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STATEMENT ON OCCUPATIONAL LUNG CANCER SCREENING

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The Collegium Ramazzini is an international scientific society that examines critical issues in occupational and environmental medicine with a view towards action to prevent disease and promote health. The Collegium derives its name from Bernardino Ramazzini, the father of occupational medicine, a professor of medicine of the Universities of Modena and Padua in the late 1600s and the early 1700s. The Collegium is comprised of 180 physicians and scientists from 35 countries, each of whom is elected to membership. The Collegium is independent of commercial interests.

Summary

Lung cancer is the most common cause of death from cancer in the world. It is also the most common lethal work-related cancer. After tobacco smoking, occupational exposures present the most frequent specific cause of lung cancer that is amenable to intervention.

Early detection and treatment can identify and cure primary lung cancer. Randomized controlled trials have demonstrated the efficacy of low dose computed tomography (LDCT) screening among persons at high risk of lung cancer. Guidelines for determining eligibility for LDCT screening have been established for the general population but have largely neglected those for whom occupational exposure to lung carcinogens is a risk factor.

The Collegium recommends that persons at risk for lung cancer from occupational exposures be offered annual LDCT if their cumulative risk of lung cancer approximates the level of risk endorsed by the guidelines promulgated by the United States Preventive Services Task Force (USPSTF) in 2021 and the National Comprehensive Cancer Network (NCCN) in the United States in 2021. At present, these agencies recommend screening for people aged 50 and over who have smoked at least 20 pack-years of cigarettes. The Collegium recommends that additional lung cancer risk factors, including exposure to known or suspected occupational and environmental lung carcinogens; family history of lung cancer (especially among first degree relatives and relatives $\leq$ 60 years of age); a personal history of chronic obstructive lung disease, pneumoconiosis, or pulmonary fibrosis; or a personal history of cancer (excluding skin cancer) be considered as part of the risk assessment for eligibility determination for lung cancer screening. Latency, or the period of time since initial occupational exposure (e.g., $\geq$15 years) is another factor that should be considered. If the presence of these additional risk factors, in combination with age and smoking history, is associated with a level of risk that meets or exceeds the level of risk identified by the USPSTF and NCCN, then an annual low dose chest CT for lung cancer screening should be offered. We do not favor a specific age cut-off at which to end screening, but we recognize that only persons who are sufficiently healthy and have sufficient life expectancy to undergo diagnostic work-up and potentially curative treatment should be offered screening for lung cancer. In view of the rising risk of occupational lung cancer over time and the potential or actual interaction between occupational lung carcinogens and cigarette smoking even after quitting, screening programs may choose to screen workers with occupational lung cancer risk for prolonged periods after they have quit smoking cigarettes. The Collegium acknowledges that there are uncertainties and assumptions entailed in this approach and that risk assessment for individual workers necessitates application of significant professional judgement. We encourage the implementation of well-organized screening programs that can further our knowledge about optimal occupation-inclusive lung cancer screening strategies.

Workers with a history of exposure to known or suspected lung carcinogens or working in occupations/trades or work tasks that are known to elevate the risk for lung cancer form the target population for lung cancer screening. Important examples of lung carcinogens include asbestos, silica, diesel exhaust, welding fumes, selected metals, and radiation.

There are well established, evidence-based procedures for the performance of lung cancer screening, preferably in well-organized programs, that apply recognized criteria for cancer screening (Wilson et al 1968; NCCN 2021):

- Screening participants should be provided with complete and comprehensible information about risks and benefits.
- Screening should be offered annually and continuously.
- Screening should be achieved through the application of low dose computed tomography (LDCT) to minimize the radiation dose delivered.
- Proper CT scan interpretation should be performed by experienced radiologists or other well-trained readers.
- Prompt, appropriate follow-up of abnormal CT scans involving relevant medical expertise is mandatory.
- Patients who are current smokers should be offered smoking cessation programs.

The Collegium calls upon occupational health and medical professionals and stakeholders (governments, employers, insurance companies, and labor unions) to identify worker populations that have excess lung cancer risk, to promote lung cancer screening, and to develop and support well-organized programs to conduct such screening in these populations.

While elimination or minimization of exposure to lung carcinogens in the workplace through environmental controls is critical for lung cancer prevention, lung cancer screening is an essential secondary intervention for reducing deaths and disabling disease from exposure to workplace lung carcinogens.
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EVIDENCE-BASIS FOR THIS STATEMENT

A. Burden of Occupational Lung Cancer

Lung cancer is the most common cause of death from cancer in the world, causing one in five (20.4%) cancer deaths in 2019 [GBD 2019]. It is the most common cause of cancer death for males in most countries, including low-, middle-, and high-income nations, and the most frequent cause of cancer death among women in China, the U.S., Australia, Scandinavia, and Canada. Tobacco smoking is the dominant cause of lung cancer, and the maturity of the cigarette smoking epidemic and variable uptake and adoption of smoking cessation determines much of the geographic and gender variation in lung cancer incidence and mortality (Bray 2018).

Lung cancer is also the dominant cause of occupational cancer (excluding non-melanoma skin cancers), causing more than 50% of all workplace-related cancers (Straif 2008). A recent analysis associated with the Global Burden of Disease Study 2016 estimated that 300,000 lung cancer deaths occurred as a result of exposure to ten IARC Group 1 lung carcinogens in 2016, representing 86% of all occupational cancer deaths (Global Burden of Disease 2016 Occupational Carcinogens Collaborators 2020). Work-related lung cancer deaths increased 55% from 1990 to

2016, from an estimated 193,000 to 300,000 deaths per year (GBD 2016 Occupational Carcinogens Collaborators 2020). Excellent reviews of occupational cancer in general are readily available (Loomis 2018; Rushton 2010; LaBreche 2019).

Occupational lung cancer remains grossly neglected by public health surveillance, clinical medicine, and worker compensation systems despite its enormous burden of illness and death. Studies in diverse populations and industries across three continents (Asia, Europe, and North America) have demonstrated that a very small fraction - less than 3% - of the total number of estimated occupational lung cancers have been attributed to occupation. In Korea, where an estimated 630 to 1,181 occupational lung cancers occur annually, only 179 work-related lung cancers, or 10 per year on average, were compensated by the Korean national worker compensation system over a nearly two-decade period (Ahn 2014; Kim 2010). In Great Britain, where 5,442 occupational lung cancer cases are estimated to occur each year (Brown 2012), only 21 cases per year (or 392 cases over a 19 year period, 1996-2014) were recorded in Surveillance of Work-Related and Occupational Respiratory Disease (SWORD), a national voluntary reporting system (Carder 2017). Similarly, in Canada, of the estimated 4,150 annual occupational lung cancer cases, only 120 occupational lung cancers were compensated each year between 2005 and 2009 (Del Bianco 2013; Labreche 2019).

