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MERJA JÄRVELÄ

METAL WORKERS' OCCUPATIONAL EXPOSURE TO PARTICLES AND ITS EFFECTS ON INFLAMMATION MARKERS AND PULMONARY FUNCTION

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ABSTRACT

Tens of thousands of Finnish workers are exposed to metal particles. Respiratory exposure levels vary between the metal industries; in fact all the particulate emissions caused by industrial processes, especially if measured in particle number concentrations, have been poorly reported. Environmental exposure to outdoor particles and occupational exposure to welding fumes are known to cause harmful lung and cardiovascular effects as well as cancer, but the detailed mechanisms mediating these effects are not fully understood. Inflammation has been associated with the development of cancer and an inflammatory response has also been implicated in the development of atherosclerosis.

The present study investigated occupational exposure to particles in welding workplaces and in a ferrochromium and stainless steel production line with particle exposures being measured in both mass and number concentrations. In addition, changes in welders' blood inflammation markers and pulmonary function were studied in both workplace and the welding exposure tests, which were performed in workers with suspected occupational asthma. Ferrochromium and stainless steel workers' blood and lung inflammatory marker levels were compared to the levels observed in unexposed workers, and the associations between stainless steel workers particle exposure and levels of systemic and pulmonary inflammation markers were studied.

In welding workplaces, the inhalable dust concentrations measured in the breathing zone were higher for welders than for sheet metal workers. Nevertheless, the exposure dose in sheet metal workers could be higher because most of the welders used effective respiratory protection while working, whereas sheet metal workers did not wear any respiratory protection. Employees using the MIG/MAG welding technique were exposed to higher concentrations of particulate matter than sheet metal workers. In the welding exposure tests, the average total particle number

conentration varied between 1.7×10^6 and 3.2×10^6 particles/cm^3. The particle size distribution was unimodal with most of the particles being about 430 nm in size.

In the production of ferrochrome and stainless steel, exposure to particle mass and number concentrations were highest at the beginning of the production, during the sintering, ferrochromium smelting and steel melting phases. In contrast, exposure was the lowest at the end of the production chain at the cold rolling mill. Workers' personal exposure was significantly reduced as compared to the process area particle concentration levels because workers spent about 85 % of their working time in control rooms where the particle concentrations were generally equivalent to the levels measured in office environments.

Welding fume exposure caused a decrease in blood hemoglobin and erythrocytes as well as increasing the levels of leukocytes and neutrophils. Exposure also resulted in changes in blood interleukin-1β and E-selectin levels. No changes were found in the lung function tests in the workplaces during the working day, but after the welding exposure tests, a slight decrease in FEV_1 and PEF values was observed.

Among ferrochromium and stainless steel workers, no associations were found between the particle exposure and the inflammation markers. However, the baseline inflammation marker levels of the chromium-exposed groups differed slightly as compared to non-exposed controls.

In conclusion, exposure to welding fume particles resulted in a mild acute systemic inflammation when measured as changes in blood inflammatory markers. Therefore, exposure to particles containing metals should be reduced by using control measures that improve occupational hygiene in all working environments where exposure to metal particles is likely.

National Library of Medicine Classification: QV 290, QZ 150, WA 450, WB 284

Medical Subject Headings: Occupational Exposure; Air Pollutants, Occupational; Workplace; Particulate Matter; Dust; Metals; Stainless Steel; Chromium; Welding; Inflammation; Cytokines; Hemoglobins; Erythrocytes; Leukocytes; Neutrophils; Interleukin-1beta; E-Selectin; Lung; Respiratory Function Tests; Asthma, Occupational

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TIIVISTELMÄ

Kymmenet tuhannet työntekijät altistuvat Suomessa metalleja sisältäville hiukkasille. Altistumistasot vaihtelevat eri metallitoimialoilla, eikä edes kaikkien teollisuusprosessien aiheuttamia hiukkaspäästöjä hiukkasten lukumääräpitoisuutena mitattuna vielä tiedetä. Ulkoilman hiukkasille ja työperäisen hitsaushuuruille altistumisen tiedetään aiheuttavan haitallisia keuhko- ja sydänvaikutuksia sekä syöpää, mutta tarkkoja vaikutusmekanismeja näiden vakavien vaikutusten takana ei kuitenkaan täysin tunneta. Viime vuosina tulehdus on yhdistetty niin syövän syntyyn kuin valtimokovettumataudinkin kehittymiseen.

Tässä väitöstutkimuksessa tutkittiin ja karakterisoitiin työperäistä hiukkasaltistumista hitsaustyöpaikoilla sekä ferrokromin ja ruostumattoman teräksen tuotantoketjussa. Hiukkasten pitoisuutta mitattiin sekä massa- että lukumääräpitoisuuksina. Lisäksi tutkittiin hitsaushuurualtistumisen aiheuttamia äkillisiä muutoksia veren tulehdusmarkkereihin ja keuhkojen toimintaan hitsaajilla niin työpaikoilla kuin ammattitautiepäilypotilaille tehtävillä hitsausaltistuskokeilla. Ferrokromin ja ruostumattoman teräksen tuotantotyöntekijöiden veren ja keuhkojen tulehdusmarkkeritasoja verrattiin kromille altistumattomien työntekijöiden tasoihin sekä tutkittiin hiukkasaltistumisen osuutta tulehdusvälittäjäaineiden pitoisuuksiin.

