Occupational exposure to carcinogens: Benzene, pesticides and fibers (Review)

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Abstract. It is well known that the occupational exposure to contaminants and carcinogens leads to the development of cancer in exposed workers. In the 18th century, Percivall Pott was the first to hypothesize that chronic exposure to dust in the London chimney sweeps was associated with an increased risk of developing cancer. Subsequently a growing body of evidence indicated that other physical factors were also responsible for oncogenic mutations. Over the past decades, many carcinogens have been found in the occupational environment and their presence is often associated with an increased incidence of cancer. Occupational exposure involves several factors and the association between carcinogens, occupational exposure and cancer is still unclear. Only a fraction of factors is recognized as occupational carcinogens and for each factor, there is an increased risk of cancer development associated with a specific work activity. According to the International Agency for Research on Cancer (IARC), the majority of carcinogens are classified as 'probable' and 'possible' human carcinogens, while, direct evidence of carcinogenicity is provided in epidemiological and experimental studies. In the present review, exposures to benzene, pesticides and mineral fibers are discussed as the most important cancer risk factors during work activities.

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1. Introduction

Occupational cancer remains a major concern due to of worker's exposure to carcinogens. Percivall Pott was the first to describe occupational cancer in the 18th century, caused by dust in chimney sweeps (1). In 1926, Muller discovered a clear association between X-rays and lethal mutations (2). Apart from such physical factors, up to the 1970s, the majority of recognized human carcinogenic factors were observed primarily in the occupational environment (3).

The association between occupational exposure and cancer has not yet been fully determined. Often, occupational exposure involves a combination of factors; only a fraction of factors is recognized as occupational carcinogens. However, in several cases, there is a significant indication of an increased risk of cancer development associated with a specific work activity (4).

Considerations and evaluations, reported by the International Agency for Research on Cancer (IARC), reveal that the majority of carcinogens are classified as 'probable' and 'possible' human carcinogens (5). Direct evidence of carcinogenicity is only provided in epidemiological and experimental studies.

Several studies have indicated that occupational exposure to specific factors, including exposure to benzene, pesticides and mineral fibers is associated with the risk of cancer development (6 and refs. therein). A similar cancer risk has been observed for subjects employed in night shift work, in which both the alterations in the circadian system and the reduction in melatonin output, associated with the exposure to light-at-night

during night shift work, remain the most valid hypotheses on the causal association between shift work and breast cancer (7).

Furthermore, work organizational factors may also cause cancer. Work-related stress has been suggested to be one of the main factors, followed by sedentary work, including that of video-terminal station workers (8-14). However, stress is only an indirect risk of developing cancer, as certain strategies employed to manage stress may involve excessive smoking, alcohol consumption, overeating and/or the use of drugs, thereby increasing the risk of cancer (15). Boyle *et al* observed that long-term sedentary work may lead to an increase in the risk of developing colon cancer (16). Apart from the risk of cancer, such physical (17-20) or organizational factors may be also associated with other injuries (21-24).

Work activities associated with the exposure to ionizing and ultraviolet radiation may induce the development of cancer, as well as the development of other diseases. There is also increasing evidence to indicate that specific non-ionising radiation may be linked to the risk of cancer caused by lethal mutations. Outdoor workers can be exposed to ultraviolet radiation from sunlight and may develop melanoma or non-melanoma skin cancers (25). Previous studies, although inconclusive, have suggested the increased risk of brain cancer in subjects exposed to non-ionizing radiation, particularly radio frequency fields emitted by mobile telephones (26). Furthermore, in occupations, such as furnace and smelter operators, or industries such as casting factories, there is some evidence to suggest that heat shock leads to deoxyribonucleic acid (DNA) damage causing cells to switch to high mutation rates for several cell generations (27).

Finally, different infectious agents may cause cancer, either through direct or indirect mechanisms (28-33). In particular, it has been observed that the activation of the immune response may induce specific B-cell clones to proliferate as a consequence of the chronic antigenic stimulation sustained by different infectious agents (34-36).

There is increasing evidence to indicate that the occupational exposure to benzene, pesticides and mineral fibers may be associated with an increased risk of cancer. In this review, such evidence is summarized and discussed in order to determine and identify strategies with which to reduce such risks during work activities.

2. Benzene

Benzene is an aromatic hydrocarbon which is widely used in the production of several polymers, resins and synthetic fibers. It is also a component of wood, gasoline and tobacco smoke.