B. Exposure to Occupational Lung Carcinogens

Over the past five decades, the International Agency for Research on Cancer (IARC) has identified 20 IARC Group 1 occupational lung carcinogens (substances or mixtures) and an additional 7 occupations, industries or work processes in which occupational epidemiology studies were instrumental in establishing specific lung carcinogenicity (Loomis 2018). These agents, occupations and industries are listed in Table 1, adapted from IARC sources (Loomis 2018; IARC 2022). Four in ten of all agent-specific IARC Group 1 carcinogens cause lung cancer. In addition, two-thirds of all occupations, industries, or processes that cause occupational cancer cause lung cancer (Table 1).

Further, there is limited evidence for an association with lung cancer of numerous other exposures, though less broadly recognized within the occupational health community. They include cobalt, 2,3,7,8 tetrachlorordibenzo-para-dioxin (dioxin), and high temperature frying emissions and total 8 agents or mixtures and 4 occupations, industries or processes (Table 1) (IARC 2019).

The number of occupational lung carcinogens are increasing. In the past decade alone, IARC has added common exposures such as diesel engine exhaust (2013), outdoor air pollution (2016), and welding fumes (2017) to its Group 1 list of carcinogens (Table 1). (Loomis 2018; IARC 2022). For additional carcinogens, there is limited evidence for an association with lung cancer: emissions from combustion of biomass fuel (2010); bitumens from roofing (2013); diazinon (2017); and hydrazine (2018).

The occupational lung cancer burden is likely to grow. Only a small fraction of the tens of thousands of chemical agents in commercial use have been evaluated for toxicity. In five decades, IARC has evaluated more than 1,000 agents, occupations and industries, but found that available scientific studies are inadequate or lacking in approximately one-half of the evaluations (Loomis 2018; Cogliano 2011). For context, there are an estimated 86,000 chemicals in the United States Environmental Protection Agency's Toxic Substances Control Act Inventory (Environmental Protection Agency 2019). Given the frequency of exposure of the respiratory system to inhaled toxicants and the demonstrated carcinogenicity of many chemical agents, it is likely that only a fraction of occupational lung carcinogens has been identified and the total burden of occupational lung cancer remains undefined.

Exposure to occupational lung carcinogens has been and remains reasonably common. National and cross-national surveys of workplace exposures have been conducted in high income countries for 4 decades, including the U.S. National Occupational Hazard and Exposure Surveys (1972-1974 and 1981-1983; CAREX (carcinogen exposure) project in the European Union (1990-1993) (Kauppinen 2000); FINJEM (Finnish job-exposure matrix) system in Finland (Kauppinen 2013; and the Canadian version of FINJEM (Peters 2015).

The most prevalent occupational lung carcinogens in high income countries over the past 30 years have been diesel exhaust, welding fumes, and silica. Based on data from Europe, Finland and Canada, more than 2% of the employed population has been exposed to each of these three mixtures or agents. This proportion has not changed in the past 3 decades. Exposure to asbestos had been a dominant exposure in these countries, but its use declined markedly in recent decades due to widely accepted bans and restrictions. Asbestos exposure continues in these countries, however, due to large quantities of asbestos-containing materials still in place. For middle- and low-income countries, national estimates of the prevalence of exposure to occupational lung carcinogens have not been identified. Given the extent and lack of adequate regulation of manufacturing, mining, and construction, exposures to said agents is likely to be more common and at higher levels than in high income countries.

For the purpose of lung cancer screening, workplace exposures that were prominent 20 to 40 years ago are highly relevant today due to the latency of asbestos-related lung cancer. Asbestos exposure was common in worksites in many high-income countries prior to the 1980's, though exposure in recent decades has declined. The prior and continuing high use of asbestos in China, Russia, India, and selected other countries is almost certainly associated with elevated risk of asbestos-related lung cancer for large populations of workers at, both at present and well into the future (Nicholson 1982; Flanagan 2016). Other highly relevant exposures, such as silica, diesel exhaust, and welding fumes, were prevalent in the past and remain prevalent in countries of all national income levels.

Salient industries and examples of occupations with current exposure to occupational lung carcinogens are provided in Table 2. Many construction workers are exposed to the most common lung carcinogens: asbestos, diesel exhaust, silica and welding. Diesel engine exhaust exposure is highly prevalent among workers who drive or maintain diesel vehicles, including buses, trucks, trains, ships and heavy equipment. Many workers in mining are exposed to diesel exhaust from mining equipment. Miners and workers in many manufacturing industries continue to have exposure to carcinogenic metals and silica.

C. Smoking and Chronic Lung Disease Amplify Occupational Lung Cancer Risk

Cigarette Smoking Occupation and, more generally, social class, are closely associated with cigarette smoking. In the United States, one-quarter or more of workers in construction, manufacturing, mining, and transportation smoke cigarettes compared to 10% of workers in professional or managerial positions (Symlal 2016). In China, for example, the prevalence of smoking among male machine operators (67%) was nearly twice that of male medical/health personnel or teaching staff (36% to 38%) (Gonghuan 2010).

Interaction of Smoking and Occupational Lung Carcinogens It is well-established that occupational lung carcinogens and cigarette smoke act in concert in some circumstances to increase the risk of lung cancer. They share mechanistic pathways and have been repeatedly shown in epidemiologic studies to increase lung cancer risk above that expected by the presence of each risk factor alone. Asbestos is the best-known example of this phenomenon. Asbestos frequently shows at least a supra-additive interaction with smoking in determining lung cancer risk (Nielsen 2014; Markowitz 2013; Wang 2012; Offermans 2014; Olsson 2017). Several large studies addressing the lung cancer risk among silica-exposed workers have been completed in the past decade, generally suggesting a supra-additive effect with cigarette smoke (de Matteis 2012; Liu 2013; Consonni 2015; LaCourt 2015; Kachuri 2014). Other occupational lung carcinogens that have been studied for interaction include diesel exhaust (Silverman 2012; Pintos 2012) and radon (Schubauer-Berrigan 2009; Leuraud 2011; Kreuzer 2018).

Chronic lung disease and lung cancer risk Occupational exposures also indirectly increase lung cancer risk by causing chronic lung diseases, namely, chronic obstructive lung disease (COPD) and pneumoconioses, such as silicosis and asbestosis (Denholm 2014; Markowitz 2020). In fact, since occupational exposures to vapors, gases, dusts or fumes raise the risk of COPD (Blanc 2019), for example, the occupational contribution to lung cancer should be considered more broadly than simply the role of the occupational agents causing lung cancer. Smoking works similarly as a major cause of COPD and as an established risk factor for idiopathic pulmonary fibrosis (Takiguchi 2014; Naccache 2018). Figure 1 illustrates the complexity of these relationships. Key aspects of these relationships have been well-studied (e.g., the smoking and asbestos interaction noted above and the contribution of asbestosis and silicosis to risk of lung cancer). Other relationships, such as the interaction between work-related COPD and lung cancer, have received relatively less attention.