Hitsaustyöpaikoilla hengitysvyöhykkeeltä mitatut hengittyvän pölyn pitoisuudet olivat korkeampia hitsaajilla kuin levysepillä. Siitä huolimatta levyseppien todellinen altistuminen saattoi olla suurempaa, koska suurin osa hitsaajista käytti tehokkaita hengityksensuojaimia työskennellessään, kun taas levysepät eivät käyttäneet hengityksen suojaimia juuri ollenkaan. MIG/MAG hitsaustekniikkaa käyttäneet työntekijät altistuivat suuremmille hiukkaspitoisuuksille kuin puikkohitsaajat. Hitsausaltistuskokeissa hiukkasten keskimääräinen kokonaislukumääräpitoisuus vaihteli 1.7×10^6 ja 3.2×10^6 hiukkasta/cm^3 välillä. Hiukkaskokojakauma oli yksimoodinen ja suurin osa hiukkasista oli noin 430 nm:n kokoisia.

Ferrokromin ja ruostumattoman teräksen tuotannossa altistuminen hiukkasten massa- ja lukumääräpitoisuuksille oli korkeinta tuotantoketjun alkupäässä, sintraamossa, ferrokromisulatossa ja terässulatossa. Tuotantoketjun lopussa, kylmävalssaamossa, altistuminen oli vähäisintä. Tuotantotyöntekijöiden henkilökohtaiseen altistumiseen vaikutti merkittävästi se, että työajasta noin 85 % vietetään valvomohuoneissa, joissa hiukkasten lukumääräpitoisuudet vastasivat pääsääntöisesti toimistoympäristöissä mitattuja tasoja.

Hitsaushiukkasille altistuminen aiheutti veren hemoglobiini- ja erytrosyyttitasojen laskua sekä leukosyyttien ja neutrofiilisten valkosolujen pitoisuuksien nousua. Altistuminen aiheutti muutoksia myös veren interleukiini-1β- ja E-selektiinipitoisuuksien tasoissa. Keuhkojen toimintakokeissa ei havaittu muutoksia työpaikoilla työpäivän aikana, mutta hitsausaltistuskokeiden jälkeen havaittiin lievää laskua sekä FEV_1- ja PEF-arvoissa.

Ferrokromin ja ruostumattoman teräksen työntekijöiden altistumisen ja tulehdusmarkkereiden välillä ei löydetty yhteyttä, vaikka kromialtistumisen mukaan jaettujen ryhmien tulehdustasot poikkesivatkin hieman toisistaan.

Yhteenvetona voidaan todeta, että hitsaushiukkasille altistuminen aiheuttaa lievää, äkillistä ja koko elimistöä koskevaa tulehdusta mitattuna veren tulehdusmerkkiaineiden muutoksina. Siksi altistumista metalleja sisältäville hiukkasille tulisi vähentää käyttäen työhygieniaa parantavia hallintakeinoja kaikissa työympäristöissä, joissa altistuminen metallihiukkasille on todennäköistä.

Yleinen suomalainen asiasanasto: altistuminen; altisteet; ilman epäpuhtaudet; työympäristö; hiukkaset; pöly; metalliteollisuus; metallit; ruostumaton teräs; ferrokromi; kromi; hitsaus; hitsaajat; levytyö; tulehdus; markkerit; sytokiinit; hemoglobiini; punasolut; valkosolut; interleukiinit; keuhkot; astma

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I express my deepest gratitude to all co-authors. The original articles could not have been completed without their contributions. Special thanks to Paula Kauppi, Jukka Uitti, Markku Huvinen and Anna-Kaisa Viitanen for their untiring encouragement and wise advice during writing the original articles. I wish also to thank Ritva Luukkonen for her guidance in statistical analyses. I also want to thank Paula Jussheikki for her help at the Outokumpu stainless steel factory site and her contribution to particle measurements.

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Kuopio, June 2018
Merja Järvelä

CONTENTS

LIST OF ABBREVIATIONS

BAL	Bronchoalveolar lavage
BLV	Biological limit value
CPC	Condensation particle counter
Cr^{3+}	Trivalent chromium
Cr^{6+}	Hexavalent chromium
CRP	C-reactive protein
DMA	Differential mobility analyzer
EBC	Exhaled breath condensate
EDX	Energy dispersive X-ray analysis
EELS	Electron energy loss signal
EIA	Enzyme immunoassay
ELPI	Electrical low pressure impactor
eNO	Exhaled nitric oxide
ENPs	Engineered nanoparticles
FCAW	Flux cored arc welding
FEV_1	Forced expiratory volume in 1 second
FIOH	Finnish Institute of Occupational Health
GMAW	Gas metal arc welding
HRV	Heart rate variability
HWE	Healthy worker effect
IARC	International Agency for Research on Cancer
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
IL-8	Interleukin 8
IOM	Institute of Occupational Medicine
IHD	Ischemic heart disease
LTB4	Leukotriene B4
MFF	Metal fume fever
MMAW	Manual metal arc welding
MS	Mild steel
NIOSH	National Institute of Occupational Safety and Health
NO	Nitric oxide
OA	Occupational asthma
OEL	Occupational limit value
·OH	Hydroxyl radical
OPC	Optical particle counter
OSHA	Occupational Safety and Health Administration, United States

PEF	Peak expiratory flow
$PM_{2.5}$	Particulate matter smaller than 2.5 μm
PPE	Personal protection equipment
ROS	Reactive oxygen species
RSW	Resistance spot welding
SIMS	Secondary-ion mass spectrometry
SMPS	Scanning mobility particle sizer
SS	Stainless steel
TEM	Transmission electron microscopy
TIG	Tungsten inert gas welding
TNF-α	Tumor necrosis factor alpha
TWA	Time weighted average
UFP	Ultrafine particles

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on data presented in the following articles, referred to by the Roman numerals I–IV.

I Järvelä M, Kauppi P, Tuomi T, Luukkonen R, Lindholm H, Nieminen R, Moilanen E, Hannu T. Inflammatory response to acute exposure to welding fumes during the working day. *Int J Occup Med Environ Health* 26: 220-229, 2013.

