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Health risk assessment by measuring plasma malondialdehyde (MDA), urinary 8-hydroxydeoxyguanosine (8-OH-dG) and DNA strand breakage following metal exposure in foundry workers

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ABSTRACT

Silica particles and metals are important occupational hazards in foundry workers, and exposure may result in DNA damage and lipid peroxidation through oxidative stress. This study aimed to compare oxidative damage by measuring the levels of plasma malondialdehyde (MDA), urinary 8-hydroxydeoxyguanosine (8-OH-dG) and DNA strand breakage in workers at two foundry plants (exposure group) and in town hall employees (control group) in central Taiwan. Air samples for metals analysis in the workplace were also collected to assess the health risk to foundry workers.

Significantly higher MDA levels (4.28 μM versus 1.64 μM), DNA strand breakage (6.63 versus 1.22), and 8-OH-dG levels (5.00 μg/g creatinine versus 1.84 μg/g creatinine) were found in exposure group compared with the control group. Higher levels of these parameters were also found in workers involved in manufacturing than in workers involved in administration. Higher air respirable dust concentrations were found in manufacturing departments (0.99 mg/m^3) than in administrative departments (0.34 mg/m^3). The health risk assessment on metals exposure showed that the cancer risk for Cd, Cr and Ni were all above 1×10^{-6}. Future studies are necessary to determine whether metals exposure can contribute to oxidative damage in foundry workers.

1. Introduction

Foundry plants have various treatment processes for reclaiming bentonite-bonded molding sands, which consist of silica sand, coal dust and clay, with particle-sizes ranging from 0.1 to 0.4 mm [1]. Two main procedures take place in a foundry: sand molding and metal casting. Sand molding includes core sand and binder, core making and then the casting process which consists basically of pouring liquid metal into a mold containing a socket into the geometry desired for the final part of the process. After casting cooling, shakeout and cleaning, the metals and sand are recovered. The flow chart in Fig. 1 refers to the report by Ribeiro and Filho [2]. The study consisted of 610 workers employed at a foundry where it was found that a total of 846 injuries were recorded on the personnel injuries files. The highest number of injuries involved foreign particles in eyes (40%), strains, pulls and tears (31%), bruises (11%), cuts and puncture wounds (9%), burns and scalds (5%), and broken bones (4%) [3]. In addition, grinders experienced more eye injuries, and molders had more strains, pulls and tears. Particle injuries were obviously more important than any of the other physical injuries recorded in the foundries. Environmental air sampling has shown that chromium species (Cr), iron (Fe) and aluminum (Al) are at high levels in the emission or ambient air outside the foundry in an area between no foundry activity and foundry activity [4,5]. Moreover, a leaching study finds high silver (Ag), arsenic (As), barium (Ba), cadmium (Cd), chromium (Cr), and lead (Pb) in foundry molding sands [6]. Although industrial foundries vary in terms of the type of metal being poured, the sand casting process, the type of furnace (induction, electric arc, and cupola) and finishing process (grinding, blast cleaning, and coating), the basic process and hazards including particles and metals remain the most important occupational hazards in the foundry industry.

Many studies have suggested that silica particles may induce reactive oxygen species (ROS) generation [7–9], which overwhelms antioxidant defenses in the lung and causes lipid peroxidation and cell damage [10]. ROS can also cause many types of DNA damage, including gene mutation, exchange of sister chromosomes

Abbreviations: ROS, reactive oxygen species; 8-OH-dG, 8-hydroxydeoxyguanosine; comet, single-cell gel electrophoresis assay; MDA, malondialdehyde; TMOM, the tail moment by Comet assay.

