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A review of the health effects and exposure-responsible relationship of diesel particulate matter for underground mines

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ABSTRACT

The increasing use of diesel-powered equipment in confined spaces (underground mines) has the potential to over expose underground miners under the threat of diesel particulate matter (DPM). Miners in underground mines can be exposed to DPM concentrations far more than works in other industries. A great number of animal and epidemiological studies have shown that both short-term and long-term DPM exposure have adverse health effect. Based on reviews of related studies, especially some recent evidence, this paper investigated the long and short-term health effects based on animal studies and epidemiological studies. The exposure-response relationship studies were also explored and compared to the current DPM regulation or standards in some countries. This paper found that the DPM health effect studies specifically for miners are not sufficient to draw solid conclusions, and a recommendation limit of DPM concentration can be put in place for better protection of miners from DPM health risk. Current animal studies lack the use of species that have similar lung functions as human for understanding the cancer mode of action in human. And finally, the DPM health hazard will continue to be a challenging topic before the mode of action and reliable exposure-response relationship are established.

1. Introduction

As diesel-powered equipment has good power performance, high economy, efficiency as well as durability, its use has continuously increased in both underground coal and metal/non-metal mines since the 1960s. Various types of diesel-powered equipment are operated in the mining industry. Compared to gasoline equipment, diesel-powered equipment is more efficient and emits less carbon dioxide (a greenhouse gas) per unit of work. Nevertheless, diesel-powered equipment emits much more particulate matter than gasoline equipment during the combustion process. This is a problem in confined spaces, such as underground mines, where it has great potential for miners to be overexposed to diesel particulate matter (DPM). Miners in underground mines can be exposed to far higher DPM concentrations than in other industries. For example, in 1996, the US nationwide average DPM exposure was estimated to be 1.4 $\mu g/m^3$. On the other hand, investigators showed that exposure for the workers in coal mines and noncoal mines ranges from 10 to 1280 $\mu g/m^3$, with environmental equivalent exposure of 2–269 $\mu g/m^3$ [1].

In 1988, based on the results of a series of animal and epidemiologic studies, the National Institute for Occupational Health and Safety (NOISH) in the US recommended that DPM had potential carcinogenic effects on humans [2]. In the following year (1989), International Agency for Research on Cancer (IARC), a part of the World Health Organization (WHO), published a monograph which classified DPM as a probable carcinogen to humans (group 2A) [3]. A number of animal studies have been conducted, which showed that long-term exposure to DPM has the potential to cause lung tumours [4–9]. There are also many epidemiological studies on humans that have suggested the association between health effects and long-term DPM exposure [10–20]. These studies concluded that long-term exposure to high concentrations of DPM could increase the lung cancer risk. In addition, many studies showed that short-term or acute exposure to DPM could also induce negative health effects, such as acute irritation, asthma, cough, lightheadedness [1,21–28]. In 2012, based on sufficient evidence of animal and epidemiological studies, IARC classified DPM as carcinogenic to humans (Group 1). For these reasons, health issues associated with DPM exposure are receiving substantial attention from the public, government agencies and academia.

In order to minimize DPM health hazards, the DPM concentration should be maintained below an acceptable standard. Germany, Canada and the USA have already set their limit or

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standard for DPM exposure for mining industries. Germany sets the DPM limit for underground noncoal mines and other surface workplaces at 0.3 and 0.1 mg/m^3, respectively. The Canada Centre for Mineral and Energy Technology sets the standard of DPM at 0.75 mg/m^3 [29]. In the US, the Mine Safety and Health Administration (MSHA) has an exposure standard of DPM for metal/nonmetal mines of 0.16 mg/m^3 (measured as total carbon) [30]. The development of regulations and standards for the DPM exposure in underground mines is still in its early stage in Australia [31]. Currently, the official limit for DPM exposure for underground mines is still not established, and the level of regulation in different states varies. In Australia, many regulatory agencies have considered 0.1 mg/m^3 (measured as elemental carbon, TWA) of DPM as a recommended exposure limit, and this is also recommended by the Australian Institute of Occupational Hygienists (AIOH) [32].

Due to the hazards of DPM, many studies of DPM have been carried out; however, very few detailing the health effects review impacts on mining workers, especially for the underground miners. The aim of this paper is to provide a review of the health effects of DPM on underground miners, especially some recent evidence, and the regulations in some major mineral producing countries with a new trend on what data is more appropriate to reflect the DPM dose. This paper conducted a scientific review of a great number of available literature published over the past three decades. Based on the published animal and epidemiological studies, this paper determined the potential relationship between both long-term and short-term DPM exposure and health effects. This paper also aims to determine whether there was an exposure-response relationship for cancer effects. Available data from animal and human studies have been used to evaluate the exposure cancer unit risk and the cancer mode of action. A recommended exposure limit of DPM for underground mining industry was concluded based on a summary of the published literature and regulation in different countries.

