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Bladder Cancer and Exposure in Ontario Mines

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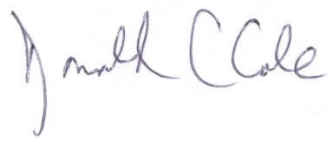

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Introduction

Miners work with and around a variety of contaminants that are known or suspected bladder carcinogens. A recent meta-analysis on occupational exposures and cancer by Micallef et al. [1] reports that bladder cancer is the second type of cancer, after lung, to be most associated with occupational exposures (namely, nine of 37 selected exposures based on IARC classifications), and this agrees with the fact that workplace exposures account for 5 to 25% of all bladder cancer cases [2]. An analysis of pooled data from case-control studies on bladder cancer in Europe between 1976 and 1996 reported that miners and quarrymen workers have a significantly higher risk of bladder cancer (Odds Ratio or OR 1.3; 95% CI: 1.02-1.64) [3]. A population-based case-control study in Canada by Gaertner et al. [4] found a statistically significant increased risk of bladder cancer (OR 1.94; 95% CI 1.18-3.17) among male miners, a category that included supervisors, drillers and hauler/machinists. A meta-analysis by Reulen et al. [5] confirmed the previous observations with an SRR (Standardized Rate Ratio) of 1.31 (95% CI 1.09-1.57) for bladder cancer in miners. Note all of these were statistically significant elevations of risk.

Among the exposures relevant to the mining industry, the International Agency for Research on Cancer (IARC) lists arsenic and inorganic arsenic compounds, x-radiation, gamma-radiation as agents with sufficient evidence to cause bladder cancer; and diesel exhaust (DE) and tetrachloroethylene as agents with limited evidence [6]. The Collaborative on Health and the Environment (CHE) Toxicant and Disease Database adds to the previous list: polycyclic aromatic hydrocarbons (PAHs) with strong evidence, solvents with good evidence and asbestos with limited evidence [7]. Numerous studies have examined the link between occupational exposures and the development of bladder cancer, resulting in strong positive evidence on the role of diesel exhaust, arsenic and ionizing radiation exposures in the development of bladder cancer and mixed conclusions about the links with other agents. In the following summary only occupational exposures relating to mining as risk factors for bladder cancer will be addressed, but the literature drawn upon includes a wide range of studies showing associations between these exposures and cancer outcomes.

A literature search was completed on EBSCO host in July 2018 using Boolean search techniques “bladder” AND “cancer” AND “mining”/“miner”/“mine”/“asbestos”/ “solvents” “arsenic”/“ionizing radiation”/“radon”/“dust”/“diesel”/“diesel exhaust”/“aluminum”/“silica” as well as “bladder 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.

Diesel exhaust exposure (DEE) (including PAHs)

Diesel exhaust is made up of gas and particle phases. The gas phase comprises carbon monoxide, nitrogen oxides and volatile organic compounds; the particle fraction comprises elemental and organic carbon, ash, sulfate and metals; and polycyclic aromatic hydrocarbons and nitroarenes are distributed within both phases [8]. Brown and colleagues' review [9] addressed the plausibility of the effect of diesel engine exhaust on the occurrence of bladder cancer in a review of occupational urinary tract cancers and state that metabolites of polycyclic aromatic hydrocarbons (PAHs) are present in diesel exhaust emissions (DEE) and are concentrated in the urine and may interact with the urothelium of the bladder. Exposure to DEE occurs in many occupational settings, and levels of PAHs in this fume are highest in emissions from heavy-duty diesel engines and lower (and comparable) in emissions from light-duty diesel engines and from petrol engines without catalytic converters [9].

PAHs derive mainly from the incomplete combustion of organic material. These include hundreds of compounds, among which the best known is benzo[a]pyrene, often used as a marker of exposure to PAHs [10]. Many PAHs are classified in IARC Groups 1, 2A and 2B; among these are benzo[a]pyrene in Group 1, and naphthalene, chrysene, benz[a]anthracene, benzo[k]fluoranthene and benzo[b]fluoranthene in Group 2B [6]. High exposure to PAH mixtures have been reported in several industries and occupations, including aluminum production, coal gasification, coke production, iron and steel foundries, coal tar and related products carbon black and carbon electrodes production and chimney sweeps [10]. Brown et al. [9] found an overall statistically significant RR (Relative Risk) of 1.4 (95% CI 1.2-1.7) for occupational exposure to PAHs and bladder cancer based on 26 studies previously reviewed by Boffetta et al. [11] regarding exposure to PAHs in aluminum production, coal gasification, coke production, iron and steel foundry work, DEE exposure, and workers exposed to coal tars and related products.