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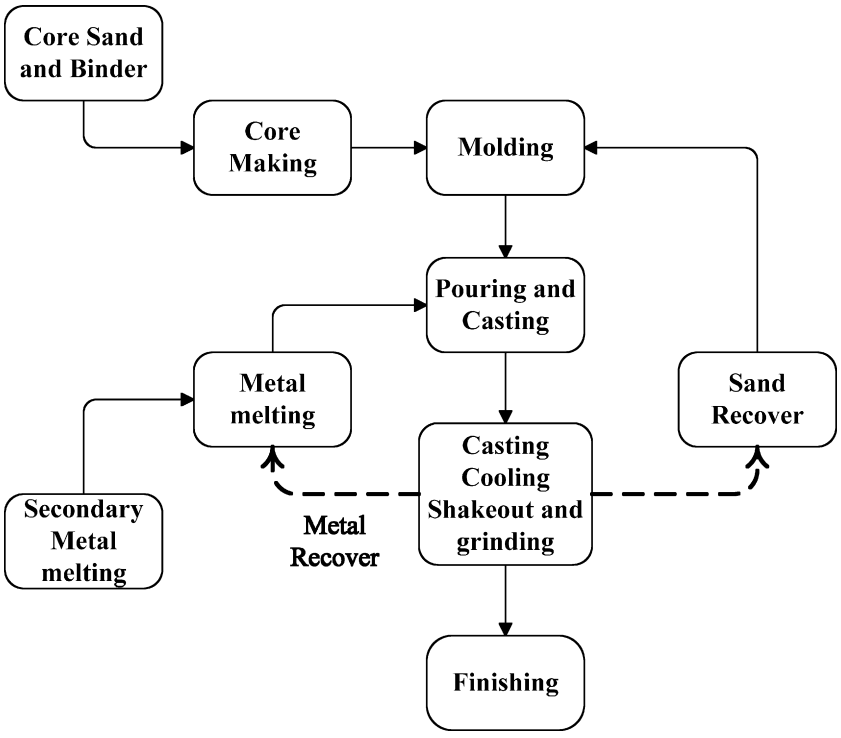

Fig. 1. Operating procedure of the foundry.

and mutagenesis in chromatids [11,12]. Hazardous substances such as metals and other organic compounds can cause an increase in oxidative damage, including malondialdehyde (MDA), 8-hydroxydeoxyguanosine (8-OH-dG), and DNA breakage (single cell gel electrophoresis of comet assay) in workers in the battery plant, cement plant, and metal recovery plants [13–15], and the studies suggest that occupational exposure to incinerators may cause harm via oxidative stress. Meanwhile, exposure to Cr results in the increased production of ROS, lipid peroxidation, and enhances the excretion of urinary lipid metabolites [16], as well as lipid peroxidation and catalase activity elevates in liver, kidney and brain of Pb exposed rats [17–19]. Ni compounds can elicit chromosome aberrations, lung cancer risk [20] and are classified as human carcinogens by the International Agency of Research on Cancer (IARC) [21]. These results suggest that exposure to silica particles and many metals may result in DNA damage and lipid peroxidation through oxidative stress.

Although many studies have indicated neuro-toxic and health effects in foundry workers [22,23], little is known about the status of oxidative stress in workers at occupational smelting factories potentially exposed to more silica particles and metals. Here, we compared the oxidative stress status by measuring the levels of plasma malondialdehyde (MDA), urinary 8-hydroxydeoxyguanosine (8-OH-dG) and DNA strand breakage in workers potentially exposed to hazardous substances, including silica sand and metals at two foundry plants (exposure group) and in town hall employees (control group) in central Taiwan. Air samples for metals analysis in the workplace were also collected to assess the health risk of foundry workers.

2. Materials and methods

2.1. Subjects

The study was conducted in two typical foundry plants in central Taiwan. Plant A typically uses an induction furnace for metal melting and plant B uses a cupola. A pre-sampling walk-through was conducted to determine the layout of each work site and its borders. In principle, the zones in the foundry plant are based on various operational functions. Areas which included: core making, smelting furnace, molding, sand shakeout, grinding, sand recovery, and administration, were selected for study.

