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Kidney Cancer and Exposures in Ontario Mines

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***Version 2 of the report corrected one typo on the Guo et al. entry in the Table on page 11, under the "Risk" column (1.07 corrected to 1.17). No other changes were made.**

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Introduction

Miners work with and around a variety of contaminants that are known or suspected kidney carcinogens. A cohort study that examined the economically-active population of Sweden showed a significantly increased standardized incidence ratio (SIR) for kidney cancer in male miners (SIR 1.57; 95% CI: 1.12-2.08) when they maintained their occupation from 1960 to 1970 [1].

A mortality analysis on a French cohort of uranium miners [2] found that miners had a statistically significant excess mortality rate from kidney cancer (Standardized Mortality Rate or SMR 2.00; 95% CI: 1.22-3.09) when compared to the male French population, which agrees with a more recent study on the same cohort (SMR 1.60; 95% CI: 1.03-2.39) [3].

The International Agency for Research on Cancer (IARC) lists x-radiation, gamma-radiation and trichloroethylene as agents with sufficient evidence to cause kidney cancer; and arsenic, cadmium, and welding fumes as agents with limited evidence [4]. The Collaborative on Health and the Environment (CHE) Toxicant and Disease Database groups arsenic, asbestos, PAHs and trichloroethylene among others as having good evidence for association with development of renal (kidney) cancer; and cadmium, solvents and others as agents with limited evidence [5]. All of these agents are present and pose potential exposures in mining operations. Numerous studies have examined the link between occupational exposures and the development of kidney cancer resulting in mixed conclusions about the links. In the following summary only occupational exposures relating to mining as risk factors for kidney cancer will be addressed.

A literature search was completed on EBSCO host in July 2018 using Boolean search techniques "kidney" AND "cancer" AND "mining"/"miner"/"mine"/"asbestos"/"ionizing radiation"/"radon"/"dust"/"diesel"/"dieselexhaust"/"cadmium"/"aluminum"/"arsenic"/"silica" /"trichloroethylene"/"arsenic" as well as "kidney cancer" AND "occupational exposure" AND "meta-analysis"/"review". IARC monographs were also consulted for every exposure that was available. The information gathered in this literature search was used to complement and update the work previously performed by OHCOW occupational hygienists, physicians and nurses on the topic.

The following table shows a range of studies showing miners and their risk of renal cell carcinoma (RCC) which is the most common type of kidney cancer representing 80 – 90% of kidney cancer cases in Canadian men (Atkins et al. 2019) [51].

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Author	Year	Number of participants/cases	Occupation	Risk	95% CI
Ji et al.	2005	11,183	Miners	1.57	1.22-3.09
Vacquier et al.	2007	5086	Miners	2.00	1.22-3.09
Rage et al.	2015	5086	Miners	1.60	1.03-2.39
Sritharan et al.[10]	2014	14,000+	Miners	2.71	1.12-6.57
Mellemgaard et al.[11]	1994	365	Miners	3.10	1.30-7.70

Note. All confidence intervals have a lower confidence interval greater than 1.

Trichloroethylene (TCE) exposure

Trichloroethylene (TCE) is a chlorinated solvent mainly used as a metal degreaser in several industries including mining mechanical and electrical workshops. The IARC monograph on TCE [11] analyzed 8 case-control studies, 17 cohort studies and 4 meta-analyses regarding trichloroethylene exposure and cancer of the kidney. The largest body of evidence to support the IARC Group 1 classification of TCE came from studies on kidney cancer, and referring to this monograph as a support, the IARC Working Group concluded that there is sufficient evidence in humans for the carcinogenicity of TCE and that TCE causes cancer of the kidney.