I. Lung Cancer Screening Recommendations in the General Population

A. Low Dose CT (LDCT) Scan Screening Studies

Three decades of research provide strong evidence that periodic low dose chest CT scans can identify lung cancers at an early stage and can reduce lung cancer mortality. In Japan and the U.S., Sone et al (Sone 1998) and Henschke et al (Henschke 1999) separately demonstrated that low dose chest CT scanning in high risk populations detected ~85% of lung cancers at Stage I. In 2006, Henschke et al. further showed that treated early CT-detected lung cancers had excellent survival: a group of 412 Stage 1 lung cancers detected by CT screening had an estimated 88% 10-year survival (Henschke 2006). Of those who underwent surgical resection within one month of diagnosis, 10-year survival was 92%, 95% CI 88-95%. These remarkable results of non-randomized studies stimulated intense interest and the initiation of randomized controlled trials of the impact of low dose CT scans on lung cancer mortality.

Two large complementary randomized clinical trials of populations at high risk of lung cancer—the U.S. National Lung Screening Trial (NLST) and the Dutch–Belgian Nederlands–Leuvens Longkanker Screenings Onderzoek (NELSON)—conclusively demonstrated that periodic low dose chest CT scanning reduces lung cancer mortality (National Lung Screening Trial Research Team 2011; de Koning 2020).

The NLST, conducted by the United States National Cancer Institute, included 53,454 enrollees aged 55 to 74 who had smoked at least 30 pack-years and, for former smokers, had quit within the past 15 years. The CT versus chest X-ray (CXR) study arms were screened annually for 5 years and followed for a median of 6.5 years. The CT scan screening arm showed a 20% reduction in lung cancer mortality versus the CXR screening arm (National Lung Screening Trial Research Team 2011).

The NELSON trial included 13,195 men and 2,594 women aged 50 to 74 years who had smoked at least 15 to 20 pack-years and, if former smokers, had quit 10 or fewer years prior to the entry date into the study. NELSON compared an intervention group who underwent 4 rounds of CT screening (baseline, year 1, year 3, and year 5.5) with a reference group who had no screening; all were followed for at least 10 years. NELSON observed a 24% and 33% lung cancer mortality reduction among men and women, respectively, in the trial (de Koning 2020).

Neither the NLST nor the NELSON trials were designed to evaluate the efficacy of lung cancer among screenees defined other than by age and smoking. Other factors would include occupational exposures, chronic lung disease, family history of lung cancer, personal history of cancer, or environmental exposure to radon, air pollution, or other non-occupational toxins.

B. Lung Cancer Prediction Models

An alternative to the use of age and smoking history alone to estimate lung cancer risk and to determine screening eligibility is the employment of a broader set of lung cancer risk factors in lung cancer risk models. More than 20 lung cancer risk prediction models based on large lung cancer datasets [e.g., Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO, developed in North America) (Tammemägi 2013); Liverpool Lung Project (LLP, developed in England) (Cassidy 2008)] have been developed, and many are inclusive of a broader and more detailed set of lung cancer risk factors than the NLST and NELSON trials (Toumazis 2020). These additional risk factors variably include gender, race, body mass index (BMI), intensity and duration of smoking, number of years since smoking cessation, chronic lung disease, especially chronic obstructive pulmonary disease (COPD), personal history of cancer, family history of lung cancer, education, and asbestos exposure. Among the better-performing models, the only occupational carcinogen included is asbestos, which is part of the Liverpool Lung Project (LLP) and Bach models (Cassidy 2008; Bach 2003). No other occupational or environmental exposures have been included in the risk prediction models. Lung cancer risk calculators derived from these models use no or little information about occupation in determining risk.

In a noteworthy comparison of the risk factor versus risk prediction approaches to the use of LDCT, ten Haaf (ten Haaf 2017) applied nine established lung cancer risk prediction models to the large data sets of the NLST and the PLCO and compared results to the risk factor eligibility criteria used in the NLST, using 5- and 6-year lung cancer incidence and mortality as outcomes. The specificity of the risk prediction models versus the NLST criteria were very similar (~62.2% to 62.6%), but four models had substantially higher levels of sensitivity (> 78%) compared to that of the NLST criteria (71.4%) with respect to lung cancer incidence. The contrast in sensitivity for lung cancer mortality between the NLST criteria and the model predictions was even greater: 73.5% for the NLST versus 85.2% for the $PLCO_{m2012}$ model and 83.8% for the TSCE (Two-Stage Clonal Expansion) and Bach models (ten Haaf 2017).

In a U.S. National Cancer Institute study of this issue, investigators compared the lung cancer mortality benefits of a risk prediction-based model versus a USPSTF guidelines-based model (restricted to age and smoking) and concluded that the former approach, which used family history, self-reported emphysema, body mass index, age and a broader range of smoking history as eligibility criteria, prevented a greater number of lung cancer deaths than a model based on USPSTF screening guidelines (see below) (Katki 2016; Tammemägi 2022).

C. Current Lung Cancer Screening Recommendations

Unites States Based principally on the results of the NLST, the United States Preventive Service Task Force (USPSTF) recommended in 2013 that annual low dose CT scanning be offered to individuals at high risk of lung cancer, who were defined as people aged 55 to 74 years who had smoked at least 30 pack-years of cigarettes and currently smoke or quit less than 15 years previously. In 2021, after publication of the NELSON trial results, the USPSTF revised its recommendations for annual LDCT eligibility to include people aged 50 to 80 years who have at least a 20 pack-year smoking history and currently smoke or have quit within the past 15 years (U.S. Preventative Services Task Force 2021). These recommendations were adopted by the U.S. Federal government and private insurance companies for use in health insurance coverage and clinical preventive practice.

Europe Recommendations based in Europe to date have adopted a more heterogeneous approach. In a March 2022 report prepared by SAPEA (Science Advice for Policy by European Academies), a consortium effort of European Scientific Academies and released, lung cancer screening with LDCT is recommended, using either a combination of age and smoking or the $PLCO_{m2012}$ model (SAPEA 2022). An expert group of European physicians and scientists who are leaders in lung cancer screening in Europe have developed a set of consensus recommendations on lung cancer screening, which were published in June 2020 (Veronesi 2020). They recommended the use of lung cancer risk thresholds (e.g., 1.51% over a 6-year period) applied to results of risk prediction models in order to determine who should be eligible for LDCT-based lung cancer screening. Of the numerous risk prediction models that have been developed, the expert group favored those derived from the Liverpool Lung Project (LLP_{v2}) and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial ($PLCO_{m2012}$).

China In China, a multidisciplinary lung cancer early detection and treatment expert group (appointed by the Chinese National Health and Family Planning Commission) established the China National Lung Cancer Screening Guidelines, recommending annual lung cancer screening with LDCT for people aged 50-74 years who have at least a 20 pack-year smoking history and who currently smoke or have quit within the past five years. (Zhou 2018).