Fifteen and 26 workers were recruited from plant A and B, respectively (exposure group) and 27 administrative staff from the town hall (control group) were also included. Each employee was asked to fill out a questionnaire asking for information about personal characteristics (gender, age, height, weight, residence neighborhood, etc.), life style (e.g., tobacco usage and alcohol intake), and occupational history (e.g., working history at current place of employment, working environment, job titles, periods of employment, and use of protective equipment). Body mass index (BMI, kg/m^2; weight in kg divided by the square of the height in meters (m)) was also calculated for each participant. The study was approved by the Ethics Committee of the Kuang Tien General Hospital (Taichung, Taiwan).

2.2. Blood collection

The sampling day was Friday, the last working day of the week. The workers completed an overnight fast before blood sampling, and Friday was chosen as it would represent the highest accumulation of hazardous chemicals for the week in this type of environment. Each participant provided 2 mL of venous blood, drawn into chemically clean tubes containing heparin. One milliliter of the blood sample was centrifuged at $1000 \times g$ for 10 min to separate blood cells and plasma. Plasma was stored at −85 °C until analysis of MDA. After cryoprotectants (1:1 ratio) had been added to the other 1 mL of blood, the samples were stored at −85 °C until the comet assay.

2.3. Urine collection

Urine samples were collected in polyethylene bottles (which had been washed with 0.2% HNO_3) from the first urination in the morn-

ing. The samples were kept at −85 °C for 8-OH-dG analysis and the assay was complete within 1 week.

2.4. MDA analysis

Plasma lipid peroxidation was measured as MDA levels. The MDA assay protocol was referred from Hong et al. report [24]. The MDA standard solution used 1,1,3,3-tetraethoxypropane (Fluka Co., No. 87670) in concentrations of 0.075, 0.1, 0.25, 0.4, 0.5, 0.75, and 1.0; values are presented as μM. Firstly, 500 μL of plasma was added to 50 μL of 0.2% butylated hydroxytoluene (BHT) and 25 μL 10N NaOH. After the mixture had been incubated at 60 °C for 30 min, it was combined with 30 mL of 1% potassium iodide (KI) and 7.2% trichloroacetic acid (TCA). The samples were then centrifuged at 2300 × *g* for 10 min, and then 1.0 mL of 0.6% thiobarbituric acid (TBA) was added to the mixture and incubated at 95 °C for 30 min. Finally, the samples were placed in ice for 5 min, and then 3.0 mL of n-butanol was added. The n-butanol extract was measured at an excitation wavelength of 515 nm and an emission wavelength of 555 nm using a fluorescence spectrophotometer (Shimadzu RF-5301pc).

2.5. Urine 8-OH-dG assay

Urinary 8-OH-dG levels were determined using a competitive ELISA immunoassay (Japan Institute for the Control of Aging, Shizuoka, Japan) [25]. Data are presented as 8-OH-dG (μg/g creatinine).

2.6. Blood comet assay for DNA strand breakage

The comet assay protocol was referred from our previous report [26]. Firstly, 150 μL of 1% normal melting point agarose (LMA) was applied to the first layer of the slide. We then mixed 50 μL of whole blood with 250 μL of 1% LMA, and applied 130 μL of that mixture to the second layer of the slide. After applying another layer of 1% NMA (150 μL), we immersed the slides in cold lysing solution (2.5 M NaCl, 100 mM Na_2EDTA, 10 mM Tris, 1% *N*-sodium lauroyl sarcosinate) for 1 h at 4 °C. The slides were then placed in an electrophoresis tank, to allow the DNA to unwind for 15 min in the alkaline solution (300 mM NaOH and 1 mM Na_2 EDTA). Electrophoresis was then carried out at 300 mA for 20 min in the same alkaline solution at room temperature. The slides were then neutralized by adding 0.4 M Tris–HCl buffer (pH 7.5) and stained with ethidium bromide. Images of DNA strand breakage were visually analyzed using comet scores according to the method of Chia et al. [26]. The tail moment (TMOM) was determined using Comet Assay IV (Perceptive Instruments Ltd., Haverhill, Suffolk, UK) according to the formula:

$$\text{TMOM} = \text{TDNA}(\text{DNA in tail as a \% of total DNA}) \times \text{TDx}(\text{DNA tail length}).$$

The breakage of DNA strands occurred due to oxidative damage and a comet was formed by electrophoresis. The longer the DNA tail length, presented the higher the percentage of breakage. The tail moment is considered one of the best indices of comet formation obtained in computerized analysis [27].

