranium or gold miners, observed that smoking rates were similar across different mining categories (uranium, gold, nickel) and they concluded that smoking could not account for the observed increased risk of lung cancer.

A 2018 update of a large German cohort of nearly 60,000 uranium miners found that adjusting for smoking had little effect on the risk estimates for lung cancer (Kreuzer et al 2018). The effect modification of smoking was analyzed in the 1960+ sub-cohort as better smoking histories were available for miners who started working after 1960. Notably, miners in the intermediate cumulative exposure category (10 to 50 WLM) had an increased lung cancer mortality risk (RR=1.29; 95% CI 1.01-1.56) when compared to the low exposure category of <10 WLM. The increase in risk was similar after adjusting for smoking (RR=1.23; 95% CI 0.98-1.50) and remained close-to statistical significance. A nearly 2-fold statistically significant increased risk was observed for uranium miners in the high cumulative exposure category of 50 to 334 WLM; (RR = 1.99; 95% CI 1.52-2.47). Adjusting for smoking had only a small effect on the risk of lung cancer; (RR = 1.85; 95% CI 1.40-2.30) and the risk remained statistically significant. This was similar to the finding in an earlier nested case-control study (421 cases and 620 controls) from

[cc] *Dose rate = duration of exposure within cumulative dose categories*
[dd] *Exposure rate = WLM per year*

the same cohort in which adjustment for smoking resulted in only marginal changes in lung cancer mortality risk (Schnelzer et al 2010).

Separate adjustment for occupational exposure to other lung carcinogens, including RCS dust and external gamma radiation or long-lived radionuclides, also resulted in only minor changes in the radon-related risk estimates.

The findings of this German study provide additional evidence for increased risk of lung cancer at low radon exposures after controlling for potential confounders such as smoking and occupational exposure to other lung carcinogens. The authors noted that although the small number of deaths in the respective smoking categories reduced the statistical power, the findings are consistent with a greater than multiplicative interaction between radon exposure and smoking.

As noted earlier, the Lane et al 2019 analysis of a joint cohort of Czech, French and Canadian uranium miners found that the statistically significant linear relationship between radon exposure and lung cancer mortality persisted after controlling for tobacco smoking.

Combined Exposure to Radon and Respirable Crystalline Silica (RCS).

There is also some evidence that combined occupational exposure to radon and RCS may be associated with greater lung cancer risk than exposure to either agent alone. The Sogl et al 2012 study of German uranium miners was large enough to investigate the combined effect of RCS and radon on lung cancer risk in uranium miners. The findings are summarized in Table 30.

Table 30 Combined Effect of Combined Exposure to RCS and Radon on the Risk of Lung Cancer

RCS (mg/m^3-years)	Radon WLM Relative Risk RR (95% CI) [number of cases]		
	< 50	**50-1000**	**> 1000**
< 10	1.0 (reference) [609]	**1.52 (1.34-1.69) [585]**	1.95 (0.83-3.07) [12]
10-20	1.10 (0.79-1.41) [54]	**2.45 (2.17-2.73) [663]**	**3.11 (2.62-3.61) [219]**
20-30	1.33 (0.26-2.41) [6]	**3.11 (2.63-3.60) [238]**	**4.29 (3.64-4.74) [420]**
30+	0	**4.75 (3.25-6.25) [42]**	**4.56 (3.72-5.42) [147]**

statistically significant risk estimates in bold
adapted from information in Sogl et al 2012

An increased risk of lung cancer was observed among radon-exposed workers with increased cumulative exposure to RCS and an increased risk among RCS-exposed workers with increasing exposure to radon. There was also a statistically significant increase in lung cancer risk with combined exposure to radon > 50 WLM < 1000 WLM in all cumulative RCS exposure categories (middle column) when compared to the reference category (< 10 mg/m^3 - years RCS and < 50 WLM radon). Further analysis found that the combined effect of RCS and radon exposure is more likely to be additive rather than multiplicative. However, the cumulative RCS and radon levels reported in the German study are somewhat higher than those experienced by Ontario uranium miners.

Combined Exposure to Radon and Diesel Exhaust (DE)

Two recent papers, by Cao et al 2017 and Chang et al 2018 evaluated the combined effect of exposure to radon and diesel exhaust (DE).

Cao et al 2017 is the first study that analyzed the possible confounding effect of exposure to DE on the risk of lung cancer associated with exposure to radon. The authors began by estimating the historical DE concentrations for the 11 mining cohorts used in the 1999 BEIR VI report. Although historical DE exposure data (i.e., concentrations of REC) were not available for the 11 uranium mining cohorts, ranges of REC exposures were calculated using the approach of Vermeulen et al 2010 that estimated the exposures in US non-metal mines for the DEMS studies (Attfield 2012, Silverman 2012). According to the estimates in the Vermeulen et al 2010 paper, the REC concentration was essentially zero in the 1950s because diesel-powered equipment was not widely used, and their use increased gradually during the late 1950s. It was estimated that the REC concentration was in the range of 20-60 ug/m^3 by 1960 and 110-350 ug/m^3 by 1970 which reflects the rapid growth in the use of diesel-powered equipment during the 1960s.