A case control by Moore et al. [12] was conducted in Central Europe with 1,097 cases and 1,476 controls, assessing occupational exposure to TCE and risk of renal carcinoma. Exposure assessment was conducted via general occupational questionnaires followed by evaluation of frequency, intensity, and confidence of exposure by a team of occupational hygiene experts. Odds ratios (ORs) were calculated in reference to unexposed for any occupational exposure, duration of exposure, cumulative exposure (ppm-years), and average intensity (ppm). For all subjects ever exposed to TCE the observed OR was 1.63 (95% CI 1.04-2.54; p-value 0.03), for average intensity ≥0.076 ppm the OR was 2.34 (95% CI 1.05-5.21; p-value 0.02) and for hours of exposure ≥1080 the OR was 2.22 (95% CI 1.24-3.99; p-value 0.001).

A consecutive hospital-based case-control study in Germany [6] reports significant excess risks for the development of kidney cancer associated with "metal greasing/degreasing" job tasks (OR 5.57, 95% CI 2.33–13.32). According to CAREX Canada, the most heavily exposed occupational group are workers who degrease metals [7] which would include mechanics, electricians, welders, solderers and brazers [8]; all of these occupations can be found in mines. A study on chronic health effects of TCE in Singapore [9] conducted personal environmental measurements via passive dosimetry of electronics plant workers that used TCE to degrease

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small metal parts (which would likely be a similar exposure to mining/smelting/milling tasks performed by electricians and mechanics) and found a range of 9 to 131 ppm with an average of 29.6 ppm; which considerably exceeds the current TLV (TWA) for TCE which is 10 ppm and STEL which is 25 ppm [10].

A case-control study by Charbotel et al. [13], was a supplementary analysis using data from a 2006 case-control study by the same authors. It was conducted in France with 86 cases and 316 controls matched for age and gender and analyzed the relevance of the national occupational exposure limits for TCE regarding kidney cancer. The authors calculated ORs for TCE exposure estimated in ppm for an average exposure of 8 hours resulting in ORs: 1.62 (95% CI 0.77-3.42) at 35 ppm, 2.80 (95% CI 1.12-7.03) at 50 ppm and 2.92 (95% CI 0.85-10.09) at 75 ppm. These results demonstrate statistical significance and trend towards a dose-response relationship as the highest tertile CI crosses 1. When assessing possible confounding by exposure to cutting fluids, they found an OR of 1.62 (95% CI 0.76-3.44) in subjects exposed to only TCE. The OR adjusted for body-mass index, tobacco smoking and exposures to other oils was 2.70 (95% CI 1.02-7.17) in subjects exposed to TCE and cutting fluids at >50 ppm.

The US Environmental Protection Agency (EPA) conducted a meta-analysis of epidemiological studies to assess TCE exposure and risk of kidney, liver, and non-Hodgkin lymphoma (NHL) cancers [14]. The search was carried out without restricting year of publication and language and the study selected if it met their four specific criteria. Twenty-four studies were eligible and fifteen were analyzed for TCE exposure and kidney cancer. The authors report a statistically significant meta-RR of 1.27 (95% CI 1.13-1.43) from both the primary random-effects and the fixed-effect model.

A meta-analysis by Karami et al. [15] evaluated the risk of kidney cancer following TCE exposure from 15 cohort studies and 13 case-control studies published up to the year 2011. The authors included studies that specifically evaluated the effects of exposure to chlorinated solvents, degreasing agents or TCE; and excluded studies focusing on dry-cleaners and on workers with low likelihood of exposure. For TCE exposure, they reported a statistically significant meta-RR (Relative Risk) for all studies of 1.44 (95% CI 1.16 to 1.70; $p < 0.001$), for cohort studies the meta-RR was 1.26 (95% CI 1.02 to 1.56; $p = 0.65$), and for case-controls the meta-OR was 1.35 (95% CI 1.17 to 1.57; $p = 0.41$).

In summary, there is sufficient evidence in the literature to support the association between kidney cancer and occupational exposure to TCE. Furthermore, various mining tasks have historically used TCE as a degreasing agent, presenting the potential for occupational exposure.