2.7. Ambient samples

The respirable dusts were sampled inside the plants using the SKC nylon cyclone with a filter loaded into a three-piece filter cassette (SKC Inc.) with 0.4-μm pores and 37-mm-diameter mixed cellulose ester filters (Nucleopore, Inc., Cabin John, MD, USA). The sampling height was about 1.5 m in the breathing zone of the workers. The filters were conditioned in the same temperature and humidity. In addition, the filters were weighed 48 h post-conditioning. The post-sampling weights were subtracted from the pre-sampling weights to provide the particle mass in the ambient sampling. Personal air pump samplers with a flow rate of approximately 1.7 L/min were used during an 8-h work shift. The sampling time was about 8 h per sample. We took 15 and 19 samples in the operating departments of plant A and B, respectively, and 3 samples in the administrative departments of each plant. In total, 34 respirable samples were collected.

2.8. Metal analysis by inductively coupled plasma-optical emission spectrometer (ICP-OES)

Particles were digested in a 1200-W microwave oven (Mars, microwave digestion system, CEM) according to Tsai [28] to ensure accurate and reliable analysis of metals in the particles. The digested solution was a mixture of 8.0 mL 65% HNO_3 and 2.0 mL 30% H_2O_2. All reagents were prepared using chemicals supplied by Merck (Analytical grade). Inductively coupled plasma-optical emission spectrometer (ICP-OES, ICP-OES Optima 2100DV, PerkinElmer) was used to analyze the metal concentrations.

2.9. Statistical methods

The JMP 5.0 (SAS Institute, Cary, NC, USA) software packages were used for data management and statistical analysis. The Wilcoxon rank sum test was carried out to evaluate differences in age, 8-OH-dG and MDA levels as well as DNA strand breakage between the exposure and control groups. Differences between the gender ratios, smoking ratios, and other factors were examined using Fisher's exact test.

3. Results

3.1. Demographic distribution of workers

Table 1 showed the distribution of demographic characteristics in the exposure and control groups. The average BMI of the control group (25.8) was significantly higher than that of the exposure group (23.6), in addition, a higher percentage of those in

Table 1
Demographic characteristic of study subjects.

	Exposure (n = 41)	Control (n = 27)	p-Value
Age[a]	46.7 ± 10.3	49.0 ± 6.4	0.419
Sex (%)[b]			0.514
Men	39 (95.1)	27 (100)	
Female	2 (4.9)	0	
BMI[a]	23.6 ± 2.5	25.8 ± 3.0	**0.001***
Smoking status (%)[b]			1.000
Yes	23 (56.1)	15 (55.6)	
No	18 (43.9)	12 (44.4)	
Alcohol intake (%)[b]			0.440
Yes	27 (69.2)	16 (59.3)	
No	12 (30.8)	11 (40.7)	
Betel nut use (%)[b]			1.000
Yes	11 (26.8)	8 (29.6)	
No	30 (73.2)	19 (70.4)	
Exercise habit (%)[b]			**<0.0001***
Yes	16 (39.0)	24 (88.9)	
No	25 (61.0)	3 (11.1)	

[a] Mean ± standard deviation, data are analyzed by Wilcoxon test.
[b] Data are analyzed by Fisher's exact test.
* p-Value < 0.05.

Table 2
MDA, 8-OH-dG and TMOM of the workers in exposure (foundry plants) and control groups.