2. Health effects of DPM

2.1. Deposition mechanisms

The main way for DPM to enter the respiratory system is inhalation. It was reported that particles could deposit within the human respiratory tract [1]. Studies showed that the filtering capacity of the nose would be very low when particles' size was less than 0.5 μm [1,34]. When the particle size is less than 1 μm, it is able to deposit in the deepest ranges of lungs. Fig. 1 shows the typical mass-weighted and number-weighted size distributions of diesel particles. As can be seen, more than 90% of the particles' diameters are below 1 μm, which are capable of entering the deepest ranges of the lungs. Many studies have shown that airborne PM, in which DPM is the main component, contributes to the respiratory mortality and morbidity [35,36].

2.2. Long-term effects

2.2.1. Laboratory animal studies

A high number of animal studies have been carried out to evaluate the potential health effects of long-term DPM exposure. Many animal studies, including on rats, mice, hamster and monkey, have demonstrated that long-term exposure to high concentrations of DPM contributes to increasing the risk of lung tumour.

Almost all the animal studies have shown a lung tumour response in rats after long-term exposure to a high concentration of DPM (>2.5 mg/m^3). Heinrich et al. conducted a long-term study with rats, mice, and hamsters exposed to unfiltered and filtered DPM to understand its carcinogenicity [4]. All experimental animals were aged 8–10 weeks before the exposure. The exposure was 19 h a day, 5 days a week. The maximum exposure duration for mice, rats and hamsters was 120, 140 and 120 weeks, respectively. The concentrations of unfiltered DPM in this study were about 4 mg/m^3. Each group included 96 animals. There was a clean air exposure chamber for the control groups with equal sample size. A high lung tumour rate in rats (18%, 17/95) had been observed after long-term exposure to DPM compared with the controls (0%, 0/96). Mauderly et al. conducted a carcinogenicity study of rats that were exposed to soot (a primary composition of DPM) at high, intermediate, and low concentrations (0.35, 3.5, 7.0 mg/m^3 respectively) for up to 30 months (7 h/day, 5 days/week) [6]. The result showed that the rate of lung tumour for high and intermediate exposure groups was 13% and 4% respectively, which was higher than that of the control group (1%). Iwai et al. conducted an inhalation study to estimate the relationship between oxidative DNA damage and lung tumour in 48 F344 female rats which were exposed to diesel exhaust at 2.1–4.9 mg/m^3 for up to 12 months (17 h/day, 3 days/week). After 12 months' exposure, the experimental rats were transferred to a clean room and maintained for another 18 months for observation [8]. The results showed that the rate of lung tumours in rats increased gradually with the exposure duration after 6 months and reached the peak at the 9th month; the exposed rats had high rates of death compared with the controls. Many other studies also showed similar results [5,7,9,37]. From the studies above, DPM is considered carcinogenic in rats after long-term exposure. However, a study conducted by Lewis et al. gave an opposite conclusion [38]. In this study, three different animals (monkeys, rats and mice) were exposed to different experimental environments for up to 2 years, including clean air (controls group), 2 mg/m^3 coal dust, 2 mg/m^3 DPM, and 1 mg/m^3 coal dust and 1 mg/m^3 DPM mixture. No significant difference in the rate of lung tumour for rats was found between four exposure groups (2%, 4%, 4% and 4%, respectively). Compared to other studies, this study lacks the post-exposure period for rats, which could be a reason for the different results. It is also noticed that the DPM concentration in this study was lower than other studies, which could also be a limitation for the results.

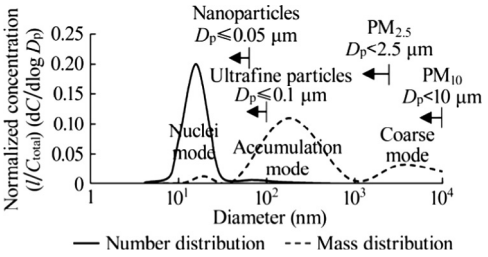

Fig. 1. Diesel particulate matter size distribution (Modified after Kittelson [33]).

Some animal studies also selected mice as one of the tested animals. However, discrepant results were achieved in some of those mice studies. Heinrich et al. pointed out that the lung tumour incidence in exposed mice (32%) was about three times that of the controls (11%) [4]. However, a carcinogenic response failed to show in his later study [5]. In this study, mice were exposed to clean air, filtered diesel exhaust (particle free) and unfiltered diesel exhaust (4.5 and 7.0 mg/m^3 DPM) for 13.5 months (18 h/d, 5 d/week). No lung tumour incidence increase was observed in the mice. Although the earlier study provided some evidence for the carcinogens of DPM, no tumorous response was observed in the larger sample size and well-designed later study. Thus, the carcinogenic effect of DPM on mice is inconclusive. The reason for the discrepant results are still not identified.

In contrast to the studies of rats and mice, a lack of significant tumorous response was found in hamsters and monkeys. In Hein-

rich et al.'s study, no tumours were observed in both the DPM exposure group and the control group for the hamsters [4]. The monkey group showed a similar result as that of rats in the report by Lewis et al. which is mentioned above [38]. In summary, DPM did not induce lung tumours either in hamsters or in monkeys. The limited observation time and the difference in lung burden ability between monkeys, hamsters and rats may cause the different results.