The association between diesel exhaust and various cancers is well documented in the literature. In the IARC monograph on diesel exhaust [8] the Working Group concluded that a positive association has been observed for diesel exhaust and cancer of the urinary bladder. It is well known that traditional diesel exhaust (TDE) from older engines, especially those used prior to tighter emission standards emitted diesel exhaust fume (particulate matter) at concentrations "orders of magnitude greater" than current standards [12]. Reported levels of exposure to elemental carbon (EC) as a surrogate for diesel exhaust in underground production/mining vary from 148 to 637 $\mu g/m^3$ (weighted arithmetic mean 135 $\mu g/m^3$), for surface miners an average of 2 $\mu g/m^3$, and an overall average for all miners of 87 $\mu g/m^3$ [8]. In 2001 the ACGIH proposed a TLV (TWA) of 20 $\mu g/m^3$ 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/m3 total carbon (approximately 308 $\mu g/m^3$ 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. There is a proposed Ontario OEL for industries other than mining of 160 μg/m^3 total carbon (123 μg/m^3 EC) and a discussion with stakeholders on the application of this threshold to the mining industry. 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].

In 2016 Health Canada conducted a detailed review on the human health risks of diesel exhaust and included studies published between the years 2000 and 2012 [17], in which they state that: *"Based on limited epidemiological evidence supporting a causal relationship between DE exposure and bladder cancer, substantial supporting evidence from toxicological studies establishing the mutagenicity and genotoxicity of DE and the fact that DE contains known human carcinogens, it is concluded that the evidence is suggestive of a causal relationship between DE exposure and bladder cancer".*

From a study of truck drivers by Steenland et al. [13] cited in IARC [8], "A significant increase in risk for those with 20 or more years of employment was seen for those employed as truck drivers". The authors reported a RR of 12 (95% CI 2.29 – 69.9) for this group of workers for urinary bladder cancer. A statistically significant trend in risk for urinary bladder cancer with increasing duration of employment was also reported in a case-control study by Silverman et al. [14], with a RR of 2.2 (95% CI 1.1 – 4.2) for truck drivers employed 25 years or more with a latent period of at least 50 years. In this same study, the age adjusted RRs for truck drivers were: RR 2 for those who smoked ≤1 pack per day; RR 3 when ≤2 packs per day; and RR 3.6 when ≥2 packs per day.

Koutros et al. [15] examined the association between lifetime occupational DEE exposure and risk of bladder cancer in 1171 cases and 1418 controls in a population based case-control study. DEE was associated with an increased risk of bladder cancer with a cumulative exposure of 0.25 mg/m^3 (250 μg/m^3) of respirable elemental carbon (REC) per year having a 35% elevated risk (95% CI = 0.86 – 2.13) compared to those with no exposure. Time-period analysis by decade of first DEE – exposed job showed a statistically significant increased risk among men first exposed in the 1950's (heavily exposed: OR = 2.73, 95% CI = 1.29 – 5.70, p-trend = 0.009). It should be noted that exposures to DEE in underground mining are much higher than other DEE exposed workers such as above ground truck drivers. Underground miners and tunnel workers have a relatively higher exposure to elemental carbon than other occupations. Therefore, considering the dose response relationship for cumulative exposure demonstrated for truck drivers employed 25 years or longer, the risk for bladder cancer in miners would be expected to be higher.

The risk from exposure to diesel exhaust and bladder cancer is elevated regardless of smoking history. For example, among non-smokers, a significant trend in risk was observed by Koutros et al. [15] with increasing exposure to cumulative REC (Respirable Elemental Carbon) (p-trend =

0.03), with heavily exposed subjects having an OR = 2.80 (CI 1.08 – 7.22). This was also demonstrated by Latifovic et al. [16], where after adjustment for smoking and with exposure to high concentrations of diesel for >10 years, a greater than twofold increase in risk was found (OR = 2.45, 1.04 – 5.74). In this study, "high concentrations" of exposure were assigned to jobs such as garage mechanics maintaining diesel engines in poorly ventilated areas and underground mine workers. It was concluded by IARC that the findings of the Latifovic et al. study *"…extend the epidemiological literature on the role of diesel emissions in occupational carcinogenesis and support the hypothesis that occupational exposure to diesel emissions is an occupational risk factor for bladder cancer"* [8]. The literature is not clear whether the combined effects of diesel emission and smoking is either additive, multiplicative (synergistic) or somewhere in between.

In summary there is sufficient evidence that occupational exposure to diesel engine emissions is a risk factor for bladder cancer and that miners are exposed to elevated levels of diesel exhaust emissions.