	Exposure ($n=41$)	Control ($n=27$)	p-Value
MDA (μM)[a]	4.28 ± 2.11	1.64 ± 0.81	**<0.0001***
8-OH-dG (μg/g creatinine)[a]	5.00 ± 4.92	1.84 ± 1.53	**0.001***
TMOM[a,b]	6.63 ± 3.99	1.22 ± 0.76	**<0.0001***

[a] Mean ± standard deviation, data are analyzed by Wilcoxon test.
[b] TMOM (tail moment).
* p-Value < 0.05.

the control group exercised regularly compared with the exposure group.

3.2. Oxidative stress markers

We found significantly higher MDA levels in the exposure group compared with the control group (4.28 μM versus 1.64 μM, respectively; $p<0.0001$), as well as greater DNA strand breakage (6.63 versus 1.22, respectively; $p<0.0001$). The differences in 8-OH-dG levels between the two groups also showed a similar trend (5.00 μg/g creatinine versus 1.84 μg/g creatinine, respectively; $p<0.0001$; Table 2).

3.3. Working status and oxidative stress markers

All workers were categorized, based on their job titles or work departments, as members of the manufacturing department ($n=38$) or administrative department ($n=3$) in the two foundry plants. MDA levels, 8-OH-dG levels and DNA strand breakage were significantly higher in manufacturing workers than in administrative workers, regardless of which foundry they belonged to (Table 3).

Table 3
MDA, 8-OH-dG and TMOM of the workers in manufacturing department and in administrative department.

Oxidative damage	Departments	
	Administrative dep. ($n=3$)	Manufacturing dep. ($n=38$)
MDA (μM)[a]	2.62 ± 0.54	4.41 ± 2.13
8-OH-dG (μg/g creatinine)[a]	1.61 ± 1.05	5.27 ± 5.01
TMOM[a,b]	4.52 ± 3.19	6.80 ± 4.03

[a] Mean ± standard deviation.
[b] TMOM (tail moment).

3.4. Environmental monitoring inside the foundry

Forty respirable air samples were collected inside the foundry, and the dust and metal concentrations are shown in Fig. 2. Higher dust concentrations were found in the manufacturing departments (0.99 mg/m^3) than in the administrative departments (0.34 mg/m^3). Levels of Al, Fe, Mn, Ni, Pb, and Zn were higher in the manufacturing departments than in the administrative departments.

3.5. Risk assessment of heavy metals exposure in foundry workers

Cd, Cr and Ni are recognized as human carcinogens or are suspected to be human carcinogens by the IARC. The health risk assessment on metals exposure showed that the cancer risk of Cd (2.34×10^{-4}), Cr (7.92×10^{-3}) and Ni (5.76×10^{-5}) were all above 1×10^{-6} (Table 4). Non-cancer risk assessment also showed that the hazard index (HI) was above 1. This means that workers exposed to Cd, Cr, Ni and Mn in foundries are at risk of bronchus cancer, lung cancer and impairment of neurobehavioral function.