In summary, almost all the studies in rats indicated an apparent increase in the risk of lung tumours except for one study [38]. None of the hamster studies showed the same increasing trend as rats in the risk of lung tumours. The results of the mice studies varied. Only one study involved monkeys, but no lung tumours were found in monkeys after long-term DPM exposure [38]. The animal studies in rats have provided sufficient evidence for the carcinogenicity of DPM, but future studies still need to be conducted to determinate the carcinogenicity of DPM exposure for other animals.

2.2.2. Epidemiological studies

Animal studies have already provided a number of evidence and experimental data for the positive link between DPM exposure and adverse health effects. Although it is possible that long-term DPM exposure contributes to lung cancers in humans, it does not mean that the dose-response information from the carcinogenicity in rats is applicable to humans. Many studies showed that it is the overload of the lung which resulted in the high risk of lung tumour in rats [5,7,8]. For humans, the clearance and burden function of the lung is much greater than rats. In other words, the deposition of DPM in lungs is different for animals and humans even when breathing the same dose of DPM. Thus, adopting the laboratory animals' DPM exposure concentration as the guidance for human DPM exposure is inappropriate [1]. For this reason, a number of occupational studies have been conducted, which provided epidemiologic evidence relevant to the association between DPM exposure and the risk of lung cancer.

In 1986, NIOSH published the report "*Evaluation of the potential health effects of occupational exposure to diesel exhaust in underground coal mines*". This report included a series of animal studies and epidemiological studies with regard to health effects of long-term DPM exposure. In 1988, NIOSH further analysed the data in the 1986 report and concluded that long-term exposure to high concentrations (over 4 mg/m^3) of diesel exhaust could significantly increase the risk of lung tumour for tested animals. However, only two epidemiological studies cited in the report illustrated that the lung cancer mortality of the railroad workers increased after long-term exposure to DPM emissions [39,40]. While another epidemiological study showed that there was no significant increase in the lung cancer mortality of workers who were exposed to the DPM emissions compared with the general group, this result is less reliable due to the small size of the analysed population [39]. Based on sufficient animal studies and limited evidence of epidemiological studies, NIOSH recommended that DPM had potential carcinogenic effects on human [2]. In 1988, IARC held a review conference with a working group of experts to evaluate the health effects of DPM exposure. Similar to the NIOSH recommendation, IARC classified the DPM as a probable carcinogen to humans (group 2A), and this conclusion was reported in the 1989s publication "*Diesel and gasoline engine exhausts and some nitroarenes*" [3]. The review mainly evaluated more than ten cohort studies related to different occupations (railroad workers, drivers and miners) and case-control studies related to various diseases (lung cancer, bladder cancer, etc.). However, the association of long-term DPM exposure and the incidence of lung cancer could not be identified due to limited evidence of epidemiological studies. After 24 years, in 2012, IARC conducted another review following the first review in 1988. A major result of this review was that DPM has been changed to be classified to be carcinogenic to humans (Group 1), and this evaluation was published in a report in 2013 [41]. The animal and limited epidemiological studies reviewed in the previous report provided the evidence to support the probable carcinogenicity of DPM [3]. In the latest report, new evidence for the association between lung cancer and DPM exposure has been provided by epidemiological studies [41]. Two studies cited in the report, an occupational cohorts study and a case-control study, in particular provided powerful evidence for the association between lung cancer and long-term DPM exposure [20,21].

A number of epidemiological studies for different job titles which were reviewed in the IARC report provided strong evidence for the carcinogenicity of DPM [41]. Garshick et al. found that the relative risk (RR) for lung cancer mortality among long-term exposure railroad workers was 1.40 (95% CI: 1.30–1.51) compared with those workers without regular exposure to DPM emissions [12]. However, this study did not adjust for the smoking history, which is a potential confounding factor for the result. For this reason, Garshick et al. conducted a further study with the smoking history adjustment [13]. The results of the study showed that the RR of lung cancer were 1.22 (95% CI: 1.12–1.32) and 1.35 (95% CI: 1.24–1.46) with and without smoking history adjustment, respectively. This data showed that there was a small difference in the risk of lung cancer mortality after considering the smoking history. A large sample size and long duration period in this study allowed reliable conclusions to be drawn. Similar results were also found in epidemiological studies of trucking industry workers, construction workers and other DPM exposure related areas [10,15–18,42,43].