The general population is exposed to benzene through the inhalation of vapors released by motor vehicles, service stations and cigarette smoke. Additionally, contamination can occur due to the ingestion of polluted foods or water. Occupational exposure to benzene occurs in a great number of industrial settings, such as factories, refineries and rubber production plants, as well as shoe manufacturing and printing factories (37). Thus, humans are unavoidably exposed to benzene both in environmental and occupational settings, and this represents a serious concern for public health (38).

Benzene has been classified as a group 1A carcinogen (5), as its toxic effects on the hematopoietic system are well known (39).

Nevertheless, epidemiological and experimental studies have suggested that the exposure to benzene can cause a great number of acute and chronic diseases, which can involve several human tissues or organs. The acute and chronic effects of exposure to benzene can involve the central nervous system (40), the reproductive and developmental system (41-43), the immune system (44,45) and the respiratory system (46). It is widely accepted that benzene can cause hematological diseases, such as acute myeloid leukemia, acute and chronic lymphocytic leukemia, non-Hodgkin's lymphoma, multiple myeloma and aplastic anemia (47,48).

Apart from the fact that benzene can cause cancer of blood components, in animal studies, benzene has also been reported to induce mammary cancer (49,50). However, studies on humans to suggest that benzene is one of the risk factors for the development of breast cancer are limited (51). Few studies have suggested that exposure to benzene can cause malignant melanoma, stomach cancer, prostatic cancer and nasal cancer (52-55). Several potential mechanisms of benzene toxicity have been proposed (56-58). It is generally recognized that its metabolism is critical in the toxicity, with the involvement of one or more reactive metabolites, which are further bioactivated by myeloperoxidases and other heme-protein peroxidases to the reactive compounds emiquinones and quinones (59). These reactive products can lead to the formation of reactive oxygen species (ROS), which can directly damage pivotal molecular targets, such as DNA, lipids and proteins, leading to the formation of new compounds and modified structures, as advanced oxidation protein products (AOPP), advanced glycation end-products (AGE) and advanced lipoperoxidation end-products (ALE) (60), which have been used as biomarkers for risk assessment in workers occupationally exposed to benzene (61). ROS can also affect critical kinases and signal transduction pathways [mitogen-activated protein kinse (MAPK) family, p38-MAPK, nuclear factor (NF)-κB and signal transducer and activator of transcription 3 (STAT3)], involved both in cellular proliferation and apoptosis (62,63). Several authors have demonstrated that the activatation of these pathways promoted by cellular stresses, such as excessive ROS or inflammatory stimuli, may lead to aberrant cell growth and carcinogenesis (64,65). In addition, the link between ROS and several cellular components can promote the formation of DNA strand breaks, sister chromatide exchange (SCE), and micronuclei and chromosomal aberrations (CA) (66,67). Smith *et al* (68) demonstrated that exposure to benzene was associated with markedly elevated levels of t(8;21) and of hyperdiploidy 8 and 21 in the circulating lymphocytes of otherwise healthy workers exposed to benzene compared to unexposed controls. This suggests a role for these aberrations in benzene-induced leukemia and that their detection in peripheral blood cells by chromosome painting may be useful biomarkers of an increased risk of developing hematological malignancies due to benzene and other potential leukemogens (68).

Bassig *et al* evaluated alterations in leukocyte telomere length (TL), which is associated with the risk of cancer, in workers occupationally exposed to benzene. The authors observed a significant increase in TL associated with very high levels of benzene exposure in factory workers compared to unexposed control workers (69).

There is evidence to suggest that exposure to benzene is associated with epigenetic alterations (70,71). Epigenetics is the

investigation of mitotically and meiotically heritable alterations in gene expression without alterations in the DNA sequence. Epigenetic biomarkers, include DNA methylation, histone modifications and microRNA expression, which are induced by exposure to a great number of environmental factors. There also data to suggest an association between exposure to benzene, epigenetic alterations and an increased susceptibility to develop several diseases, such as cancer and inflammatory diseases (72).

Both the toxic and carcinogenic effects of benzene depend on several factors, such as the duration and levels of exposure, the route of exposure (inhalation, ingestion or cutaneous contact) and individual susceptibility factors (age, gender, lifestyle and pre-existing diseases or disorders).