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Diesel exhaust exposure

IARC [4] lists diesel exhaust as a human carcinogen (group 1) with sufficient evidence in humans for carcinogenicity, and there is research that suggests an association between diesel exhaust exposure and kidney cancer (16).

Most notably, a recent Canadian case-control study which included 712 cases of kidney cancer, showed a correlation to workers who had ever been exposed to diesel exhaust 1.23 (95% CI; 0.99-1.53) (49)

As noted by CAREX, miners are amongst those exposed to the highest levels of diesel exhaust emissions, and truck drivers represent the largest exposed occupation (CAREX Canada n.d) [7].

The IARC monograph on diesel exhaust [16] cites six cohort studies of cancer in miners, out of which two evaluated their risk of kidney cancer. Attfield et al. conducted a mortality study [17] on a cohort of 12,315 workers at 8 US non-metal mines and estimates of exposure to diesel exhaust were based on respirable elemental carbon REC) personal measurements. The authors reported a small risk in ever-underground workers with an SMR of 1.11 (0.53-2.04). The second cohort study cited by IARC was conducted by Guo et al. [18] and followed all economically-active Finns who participated in the census of 1970, including mining as occupation and industry. Diesel exhaust exposure estimates were derived from FINJEM and they used NO_2 as a surrogate agent for diesel exhaust. The authors found a statistically significant risk of kidney cancer with lowest cumulative exposure (<2.0 mg/m^3-years) in men with an RR of 1.17 (1.05-1.30; 465 cases).

Reported levels of exposure to elemental carbon (EC) as a surrogate for diesel exhaust in underground production/mining vary from 148 to 637 µg/m^3 (weighted arithmetic mean 135 µg/m^3), for surface-only miners an average of 2 µg/m^3, and an overall average for miners of 87 µg/m^3 [16]. In 2001 the ACGIH proposed a TLV (TWA) of 20 µg/m^3 EC [43]; however, this limit was never adopted. It is clear from the literature that underground miner exposure has been at least an order of magnitude greater than this value. The current Ontario occupational exposure limit (OEL) for diesel exhaust in mining (Regulation 834) is 400 µg/m^3 total carbon (approximately 308 µg/m^3 EC); though relying on total carbon as a surrogate for diesel particulate matter has been demonstrated to be a less sensitive and less accurate measure than elemental carbon. The Occupational Cancer Research Centre (OCRC) recommends lowering the OEL to 20 µg/m^3 EC for the mining industry and 5 µg/m^3 EC for all other workplaces [44]. A cohort study by Boffetta et al. [19] studied the Swedish Cancer Environment Register III with

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data on cancer incidence during 1971-1989. Miners were included in the cohort and classified by the authors as an occupation at high probability of exposure to diesel engine emissions (i.e. a job with 75-100% probability of exposure to diesel exhaust). A statistically significant increase in risk of kidney cancer was found in men (SIR 1.06; 95% CI 1.02-1.11; 2243 cases). When they restricted the analysis to subjects with high probability of exposure, it confirmed the risk of kidney cancer (SIR 1.10, 95% CI 1.02-1.19) with diesel exhaust exposure. The Swedish cohort study by Ji et al. found a significantly increased SIR for kidney cancer in male miners (SIR 1.57; 95% CI: 1.12-2.08) when they maintained the same occupation from 1960 to 1970 [1]. The authors state that diesel exhaust as a risk factor for kidney cancer is one of the occupational exposures that does not seem to be confounded by smoking and therefore appears to be a true occupational risk factor for the disease.

The association between diesel exhaust exposure and kidney cancer has been extensively documented in professional drivers. Soll-Johanning et al. [20] reported an association with kidney cancer (SIR 1.6; 95% CI 1.3-2.0; 83 cases) in urban bus drivers and tramway employees in Denmark which was stronger but similar to a later study by Jarvohln & Silverman [21] on truck drivers (SIR 1.12; 95% CI 1.12; 23 cases). Elevated risk of kidney cancer has also been found among heavy equipment operators, railroad workers, firefighters and automotive repairers/mechanics [16] which further suggest that diesel may be an etiologic factor associated with kidney cancer.