The latest Chinese guidelines developed by the National Cancer Center of China recommends lung cancer screening eligibility including: 1) current smokers with ≥30 pack-years or former smokers with ≥30 pack-years who have quit within 15 years; 2) secondhand smokers who have lived or worked with smokers for at least 20 years; 3) people with COPD; 4) participants who have exposure ≥1 year to asbestos, radon, beryllium, chromium, cadmium, nickel, silica, or soot; 5) people with first degree relatives have confirmed lung cancer (He et al. 2021).

South Africa The South African Thoracic Society recently issued recommended guidelines for lung cancer screening. They recommend that annual LDCT should be offered to people between 55–74 years of age who are current or former smokers (having quit less than 15 years previously) with a history of ≥ 30-pack years of smoking. Participants should have no history of lung cancer and be in reasonable health and able and willing to be treated for lung cancer. They note that the high prevalence of tuberculosis in South Africa requires that only lung nodules ≥ 6 mm need follow-up (Koegelenberg 2019)

III. Dearth of Recommendations for Occupational Lung Cancer Screening

A. Current Recommendations

Occupation is generally ignored in current screening recommendations, whether they are based on selected risk factors (age and smoking) or on risk prediction models. Exceptions in the U.S. include guidelines developed by the National Comprehensive Cancer Network (NCCN) and the American Society of Thoracic Surgeons. Their guidelines include using additional risk factors to determine screening eligibility, i.e., family history, history of chronic lung disease and occupational exposures. Specifically, NCCN Group 2 eligibility criteria, first used in 2014, recommended screening people aged ≥50 years with a 20 pack-year smoking history if they have an additional risk factor for lung cancer, such as exposure to occupational lung carcinogens, chronic lung disease, or a family history of lung cancer and had an aggregate 6 year risk of lung cancer ≥ 1.3% (Wood 2018). More recently, NCCN recommended a 20 pack-year screening threshold for everyone aged 50 years and over but occupation and other risk factors can additionally be considered in determining eligibility for screening (National Comprehensive Cancer Network Clinical Practice Guidelines 2022)). Occupational lung carcinogens named include silica, cadmium, asbestos, arsenic, beryllium, chromium, diesel exhaust, nickel, coal smoke, and soot.

In 2014, a group of international experts in asbestos-related diseases met in Helsinki and recommended that the lung cancer risk level associated with the NLST study population be used as the threshold risk level in organized low dose CT scan programs for screening asbestos-exposed workers for lung cancer (Wolff 2015). The Helsinki recommendation was made before completion of the NELSON clinical trial, numerous modeling studies, and revision of the USPSTF eligibility guidelines in 2021.

In 2017, an expert working group in France made recommendations for the application of LDCT for lung cancer screening for workers who have a history of exposure to Group 1 IARC occupational lung carcinogens, including asbestos (Delva 2017). They conducted a scientific literature review and developed an expert consensus on how to identify the magnitude of lung cancer risks associated with these Group 1 carcinogens, alone and in combination with cigarette smoking, and identified the combinations that equaled or exceeded the lung cancer risk associated with NLST eligibility criteria. They assumed a multiplicative (and not a supra-additive or additive) joint effect between the occupational carcinogenic agent and tobacco in estimating the relative risks. They estimated that the relative risk of lung cancer associated with the NLST study eligibility criteria (≥30 pack-year history of cigarette smoking) was 30. Using the target relative risk level of 30, exposure to each of the IARC Group 1 lung carcinogens in combination with 20–29 pack years of smoking met or exceeded the target risk level. Never smokers who were occupationally exposed to lung carcinogens at any level did not reach a relative risk sufficient to justify lung cancer screening with the possible exceptions of plutonium and bis-chloromethyl ether (Delva 2017).

Since the publication of this set of French recommendations in 2017, the results of the NELSON trial and modeling studies led the USPSTF to lower the age and smoking levels for eligibility for LDCT-based lung cancer screening (≥age 50 years and ≥20 pack-years). The associated estimated relative risk level of lung cancer in the French analysis would be 20. Accordingly, under these French guidelines, workers with intermediate asbestos exposure ≥10 years and workers with ≤ 5 years of high asbestos exposure would be recommended for lung cancer screening even among ever smokers with a smoking history of less than 20 pack-years.

B. Empirical Studies of LDCT in Occupational Populations at Risk

Studies of lung cancer screening among occupational populations at high risk of lung cancer are limited to date. Two types of occupational settings have been studied: asbestos-exposed groups and United States nuclear weapons workers.

Asbestos Nine non-randomized studies of asbestos-exposed populations with ≥150 participants reported results of LDCT screening for lung cancer between 2002 to 2019 (Titola 2002; Minniti 2005; Das 2007; Fasola 2007; Vierreko 2007; Mastrangelo 2008; Roberts 2009, Clin 2009; Kato 2018; Maisonneuve 2019; and Brims 2023). Age, smoking history, and asbestos exposure were principal or exclusive eligibility criteria with frequent use of broader age and smoking ranges than those used in NLST or NELSON. These studies were included in a published systematic review and meta-analyses by Ollier et al (Ollier 2014) and Maisonneuve et al (Maisonneuve 2019).

None of these studies used risk prediction models, NLST, or NELSON eligibility criteria to determine eligibility. Comparison with NLST or the NELSON results is precluded by the heterogeneity of the study populations and the lack of sufficient detail on smoking history and age in the published studies.

Combining the screening yield results of these nine studies yielded 86 lung cancers detected among 5,548 ever smokers (1.55%) and 6 lung cancers detected among 1,787 never smokers (0.33%).

Parameters of asbestos exposure varied widely among the nine studies by industry, occupation, duration of employment, presence or absence of pleural plaques, and other variables. One-half of published studies screened people only if they had a history ≥ 15 years of asbestos exposure, while one-half used a history of 1 or 5 years of significant asbestos exposure as a screening criterion. The studies with the highest lung cancer detection yields by LDCT also tended to have study populations with the highest prevalence (43% to 89%) of pleural plaques on low-dose CT scans (Das 2007; Roberts 2009; Kato 2018). The pleural plaques were generally identified by LDCT.

Only one study reported on lung cancer mortality follow-up of application of LDCT among an asbestos-exposed population. Barbone and colleagues examined nine-year mortality follow-up of a non-randomized study of 926 asbestos-exposed workers who were enrolled in an asbestos surveillance program in Northeastern Italy, a major shipbuilding area. The group had undergone at least two periodic LDCT scans beginning in 2002 (Fasola 2007; Barbone 2018). They were mostly men with a mean age of 58 years at study onset and a mean duration of 30 years of exposure to asbestos; one-third never smoked, and median pack-years of cigarettes among smokers was 18.5. The comparison group of 1,507 people had more smokers but a lower average level of asbestos exposure and underwent chest-rays (CXR). The LDCT study group showed a lung cancer SMR of 0.55 (95% CI: 0.24–1.09), and the CXR study group had a lung cancer SMR of 2.07 (95% CI: 1.53–2.71) in comparison with regional mortality rates. In a Cox proportional hazard analysis adjusting for age, smoking, and asbestos exposure level, the LDCT study group showed a hazard ratio for lung cancer of 0.41 (95% CI: 0.17–0.96) versus the CXR study group. Differences in the lung cancer risk factor profile between the study groups and the non-random nature of the study likely accounted for some of the observed difference in lung cancer mortality.