Compared to other diesel engine related jobs, underground miners usually are exposed to higher concentrations of DPM due to the confined working space and poor ventilation conditions. However, only three epidemiological studies on underground mines in the last decade have been found. These studies provide strong evidence for the association between high risk of lung cancer and long-term DPM exposure. In a cohort mortality study, a large sample size of 12,315 mineworkers who were exposed to DPM emissions at 8 American non-metal mines was selected [19]. All the workers had been employed for more than 1 year during which time the diesel equipment was used in the mine. The mortality information for miners was followed until the end of 1997. The study selected the respirable EC as the surrogate of DPM for each case study at eight mining facilities (including all kinds of surface and underground jobs). In the assessment, the exposure was estimated based on the measurement of personal respirable EC (REC) levels between 1998 and 2001. The historic REC concentration (before 1998) was speculated based on the data collected between 1998 and 2001. This study also takes other factors, such as sex, job titles, date of birth, into consideration. However, smoking history was not available to use in the study. The results of the study showed that the mean DPM concentration for the surface workers and underground workers were 1.7 and 128.2 μg/m^3, respectively. The RR of lung cancer mortality for ever-underground workers and surface only workers were 1.21 (95% CI: 1.01–1.45) and 1.33, respectively. When the cumulative DPM concentration was above 946 μg/m^3 a year, the RR for underground miners was 2.21 (95% CI: 1.19–4.09). This data illustrated that the high DPM concentration exposure group (underground miners) has a higher risk of lung cancer mortality than that of the low-exposure group (surface miners). Also, the results showed a rising trend in the hazard ratios for lung cancer mortality with increasing DPM exposure time. Based on this study, a nested case-control study was conducted by Silverman et al., with the same group of miners as the research sample [20]. With the inclusion of smoking history and previous respiratory disease as factors, the adjusted results still supported the conclusions of the original

study by Attfield et al. [19]. For both smokers and non-smokers, the risk of lung cancer mortality increased with the increasing exposure time (15-year lag). The underground miners who were exposed to high concentrations of DPM for a long-term (15 years or more) had a higher risk of lung cancer mortality (4 times) than surface miners who were exposed to a lower concentration of DPM. In another cohort study, 5,862 German potash miners were followed from 1970 to 2001 [44]. Total carbon (TC) was selected as a surrogate of DPM. Cumulative diesel exposure was estimated by multiplying the concentrations of TC by the miners' exposure period. Smoking history of miners was considered as a confounder factor in this study. The standardized mortality ratio (SMR) for lung cancer was 0.73 (95% CI: 057–0.93); the lung cancer SMR for the whole cohort and sub-cohort were 1.28 (95% CI: 0.61–2.71) and 1.50 (95% CI: 0.66–3.43), respectively, at the cumulative DPM exposure of 4.9 mg/m^3-years compared with the low exposure group after smoking adjustment. The results showed a positive link between the mortality of lung cancer and DPM exposure, and the RR grows with increasing exposure time.

However, the study conducted by Möhner et al. drew a different conclusion [45]. This study reanalysed Neumeyer-Gromen's study and aimed to reassess the cancer risk in potash miners after long-term exposure to DPM [44]. EC was used to represent the level of total DPM. The results indicated that there was no apparent relationship between cumulative DPM exposure and lung cancer risk. However, the result is not convincing due to the small sample size.

To summarize, the epidemiologic studies have supported the positive relationship between the long-term DPM exposure and the risk of lung cancer, which is unlikely to be caused by chance. Only a few studies were found directly on underground miners, but three of such studies indicated a positive relation between lung cancer mortality and prolonged high DPM concentration exposure. Further studies are still needed to focus on the underground miner group as the DPM concentrations underground are higher than other workplaces. Besides, other contaminants, such as dust, should also be considered in the study, because such contaminants might exacerbate the health effect of DPM.

2.3. Short-term effects

Although the diesel exposure studies were mainly focused on the carcinogenicity of long-term DPM exposure (i.e., lung cancer), health effects of short-term or acute DPM exposure are also investigated in various studies. These studies are divided into laboratory animal studies and human studies in this section.

2.3.1. Laboratory animal studies

Due to the similar non-carcinogenic responses to the short-term DPM exposure in human and experimental animals, many animal studies are used to evaluate the DPM short-term effect. Rat is the preferred animal species in such studies, and the DPM dosage is either through exposing the animal to the DPM environment or through intratracheal instillation or injection of a dose of DPM directly into the test animal.