II Kauppi P, Järvelä M, Tuomi T, Luukkonen R, Lindholm T, Nieminen R, Moilanen E, Hannu T. Systemic inflammatory responses following welding inhalation challenge test. *Toxicology Reports* 2: 357-364, 2015.

III Järvelä M, Huvinen M, Viitanen AK, Kanerva T, Vanhala E, Uitti J, Koivisto AJ, Junttila S, Luukkonen R, Tuomi T. Characterization of particle exposure in ferrochromium and stainless steel production. *J Occup Environ Hyg* 13: 558-568, 2016.

IV Uitti J, Huvinen M, Kanervo A, Järvelä M, Oksa P, Lehtimäki L, Toivio P, Tuomi T, Moilanen E, Sauni R. Pulmonary inflammation markers in workers exposed to metal dusts and fumes in ferrochromium and stainless steel production. *Submitted 2018*.

AUTHOR'S CONTRIBUTION

The publications in this dissertation are original research papers investigating the exposure of workers to particles and short-term health effects in metal industry.

Studies with welders in workplace and laboratory challenge experiments (Papers I and II): The author designed and conducted the particle measurements. She gathered and processed both exposure and clinical measurement data. She wrote manuscript I and participated in writing manuscript II with significant editorial input from all of the co-authors.

Exposure and clinical study among stainless steel production workers (Papers III and IV): The author participated in developing the study design and conducted the particle exposure measurements with the help of Outokumpu Stainless Ltd's occupational hygienists. She collected and processed the exposure data and conducted the personal particle exposure evaluation. Manuscript III was mainly written by the author. She also participated in the writing of manuscript IV.

1 INTRODUCTION

Airborne dust and particles can be described as aerosols. The term, "aerosol" refers to a suspension of liquid or solid particles in gaseous media, usually in air. The particle size-ranges of aerosols can vary from about 1 nm to more than 100 μm.

Particles are present everywhere; in ambient air as well as in indoor environments (e.g. homes, schools, offices and industrial facilities). Particles are formed via condensation or by mechanical or chemical processes. It is known that exposure to ambient air particles causes adverse health effects (Seaton et al. 1995). Exposure to airborne fine particles ($PM_{2.5}$) is associated with an increased risk of mortality (Dominici et al. 2003) and cardiovascular and pulmonary hospitalizations (Bravo et al. 2016, Lanzinger et al. 2016, Dominici et al. 2006).

In workplace conditions, particle concentrations can be much higher than ambient air levels. Atmospheric aerosol mass concentrations are about 20-200 $\mu g/m^3$ depending on the air pollution level, whereas mass concentrations in polluted industrial environments can reach several milligrams per cubic meter (Kulkarni et al. 2012). However, the association between occupational particle exposure and adverse acute health effects is less evident in comparison to research results obtained from ambient air studies. This may be due to the healthy worker effect (HWE) which refers to the most sensitive and symptomatic individuals opting out of jobs where occupational exposure occurs. An HWE causes better health status of workers relative to the general population.

In the metal industry, workers are exposed to fumes and dusts which contain different sizes of particles; coarse particles (diameter 2.5-10 μm) as well as ultrafine particles (UFP) with diameters smaller than 100 nm. Particles are generated in high temperature processes e.g. in smelting, rolling and welding, as well as in mechanical operations such as cutting and grinding. Metal processing and welding produces aerosols containing metal oxides originating from materials and techniques used in metal alloy production or welding. Metal particles are reported to cause hazardous effects on workers' health and their toxicity may depend on the oxidation state of the metal. For example, both trivalent (Cr^{3+}) and hexavalent (Cr^{6+}) chromium have been shown to exist in workplace air during the manufacture of stainless steel (SS) (Huvinen et al. 1993) and in SS welding operations (Perch et al. 2015, Matczak & Chmielnicka 1993). The mechanisms underpinning the increased health risks attributable to metal particle exposure are not clear, but recent studies suggest that inflammation mediators are associated with many of the health outcomes, e.g. lung illness (Suri et al. 2016) or changes in cardiac autonomic dysfunction indices (Umukoro et al. 2016, Ohlson et al. 2010).

In this thesis, occupational exposure to particles and the acute effects on health in welding, and in ferrochromium and stainless steel production were investigated. The aim was to study short-term inflammatory systemic and pulmonary effects in workplace conditions as well as in a controlled exposure study with welders with

suspected occupational asthma. The clinical study was accomplished by analyzing selected blood inflammation markers and conducting lung function measurements before and after metal particle exposure.

2 LITERATURE REVIEW

2.1 OCCUPATIONAL EXPOSURE TO PARTICLES

2.1.1 Exposure routes

Inhalation is the most relevant route for occupational exposure to particles. After gaining access to the body via either nose or mouth breathing, inhaled particles deposit in the extrathoracic (nasal, pharyngeal, laryngeal), tracheobronchial and alveolar regions of the respiratory tract (Figure 1). The regional deposition efficiency depends mostly on the particle size and shape as well as the effective density. Ultrafine particles are effectively deposited in all respiratory tract regions due to their high diffusion properties whereas larger particles remain in the upper airways (ICRP 1994, Oberdörster et al. 2005).