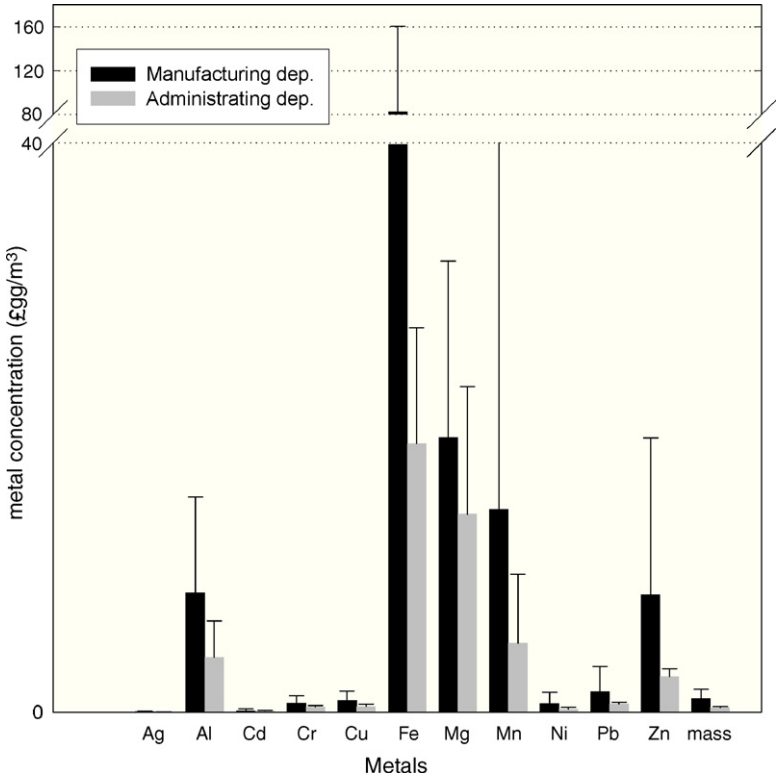

Fig. 2. Particle mass (mg/m^3) and metal concentration (μg/m^3) of respirable particles between manufacturing department and administrating department in the foundry plants (manufacturing department: sample size = 34, administrating department: sample size = 6).

Table 4
Health risk assessment for metals in manufacturing departments in foundry.

	Cd	Cr	Ni	Mn
Impairment	Lung, trachea, bronchus cancer [35]	Lung cancer [34]	Lung cancer [33]	Impairment of neurobehavior function [36]
Unit risk ($\mu g/m^3$)$^{-1}$	1.8×10^{-3}	1.2×10^{-2}	2.4×10^{-4}	Group D
RfC ($\mu g/m^3$)	–	–	–	5×10^{-4}
Air levels ($\mu g/m^3$)	0.13	0.66	0.24	14.26
Risk of carcinogenesis[a]	2.34×10^{-4}	7.92×10^{-3}	5.76×10^{-5}	–
Risk on non-carcinogenesis[b]	–	–	–	28520

[a] Risk on cancer = air levels($\mu g/m^3$) × unit risk ($\mu g/m^3$)$^{-1}$.
[b] Hazard index (HI) = air levels($\mu g/m^3$)/RfC ($\mu g/m^3$).

Table 5
Summary presentation of research findings related to metallic profiles in aerosol ($\mu g/m^3$) from various industrial sources.

Character	Size	Ag	Al	Cd	Cr	Cu	Fe	Mg	Mn	Ni	Pb	Zn	Reference
Ferroalloy smelter	PM_{10}	–	–	–	–	–	–	–	0.80	–	–	–	[29]
Foundry	TSP	–	–	–	–	–	–	–	5.0–39	–	–	–	[47]
Manganese alloy plant	PM_{10}	–	–	–	–	–	–	–	301	–	–	–	[23]
Iron and steel industry	TSP	–	0.59	–	0.02	0.10	1.25	–	0.07	0.01	0.15	0.19	[32]
Industrial area	$PM_{2.5}$	–	0.07	–	0.01	0.01	0.30	–	0.01	0.004	0.01	0.04	[48]
Industrial area	$PM_{2.5}$	–	0.33	–	0.01	0.04	0.48	0.20	0.02	0.01	0.09	0.38	[46]
Industrial complex	PM_{10}	–	–	0.003	0.03	0.04	1.63	–	0.05	0.04	0.24	0.24	[9]
Industrial area	PM_{10}	–	0.57	0.01	0.04	0.02	1.07	0.29	0.06	0.02	0.18	0.48	[30]
Blast furnace during operation	$PM_{2.5}$	0.06	17.13	0.12	0.09	0.36	40.00	25.13	0.27	0.04	1.15	31.07	[31]
Manufacturing dep.	PM_{10}	0.05	8.42	0.13	0.66	0.86	83.03	19.31	14.27	0.62	1.50	8.28	This study
Administrating dep.	PM_{10}	0.03	3.88	0.10	0.40	0.44	18.89	13.92	4.85	0.24	0.59	2.53	This study

–: No data available.