A number of inhalation studies showed that short-term exposure to DPM could affect the brain, cardiovascular and lung system, but these effects are reversible after a period of stay in a DPM-free environment. Campen et al. conducted a study to estimate the association of acute DPM exposure and cardiovascular effects in spontaneously hypertensive rats [46]. The study exposed rats to five different levels of DPM (0, 0.03, 0.1, 0.3, 1 mg/m^3) for 6 h/day for one week. Mild effects on lungs for the exposure group were observed in this study. Both HR and PQ intervals showed a significant difference in the male exposure rats, but less difference was found in the female exposure group. The limited experimental data in this study prevented the result providing enough evidence to reveal the association between cardiovascular effects and DPM exposure. This association was further studied by Campen et al. using mice as the study subject. The results showed that both DPM and non-particle compounds in the diesel exhaust had adverse effects on cardiovascular systems [47]. Berlo et al. conducted a study to estimate the relationship between short-term DPM exposure and adverse effects on rat lungs and brains [48]. This study exposed male Fischer F344 rats, aged 9 weeks, to 1.9 mg/m^3 DPM and purified air (controls) for 2 h and then followed by a 4 or 18 h recovery exposure. The results showed that an increase in HO-1 level, a material to protect the brain from injury, was observed in the brain for the exposure group. However, only light inflammation was observed in the lungs. Thus, concluding that short-term DPM exposure has adverse effects on the brain but limited effects on the lungs. Hazari et al. exposed male spontaneously hypertensive rats to low (0.5 mg/m^3) and high (0.15 mg/m^3) concentrations of whole diesel exhaust (wDE) and filtered diesel exhaust (fDE) and filtered air (controls) for 4 h to study the link between increased risk of triggered arrhythmias and diesel exhaust exposure [49]. Slightly higher heat rates were observed in wDE and fDE exposure groups compared with the controls. The findings illustrated that a high rate of arrhythmias could be triggered by short-term exposure to DE for that heart sensitivity group. Gordon et al. exposed 12 male Wistar-Kyoto rats to 3 experimental environments (unfiltered DPM, filtered DPM and clean air) for 2 exposure periods (2 days and 4 weeks) [50]. The results showed a reduction in BP and HR in both filtered and unfiltered DPM exposure groups after 4 weeks exposure compared with the controls, but there was no apparent difference in HR between the 3 groups in the first exposure week. Apparent inflammation in the lungs was found in both the 2 days and 4 weeks exposure groups. Apparent reduction of cardiac contractility was observed only in the unfiltered DPM exposure group after 4 weeks exposure. However, all the adverse effects disappeared after a period of recovery. This study indicated that short-term DPM exposure can cause adverse effects on both heart and lungs, but the adverse effects are reversible after a period of recovery. Overall, short-term DPM exposure could result in a series of adverse effects on the brain, lungs and cardiovascular system. From the study, it is concluded that the brain and cardiovascular system are more sensitive to the DPM exposure than the lungs. However, the adverse effects will disappear after a period of recovery in clean air.

Some instillation and injection studies also linked the DPM to the adverse effects on the lungs and cardiovascular system, such as inflammation in lungs, arrhythmia and myocardial ischemia. Yokota and his co-workers conducted a series of intratracheal instillation studies to estimate the DPM's adverse effects on the cardiovascular system and lungs in rats [51–53]. In the study, a pre-instillation of 1 mg DPM dose was received by rats before the ischemia/reperfusion experiment. Arrhythmia and inflammation in lungs were observed in the experiment, which indicated that short-DPM exposure might cause dysfunction on lungs and the cardiovascular system. Nemmar et al. conducted an injection study to demonstrate the cardiovascular and lung inflammatory effects induced by DPM in rats. Different doses of DPM (0.02. 0.1 and 0.5 mg/kg) were injected into the tail vein of rats [54]. The study supports the same conclusion that the existence of DPM in systemic circulation can induce pulmonary inflammation and cardiovascular changes. However, there was no post-exposure procedure in these studies, which leads to uncertainty for its reversibility.

2.3.2. Human studies

The available human research indicated that short-term or acute exposure to DPM results in some non-cancer health effects,

such as acute irritation, asthma, cough, light headedness. Especially for asthma patient and sensitive groups, who are more easily affected by the DPM.

A series of studies have been conducted by Rudell et al. to access the health effects of short-term DPM exposure on humans [23–26]. These studies exposed healthy non-smoking volunteers to DPM exhaust for a short-period. The results suggested that short-term exposure could cause bronchial inflammation, eye irritation, nasal irritation and headache, etc. Salvi et al. conducted some similar studies on healthy human volunteers [26,27]. These studies demonstrated that acute or short-term exposure to high concentration DPM could cause a pulmonary inflammatory response in the lungs and cause respiratory health effects. However, the DPM level data was not available in these studies. Nordenhall et al. conducted studies of the adverse effects of short-term DPM exposure on the airway in humans [55,56]. In these studies, 15 non-smoking healthy and 14 asthmatic volunteers were exposed to diesel exhaust at a PM_{10} concentration of 0.3 mg/m^3 and clean air (controls) for 1 h. Inflammation in airways was observed both in the healthy and asthmatic groups 6 h after the exposure. For the asthmatic group, significant airway hyper responsiveness, which is the fatal factor of asthma, was found in the DPM exposure group but not in the controls. This means that asthma could be triggered after short-term exposure to DPM among asthmatics. To estimate the health effects of short-term DPM exposure on vascular and endothelial function in humans, Mills et al. exposed 30 non-smoking healthy male volunteers to 0.3 mg/m^3 DPM and clean air for 1 h [57]. During the exposure, the volunteers were asked to do intermittent exercise. The adverse effects on vascular and fibrinolytic function were observed in the DPM exposure group, but there was less effect on the heart rate and blood pressure for the same group. Mills et al. conducted a similar study to estimate the effects of short-term DPM exposure on myocardial, vascular and fibrinolytic functions in coronary heart disease patients [58]. The results showed that short-term DPM exposure could aggravate the impairment of myocardial and vascular functions for stable coronary heart disease patients when doing exercise. The two studies indicated a positive relationship between short-term DPM exposure and adverse effects on cardiovascular functions. Lucking et al. conducted a study to estimate the particle capture effects of particle traps [28]. This study exposed 19 healthy male volunteers to 0.3 mg/m^3 DPM with and without particle traps for an hour. The results showed a higher rate of vascular function impairment and thrombus formation in the exposure group without particle traps compared to the group with particle traps. Although the aim of this study is to evaluate the performance of the particle traps, the findings provided the support for the positive association between short-term DPM exposure and the adverse effects of cardiovascular functions.