Loewen and colleagues used LDCT to study a population with mostly environmental exposure to Libby amphibole asbestos in Libby Montana. The population was aged 50 to 84 years, had a >20 pack-year history of tobacco use, and had a history of asbestos-related pleural or pulmonary fibrosis on a previous high-resolution CT scan. Seventeen lung cancers were detected: 71% were Stage 1 (59%) or Stage 2 (11%) (Loewen 2019).

In Germany, the German Statutory Accident Insurance offers annual LDCT screening to those who are $\geq$ 55 years of age, have smoked > 30 pack-years and have been exposed to asbestos $\geq$ 10 years before 1985 or who have parenchymal asbestosis or pleural fibrosis. As of mid-1991, 10,306 of 20,253 people who met these criteria and had physician counseling underwent baseline LDCT screening with 5,476 undergoing a second round of screening and 1,725 have additional screening rounds. Preliminary data show that 133 people in the program have been detected as having lung cancer (Heidrich 2022).

In Australia, Brims and colleagues applied LDCT for 5 years to 1,743 people with asbestos exposure, including one-third from the Wittenoom environment (workers or residents). Non-Wittenoom participants had >3 months of cumulative occupational exposure to asbestos or radiographic evidence of pleural plaques. Median cumulative asbestos exposure was modest (0.7 fiber/cc-years, but 61% had pleural plaques and 35 % had parenchymal asbestosis on the baseline LDCT scan. Only 7% of the population were current smokers, and one-third of the population never smoked; median pack-years was 20 for ever smokers. LDCT detected 22 lung cancers, and an additional 4 lung cancers were detected in follow-up (3 were interval cancers). 19 of the 22 (86.4%) LDCT-detected cancers were Stage I lung cancers. The authors applied the 2021 USPFTF, $PLCO_{2012}$, the LLP, and a combined $PLCO_{2012}$/LLP eligibility criteria to the study population and found that no more than 25% of the program participants would have been screened under these various alternative criteria. Consequently, no more than 35% of the 26 lung cancers detected by the program would have been detected by application of these alternative eligibility criteria. Brims et al conclude that existing lung cancer screening criteria do not adequately account for occupational exposures. (Brims 2023).

Asbestos-Exposed Never Smokers Compared to Smokers Kato et al. performed a one-time LDCT screening of 2,132 asbestos-exposed workers, principally from shipbuilding, construction, and manufacturing sectors in Japan. Eligibility criteria included: (1) work in asbestos manufacturing for ≥ 1 year; or (2) work in other asbestos-exposed industries for > 10 years; or (3) evidence of pleural plaques on CXR or chest CT scan. In total, 89% of participants had pleural plaques on CT scan. Among 444 never smokers, 3 lung cancers were detected (0.7%), and 42 lung cancers were found among 1651 smokers (2.5%) (Kato 2018).

In the Brims et al study summarized above, 4 lung cancers were detected among 596 (0.7%) never smokers, representing 15% of all lung cancers detected in the program. Details regarding the asbestos exposure or findings of radiographic scarring are not available. (Brims 2023)

C. U.S. Nuclear Weapons Workers

For two decades, Markowitz, Miller and colleagues have used low-dose chest CT scanning to screen ~14,000 workers who had worked at nuclear weapons facilities in 13 mostly non-metropolitan U.S. communities with variable exposure to asbestos, radiation, beryllium, nickel, chromium, and other toxins. Eligibility criteria included age (≥50 years), smoking, occupation (production, maintenance or laboratory worker), and, if present, asbestos-related radiographic parenchymal or pleural fibrosis and/or a positive beryllium lymphocyte proliferation test. In a 2018 report on 7,189 of these workers, all of whom had a smoking history, the proportions with screen-detected lung cancer were 0.83% at baseline and 0.51% on annual scan. Stage distribution at diagnosis was favorable: of 80 detected lung cancers, 59% (n = 47) were Stage 1, and 10% (n = 8) were Stage 2. Study strengths included high study compliance; high credibility with the study population through labor union co-sponsorship; implementation in community settings; excellent follow-up; and use of a standardized protocol with demonstrated quality (Markowitz 2018).

To delineate the occupational contribution to aggregate lung cancer risk, Markowitz et al. compared two sub-groups of the study population: Group A met NLST eligibility criteria for age (≥55 years) and smoking history (≥30 pack-years); Group B did not meet these NLST study criteria but met National Comprehensive Care Network (NCCN) Group II criteria (age ≥ 50 years, 20–29 pack-year smoking history, and occupational risk). Both groups had occupational exposures. Group B had a lower overall lung cancer risk compared to the NLST study based on age and smoking profile but had occupational risk of lung cancer. The lung cancer screening yield of Group A (1.5%, 95% CI: 0.88–2.12%) was similar to that of Group B (1.36%, 95% CI: 0.85–1.87%). Both were statistically similar to the screening yield of the original NLST study (1.0%, 95% CI: 0.88–1.12%). These results indicate that, in the presence of occupational risk, younger people with lesser smoking histories could nonetheless benefit from LDTC screening (Markowitz 2018).

Although the Markowitz et al. study did not include mortality follow-up, the shift in diagnosis of earlier stage lung cancers with LDCT screening is consistent with the NLST and NELSON trials that demonstrated favorable mortality reductions (Markowitz 2018).

A second study of LDCT screening among US nuclear weapons workers—construction workers—was completed by Welch, Dement, and others (Welch 2019). The study group had a lower age and smoking threshold than the NLST study criteria (age $\geq$ 50 years and smoking $\geq$ 20 pack-years), but they had additional lung cancer risk, as defined by 5 years of work in the construction industry (exposure to asbestos, silica, beryllium, chromium, radiation, or welding), evidence of radiographic asbestosis or pleural plaques, or spirometric evidence of chronic obstructive pulmonary disease. Stage distribution among CT-detected cancers was favorable: 20 of 30 (67%) detected lung cancers were Stage 1 (57%) or Stage 2 (10%) disease. The lung cancer screening yield at baseline scan was 1.7% (21 of 1,260 participants), a result that was similar to the NLST results, despite the fact that less than one-half of participants met the NLST eligibility criteria (Welch 2019).