The majority of epidemiological and experimental studies have evaluated the health effects of exposure to high doses of benzene, both in living and working settings. Moreover, a number of studies have referred to an inhalation exposure (73,74), while only in a few cases, exposure by ingestion (75,76) or dermal contact (77,78) has been reported. The progressive reduction of the levels of exposure both in environmental and occupational settings have led researchers to focus their attention on the health effects observed with low doses of benzene, particularly those related to cancer. Further elucidation of the mechanisms through which benzene alters gene expression is required in order to better comprehend the toxic potential of this pollutant and to identify more appropriate preventative measures, particularly for occupationally-exposed subjects.

3. Pesticides

Pesticides are chemical compounds which can be distinguished into different classes by chemical structure, target organisms or the type of health hazard produced. They have been widely used to control, repel and destroy any pest both in agricultural and domestic use (79). Thus, it has been hypothesized that exposure to pesticides could be classified as residential, para-occupational and domestic. The first is characterized by living close to a treated field. Domestic exposure is defined as any domestic use by a household member or gardener. Para-occupational exposure is defined as the occupational use of pesticides by one or more household members (80).

Occupational exposure to pesticides occurs during the preparation and handling of pesticides and it is considered greater than that of the general population, which occurs normally at relatively low doses (81). However, the widespread use of pesticides represents a potential risk to human and environmental health. Over the past years, a growing number of epidemiological and experimental studies have evaluated the possible associations between pesticide exposure and the development of adverse health effects. Significant associations between pesticide exposure and cancer have been previously described (51,82-88). However, the exposure to pesticides may also cause the development of other pathological conditions, such as amyotrophic lateral sclerosis (89), asthma (90), type II diabetes (89), and Alzheimer's and Parkinson's disease (92,93).

The knowledge of the association between pesticide exposure and cancerogenesis is actually one of the main challenges in occupational and environmental toxicology. As a carcinogen, a pesticide can act as genotoxic tumor promoter and endocrine disruptor. Pesticides are also considered as chemicals which induce immunotoxicity, influencing the activity of cells, macrophages and the secretion of cytokines, such as interleukin (IL)-17, IL-22, IL-2, IL-8 and interferon (IFN)-γ (94,95). These modifications can alter cancer immunosurveillance and can compromise any of the 3 Es of cancer immunoediting: elimination, equilibrium and escape. Moreover, pesticides may promote cancerogenesisby, inducing innate immune dysfunctions, leading to chronic inflammation (96). Among organochlorine pesticides, there are a few still in use (endosulfan, lindane and dicofol) which have been associated with the risk of breast cancer. The study by Fenga demonstrated that organochlorine pesticide mixtures, including aldrin, p,p'-DDE and dichlorodiphenyldichloroethane play a relevant role in the development of breast cancer (51).

Van Maele-Fabry *et al* investigated the link between prostate cancer and pesticide exposures in manufacturing workers. The results of their study showed that although epidemiological evidence did not allow the identification of a specific pesticide as responsible for an increased risk of prostate cancer, occupational exposure to pesticides emerged as a possible risk factor for this tumor (97).

Lee *et al* examined the incidence of lung cancer among pesticide applicators exposed to chlorpyrifos. The authors showed a statistically significant increased risk of lung cancer adjusting for cigarette smoke or other confounding factors (98). The same group of researchers investigated a potential correlation between exposure to aldicarb and chlorpyrifos and colorectal cancer, demonstrating a significant association (99).

As regards pancreatic cancer, the available data are controversial. Some authors have demonstrated a possible association between the exposure to pesticides and an increased risk of pancreatic cancer (100), while others have not revealed a consistent association (101). Epidemiological studies have shown that pesticide exposure may increase the risk of developing hepatocellular carcinoma (HCC), through mechanisms of genotoxicity, cytotoxicity, tumor promotion, immunotoxicity and hormonal action (83). In particular, exposure to organochlorine pesticides has been associated with an increased risk of developing HCC among California male residents of agriculturally intensive areas (102). It has also been observed that organochlorine pesticides possess carcinogenicity and can induce liver cancer (103).

A previous study conducted a geo-epidemiological study on a population in Crete in order to understand and relate environmental factors to the pathogenesis of disease. The results of their study revealed a higher than expected spatial distribution of HCC in an area with a widespread use of pesticides (104). As regards the mechanisms through which pesticides can induce HCC, recently, it has been demonstrated that methyl parathion and chlorpyrifos negatively modulate the expression of the paraoxonase 1 (PON1) gene in human HCC (HepG2) cells through a mechanism that involves the induction of inflammatory cytokines, such as tumor necrosis factor (TNF)-α, IL-6, and IL-1β. A decrease in the expression of the PON1 gene may increase susceptibility to organophosphate intoxication and the risk of diseases related to inflammation and oxidative stress (79,105).