In summary, generally there is more literature than less to support the association between kidney cancer and occupational exposure to diesel exhaust. Furthermore, there is the potential for considerable occupational exposure to diesel exhaust in mining operations.

Ionizing radiation/radon exposure

Workers in the mining industry are exposed to external gamma radiation emitted by minerals containing uranium, potassium or thorium, and to alpha radiation from naturally occurring radioactive materials which can be ingested or inhaled [22]. Radon-222 and its decay products are classified as an IARC Group 1 carcinogen [4]; radon decay products include gamma radiation emitters which is listed as a kidney carcinogen with sufficient evidence. A study in 2002 reported that the kidney is the organ to receive the second-highest dose of inhaled radon progeny, an order of magnitude lower than in the respiratory tract [23]. The workers at risk of highest exposure to radon are those working in underground mines [7] and the 2017 National Dose Registry (NDR) reports that close to 4,000 workers in the mining industry are exposed to a dose of up to 10 mSv (2 Working Level Months or WLM), 99.7% of them being exposed to up to

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5 mSv (1 WLM) [24]. A German uranium miners' cohort [38] employed from 1946 to 1989 reports a mean cumulative exposure to radon of 279 WLM (median= 30.8 WLM) and to external gamma radiation of 48.6 mSv (median=16.5 mSv). A cohort of 4320 uranium miners in West Bohemia [45] followed up to the end of 1990, reported an average cumulative radon exposure of 219 WLM, with 62.8% of the miners cumulatively exposed to a range of 100-299 WLM. Ontario regulation 854 states a limit of 1 WLM in mines.

A study on extrapulmonary cancers in the German uranium miners' cohort [38] observed a statistically significant relationship with cumulative radon exposure for all extrapulmonary cancers (Excess Relative Risk/Working Level Month or ERR/WLM=0.014%; 95% CI: 0.006–0.023%). Two independent studies, both on the same cohort of French Uranium miners, have found a statistically significant excess in kidney cancer mortality in this occupation (SMR 2; 95% CI 1.22-3.09 [2] and SMR 1.60; 95% CI 1.03-2.3[3]). This cohort was extended recently by adding workers employed in the Jouac mines, giving a total of 5,400 workers in the extended cohort. In this analysis the SMR and 95% CI remained significant and similar to those from the main cohort (SMR 1.58; 95% CI 1.01-2.39 [26]). A recent study conducted by the OCRC and prepared by Navaranjan et al. [25] failed to find a dose-response relationship for kidney cancer and radon exposure: with cumulative exposure of radon of ≥2 to <5 WLM the RR was 0.72 (95% CI 0.44-1.17) and at ≥15 WLM the RR was 0.66 (95% CI 0.40-1.10). The consistency in excess mortality of kidney cancer among uranium miners and ionizing radiation's ability to damage the genetic material of virtually any cell, makes it important for increased research efforts in the matter.

In summary, there is sufficient evidence in the literature to support the association between kidney cancer and occupational exposure to ionizing radiation (radon and gamma radiation from minerals). Furthermore, there is the potential for considerable occupational exposure to ionizing radiation in mining operations.

Cadmium exposure

CAREX Canada reports that the largest occupational group exposed to cadmium is welders, where exposure to cadmium or cadmium compounds can occur when welding stainless steel containing cadmium or surfaces that are cadmium coated or plated; welders are employed in many different industries including mining [7]. Cadmium and cadmium compounds are classified as an IARC Group 1 carcinogen with limited evidence for kidney cancer [4] and appear under that same strength of evidence category in the CHE database [5]. Cadmium has a long residence time in the renal cortex and nephrotoxic effects associated with occupational and environmental exposures have been observed [27].