Using the REC concentration ranges estimates by Vermeulen et al 2010, Cao et al 2017 estimated the historical REC levels for the BEIR VI uranium mining cohorts. The cumulative exposure to DE was then estimated for the same period of the radon exposure and the relative risk (RR) was calculated for each BEIR VI uranium mining cohort using the concentration range estimates provided by Vermeulen et al 2010 and the exposure-response relationship derived by Vermeulen et al 2014 for the DEMS studies.

The cumulative DE exposure (i.e., dose) for the Ontario uranium mining cohort was estimated to have ranged from 190 ug/m^3-years to 598 ug/m^3-years during the period the cohort was exposed to radon (1963-1986). The corresponding relative risk of lung cancer from the estimated DE cumulative exposure (RR_{DE}) ranged from RR_{DE} = 1.20 (95% CI 1.11-1.31) to RR_{DE} = 1.80 (95% CI 1.39-2.32) and was statistically significant.

Cao et al 2017 used two models to assess the joint effect of radon and DE on the risk estimates for lung cancer: a multiplicative model that implies that the effect of radon depends on the effect of DE exposure ($RR_{radon,\ modified} = RR_{radon} \div RR_{DE}$) and an additive model that implies that the effect of radon exposure and DE exposure are considered to be independent ($RR_{radon\ modified} = RR_{radon} - RR_{DE}$).

Using these models, and the estimated RR_{DE} calculated as described above, a modified exposure-response coefficient for radon (ERR/WLM or $\beta_{radon\ modified}$) was then calculated for each of the BEIR VI uranium mining cohorts.

Cao et al 2017 observed that the modified β_{radon} was reduced in all 9 of the uranium mining cohorts. They concluded that the overall radon exposure-response coefficient (β_{radon}) may be overestimated by 9% to 26% after accounting for exposure to DE. The decline of the β_{radon} varied greatly across each cohort and decreased more with the modification in the multiplicative model (up to 26%) than in the additive model (up to 16%). Generally, the excess risk from radon exposure was reduced more in the mines that had

longer duration of exposure and later first year of exposure to radon. This was attributed to the higher DE exposures in those mines estimated from historical data. The Ontario, Chinese, and French cohorts had the greatest decline in β_{radon} which coincided with these cohorts having the highest estimated cumulative exposure to DE. The estimated range of relative risk for lung cancer deaths from DE exposure for the Ontario cohort (RR_{DE} = 1.20 to 1.80) exceeded the relative risk for lung cancer from radon exposure (RR_{radon} = 1.28).[ee]. This finding suggests that historical DE exposure may be a larger contributor to the risk of lung cancer among Ontario uranium miners than exposure to radon alone.

Chang et al, 2018[ff] reanalyzed the lung cancer mortality reported in the DEMS studies (Attfield et al 2012, Silverman et al 2012) using alternative exposure estimates for DE and adjustment for radon exposure. The DE exposures (REC levels) were estimated from diesel engine horsepower data and mine air-ventilation rates rather than the approach of Vermeulen at al 2010 that was used in the DEMS studies that estimated REC levels from historical carbon dioxide (CO) measurements. The average radon exposure levels in the DEMS cohort were low; across all mine types in the complete cohort, the mean radon exposure was 0.008 WL, with mine-specific averages ranging from 0.008 to 0.017 WL (Attfield et al 2012). Among ever-underground workers the mean radon exposure intensity was 0.011 WL, ranging from 0.008 to 0.017 WL. Both the Attfield et al 2012 DEMS study and the 2018 Chang study detected a significant positive association only in the limestone mine and not in the other mines (potash, salt, trona). A nested case-control study based on the DEMS cohort by Silverman et al 2012 reported odds ratios of 1.08; 95% CI 0.63-1.84) for cumulative radon exposures ≥ 1.9 and <3.0 WLM and 1.32; 95% CI 0.76-2.29 for ≥ 3.0 WLM versus no exposure to radon.

Without controlling for radon exposure, several statistically significant positive exposure-response associations were found with cumulative REC and average REC intensity, based on both the DEMS REC data and the alternate REC data, among ever-underground workers, surface only workers, and all workers combined, but not among underground-only workers. Controlling for radon resulted in substantially weaker associations between cumulative DE exposure or average DE exposure intensity and lung cancer mortality among ever-underground, underground-only and all workers. Nearly all significant positive associations after control for radon were found only among ever-underground and all workers with cumulative DEMS REC exposure of < 1,280 ug/m^3-years.