From the studies above, it is concluded that short-term DPM exposure is associated with adverse health effects on humans, including respiratory and cardiovascular disease. Especially for the sensitive population, they are more easily affected by acute DPM exposure. However, no cancer effects have been observed for short-term DPM exposure. In fact, many cancers are caused by one or more risk factors, like long-term exposure.

3. Exposure-response relationship and regulation

3.1. Exposure-response relationship

Understanding the exposure-response relationship may help to control the DPM effectively. Currently, there are mainly two ways to evaluate the exposure-response relationship [1]. The first approach is to evaluate the relationship between the potential cancer risk to humans and certain levels of long-term DPM exposure (mg/m^3). Another way is by the cancer mode-of-action information.

The first approach could be achieved by evaluating the available human and animal data. Many animal studies showed that lung cancer response in rats had been observed under a high concentration of DPM exposure, but this concentration is not suitable for humans because of the difference in burden ability of lungs. Therefore, the human data is more applicable than animal data. A number of occupational epidemiological studies mentioned above have provided substantial data to evaluate the exposure-response relationship. According to these studies, a positive relationship between the incidence of lung cancer and long-term DPM exposure has been demonstrated. Several epidemiological studies for underground miners have provided some available data for the evaluation of exposure-response relationship. Neumeyer-Gromen et al. concluded that the smoking adjusted ratio of lung cancer mortality for miners (15-year duration of exposure) was 1.0 (baseline) when the cumulative DPM exposure levels were below 1.29 mg/m^3-year (measured as TC) [44]. The mortality ratio (MR) increased with increasing levels of DPM exposure. When the DPM exposure levels were above 4.9 mg/m^3-year, the MR rose to 1.28 (95% CI: 0.61–2.71) and 1.50 (95% CI: 0.66–3.43) for whole cohort and subcohort, respectively. Attfield et al. indicated that the RR (not adjusted for smoking habit) of lung cancer mortality for the underground miners (15-year lag) was 1.0 (baseline) when the cumulative DPM exposure levels were below 0.108 mg/m^3-year (measured as EC) [19]. The RR increased to 2.21 (95% CI:1.19–4.09) when the cumulative DPM concentration was above 0.946 mg/m^3-year (measured as EC). On the basis of Attfield et al.'s study, Silverman et al. adjusted the smoking habit in his study. This study showed that the smoking adjusted ratio of lung cancer mortality for underground miners was 1.0 (baseline) when the cumulative DPM concentration was below 0.003 mg/m^3-year (measured as EC) [19–20]. When the concentration was above 0.536 mg/m^3-year (measured as EC), the SMR increased to 2.83 (95% CI: 1.28–6.26). Overall, although these epidemiological studies have provided some available data, they are inadequate to determine the exposure-response relationship. In another words, cancer unit risk cannot be identified by the available data. First, different measurements (TC and EC) of DPM could lead to different DPM levels. Compared with TC, EC is a more sensitive and specific surrogate of DPM. In addition, baseline exposure is not the normal environmental exposure. Comparing the specific occupational exposure (underground mines) with the normal environmental exposure could provide more information to the evaluation of the response-exposure relationship. However, the data still provides some useful information. An increasing trend of lung cancer mortality risk with increasing concentrations of DPM exposure could be observed from the data.

Another way to evaluate the exposure-response relationship is based on the cancer mode-of-action information. Many animal studies used a bio-maker to evaluate the effects of DPM exposure. Nikula et al. pointed out that alveolar epithelial hyperplasia could be considered as the beginning of lung tumours in rats exposed to DPM [7]. Iwai et al. selected 8-OH-dG production to detect the DNA damage in lungs in the DPM exposure rats [8]. In addition, heart rate, PQ interval, neutrophil count, oxygen radical production, HO-1 level, arrhythmias, etc., have been used to assess the health effects of DPM exposure in rats [46,48–51]. For humans, some symptoms, like nose and eyes irritation, headache, bad smell and bronchial inflammation, have been selected to evaluate the health effects of short-term DPM exposure on humans. Most of the animal and human studies only provided the mode of non-cancer action information. However, the cancer mode-of-action for long-term DPM exposure in humans has not been established. The current

studies mainly focused on the association between the incidence of lung cancer and long-term DPM exposure. Fewer studies mentioned the mechanism of DPM that induces the lung cancer. In some animal studies, the lung overload response in rats could be treated as a cancer mode-of-action. However, this is not applicable for humans. Further studies are needed to evaluate the cancer mode-of-action or carcinogenesis mechanism of DPM.

3.2. Regulation

To protect miners, many countries have assigned limits or passed regulations to control DPM levels for underground mines based on available studies.

Germany was the first to set the limit for DPM in underground mines. In 1990, Germany classified DPM as a carcinogen. The government then set the limit for DPM at 0.2 mg/m^3 for general surface workplaces and 0.6 mg/m^3 for non-coal underground mines [59]. With the development of the limit, Germany reduced the DPM limit for underground non-coal mines and other surface workplaces to 0.3 and 0.1 mg/m^3, respectively [31].