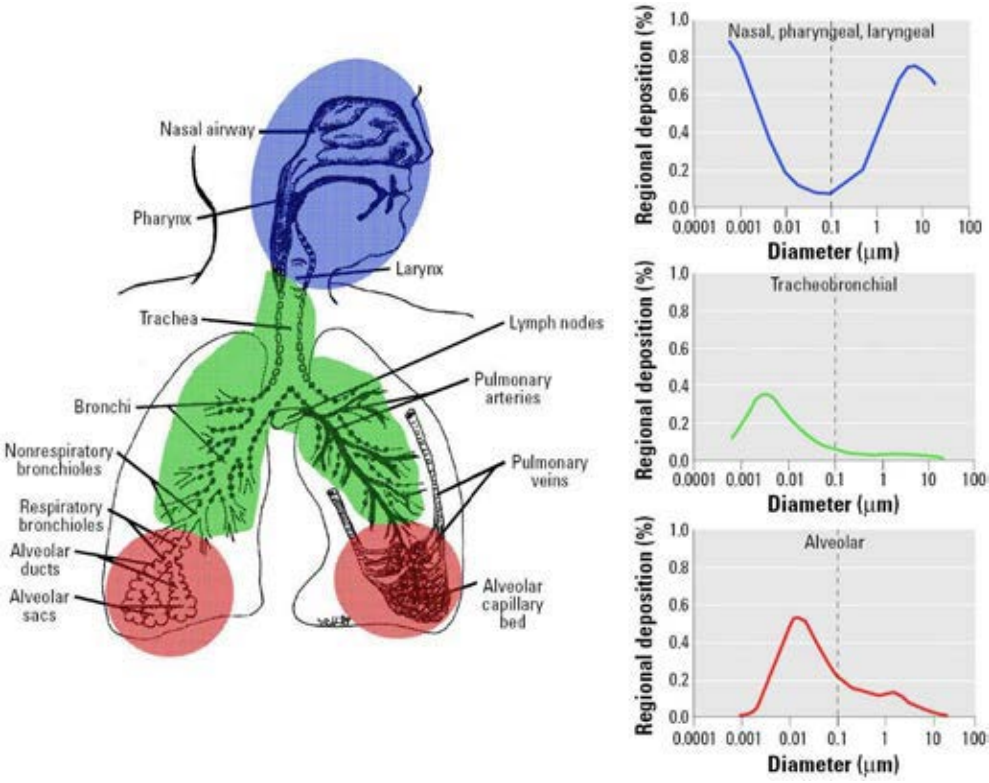

Figure 1. Predicted fractional deposition of inhaled particles in the nasopharyngeal, tracheobronchial, and alveolar region of the human respiratory tract during nose breathing. (Reproduced from Oberdörster et al. (2005). Copyright Environmental Health Perspectives).

Furthermore, particle exposure may occur via either the gastrointestinal (GI) tract or the skin. Particles initially inhaled and then cleared by mucociliary movement, can be swallowed and gain access to the GI tract. There is growing concern that ingested particles increase the risk of toxicity and carcinogenicity to the internal organs (Kim et al. 2014). Dermal exposure and particle penetration through the epidermal barrier have been topics of interest for the last decade since manufacturing and use of engineered nanoparticles (ENPs) have expanded considerably. In particular, the safety of cosmetic products containing ENPs (e.g. sunscreens) has been a cause of concern (McSweeney 2016). According to our current knowledge, the significance of particle exposure via the dermal route is less important than that of inhalation exposure even for the smallest, nanosized particles (Landsiedel el al. 2012). However, there is evidence that the penetration of nano-sized metal oxide particles can become elevated through injured and atopic skin (Ilves et al. 2014).

The respiratory system can clear deposited solid particles by physical and chemial processes. Physical clearance mechanisms include mucociliary movement, macrophage phagocytosis and epithelial endocytosis. Chemical clearance processes can clear biosoluble particle components via dissolution, leaching and protein binding (Oberdörster et al. 2005).

Deposited particles can be translocated to secondary organs via the lymphatic and blood circulation and sensory neurons (Balasubramanian et al. 2013). There are some studies indicating that nanosized metal particles deposited in the olfactory region of the nose can migrate to the brain along the olfactory nerve (Hopkins et al. 2014, Balasubramanian et al. 2013, Oberdörster et al. 2004). Apart from nervous system translocation, inhalation studies with animal experiments have revealed particle translocation to cardiovascular and digestive systems as well as to internal organs like spleen, kidneys and liver (Balasubramanian et al. 2013). However, at the moment, the biological significance of particle translocation via the nervous, cardiovascular or digestive routes is far from clear.

2.1.2 Exposure measurements

Particle measurements are needed to quantify and qualify occupational exposure and to monitor emissions from different indutrial processes. Workplace risk assessment and compliance with regulations can be based on exposure measurement data. European standard EN 481 defines sampling protocols for three particle size fractions according to their deposition properties: inhalable, thoracic and respirable fractions (European Standardization Committee 1993) (Figure 2). Thus, measurements conducted with instruments in accordance with the standard will ensure the best association between concentrations and impacts on human health.