Dement and colleagues used this nuclear weapons construction worker cohort and a related larger construction worker population to develop a lung cancer risk prediction model (BTMed model) that includes age, gender, race, smoking history, spirometry, chest X-ray finding of parenchymal fibrosis and/or pleural plaques, occupational history of $\geq$ 5 years of work in construction, body mass index, respiratory symptoms, and personal history of cancer (Dement 2020). Applying the lung cancer screening criteria described above in the Welch et al. study yielded an 85.6% sensitivity, a 56.8% specificity, and a 4.2% positive predictive value. The BTMed model calibrated to scan the same number of individuals as the $PLCO_{m2012}$ model demonstrated a sensitivity of 76.0%, specificity of 70.9%, and a 5.5% positive predictive value. This level of sensitivity compares favorably with that of the $PLCO_{m2012}$ model applied to this cohort (70.5%), and specificity was comparable (70.9% for BTMed and 70.8% for $PLCO_{m2012}$)... Dement et al. applied the 2013 USPSTF-recommended screening criteria (age 50–80 years, $\geq$ 30 pack-years of smoking, and quitting <15 years in past) to their dataset and obtained a 50.9% sensitivity, an 81.2% specificity, and a 5.7% positive predictive value (Dement 2020). This large decline in sensitivity, from 85.6% to 50.9%, using the different eligibility criteria, represents a failure of the 2013 USPSTF criteria (which exclude occupation) to detect as many as 40% of the lung cancers detected in the Welch et al study.

RECOMMENDATIONS

1. <u>Pre-eminence of Primary Prevention of Occupational Lung Cancer</u>

Primary prevention of occupational lung cancer through the control of exposure to lung carcinogens in the workplace is key to avoiding future suffering from occupational lung cancer. Elimination of current and future exposures to occupational lung carcinogens, education of workers, employers and other parties to the workplace, and regulations by governments and authorities play key roles in this form of prevention.

Secondary prevention of occupational lung cancer promotes the avoidance of unnecessary morbidity and mortality through the early detection of the cancer, after occupational exposure to a lung carcinogen has occurred and at a stage at which it is potentially curable. LDCT-based lung cancer screening provides the basis for this secondary prevention and also provides an excellent opportunity to promote smoking cessation, which is a second form of primary prevention. LDCT screening does not prevent the occurrence of lung cancer but it can prevent lung cancer mortality.

Finally, tertiary prevention of occupational lung cancer aims to reduce the consequences of living with lung cancer and its treatment. Recent advancements in the treatment of lung cancer are considerable and translate into longer survival for many people with the disease. Job accommodation is important to allow people with lung cancer to return to work if able and to continue to earn income and thereby lessen the impact of the diagnosis on themselves and their families. Just financial compensation for occupational lung cancer as an occupational disease can also play an invaluable role in softening the impact of a frequently devastating disease for workers and their families.

2. <u>Underlying Principles for LDCT in Occupational Populations</u>

The Collegium Ramazzini recognizes key principles supporting lung cancer screening among workers at risk.

First, the urgency presented by the magnitude of occupational lung cancer in combination with current evidence in favor of lung cancer screening efficacy supports the use of LDCT screening for workers at risk.

Second, in recognition of the principles of respect for autonomy and justice, the Collegium believes that at risk workers should be provided with a choice about undergoing lung cancer screening. This decision should be made in consultation with their doctors who, together with other members of the medical and scientific community, are duty-bound to provide ample and accessible information to enable good decision-making. Such information should include the limits and risks of annual low dose CT scans, including the possible detection of health conditions for which current treatment is inadequate (e.g., malignant mesothelioma of the pleura). Participation in lung cancer screening should be voluntary.

Third, working populations have often been kept uninformed about their occupational exposures to lung carcinogens. Even if informed, conditions of the workplaces frequently prevented avoidance of such exposures. The identification of resources to support lung cancer screening and subsequent diagnosis and treatment for these workers should be a high priority for unions and other organizations representing them, and for government agencies and employers responsible for a safe and healthy workplace - i.e., for primary prevention.

Fourth, additional research to determine the optimal parameters to ensure effective occupational lung cancer screening should be funded and undertaken. Of particular concern is whether non-malignant chronic lung disease associated with asbestos, silica, beryllium, and other lung carcinogens significantly alters the risk:benefit ratio of the use of annual LDCT. In addition, the co-morbidities due to smoking may affect screening outcomes in occupational populations whose eligibility criteria include a lesser tobacco use history in combination with exposure to workplace lung carcinogens. The Collegium encourages research collaboration and data pooling in occupational lung cancer screening studies that include long term mortality follow-up to develop an improved understanding of the effectiveness of screening working populations at increased risk of lung cancer and certain workers within those populations, such as those with pneumoconiosis.

3. Eligibility for LDCT Screening

Workers at risk for occupational lung cancer will benefit from determination of eligibility for lung cancer screening that takes into account a) age and smoking, and b) a number of other lung cancer risk factors. These include occupational exposure to a lung carcinogen(s), personal history of cancer (excluding skin cancer), personal history of chronic lung disease, family history of lung cancer, and other demonstrated lung cancer risk factors.

The Collegium recommends that persons at risk for lung cancer from occupational exposures be offered annual LDCT if their cumulative risk of lung cancer approximates the level of risk endorsed by the guidelines promulgated by the United States Preventive Services Task Force (USPSTF) in 2021 and the National Comprehensive Cancer Network (NCCN) in the United States in 2021. At present, these agencies recommend screening for people aged 50 and over who have smoked at least 20 pack-years of cigarettes. The Collegium recommends that additional lung cancer risk factors, including exposure to known or suspected occupational and environmental lung carcinogens, family history of lung cancer (especially among first degree relatives and relatives $\leq$ 60 years of age), a personal history of chronic obstructive lung disease, pneumoconiosis, or pulmonary fibrosis,, or a personal history of cancer (excluding skin cancer) be considered as part of the risk assessment for eligibility determination for lung cancer screening. The period of time since initial occupational exposure (latency) is another factor that should be considered (e.g., $\geq$15 years). If the presence of these additional risk factors, in combination with age and smoking history, is associated with a level of risk that meets or exceeds the level of risk identified by the USPSTF and NCCN, then an annual low dose chest CT for lung cancer screening should be offered. We do not favor a specific age cut-off at which to end screening, but we recognize that only persons who are sufficiently healthy and have sufficient life expectancy to undergo diagnostic work-up and potentially curative treatment should be offered screening for lung cancer. In view of the rising risk of occupational lung cancer over time and the potential or actual interaction between occupational lung carcinogens and cigarette smoking even after quitting, screening programs may choose to screen workers with occupational lung cancer risk for prolonged periods after they have quit smoking cigarettes. The Collegium acknowledges that there are uncertainties and assumptions entailed in this approach and that risk assessment for individual workers necessitates application of significant professional judgement. We encourage the implementation of well-organized screening programs that can further our knowledge about optimal occupation-inclusive lung cancer screening strategies.

It is the responsibility of occupational health and medical professionals and stakeholders (governments, employers, statutory insurance agencies and labor unions) to identify worker populations that have excess lung cancer risk. Such populations include those with known exposure to known or suspected lung carcinogens or working in occupations/trades or work tasks with known elevated risk for lung cancer. As a general rule, having worked in such conditions for $\geq$ 5 years constitutes significant risk, though shorter periods of exposure also may be significant, depending on intensity and frequency of exposures.