The majority of evidence of the adverse health effects of pesticides in human adults is derived from studies on male

subjects occupationally exposed to pesticides. Relatively less is known about the pesticide-related health effects in women. This is probably due to the fact that male workers are more engaged in pesticide handling compared to female subjects (95). Furthermore, further limitations can be highlighted, including biological matrices used to estimate exposure and target populations, differences in pesticide exposure levels, distinct ethnicities, age groups and/or dietary characteristics.

Based on these findings, it is important to investigate the health effects of long-term exposure to pesticides, in addition to the acute toxicity data.

4. Fibers

Over the past decades, a growing number of scientific evidence has demonstrated the carcinogenic role of asbestos and other mineral fibers, known as asbestos-like fibers, in workers occupationally- or environmentally-exposed to these fibers, such as vitreous, ceramic and organic fibers, suggesting a pathological mechanism based on their physical structure and not only to their chemical function (106).

The first evidence of a causal link between asbestos exposure and development of cancer of the pulmonary apparatus came from Wagner *et al* that in 1960s, for the first time, described the carcinogenic activity of asbestos fibers in a cohort of workers occupationally exposed to this contaminant (107).

Over the past years, asbestos has been widely used in many industrial contexts for its extraordinary thermal isolation properties. Millions of tons of asbestos have been processed worldwide and used for railway construction, thermal isolation and building construction, making asbestos one of the most widespread contaminants.

The main type of asbestos (90%) employed in the construction works is the chrysotile, or white asbestos, while amphibolic asbestos, which includes crocidolite and amosite (blue and brown asbestos, respectively), is less used (108). However, the toxic effects of both chrysotile and amphibolic asbestos have been known for 50 years.

Several studies have described the molecular mechanisms that lead to cancer development in individuals exposed to asbestos or asbestos-like fibers. In particular, the inhalation of these fibers has been proven to be responsible for the development of pleural mesothelioma even after a long period of absence of exposure (1079-111).

Indeed, the development of pleural mesothelioma, due asbestos or mineral fiber exposure, is a slow process with a period of latency ranging from 20 to 60 years. For these reasons, the highest worldwide incidence of pleural mesothelioma and lung cancer diseases is estimated to occur in the year 2020, with a peak of incidence for these pathologies in the areas of occupational or environmental exposure to these fibers (112,113).

The most important features for the pathogenic potential of a fiber are the size, diameter and length. In particular, the aerodynamic diameter (Dae) is the major determinant which can be used to predict the toxicity of fibers into the respiratory system (106).

Indeed, fibers ranging from 5 to 10 microns in length can reach the interstitial and serous lung, where they cause severe injury in the form of interstitial and pleural fibrosis, thickening and pleural plaques, as well as tumors. Fibers longer than 10 microns, stop at the alveolar level where they can cause asbestos-related alveolitis (114,115).

Another mineral fiber with asbestos-like effects is fluoro-edenite (FE). FE is a mineral fiber of volcanic origin from the calcic clino-amphibole subgroup, similar to amphibole tremolite and actinolite antophyllite (116).

FE was firstly identified in 1997 near the area of Biancavilla, in eastern Sicily. For years, this mineral was extracted from Mount Calvario and used for the construction of houses in the urban areas near Mount Etna (117,118).

In particular, various types of airborne mineral fibers were identified in the volcanic area of Mount Etna and may represent the cause of the increased incidence of mesothelioma and lung cancer and other lung diseases (119).

Although currently a clean correlation between the amount of inhaled fibers and the occurrence of related diseases has not been demonstrated, several studies and meta-analyses have suggest a dose-risk linear without a threshold effect (120 and refs. therein).

Several studies have provided strong evidence that the development of malignant mesothelioma is associated with asbestos and asbestos-like fibers, particularly amphibole asbestos (121 and refs. therein).

The early detection of asbestos-related diseases is one of the major goals of health surveillance in workers exposed to mineral fibers (122). However, the protocols adopted for workers exposed to asbestos do not have sufficient specificity and sensitivity to ensure early diagnosis (123). Even the IARC highlighted that occupational and environmental exposure to mineral fibers is the leading cause of asbestos-like and asbestos-induced disease (124,125).