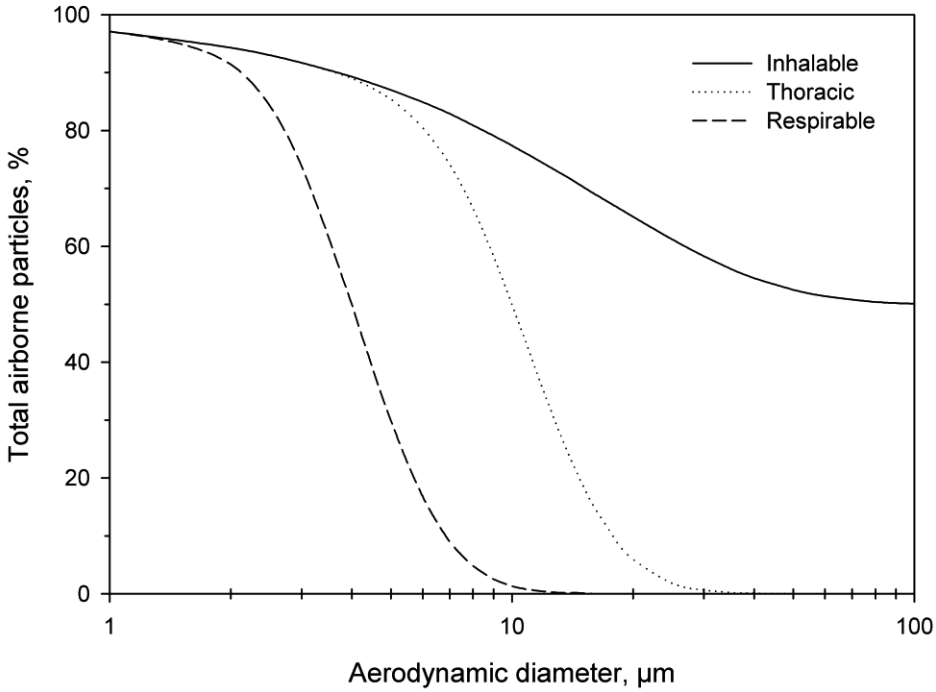

Figure 2. Particle fraction conventions as percentages of total airborne particles according to EN 481 Standard (European Standardization Committee 1993).

Mass concentration is the most commonly measured parameter when assessing particle exposure. Mass concentration refers to the particle mass in a unit volume of air, typically represented in mg/m^3 or µg/m^3 (Hinds 2012). Number concentration, i.e. particles/cm^3, is another common way to express particle concentration in both ambient and workplace air. Furthermore, particle size distributions and chemical composition have been exploited to characterize particle exposure. Particles can be chemically homogeneous or they can contain a variety of elements and chemical compounds (Kulkarni et al. 2011) and furthermore they can vary in their primary shape, ranging from equidimensional to fibres and plates or other irregular forms as well as existing as singlets, aggregates and their agglomerates. The most common particle measurement techniques used in occupational environments are described briefly below and listed in Table 1.

When evaluating workers' exposure to particles, measurements are generally conducted using filter sampling methods; these tend to measure size-selective mass concentrations, such as respirable and inhalable dust or total suspended particulate matter. This is due to the fact that filter sampling allows personal exposure assessment, and that health-based occupational exposure limit values (OELs) to

workplace dusts are defined in mass concentrations. Particles are collected on filters using a size-selective sampling head, e.g., a cyclone, connected to a pump that controls the volume sampling rate. The filter materials used in occupational exposure measurements are typically glass or quartz fibers and cellulose nitrate or acetate membranes. Sampled particles can be analyzed gravimetrically and chemically, and individual particles can be analyzed with different forms of electron microscopy and spectroscopy to examine particle size, structure and shape (Kulkarni & Baron 2011). There are two common electron imaging methods 1) transmission electron microscopy (TEM) and 2) scanning electron microscopy (SEM). TEM is suitable for imaging particles smaller than 0.5 mm in diameter since the image is formed by electrons that pass through the sample. The image is observed on a phosphor screen, typically at magnifications ranging from 1000 to about 1 000 000 times. With SEM, the particle sample can be observed at magnifications from 10 times up to about 100 000 times. SEM uses a focused electron beam that is rastered over the sample area. The beam's position is combined with the detected signal to form an image that is recorded digitally (Fletcher et al. 2011). Furthermore, individual particles can be analyzed using energy dispersive X-ray analysis (EDX) to obtain information about the elemental composition of the particles. In addition, there are other in situ identification analyses available, for example, electron energy loss signal (EELS) and secondary-ion mass spectrometry (SIMS).

Optical particle measurement techniques are widely used in occupational dust measurements. An optical particle counter (OPC) measures the size and number concentration of particles and the technique is based on the light scattering attributable to single particles. First, a stream of aerosol is drawn through a light beam. Next, the light scattered from the single particles is detected by a photodetector and converted into electrical pulses. Particle number is determined by counting the pulses of scattered light reaching the detector and the particle size is derived from the height of the electrical pulses (Sorensen et al. 2011). The particle mass concentration cannot be accurately assessed by a number measurement due to the different density of particles with diverse compositions. There are commercially available particle measurement instruments based on optical detection e.g. DustTrak™ models 8530 and 8532, Optical Particle Sizer model 3330 (TSI Incorporation, USA) and Aerosol spectrometer 11-A (Grimm Aerosol Technik, Germany). SidePak™ (TSI Inc., USA) is an OPC that is suitable for personal particle mass measurement. In addition, real-time aerodynamic measurements of particles from 0.5 to 20 μm can be measured with TSI Aerodynamic Particle Sizer 3321 (APS™ spectrometer).

Particles smaller than 0.1 μm that are optically difficult to measure, can be measured by either growing the particles after their condensation or by measuring the mobility of the particles in an electric field. The operating theory behind condensation particle counters (CPCs) is based on the supersaturation of condensing fluid (water or alcohol) to enlarge particles by condensation of vapors to a size that can be detected optically (Cheng 2011). CPCs' detection limits vary depending on the

instrument, ranging from 2.5 to 10 nm, and they can measure particles up to 3 µm. The particle size distribution is obtained using a differential mobility analyzer (DMA) in parallel with CPC. Commercial instruments for particle number size distribution measurements are TSI's SMPS 3938 (scanning mobility particle sizer) and Grimm's SMPS+C.

Cascade impactors are also used for measuring particle number concentrations and number size distributions. The measurement principle is based on the particle's inertia, which is used in the classification of particles. The electrical low pressure impactor (ELPI; Dekati Ltd., Finland) is one type of cascade impartors where particles are first charged in a unipolar diffusion charger and then classified according to their size in a cascade impactor and finally the collected particles are measured electrically (Järvinen et al. 2014, Keskinen et al. 1992). ELPI is suitable for stationary sampling, but also personal samplers based on inertial sizing are available (Marple & Olson 2011). For example, the Sioutas Cascade Impactor (SKC Inc., USA) and the Marple Personal Cascade Impactor (Thermo Scientific, USA) are commercially available personal cascade impactors.