The authors concluded that the findings of only positive associations with both REC (without radon adjustment) and the unexpected lack of association with REC among underground-only workers, are not readily explained in the context of a positive exposure-response association between REC exposure and lung cancer mortality. The authors attributed the findings for the limestone mine to the high frequency of detectable radon, poor natural ventilation and a unique ore transport system that required high-horsepower diesel equipment. The higher average REC levels in the limestone mine as well as longer

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[ee] *Using the approach outlined in Cao et al 2017, the RR_{radon} for the Ontario uranium mining cohort may be estimated from the ERR/WLM or β_{radon} value of 0.0089 per WLM and the mean radon exposure of 31 WLM: RR_{radon}= 0.0089 x 31 WLM + 1 = 1.28*

[ff] *It is important to note that this study was sponsored by a coalition of trade organizations from the Truck and Engine Manufacturers Association*.

exposure due to earlier dieselization could have contributed to the positive associations with REC in that mine only.

Similarly, the weak associations between REC and lung cancer mortality among underground-only workers did not support a positive exposure-response relationship between REC and lung cancer as these workers were most heavily exposed to DE. It is also difficult to explain that after adjusting for radon, the only significant association between cumulative REC or average REC intensity was only found among those workers with cumulative REC of < 1,280 ug/m^3-years. Workers with cumulative REC >1,280 ug/m^3-years would have been the oldest and most highly exposed workers in the cohort and would have been expected to have the highest risk of lung cancer. The observation of positive associations only after excluding those workers with the highest exposures does not fit with a monotonic exposure-response effect of DE. Chang et al 2018 concluded that the mutual confounding between REC and radon makes it difficult to disentangle associations of each exposure with lung cancer mortality.

Other Mining (Gold, Nickel, Copper)

Many of the uranium miners in the Ontario cohort also worked in gold, nickel and copper mines. The 1993 Kusiak et al update of the Ontario Uranium Miners Cohort analyzed the combined effect of mining uranium, gold, nickel and copper in different time periods. These findings are summarized in Table 31.

Table 31 Lung Cancer Mortality in Uranium Miners: combined effect of mining uranium, gold and nickel and copper in different periods

Year miner first mined gold in Ontario	Never mined nickel and copper SMR (95% CI) [number of miners]	Ever mined nickel and copper in Ontario SMR (95% CI) [number of miners]	Total SMR (95% CI) [number of miners]
Never	**230 (1.64-3.09) [6730]**	151 (0.92-2.24) [3226]	**195 (1.49-2.48) [9956]**
≤ 1945	**270 (1.77-3.85) [306]**	**302 (1.85-4.42) [233]**	**238 (2.08-3.70) [539]**
≥ 1946	**177 (1.11-2.59) [1683]**	**287 (1.83-4.11) [1291]**	**221 (1.62-2.90) [2974]**
Total	**223 (1.79-2.72) [8719]**	**227 (1.75-2.86) [4750]**	**225 (1.91-2.62) [13469]**

adapted from Table 1 in Kusiak et al 1993 (confidence intervals calculated by PS); statistically significant results in bold

The increased mortality from lung cancer in uranium miners who also worked in nickel and copper mines (SMR=227) was similar to the risk for miners who did not work in nickel and copper mines (SMR=223). However, a larger excess of lung cancer deaths was observed in uranium miners who also worked in gold mines compared to uranium miners who never worked in gold mines (SMR=195).

The 2015 update by OCRC confirmed that uranium miners who also had gold mining experience had an increased risk of lung cancer incidence and mortality. As shown in Table 32, when compared to uranium miners with no gold mining experience, those with gold mining experience had an approximately 20% increase in risk of lung cancer incidence (SIR 1.41 compared to 1.18) and mortality (SIR 1.42 compared to 1.25).

Table 32 Cancer Incidence and Mortality in Ontario Uranium Miners with and without Gold Mining Experience		
Type of Mining	**Incidence (1969-2005) Standardized Incidence Ratio SIR (95% confidence intervals)**	**Mortality (1954-2007) Standardized Mortality Ratio SMR (95% confidence intervals)**
Uranium miners with gold mining experience	**1.41 (1.30-1.52)**	**1.42 (1.31-1.54)**
Uranium miners without gold mining experience	**1.18 (1.08-1.28)**	**1.25 (1.15-1.36)**

adapted from Tables 9 and 11, OCRC 2015

Arsenic Exposure

Gold mining in Ontario has historically been a major source of exposure to arsenic and RCS (Kusiak et al 1993, Muller et al 1989, OCRC 2015). Few measurements of airborne concentrations of arsenic in Ontario mines are available; however, the concentration of arsenic in the rocks from which the gold was mined is known. The concentration of arsenic in the rock found in Ontario gold mines ranges from less than 0.02% to over 1.0%. By comparison the arsenic in the rocks in uranium mines is much lower and is in the range of 0.01% to 0.06% (Kusiak et al 1993).