The mechanisms that lead to the development of mesothelioma in patients exposed to mineral fibers are still not completely known. Recently, it has been shown that in subjects exposed to such fibers, tumor expansion is associated with the activation of fibulin-3 (126). High levels of fibulin-3 were detected in plasma samples of street cleaners from Biancavilla (Sicily), which are at high risk of FE exposure (126).

Intriguingly, it was demonstrated that plasma levels of fibulin-3 were significantly lower in the group of workers exposed to asbestos fibers compared to those exposed to FE (126), suggesting that asbestos disposal workers properly used the personal protective equipment according to the current regulations. By contrast, other workers, such as street cleaners exhibited high levels of fibulin-3, indicating that these workers should be better equipped in order to prevent injury caused by FE found in dust deposited on the ground (126).

Accordingly, our most recent *in vitro* study indicated that fibulin-3 was overexpressed in mesothelial cells following treatment with FE and not following treatment with other particulates at both the transcript and protein level (126). Therefore, it was hypothesized that the detection of high plasma levels of fibulin-3, observed in street cleaners from the Biancavilla area, may be due to FE exposure. However, volcanic particulate exposure did not affect fibulin-3 expression (126,127).

The development of mesothelioma is not only directly caused by exposure to mineral fibers. Chronic exposure to asbestos-like fibers may cause chronic inflammation and hence pro-carcinogenic stimuli (128). Chronic inflammation results in the production of several cytokines and growth factors that promote cellular proliferation and inhibit apoptosis (128,129).

It has also been demonstrated that p27 is downregulated in mesothelial cells follwoing treatment with FE fibers (130). Notably, p27 is considered a tumor suppressor gene due to its function as a regulator of the cell cycle and in cancer it is often inactivated (131). It has also been demonstrated that low levels of p27 are associated with stathmin upregulation, determining an aggressive phenotype of tumor cells (131). Our previous computational evaluation showed that stathmin is overexpressed in lung cancer patients with a history of asbestos exposure compared with those not exposed to any fibers (126). Accordingly, we can speculate that both fibulin-3 overexpression and stathmin activation may be the underlying mechanisms reponsible for the transformation of mesothelial cells following exposure to mineral fibers.

Apart from conventional risk factors described above, nanomaterials, such as carbon nanotubes may also represent emerging risk factors for cancer development (132). Long-term animal studies demonstrated that the intratracheal instillation of nanostructured carbon black, aluminium silicate, aluminium oxide, titanium dioxide (hydrophilic and hydrophobic) and amorphous silicon dioxide resulted in tumors induced by all tested nanomaterials (132 and refs. therein). A fraction of these carbon nanotubes may lead to asbestos-like effects. Former investigations suggested that lung tumors occur in cases of lung overload and subsequent reactions, such as inflammation and fibrosis. Accordingly, tumor development depends on pre-cancerous lesions, including inflammation and fibrosis. However, other studies support the notion that such particles directly interact with DNA, causing molecular alterations and in turn, tumor formation (132 and refs. therein).

5. Conclusions

The correlation between occupational exposure and the development of cancer is of particular interest to several investigators. In addition to work exposure risk factors, cancer may be caused by incorrect life style habits, as previously observed (133).

Environmental and occupational exposure to hazardous stimuli has been linked to the development of several types of cancer (4). These environmental stimuli may involve the p53, Raf/MEK/ERK and PI3K/AKT pathways in solid and hematological cancers, providing further insight into the mechanisms responsible for malignant transformation (134-136). On the other hand, chronic exposure to occupational carcinogens can modulate the immune system response, leading to an increase in the production of cytokines and inflammatory cytokines. These molecules promote the occurrence of a chronic inflammation status that that could lead to the development of tumors (96,137).

The present review aimed to determine the association between the exposure to occupational carcinogens and the development of cancer, and the impact that these contaminants may have on public health. However, the evaluation of exposure levels to a carcinogen is challenging. Exposure levels can vary widely under the same conditions widely according to physical or environmental factors. Even between individuals in the same workplace there are exposure variations. On these bases, several studies have indicated that a worker's specific employment is one of the most important elements for personal exposure that could determine significant variations from the estimated exposure values based on environmental data or epidemiological data. In our opinion, this indicates that previous evaluations based on registers or questionnaires may be considered not completely reliable.

Future studies aimed to highlight the real correlation between environmental and occupational exposure to risk factors should use an objective method for the assessment of carcinogen exposure levels. These procedures may ensure a better health surveillance and a more effective evaluation of the risk in exposed workers.

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