In Canada, the exposure standard for DPM was set by each individual province. Most provinces set 1.5 mg/m^3 for DPM measured as RCD (respirable combustible dust) as the standard exposure for non-coal mines at first. This standard had remained constant for a long time. Then, the Canada Centre for Mineral and Energy Technology finally reduced the standard for DPM to 0.75 mg/m^3 for the underground mines [29]. Quebec then changed this standard to 0.6 mg/m^3 (measured as RCD), while other provinces still use 1.5 mg/m^3 of DPM as the exposure standard [60].

In the US, MSHA published a final rule for DPM exposure in January 2001, which recommends the interim limit for DPM concentration at 0.4 mg/m^3 (measured as TC) for metal/nonmetal mines [61]. In 2005, MSHA changed the interim exposure limit to permissible exposure limit, and regulated the new DPM exposure standard at 0.308 mg/m^3 (measured as EC) [62]. In 2006, MSHA set the final DPM exposure standard at 0.16 mg/m^3 (measured as TC), and this limit has been implemented from 2008 [30].

In Australia, the regulation and standard for the DPM exposure for underground mines are still at its developing stage [31]. The official limit for DPM exposure for underground mines is still not established, and the limit of DPM concentration varies for different states. In the past, the old NSW guideline recommended the limit of DPM exposure at 0.2 mg/m^3. Currently, many regulatory agencies in Australia have adopted 0.1 mg/m^3 of DPM concentration (measured as EC) as the standard limit for underground mines. In 2008, the NSW Department of Primary Industries published a new guideline for DPM management in underground mines, which adopted 0.1 mg/m^3 for DPM concentration for 8 h (one work shift) as a recommended exposure standard [63]. In 2012, the Queensland Mines Inspectorate adopted the same DPM exposure limit for its underground mines; in the same year, the Department of Mines and Petroleum in Western Australia (WA) published a guideline (draft) with a recommended exposure standard of 0.1 mg/m^3 as well [31]. Based on the available information, AIOH adopted 0.1 mg/m^3 DPM concentration for 8 working hours as a recommended DPM exposure standard for underground mines in Australia [31].

4. Discussion

The available animal and epidemiological studies have shown that both short-term and long-term exposure to DPM could pose a risk to health. From the animal studies, it is suspected that long-term DPM exposure can increase the risk of lung tumour. The available animal studies showed that four animal species had been used: rats, hamsters, mice and monkeys. Rat is the most sensitive animal to DPM exposure among the four species. The lung tumour response in rats had been observed after long-term exposure to a high concentration of DPM (>2.5 mg/m^3). However, this exposure-response relationship cannot be used for humans directly. An impaired clearance function of lungs had been found among the rats. The overload of DPM in lungs resulted in the high risk of lung tumours in rats. The lung clearance and burden function of human beings are much greater than that of rats. In addition, the occupational environmental DPM concentration is usually lower than the animal experimental DPM concentration. For these reasons, an overload condition in a human's lungs is not expected to happen. Besides, one study showed that monkeys did not develop lung tumours after two years exposed to whole diesel exhaust (2 mg/m^3 of DPM) [38]. Therefore, the increased risk of lung tumours in rats is inadequate to evaluate the exposure-response relationship for humans. Further animal studies should be carried out to solve this problem. Two suggestions have been given for further studies:

(1) More species of animals should be considered in the study, especially for some animals which have similar lung clearance function as humans, examples such as apes and orangutans.
(2) Long-term exposure time is necessary. In Lewis et al.'s study, monkeys did not develop lung tumours. One possible reason for this result is the short exposure period [38].

The epidemiological studies indicated that long-term exposure to DPM resulted in a higher risk of lung cancer. The epidemiological studies included miners, railroad workers, trucking industry workers and construction workers. The relative risk of lung cancer ranged from 1.13 to 5.10 under different DPM exposure conditions (duration, concentration, smoking history, etc.). Although a number of epidemiological studies have been carried out to determine the carcinogenicity of DPM, few studies are related to miners. However, compared to other occupations, the miners, particularly underground miners, have the potential to be in a higher concentration DPM environment due to the confined spaces. Four epidemiological studies for miners have been conducted. Three epidemiological studies for underground miners have demonstrated the positive relationship between high risk lung cancer mortality and long-term DPM exposure based on the large samples [19,20,44]. However, there were still several limitations in the studies preventing an accurate result. In Neumeyer-Gromen et al.'s study, TC was selected as the surrogate of DPM [44]. Compared with EC, TC is more easily influenced by other interferences, like cigarette smoke, coal dust and oil mist [64,65]. The selection of surrogate for DPM will directly influence the accuracy of the study results. Another limitation is the sample size. Only 3087 participants' exposure and smoking behaviour were validated in this study. If a large sample size was selected, more reliable conclusions will be drawn. Attfield et al. did not take smoking history into consideration. Smoking could be an interference factor for the relative risk of lung cancer, so it is necessary to control for the smoking effects on the results [19]. Besides, no historical exposure data are available for DPM concentration in both Attfield and Silverman et al.'s studies [19,20]. All the past data was estimated based on the measurement of personal respirable EC (REC) levels between 1998 and 2001. For this reason, the historical exposure data might be overestimated or underestimated. Although limitations exist in these studies, they still provide strong evidence for the relationship between long-term DPM exposure and a high risk of lung cancer. Another epidemiological study conducted by Moher et al. drew a different conclusion with that concluded by other scholars. The sample size could be one possible reason for this different result