4. Elements of High-Quality Occupational Lung Cancer Screening

Lung cancer screening is effective if it is conducted as part of a systematic approach that has the following elements (Wilson 1968; NCCN 2021):

a. Eligibility determination, including ability to undergo potentially curative treatment of lung cancer
b. Provision of information on lung cancer risks, risks and benefits of screening, screening process and outcomes, and expected follow-up
c. Informed decision-making
d. Advice on smoking cessation
e. CT scan acquisition with control over quality and radiation dose
f. CT scan interpretation by experienced readers and with use of a standardized reading protocol
g. Follow-up of CT results with appropriate health care providers according to recognized guidelines
h. Access to and plan to involve appropriate medical specialties for work-up and treatment of lung cancer, as well as unanticipated findings that require further medical evaluation.

Ideally, lung cancer screening will be conducted under the auspices of an organized screening program or research study that can provide all of the elements listed above. However, it is unlikely that all workers at risk of occupational lung cancer on a global basis will have access to such programs. And lung cancer screening cannot be effectively restricted to wealthy countries with the resources to establish such dedicated programs. Simplified schemes that can be endorsed by conscientious health care providers that can meet local conditions based on available resources need to be developed. Keys to success will be the physical accessibility of screening sites for at-risk worker populations and implementation of methods that can monitor and assure quality of the screening process.

Advances in lung cancer screening have brought this domain closer to other accepted cancer screening methods such as screening for colon, breast and cervical cancer. As such, in the presence of radiologic expertise in the use of LDCT scans to screen for lung cancer and pulmonary, oncologic and surgical expertise in the diagnosis and treatment of lung cancer (significant barriers, admittedly), lung cancer screening can become a part of the occupational health service (OHS) or primary health care. Key to success is the OHS or primary health care provider's role in taking a good occupational history to identify work-related risks.

The recommendations contained in this Statement are based primarily on a high likelihood of mortality reduction in the screened population and do not address issues of cost-effectiveness.

5. Responsibilities of Parties to Promote Lung Cancer Screening

Uptake of lung cancer screening in the Unites States, where low dose CT scanning for this purpose has been approved since 2013, has been disappointingly slow. It currently stands at less than 20% of the people who are eligible for low dose CT scanning based on age and smoking criteria (ref).

The Collegium Ramazzini recognizes that achieving widespread lung cancer screening for workers at risk will be an enormous challenge. The challenges are manifold: organizational, educational, fiscal, regulatory, and political. Even the first step is rarely taken: workers are unaware of their health risks and their health providers evince little or no interest in the health consequences of work.

The Collegium calls upon governments and other stakeholders to undertake organized activities to promote lung cancer screening among workers who are at elevated risk of lung cancer. These activities can include public education campaigns to increase awareness among both workers and health care providers of occupational lung cancer risk and the importance of lung cancer screening; development of lung cancer screening eligibility guidelines and reimbursement policies that address occupational lung cancer risks; initiation or enhancement of mechanisms to identify, educate and motivate occupational populations at increased risk of lung cancer, including use of exposure registries; development of programs with organized labor and employers to encourage use of lung cancer screening; and support of research to understand and apply effective methods of increasing participation in lung cancer screening by blue collar workers.

Developing and implementing a system of workplace-based funded and independently-administered occupational health care – from primary prevention to tertiary prevention - would greatly enhance both the reduction or elimination of exposure to occupational lung carcinogens and the early detection and treatment of lung cancer.

6. Equity Challenges Within and Across Countries

The Collegium acknowledges the enormous variation in resources and capacities among and within different countries in provision of health care, including support for cancer screening. Lung cancer screening involves the use of costly CT scanners and the participation of skilled radiologists, representing a challenge for all countries, especially low- and middle-income countries. These expenses are amplified by the costs and sophisticated medical care associated with the diagnosis and treatment of lung cancer.

This challenge is intensified by the fact that the highest smoking rates in the world are nowadays in low- and middle-income countries, which will therefore face an enormous burden of lung cancer in the future. These countries include especially those in Asia and Eastern Europe (World Population Review 2022). Many of these same countries likely have widely prevalent exposures to insufficiently controlled occupational lung carcinogens and agents known to be associated with chronic obstructive and fibrotic lung disease.

We note that among the largest lung cancer screening programs in the world has been undertaken by a middle-income country – China (Li 2022).

The Collegium supports efforts to decrease the cost of lung cancer screening through the application of automated artificial intelligence (AI) interpretation of CT scans, development of cost-effective lung cancer screening programs, and the mass utilization of less expensive CT scanners that can nonetheless obtain images sufficient for lung cancer screening.

More challenging in many parts of the world will be ramping up the human and facility resources of the existing health care systems to ensure proper diagnosis and treatment for people identified as having likely lung cancers as part of screening programs. This is no small feat in countries where lung cancer death rates are increasing – low and middle income countries.

In addition, strenuous efforts should be made within countries to ensure an equitable application of lung cancer screening across racial and ethnic groups within occupational populations at risk. The issue is not only a matter of basic equity, but it is likely that many of the workers who have been most highly exposed to occupational lung carcinogens belong to economically deprived racial and ethnic groups.

7. Ethical considerations

The Collegium emphasizes the rights of workers to a safe and healthy working environment free from exposure to any cancer risks. The Collegium Ramazzini takes note of the resolution recently passed by the United Nations Human Rights Council endorsing a "human right to a clean, healthy and sustainable environment." In June 2022, the International Labor Organization (ILO) amended the ILO Declaration on Fundamental Principles and Rights at Work to include "a safe and healthy working environment" as a fundamental principle and right at work. However, in the absence of such a clean work environment, workers also have the right to make decisions freely about how they want to mitigate such risks once they have incurred these risks. These rights are foundational to fair and equitable approaches to occupational health.

The Collegium therefore recognizes the need to advocate for the concurrent introduction of lung cancer screening in current occupational and primary care practice alongside simultaneous with important systematic efforts to understand, identify and prevent exposures to lung carcinogens in the workplace.

Once introduced, lung cancer screening should only be offered on a voluntary basis with a procedure for ensuring the consent of the participant is fully informed about benefits as well as risks.

Workers should be informed, as in all disease screening efforts, of the risks and benefits of screening for lung cancer. Among such risks (and benefits) are incidental health findings for which there is presently little curative treatment, such as malignant mesothelioma among asbestos-exposed workers.

Further research concerning the effectiveness and the optimal application of lung cancer screening for occupational populations is needed (see recommendations 2 and 9). However, the need for additional knowledge should not serve as a pretext for inaction in the conduct of lung cancer screening among workers at risk, even as additional research is undertaken.

8. Role of smoking cessation

All lung cancer screening programs should include an evidence-based smoking cessation component. The health benefits of smoking cessation importantly apply to lung cancer risk but additionally have an enormous benefit for the prevention of many types of cancer and other causes of mortality.