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Three independent population-based case-control studies on occupational risk factors for kidney cancer have reported a significant elevated risk for self-reported exposure to cadmium and cadmium salts among male workers, regardless of occupation. The first study by Mandel et al. [28] reported a RR of 2.0 (95 %CI 1.0–3.9), the second one by Hu et al. [29] an OR of 1.4 (95 % CI = 1.1–1.8), and the third one by Pesch et al. [30] an OR of 1.4 (95% CI 1.1–1.8) in men and in women an OR of 2.5 (95% CI 1.2–5.3) with high exposure to cadmium. A meta-analysis of observational studies [31] also found that high levels of exposure to cadmium were associated with increased renal cancer risk (OR 1.47; 95% CI 1.27-1.71) when compared to the lowest exposure category. Furthermore, the association was stronger and statistically significant for occupational exposure (OR 1.47; 95% CI 1.26–1.72) compared to non-occupational exposure (OR 1.39; 95% CI 0.43–4.54).

In summary, there is evidence in the literature to support the association between kidney cancer and occupational exposure to cadmium. Furthermore, there is the potential for occupational exposure to cadmium in mining tasks such as welding.

Arsenic exposure

Arsenic and inorganic arsenic compounds are classified as IARC Group 1 carcinogens, and the IARC states that a positive association has been observed between exposure to arsenic and kidney cancer [32]. The Collaborative on Health and the Environment (CHE) Toxicant and Disease Database lists arsenic as having good evidence for the association with development of kidney cancer [5]. Groundwater contamination by arsenic is the main route of environmental exposure and inhalation of airborne arsenic or arsenic-contaminated dust is a common health problem in gold, tin and uranium mines [33]. Gold ore typically contains arsenic-bearing materials such as pyrite, galena, chalcopyrite and dominantly arsenopyrite (which is 46% arsenic by weight) [34]. The arsenic content of gold ores may range from traces to a value greater than 5,000 mg/kg [35]. Underground tin miners in China have been reported to be exposed to 0.1 to 38.3 µg/m^3 of respirable arsenic [36]. A study on lung cancer and arsenic exposure [37] based on male German uranium miners who died from lung cancer during 1957-1990 reported a mean cumulative exposure of arsenic of 181.2 1 µg/m^3 x years. A German uranium miners' cohort [38] employed from 1946 to 1989 reports cumulative exposure of 17,554 miners to an average of 122.5 dust-years (1 dust-year= exposure to 1 µg/m^3 for arsenic over 220 shifts each at 8 h). The Ontario OEL for arsenic is a TWA of 10 µg/m^3 [46] which agrees with the ACGIH TLV and a STEL of 50 µg/m^3 (no ACGIH STEL exists) [10]; though NIOSH set its

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recommended exposure limit (REL) STEL to 2 µg/m^3 based on arsenic's carcinogenic properties [47].

The IARC monograph on arsenic and arsenic compounds reviewed 25 epidemiological studies of arsenic in drinking water and bladder and kidney cancer, 17 of which reported statistically significant elevated risks of these cancers and many reported a dose-response relationship among men and women [32]. A cohort study conducted in an arseniasis-endemic area in Taiwan [39] reported significantly increased incidence of urinary cancers for the study cohort compared to Taiwan's general population (SIR 2.05; 95% CI 1.22-3.24) and a significant dose-response relation after adjustment for age, sex, and cigarette smoking. The subjects' risk of developing kidney cancer specifically was significantly high with an SIR of 2.82 (95 % CI: 1.29-5.36). A systematic review [40] of epidemiological studies published between 1983 and 2013 reports that ten studies showed an association with kidney cancer and that mortality rates at 150 ug/L were about 30% greater than those at 10 µg/L (no meta-risk estimate calculated due to insufficient studies reporting on kidney cancer incidence).

In summary, there is evidence in the literature to support the association between kidney cancer and occupational exposure to arsenic. Furthermore, there is the potential for considerable occupational exposure to arsenic-containing particulate matter during a variety of mining tasks.