Table 1. Instruments used for measuring occupational particle exposure.

Measurement method	**Instrument**	**Real time (R), off-line (O), particle mass (M), particle number (N)**	**Personal (P) / stationery (S) sampling**	**Cut point D_{50} / size range**
Filter sampling; mass concentration	IOM-sampler, IOM with MultiDust foam discs, Total dust-sampler, SKC Respirable Cyclone	O, M	P, S	IOM: D_{50} 100 µm, with MultiDust 4 µm SKC Respirable Cyclone: D_{50} 4 µm
particle characterization	Electrostatic precipitator + TEM/EDX	O		
Optical detection	OPC	R, M, N	S	0.1 – 30 µm
Condensation, optical detection	CPC	R, N	S	2.5 nm – 3 µm
Electrical mobility	SMPS	R, N	S	1 nm – 1 µm
Inertial classification	ELPI	R, N	S	6 nm – 10 µm

TEM/EDX = Transmission electron microscopy/energy dispersive X-ray analysis; OPC = optical particle counter; CPC = condensation particle counter; SMPS = scanning mobility particle sizer; ELPI = electrical low pressure impactor

2.1.3 Occupational exposure limit values (OELs)

In Finland, the health-based occupational exposure limit value for the 8-hour time weighted average (TWA) concentration of inorganic dust is 10 mg/m^3 (Ministry of Social Affairs and Health, Finland 2016). An OEL is provided for inhalable dust as defined in EN 481 (European Standardization Committee 1993). OELs and reference values as 8-hour TWA in different countries for inhalable and respirable fractions and for some metal components in the respirable fraction are presented in Table 2.

The Finnish OEL for trivalent chromium (Cr^{3+}) is 0.5 mg/m^3; for hexavalent chromium (Cr^{6+}), it is 0.005 mg/m^3. The exposure limit value for Cr^{6+} is the same in Sweden and USA (IFA 2016). Workers' exposure to Cr^{6+} can also be determined by measuring the chromium content of their urine samples. The biological limit value (BLV) for Cr^{6+} is 0.2 μmol/l in Finland (Ministry of Social Affairs and Health, Finland 2016).

Furthermore, Finnish OELs for iron and zinc in fumes are 5 mg/m^3 and 2 mg/m^3, respectively (Ministry of Social Affairs and Health, Finland 2016). Values are in concordance with OELs of other European countries, where the limit values for iron in fumes or in respirable dust vary from 3.5 to 6 mg/m^3 and for zinc from 2.0 to 5 mg/m^3 (IFA 2016). Finland and Germany have both an OEL value of 0.02 mg/m^3 for manganese in the respirable dust fraction (Ministry of Social Affairs and Health, Finland 2016, IFA 2016).

Table 2. Occupational exposure limit values in different countries for inhalable and respirable particle fractions and for some metals.

Country	Fraction, dust/component	8 h-TWA, mg/m^3	15 min TWA, mg/m^3	Reference
Finland	Inhalable, inorganic dust	10	-	Ministry of Social Affairs and Health, Finland 2016
	Inhalable, organic dust	5	10	
	Inhalable, trivalent chromium	0.5	-	
	Inhalable, hexavalent chromium	0.005	-	
Austria	Inhalable dust	10	20	IFA 2016
	Respirable dust	5	10	
	Inhalable, copper	1	-	
Belgium	Inhalable dust	10	-	IFA 2016
	Respirable dust	3	-	
France	Inhalable dust	10	-	INRS 2016
	Respirable dust	5	-	
Germany	Inhalable dust	4	-	DFG 2012b
	Respirable, insoluble particulates	0.3[2]	2.4	DFG 2012a
	Respirable aerosol, manganese	0.02	0.16	DFG 2012b
Sweden	Inhalable, inorganic dust	10	-	AFS 2015:7
	Respirable, inorganic dust	5	-	
	Total aerosol, hexavalent Cr	0.005	-	
USA (OSHA)	Inhalable dust	15	-	OSHA 2018
	Respirable dust	5	-	
	Inhalable, hexavalent chromium	0.005	-	

[1]for dusts with a density of 1 g/cm³

2.2 PARTICLE EXPOSURE IN METAL INDUSTRY

In Finland, there are about 110 000 workers employed in the metal processing industry as well as in the manufacturing of metal products and transport equipments (Statistics Finland 2012). The metal processing industry comprises smelting and refining processes of metal ores and scrap metal to obtain pure metals. In addition, fabrication processes include sintering, casting, hot and cold forging and cutting operations. The metal working industries processs metals in order to manufacture machine components and machinery as well as a variety of instruments and tools for different sectors of the economy (ILO 2016).

2.2.1 Particle exposure in welding

Welding is a process in which metal pieces are joined together; it is a widely used technique in the metal working industy. Welding processes can be divided into different categories, with the two most ubiquitous being arc and gas welding techniques. The most common types of arc welding processes are 1) manual metal arc welding (MMAW; also called shielded metal arc welding, SMAW), 2) gas metal arc welding (GMAW) 3) tungsten inert gas welding (TIG) and 4) flux cored arc welding (FCAW) (Antonini 2003). About 6 900 welders (including gas cutting workers) are employed in Finland (Statistics Finland 2014), and it is estimated that there are at least 2 000 000 welders worldwide (NIOSH 1998).