Arsenic exposure

Arsenic and inorganic arsenic compounds are classified as IARC Group 1 carcinogens with sufficient evidence to cause cancer of the urinary bladder [6]. The Collaborative on Health and the Environment (CHE) Toxicant and Disease Database lists arsenic as having strong evidence for a causal association with kidney cancer [7]. 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 [18]. Gold ore typically contains arsenic-bearing materials such as pyrite, galena, chalcopyrite and dominantly arsenopyrite (which is 46% arsenic by weight) [19]. The arsenic content of gold ores may range from traces to a value greater than 5,000 mg/kg [20]. Underground tin miners in China have been reported to be exposed to 0.1 to 38.3 $\mu g/m^3$ of respirable arsenic [21]. A study on lung cancer and arsenic exposure [22] based on male German uranium miners who died from lung cancer during 1957-1990 reported a mean cumulative exposure of arsenic of 181.2 $\mu g/m^3$ x years. A German uranium miners' cohort [23] 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 $\mu g/m^3$ for arsenic over 220 shifts each at 8 h). The Ontario standard OEL for arsenic is a TWA of 10 $\mu g/m^3$ which agrees with the ACGIH TLV and a STEL of 50 $\mu g/m^3$ (no ACGIH STEL exists) [40]; though NIOSH set its recommended exposure limit (REL) STEL to 2 $\mu g/m^3$ based on arsenic's carcinogenic properties [45].

The 2012 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 [24]. A cohort study conducted in an arseniasis-endemic area in Taiwan [25] reported significantly increased incidence of urinary cancers for the study cohort compared to Taiwan's general population (Standardized Incidence Ratio (SIR) 2.05; 95%

CI 1.22-3.24) and a significant dose-response relation after adjustment for age, sex, and cigarette smoking especially for transitional cell carcinoma. A dose-response relation between arsenic and bladder cancer was also found in a study by Kurttio et al. [26] which examined lower levels of exposure to arsenic. The authors reported RRs for the arsenic categories of 0.1–0.5 μg/liter and ≥0.5 μg/liter relative to the category of <0.1 μg/liter were 1.53 (95 % CI: 0.75-3.09) and 2.44 (95 % CI: 1.11-5.37), respectively. A later case-control study in Tunisia [27] also found a relationship with low-level arsenic exposure when looking at blood arsenic levels of 0.70-167 μg/liter with OR 2.44 (95% CI 1.11–5.35, p=0.026) after adjustment for age and smoking (current cigarette smoking status).

A systematic review [28] of epidemiological studies published between 1983 and 2013 reports that 28 studies observed an association between arsenic in drinking water and bladder cancer. The meta-analyses showed the predicted risks for bladder cancer incidence were 2.7 (95% CI 1.2–4.1); 4.2 (95% CI 2.1–6.3) and; 5.8 (95% CI 2.9–8.7) for drinking water arsenic levels of 10, 50, and 150 μg/L, respectively. They also stated that with exposures to 50 μg/L, there was an 83% probability for elevated incidence of bladder cancer and a 74% probability for elevated mortality.

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

Ionizing radiation 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 [29]. Radon-222 and its decay products are classified as an IARC Group 1 carcinogen [6]; radon decay products include gamma radiation emitters which is listed as a bladder carcinogen with sufficient evidence. The workers at risk of highest exposure to radon are people working in underground mines [30] 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 milliSievert (mSv) or 2 Working Level Months or (WLM), 99.7% of them being exposed up to 5 mSv (1 WLM) [31]. A German uranium miners' cohort [23] 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 [43] 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.

Significant excess risk for cancer of the urinary bladder has been reported in the Life Span Studies (LSS) (cited in IARC [32]) from exposure to x-ray and gamma-radiation, with an Excess Relative Risk/Sievert (ERR/Sv) of 1.23 (90% CI 0.59-2.1) from an analysis of cancer incidence, ERR/Sv of

1.1 (90% CI 0.2-2.5) from an analysis of cancer mortality in men and 1.2 (90% CI 0.10-3.1) in women [33,34]. There is strong evidence of excess risk in three other medical radiation cohorts included in the IARC monograph: ERR/Grey (Gy) 0.24 (95% CI 0.09-0.41) based on 71 deaths [35], ERR/Gy 0.07 (90% CI 0.02-0.17) based on 273 cases [36] and SMR 3.01 (95% CI 1.84-4.64) based on 20 deaths [37]. A study on extrapulmonary cancers in the German uranium miners' cohort [23] observed a statistically significant relationship with cumulative radon exposure for all extrapulmonary cancers (ERR/WLM=0.014%; 95% CI: 0.006–0.023%). In addition, IARC notes that underground mining with exposure to radon is carcinogenic to humans [32].

In summary, there is sufficient evidence in the literature to support the association between bladder 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.

Solvent exposure

The CHE database [7] lists solvents in general as having good evidence to cause bladder cancer and IARC specifically lists tetrachloroethylene as having limited evidence [6].