4. Discussion

4.1. Metals in foundries

Foundry particles from molding sand are composed of a complex chemical mixture which includes silica [1], Al and Fe [5], Mn [29], Cr and others [2,4], and the leaching procedure also results in high levels of Ag, As, Ba, Cd, Cr and Pb in molding sand [6].

A comparison of the metal concentrations in the present study to previous studies (Table 5), showed that the air metal concentrations were higher in foundry plants than in a ferroalloy smelter [29] and other industrial areas [9,30], regardless of whether the samples were taken from administrative departments or manufacturing departments. This means that administrative departments are not completely separate from manufacturing departments, and that administrative workers also need to be protected in the foundry. By comparing the metal concentrations in the present study to those in a blast furnace during operation [31], the manufacturing departments in the present study showed higher Cr, Cu, Fe, Mn and Ni levels than those in a blast furnace during operation. The metal concentrations in the administrative departments were also significantly higher than those collected in the vicinity of industrial areas [9,30,32]. It may be interpreted from these findings that administrative workers have a higher risk of exposure to metals emitted during the operating process in a foundry. The health risk assessment on metals exposure showed that the risk of Cd, Cr and Ni were all above 1×10^{-6}, while, non-cancer risk assessment also showed that workers were exposed to predominant metals. However, none of them exceeded the threshold limit values of the metals. Therefore, future studies should follow health outcomes including bronchus and lung impairment [33–35], and disorders of neurobehavioral function in foundry workers [36].

4.2. Metal exposure and oxidative damage

The relationship between metal exposure and neuropsychological function [22,37,38], oxidative mechanisms [16], and lung cancer risk [20] are under discussion. Levels of 8-oxo-dG in lymphocyte DNA and markers of oxidative damage to lipids and proteins in plasma are associated with environmental $PM_{2.5}$ exposure [39], and epidemiological evidence suggests that exposure to As and Cr may mediate oxidative stress, apoptosis, and carcinogenesis [40]. Massive DNA damage, along with deregulation of cell homeostasis, leads to malignant diseases [41]. Casado et al. [42] indicated that Pb exposure may cause GSH oxidation to GSSG, which shows that the stress index increases significantly, and that lipid peroxide formation is mediated by a metal-driven Fenton reaction. MDA increases under heavy metal stress, and an increasing amount of MDA represents the formation of free radicals in the test microorganism under heavy metal stress [43]. In an *in vitro* study, Cu significantly raises the MDA level more than Cd, whereas catalase activity is significantly reduced by Cd than by Cu [44]. These results provide evidence that metals treatment or metals exposure can induce oxidative stress, as measured by ROS, oxidative enzyme activities or MDA. In this study, significantly higher lipid peroxidation and DNA damage are observed in foundry workers compare to town hall employees. In addition, the levels of these parameters are higher in workers from manufacturing departments than in those from administrative departments, even though they all work in the same foundry. Compared with our previous study, the MDA levels in foundry workers in this study were higher than 0.58–3.20 μM which was found in workers from a bottom ash recovery plant and from fly ash treatment plants [45], and higher than 1.79–2.54 μM which was found in workers from a Cu smelter and from Zn recovery plants [13]. However, the 8-OH-dG level in this study (5.00 μg/g creatinine) was not different from the level in workers from a bottom ash recovery plant and from fly ash treatment plants [45]. These results suggest that blood MDA level may be a sensitive oxidative marker for exposure to occupational hazards, such as heavy metals.

5. Conclusion

The present study demonstrated that workers at foundry plants (exposure group) have significantly higher plasma MDA, DNA damage and 8-OH-dG than town hall employees (control group). Together with air sampling, the data showed that larger quantities of metals were leached from manufacturing departments than administrative departments, indicating that elevated oxida-

tive damage in foundry workers was reasonable. However, it is not negligence that administrative workers in foundries were also likely to be exposed to heavy metals emitted from the foundry operating process. In addition, it remains to be determined whether oxidative damage can be attributed to particular metals and particular levels of metals in foundry plants.

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