Welders work in different environments outdoors and indoors in open or confined spaces, in high construction sites, sometimes even underwater. Welding is often conducted in conditions with poor ventilation such as ship hulls, metal tanks, or narrow pipes leading to a greater potential for exposure. Welding fumes are complex mixtures of gases and particles consisting of metal oxides, silicates and fluorides. Aerosols are formed primarily through the nucleation of metal vapors followed by condensation and coagulation processes. The composition of the fumes is variable according to which metals and coatings (e.g. zinc and other metal coatings, oil films and paints) are being used. In addition, the type of the rod and stick influences the formed fume content and exposure levels (Palmer & Eaton 2003, Wallace et al. 2001, Zimmer & Biswas 2001). The most common metal components in welding fumes include chromium, nickel, iron, manganese, zinc and silica. Fumes generated from mild steel (MS) electrodes contain usually more than 80 % iron and manganese 1-15 % but no chromium or nickel. Stainless steel (SS) welding fumes consists of approximately 20 % chromium and 10 % nickel in addition to iron and manganese (Antonini at al. 2004). In addition to the fumes, welding produces gaseous byproducts such as carbon dioxide, carbon monoxide, nitrogen oxides and ozone. The physical hazards of welding include ultraviolet and infrared radiation, heat, noise and vibration (Antonini 2003).

Workers are often exposed to particles which have been formed nearby, i.e. in cutting, grinding and drilling operations, and welding is not the only source of particle exposure. For this reason, in many cases, particle concentration values measured in real workplace conditions contain particles from other sources in addition to those produced during welding. Nevertheless, welding can generate very high fume concentrations; these can be as high as several hundred mg/m^3 just above the arc (Ulfvarson 1981). The recent study of Cena et al. (2016) reported that the average mass concentration in a welding fume near to the arc was 45 mg/m^3 which declined to 9 mg/m^3 at two meter distance from the source. The typical worker's breathing zone concentration range from 1 to 5 mg/m^3 depending the welding methods and materials used, ventilation and the volume of the space where the welding was being performed (Antonini et al. 2004, Buonanno et al. 2011). In addition, repeated exposure studies have shown that exposure variations in an individual welder can be high (Hedmer et al. 2014). For example, workers' individual work practices can influence exposure levels between welders.

In the study of Elihn and Berg (2009), the particle number concentrations measured in metal plants where MIG, MAG and spot welding were being operated ranged from 30 to 100 × 10^3 cm^{-3}. The measured peak concentration was 267 × 10^3 cm^{-3}. Buonanno et al. (2011) detected a high particle concentration (800 × 10^3 cm^{-3}) in a welding shop where a general ventilation system was lacking.

The particle number size distribution of welding fumes is typically bi- or multimodal (Moroni & Viti 2009, Zimmer & Bisvas 2001), although a unimodal number size distribution has also been reported in a workplace study of Elihn et al. (2011). The welding technique can influence the size of the aerosols generated during welding. Zimmer and Biswas (2001) observed that GMAW generated smaller individual particles than FGAW. They also noticed that as the sample height increased, the modes of the multi-modal distributions shifted towards larger particle sizes. Measurements in workplace conditions have revealed that the welding fume particles in the breathing zone are 0.5-2.0 μm in aerodynamic diameter (Hedmer et al. 2014, Moroni & Viti 2009, Antonini et al. 2004), although also smaller particles have been reported to predominate. Elihn et al. (2011) reported a mean particle size in the range 0.2-0.5 μm in a manufacturing plant undertaking welding and laser cutting of steel. According to Antonini (2006) and Dasch & D'Arcy (2008), ultrafine particles mass account for 5-10 % of welding fume particles. However, Elihn and Berg (2009) observed a much higher UFP fraction in welding operations: 26-59 % of all particles measured with SMPS were in the ultrafine size range. Table 3 provides a list of workers' particle exposure levels measured in welding shops.

2.2.2 Particle exposure in ferrochromium and stainless steel production

Stainless steel manufacturing comprises several stages starting from the mining of the ore, proceeding to pelletizing and sintering processes, and after that, to steel

melting, casting and grinding phases and finally to hot and cold rolling, where SS strips are formed. The process is described in more detail in Paper III and in Huvinen 2002. Stainless steel is widely used in many applications of industry, construction and infrastructure. In homes, SS can be found in cooking utensils due to its safe, durable and easy-to-care properties.

Occupational particle exposure data from workers manufacturing SS is much more limited as compared to welding. In particular, there is virtually no data on steel workers' exposure to particle number concentrations. For example, in a Finnish study, SS workers' personal exposure to total particle mass concentrations was 1.5 mg/m^3 in a ferrochromium smelter, 1.8 mg/m^3 in a stainless steel melting shop and 0.3–0.5 mg/m^3 in cold rolling (Huvinen et al. 1993). Johnsen and her colleagues (2008) studied dust exposure in smelters among two different production groups: 1) ferrosilicon and 2) other ferroalloys (ferrochrome, silicomanganese and ferromanganese) smelters. They reported that in group 2 smelters, the average total dust exposure was 2.4, 2.0 and 11.6 mg/m^3 in the furnace house, electrode and sintering plant, respectively.

Table 3. Occupational exposure to welding fumes. Different welding methods, materials and measurement instrumentation and protocols were used in the studies.