Silica exposure

IARC classified crystalline silica as a Group 1 carcinogen to humans in 1997; since then, substantial amounts of data have become available on its carcinogenicity on different organs [4]. IARC's Monograph on crystalline silica dust [41] reported on a group of 8 studies with data on silica exposure and kidney cancer, out of which 5 had RRs > 1.0 including two that were significantly elevated. Verma et al. [42] presents some historical data for the late 1970s based on a study conducted by the Ontario Ministry of Labour in 1978-1979 in eight gold mines, and reported a range of respirable dust of 0.08-5.73 mg/m^3 and of respirable silica (quartz) 0.01-0.85 mg/m^3. The exposure levels also varied with occupations with a mean of respirable quartz of 0.05 mg/m^3 in stoping as the lowest exposure in a specified occupation and the highest being for conveying and transporting with a mean of 0.17 mg/m^3 and tramming with 0.12 mg/m^3. All of these exposure estimates substantially exceed the ACGIH TLV (TWA) of 0.025 mg/m^3 [10].

A quantitative exposure-response study by Attfield and Costello [48], conducted a person-years analysis by cumulative exposure group based on mortality and respirable silica dust

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concentration data. They found a high but non-statistically significant SMR of 1.37 for all cumulative silica exposure levels for malignancy of the kidney with a monotonic increase with increasing exposure, a trend that flattened towards the middle of the exposure range (>1.5 mg/m^3-yrs). A significant elevation in risk (SMR 3.12) was also found when exposure to silica dust was between 3.0 and 6.0 mg /m^3-yrs. Epidemiological evidence has not yet been sufficient to establish a clear causal relationship between crystalline silica exposure and kidney cancer, though recent research suggests silica as a causative agent of kidney cancer and must be further investigated.

In summary, there is recent evidence in the literature to support the association between kidney cancer and occupational exposure to silica. Furthermore, there is the potential for considerable occupational exposure to silica-containing particulate matter during many mining tasks.

Conclusion

By reviewing the scientific literature available to date, OHCOW has identified occupational exposure to TCE, diesel exhaust, ionizing radiation, cadmium, and arsenic as likely independent risk factors for the development of kidney cancer and silica as possible risk factor. In addition, miners work with these and many more contaminants simultaneously and so the possibility of a combination effect should not be dismissed when assessing the work-relatedness of kidney cancer.

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The following table summarizes the risk of renal cell carcinoma and exposures typically found in mining.

Occupational Exposures and RCC

Author	Year	Number of cases/participants	Exposure	Risk	95% CI
Guo et al.	2004	7366	Diesel exhaust (<2.0 mg/m^3)	1.17	1.05-1.30
Boffetta et al.	2001	2243	Diesel exhaust	1.06	1.02-1.11
Peters et al.	2018	712	Diesel	1.23	0.99-1.53
Attfield et al.	2004	5414	Silica	1.37	NR
Chiou et al.	2001	8102	Arsenic	2.82	1.29-5.36
Saint-Jacques et al.	2014	Meta-analysis	Arsenic	~1.30	NR
Moore et al.	2010	1097	TCE	1.63	1.04-2.54
Brüning et al.	2003	134	Metal degreasing	5.57	2.33-13.32
Mandel et al.	1995	4041	Cadmium	2	1.0-3.9
Hu et al.	2002	6649	Cadmium	1.4	1.1-1.8
Pesch et al.	2000	3220	Cadmium (men)	1.4	1.1-1.8
		2013	Cadmium (women)	2.5	1.2-5.3
Kun Song et el.	2015	Meta-analysis	Cadmium	1.47	1.27-1.71
Vaquier et al.	2007	5086	Ionizing radiation	2	1.22-3.09
Rage et al.	2015	5086	Ionizing radiation	1.6	1.03-2.3
Rage et al.	2017	5400	Ionizing radiation	1.58	1.01-2.39

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