A 1991 Ontario gold mining study found that in gold miners who did not mine uranium, mortality from lung cancer was associated with exposure to radon in gold mines and to arsenic before 1946 but not with exposure to arsenic after 1946 (Kusiak et al 1991). Analysis of the joint effect of exposure to radon and arsenic showed that each exposure acted independently so that the risk to a gold miner exposed to both radon and arsenic is the sum of the risk from each exposure.

In contrast, the 1993 update by Kusiak et al of the Ontario Uranium Cohort concluded that mortality from lung cancer in Ontario uranium miners who also mined gold was associated with exposure to radon and also exposure to arsenic before and after 1946. The joint effect of exposure to radon and arsenic for uranium miners who also mined gold, was more complicated than for gold miners who never mined uranium. For uranium miners whose exposure to radon (lagged 15 years[gg]) was < 40 WLM, the rate of lung cancer increased in a linear fashion which was similar to that found for gold miners who never mined uranium and were exposed to < 40 WLM of radon (Kusiak et al 1991).

However, for uranium miners who also mined gold, and were exposed to radon (lagged 15 years) > 40 WLM, the association between lung cancer mortality and exposure to arsenic was curvilinear. Lung cancer mortality was observed to increase at a faster rate as exposure to arsenic increased but at higher exposures to arsenic (~> 3.5 % As-year[hh]) the mortality rate levelled off or declined. This study

[gg] *Lagging refers to the number of years of exposure before diagnosis that are not considered in estimating the risk of lung cancer*
[hh] *% As-year = percentage (%) of arsenic (As) in the rock x years of exposure*

concluded that the amount of exposure to radon seemed to determine the size of the increase in mortality from lung cancer caused by exposure to arsenic.

The 1993 Kusiak et al uranium mining study also suggested that that the timing of exposures to arsenic and radon is important in lung cancer mortality. Their analysis found that in Ontario uranium miners the increased risk of death from lung cancer began about 20 years after exposure to arsenic and the risk from radon exposure began about 5 years after exposure. They pointed out that the dose from radon is delivered to lung tissue within hours of inhalation, but inhaled arsenic may be retained in the lungs for several years, depending on its chemical and physical characteristics. However, it is difficult to measure the timing of the doses to the lung tissue for these exposures based only on the time of exposure in the mines.

The current WSIB Policy 23-02-03 "Lung Cancer Among Workers in the Uranium Industry" does not include any consideration of arsenic exposure since it assumed that uranium mines had minimal arsenic exposures.

However, the WSIB Policy 16-02-07 "Lung Cancer – Gold Miners" takes arsenic and radon exposure for gold miners into account. Based on the Kusiak et al 1991 Ontario gold mining study the WSIB uses the following equation, as described by Kabir et al 1993 to estimate the risk of lung cancer for gold miners:

Risk = 1.00 + (0.05 x years of dusty gold mining exposure[ii]) + (0.14 x arsenic index[ij]) + (0.0005 X WLM)

According to this equation, the additional contribution from arsenic and radon exposure is small compared to the risk from the "dusty gold mining" exposure. This is because the percentage of arsenic in the rock and radon exposures in Ontario gold mines are low.

Conclusion

When taken together, the published scientific literature to date provides compelling evidence that Ontario hard rock miners are at increased risk of lung cancer from occupational exposure to RCS, DE, radon and arsenic. These exposures pose an individual risk for lung cancer and there is epidemiological evidence that the risk from combined exposure to these carcinogens is greater than the risk from exposure to the individual carcinogens (i.e., additive or multiplicative effects).

Although the WSIB has policies on lung cancer and uranium mining (Policy 23-02-03) and lung cancer and gold mining (Policy 16-02-07), the epidemiological evidence used to support these policies is now more than 20 years out of date. More recent findings from the scientific literature indicate a need for modification of these policies to be consistent with the new analyses of the risk of lung cancer among hard rock miners.

[ii] *"dusty gold mining" refers to concentrations of dust > 500 ppcc. The reader is referred to the WSIB Lung Cancer – Gold Miners Policy and the OHCOW companion document "Background and Development of the WSIB Lung Cancer – Gold Miners Policy 16-02-07" for further information.*

[ij] *Arsenic Exposure Index = number of years of gold mining x percentage of arsenic in the rock of the gold mine where the miner worked*

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