9. Research needs

Gaps in knowledge about lung cancer screening in people exposed to workplace risks are considerable, but, as noted above, it should not be cause for delaying its application. It is important to recognize that the question of whether lung cancer screening is beneficial has been answered resoundingly in the affirmative. Lung cancer screening programs, once introduced, provide the basis for addressing many of the items provided they are designed to appropriately collect the needed data.

We acknowledge that limited progress has been made in developing and validating a generalizable lung cancer risk model that include a wide variety of occupational lung cancer risks. We recognize, however, that this important area of cancer prevention is highly dynamic, and the occupational health community is encouraged to both track ongoing research and undertake screening research studies to better understand which workers will benefit from the application of low dose CT scan-based screening. Pooling occupational screening studies with mortality follow-up would be an important step to addressing current important knowledge gaps.

Important research issues remain beyond the critical ones of evaluating LDCT efficacy and effectiveness in screening participants identified via a combination of a smoking history and additional occupational risk factors for lung cancer. They include, at a minimum, optimizing LDCT and risk factor information to tailor the application of screening; cost-effectiveness; the integration of biomarkers to improve risk stratification (Freitas 2021) and cancer identification; identifying the best screening intervals; and how best to implement LDCT screening in target occupational populations [Oudkerk 2021]. For workers at risk of occupational exposure-related co-morbidities, such as asbestosis, silicosis, and chronic obstructive lung disease, it will be important to understand the impact of these co-morbidities on the real world effectiveness of lung cancer screening, diagnosis and treatment.

Table 1

IARC Agents and Processes
with Sufficient and Limited Evidence for Lung Cancer Causation

	Sufficient	**Limited**
Agent	Arsenic and inorganic arsenic compounds Asbestos (all forms) Beryllium and beryllium compounds Bis(chloromethy)ether; chloromethyl methyl ether (technical grade) Cadmium and cadmium compounds Chromium (VI) compounds Coal, indoor emissions from household combustion Coal tar pitch Engine exhaust, diesel Nickel compounds Outdoor air pollution Particulate matter in outdoor air pollution Plutonium Radon-222 and its decay products Silica dust, crystalline, in the form of quartz or cristobalite Soot Tobacco smoke, secondhand Welding fumes X- and Gamma-radiation	Acid mists, strong organic Benzene Biomass fuel (primarily wood), indoor emissions from household combustion of Bitumens, occupational exposure to hard bitumens and their emissions during mastic asphalt work alpha-Chlorinated toluenes (benzal chloride, benzotrichloride, benzyl chloride) and benzoyl chloride (combined exposures) Cobalt metal with tungsten carbide Creosotes Diazinon Hydrazine Non-arsenical insecticides (occupational exposures in spraying and application of) 2,3,7,8 Tetrachlorordibenzo-*para*-dioxin Trivalent antimony
Occupation, industry or process	Acheson process, occupational exposures associated with aluminum production Coal gasification Coke production Hematite mining (underground) Iron and steel founding Painting Rubber manufacturing industry	Art glass, glass containers and pressed ware (manufacture of) Carbon electrode manufacture Frying, emissions from high-temperature Insecticides, non-arsenical, occupational exposures in spraying and application Printing processes (occupational exposures in)

IARC. List of Classifications by cancer sites with sufficient or limited evidence in humans, Volumes 1 to 125. International Agency for Research on Cancer: World Health Organization website. https://monographs.iarc.fr/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf. Accessed October 14, 2022.

Table 2

Common Occupational Lung Carcinogens by Industry and Selected Occupations*

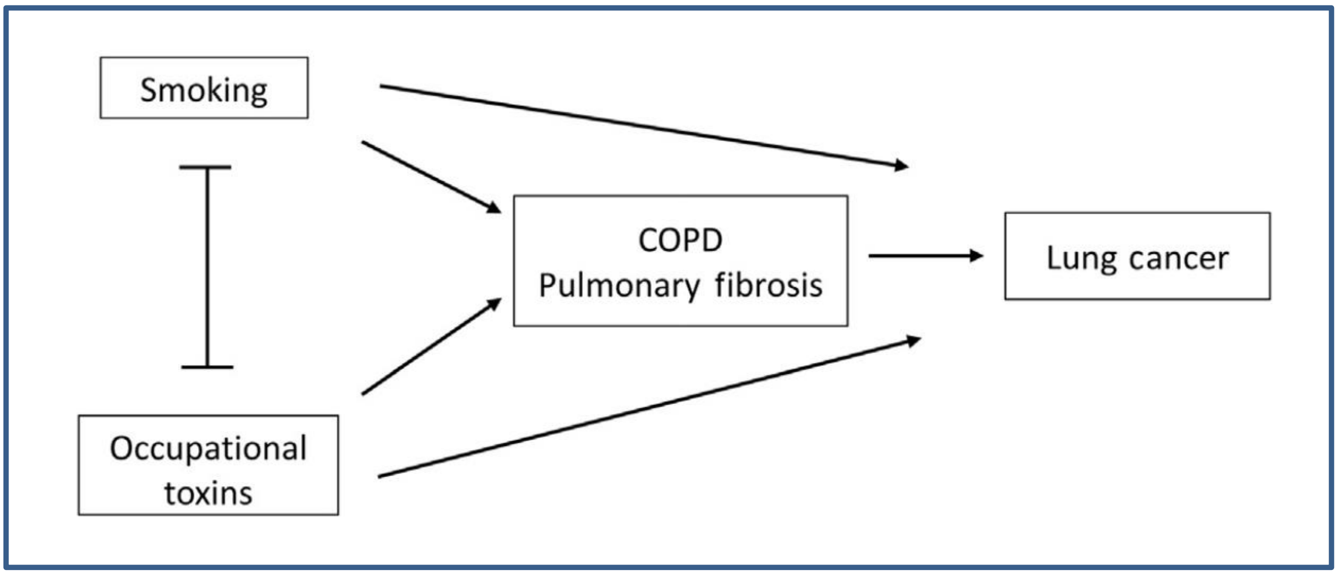
Industry	Lung Carcinogen	Examples of Occupation
Manufacturing	silica, chromium, nickel, cadmium	Metal fabricators, assemblers Metal processors, shaping workers Clay, stone, glass processors Forging workers Boilermakers, platers
Construction	silica, diesel exhaust, painting, welding, coal-tar pitch, asbestos outdoor air pollution	Excavators Welders Painters Plumbers Other construction
Transportation	diesel exhaust, PAH, outdoor air pollution	Bus drivers Truck drivers Mechanical maintenance
Mining, oil, gas extraction	silica, diesel exhaust radon	Drillers, blasters Miners, quarry workers Mineral ore treaters

*Occupations listed are examples of workers with exposure within designated industries and do not represent a complete list of such occupations.

Adapted from Markowitz 2020

Figure 1

Occupation and Smoking: Nexus of Chronic Lung Disease and Lung Cancer



From: Markowitz et al 2020

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