Trichloroethylene (TCE) and tetrachloroethylene are chlorinated solvents and TCE is mainly used as a metal degreaser in several industries. According to CAREX Canada, the most heavily exposed occupational group are workers who degrease metals [30] which would include: mechanics, electricians, welders, solderers and brazers [38]; all of these occupations can be found in mines. A study on chronic health effects of TCE in Singapore [39] conducted personal environmental measurements via passive dosimetry of electronics plant workers that used TCE to degrease 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 exceeds significantly the current TLV for TCE which is 10 ppm and STEL (a 15-minute time-weighted average exposure that should not be exceeded at any time during the workday) which is 25 ppm [40].

A recent population based case-control study by Hadkhale et al. [41] based on the Nordic Occupational Cancer database which includes 113,343 bladder cancer cases found increased risks of bladder cancer with exposures to: TCE (Hazard Ratio or HR 1.23, 95% CI 1.12–1.40), toluene (HR 1.20, 95% CI 1.00–1.38), benzene (HR 1.16, 95% CI 1.04–1.31), aromatic hydrocarbon solvents (HR 1.10, 95% CI 0.94–1.30) and aliphatic and alicyclic hydrocarbon solvents (HR 1.08, 95% CI 1.00–1.23) at high exposure level versus no exposure.

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

Conclusion

By reviewing the scientific literature available to date, OHCOW has identified occupational exposure to diesel exhaust/PAHs, arsenic, and ionizing radiation as likely independent risk factors for the development of bladder cancer and solvents as a potential risk factor. The table in Appendix 1 summarizes key selected epidemiological findings for the various risk factors including confidence intervals as an indication of statistical strength of the associations. In addition, miners work with these and many more contaminants simultaneously and so the possibility of a combination or synergistic effect should be considered when assessing the work-relatedness of bladder cancer.

Appendix 1 - Summary of Epidemiological Studies Investigating Association of Various Risk Factors with Bladder Cancer

Reference	Exposed Group	OR	RR	SRR/ERR	HR
3. Kogevinas (2003) pooled analysis	miners and quarrymen - Europe	1.3 (1.02 - 1.64)			
4. Gaertner (2004)	male miners (supervisors, drillers, hauler/machinists) - Canada	1.94 (1.18 - 3.17)			
5. Reulen (2008) meta-analysis	miners (international meta-analysis			1.31 (1.09 - 1.57) SRR	
9. Brown (2012) review	PAHs and bladder cancer		1.4 (1.2 - 1.7)		
13. Steenland (1987)	truck drivers >20 years		12 (2.29 - 69.9)		
14. Silverman (1986)	truck drivers (significant trend - risk^ with duration^)		2.2 (1.1 - 4.2)		
15. Koutros (2014)	DEE heavily exposed in 1950s	2.73 (1.29 - 5.70)			
16. Latifovic (2015)	high DEE exposure >10 years adjusted for smoking	2.45 (1.04 - 5.74)			
26. Kurttio (1999)	arsenic in drinking water 10 ug/L		2.7 (1.2 - 2.4)		
	arsenic in drinking water 50 ug/L		4.2 (2.1 - 6.3)		
	arsenic in drinking water 150 ug/L		5.8 (2.9 - 8.7)		
33 . Preston (2007)	X-ray and gamma radiation – atomic bomb survivors			1.23 (90% CI 0.59 – 2.1) ERR/Sv	
41. Hadkhale (2017)	Trichloroethylene				1.23 (1.12 - 1.40)
	toluene				1.2 (1.00 - 1.38)
	benzene				1.16 (1.04 - 1.31)
	aromatic hydrocarbon solvents				1.10 (0.94 - 1.30)
	aliphatic and alicyclic hydrocarbon solvents				1.08 (1.00 - 1.23)
DEE (Diesel Exhaust Exposure); OR (Odds Ratio); RR (Relative Risk); SRR (Standardized Rate Ratio); HR (Hazard Ratio) – terms explained on following page		95% Confidence Intervals are shown in parentheses			

$$\text{OR = odds ratio} = \frac{\text{exposed cases/unexposed cases}}{\text{exposed referents/unexposed referents}}$$

RR = relative risk = rate of disease in exposed group/rate of disease in reference group

SRR = standardized rate ratio = A rate ratio in which the numerator and denominator rates have been standardized (weighted) to the same (standard) population distribution

ERR = excess relative risk = relative risk minus 1 (e.g. if RR is 3 then ERR is 3 – 1 = 2)

HR = hazard ratio the ratio of the disease rates corresponding to two levels of exposure (e.g. if the exposed population develops the disease at twice the rate per unit time as the control population then the hazard ratio would be 2). Hazard ratios differ from relative risks and odds ratios in that RRs and ORs are cumulative over an entire study, using a defined endpoint, while HRs represent instantaneous risk over the study time period, or some subset thereof. Hazard ratios suffer somewhat less from selection bias with respect to the endpoints chosen and can indicate risks that happen before the endpoint.

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