[45]. Therefore, further study is still needed to arrive at a more reliable result. Three suggestions have been given for the further studies:

(1) To get a more accurate and reliable result, EC should be chosen as the surrogate of DPM because TC is more easily influenced by other interferences, especially in some high dust concentration environments.
(2) Large sample size and long duration should be considered in the studies because these factors allow reliable conclusions.
(3) More potential confounders such as smoking and previous employment history should be controlled during the study in order to obtain reliable results.

From the short-term animal studies, it is concluded that short-term DPM exposure, injection or instillation DPM dosage can cause adverse effects on the brain, lungs and cardiovascular system. Most of these effects are reversible after a period of recovery. In addition, it is noticed that rat is still the main experimental animal species. Only Campen et al. selected mice as the experimental animal. In order to get a more convincing result, different kinds of animal could be used in further study, especially some kinds of primates [47]. The human studies indicated that short-term DPM exposure is linked with some non-cancer adverse health effects, such as acute irritation, asthma, cough, light headedness. From three studies, it is noticed that the sensitive group, such as asthmatics and heart disease patients, is more likely to be affected by DPM [55,56,58]. Therefore, more attention should be paid to this group of people when working in a high DPM concentration environment.

The exposure-response relationship could be evaluated by DPM exposure data (a cancer unit risk potency for DPM) and the mechanisms or mode of cancer action information in studies. Understanding the exposure-response relationship may assist to better control DPM and protect miners from DPM health risks. However, the exposure-response relationship cannot be established based on the available animal and human studies. The animal studies did provide some exposure data, but this data was not suitable for humans due to the different lung clearance capacity and burden function of rats and humans. Epidemiological studies also provided limited information due to the uncertainties in these studies, such as different surrogates of DPM, confounding (smoking history) in the studies. Currently, it is noticed that the available animal and human studies provided limited mechanisms or mode of cancer action information. Not too many studies focused on the mechanism by which DPM induces lung cancer in humans. Overall, further studies are still needed before the mode-of-action and reliable exposure-response relationships are established.

Many countries have developed limits or regulations for DPM for mining industries to protect the underground miners. From the regulations, many markers (TC, EC and RCD) have been selected as a dosimeter for DPM and all these markers are measured in mass units (mg/m^3). However, TC and RCD are easily influenced by other interferences, like cigarette smoke, coal dust and oil mist [64,65]. EC has been considered as an accurate and reliable dosimeter for DPM because it could be monitored even at a low concentration and there are no other known interferences for EC in underground mines. In addition, EPA's report indicated that respirable-sized particles could also be used as dosimeters for DPM [1]. However, there are several uncertainties related to using respirable-sized particles as the dosimeter. First, compared with other dosimeters, historical data of respirable-sized particles is not available. Second, the accuracy and reliability are not mentioned in EPA's report. Due to these uncertainties, future studies are needed to determine the most accurate and reliable dosimeter for health effect purposes.

5. Conclusions

Based on the available health effects' data, this review has demonstrated that both short-term and long-term exposure to DPM are contributing to adverse health effects, especially in a high DPM concentration environment (underground mine). For this reason, many DPM regulations have been developed to guarantee underground miners' health.

A number of epidemiologic and animal studies have demonstrated that long-term exposure to high concentrations of DPM could increase the risk of lung cancer. Two recent epidemiologic studies provided strong evidence for the positive association between long-term DPM exposure and high risk lung cancer mortality among underground miners. Short-term or acute exposure to high concentrations of DPM ($0.3\ mg/m^3$) can cause acute irritation, asthma, cough, light-headedness, etc., but no evidence demonstrated the relationship between short-term or acute exposure to high concentrations of DPM and lung cancer. However, the exposure-response relationship or a cancer unit risk potency for DPM could not be determined due to the limitation of animal study data and uncertainties in the available epidemiologic data. Many countries have developed their own DPM emission standard or limit to guarantee their underground miners' health. Germany set the DPM limit for underground non-coal and other surface workplaces at 0.3 and $0.1\ mg/m^3$, respectively. In Canada, most provinces set $1.5\ mg/m^3$ for DPM measured as RCD (respirable combustible dust) as the standard exposure for non-coal mines. America and Australia recommended the exposure standard for DPM at $0.16\ mg/m^3$ (measured as TC) and $0.1\ mg/m^3$ (measured as EC). These limits or standards are developed based on various dosimeters for DPM measurement. With the studies continuing, an accuracy and proper dosimeter will be selected to measure the DPM standards for the underground mining industries.

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