Workplace and settings	Methods	Mass concentration, mg/m^3	Particle number concentration, cm^{-3}	Workplace conditions and use of respiratory protection	Reference
24 welders in a welding school, MMAW, TIG welding, and laser cutting, grinding operations	Personal exposure to $PM_{2.5}$	Median 1.69			Kim et al. 2005
26 boilermakers, MMAW welding	Personal exposure to $PM_{2.5}$	Median 8h TWA 0.39 (range 0.03-2.62)		Local exhaust ventilation	Fang et al. 2010
16 workers at two mechanical workshops: plant A) welding and laser cutting, plant B) welding and grinding	Personal exposure measurements with 25 mm open-face cassette and filter	Plant A) AM 1.1 Plant B) AM 0.49		Few subjects used respiratory protection. Plant A: Bad general ventilation in welding area, local exhaust ventilation in laser cutting. Plant B: Good general ventilation	Ohlson et al. 2010
241 stainless steel welders, different welding techniques	Personal exposure measurements. Inhalable particles: German sampler GSP 3.5; respirable particles: PGP-EA sampler	Median exposure to respirable particles: GMAW 1.64; FCAW 6.87; TIG <0.42; MMAW <0.50 Median exposure to inhalable particles: GMAW 2.71; FCAW 6.24; TIG <0.58; MMAW 0.82		Local exhaust ventilation in all companies. Of the participants, 11 % used powered air purifying respirators, 20 % dust masks, and 69 % did not use respiratory protection	Weiss et al. 2013
101 welders from 10 medium size companies producing e.g. heavy vehicles, lifting tables, stoves, heating boilers and pumps	Personal exposure measurements with 37 mm cassette with respirable dust cyclone	Median exposure 1.1			Li et al. 2015

Table 3. Continued.

Workplace and settings	Methods	Mass concentration, mg/m^3	Particle number concentration, cm^{-3}	Workplace conditions and use of respiratory protection	Reference
108 welders in 11 medium sized companies operating mild steel welding	Personal exposure measurements to respirable dust with 37 mm cassette and filter	AM: 2.3 (range 0.1-38.3)		General ventilation in all companies. Some of the participants used respiratory protection, but measurements were conducted outside.	Hedmer et al. 2014
45 male boilermakers, mainly MMAG and GMAW	Personal $PM_{2.5}$ concentrations using DustTrak Aerosol Monitor, TSI	Mean $PM_{2.5}$ 0.35 (range 0.01-2.96)			Umukoro et al. 2016
241 welders, 25 companies (5 shipyards, 13 manufacturers of containers and vessels, 4 manufacturers of machines and tools), different welding techniques	Personal exposure measurements. Inhalable particles: German sampler GSP 3.5; respirable particles: PGP-EA sampler Static measurements of particle number concentrations: SMPS, TSI Inc.	Median exposure to inhalable particles: GMAW 3.65; FCAW 8.02; TIG <0.58 Median exposure to respirable particles: GMAW 2.08; FCAW 7.11; TIG <0.42	GMAW 127 × 10^3; FCAW 122 × 10^3; TIG 151 × 10^3	Local exhaust ventilation in all companies. Of the participants, 11 % used powered air purifying respirators, 20 % dust masks, and 69 % did not use respiratory protection	Lehnert et al. 2012
Three automotive plants, RSW, MIG and TIG welding of aluminum and steel	Static $PM_{2.5}$ mass and particle number concentrations	The highest $PM_{2.5}$ in MIG welding of aluminum 0.25 and in RSW steel welding 0.25	RSW aluminum welding: mean 72 × 10^3, max. 130 × 10^3 RSW steel welding: mean 67 × 10^3, max. 170 × 10^3	Recirculating general ventilation, local exhaust ventilation in steel and aluminum MIG/TIG welding locations	Dasch & D'Arcy 2008
Two mechanical workshops: plant A) MIG and MAG welding and laser cutting, plant B) spot welding and grinding	Static particle mass sampling with MOUDI, MSP Corp. and calculation of PM10 from the MOUDI data; particle number sampling with P-Trak, TSI Inc.	Plant A) PM10: 1.00 Plant B) PM10: 0.4	Plant A) 69 × 10^3 Plant B) 33 × 10^3	Plant A: Bad general ventilation in welding area, local exhaust ventilation in laser cutting. Plant B: Good general ventilation	Elihn & Berg 2009

Table 3. Continued.

Two mechanical workshops: plant A) welding and laser cutting, plant B) welding and grinding	Static sampling with SMPS, TSI Inc.	Plant A) AM 1.29. Plant B) AM 0.61.	Plant A) 78 × 10^3 Plant B) 64 × 10^3	Plant A: Bad general ventilation in welding area, local exhaust ventilation in laser cutting. Plant B: Good general ventilation	Elihn et al. 2011
Three automotive plants, different welding techniques.	Static sampling with CPC 3775 and 3781, TSI Inc.		Plant A) Mean concentration in GMAW: 96 × 10^3, max. conc. 800 × 10^3 Plant B) max. conc. 200 × 10^3 Plant C) max. conc., 200 × 10^3	Plant A: Lack of general ventilation system in In some welding locations, local exhaust ventilation assembled Plant B: Local exhaust and general ventilation Plant C: Local exhaust and general ventilation	Buonanno et al. 2011
Mechanical engineering factory, TIG welding	Static measurements of inhalable, thoracic and respirable fractions with Grimm 1.109 Aerosol Spectrometer, UFP measurements with Grimm portable NanoCheck 1.320, total particle number measurements with ELPI, Dekati Ltd.	Inhalable particles: AM 0.34. Thoracic particles: AM 0.22. Respirable particles: AM 0.11.	UFP: 38 × 10^3 Total particles: 64 × 10^3	Local exhaust ventilation	Iavicoli et al. 2013

UFP= ultrafine particles; $PM_{2.5}$ = particulate matter smaller than 2.5 μm; AM = arithmetic mean

2.3 HEALTH EFFECTS ASSOCIATED WITH PARTICLE EXPOSURE IN WELDING AND STAINLESS STEEL INDUSTRY

Particle size, chemical composition, and particle concentration are the primary health outcome determinants associated with particle exposure. However, the underlying mechanisms responsible for the adverse health outcomes are not precisely known. It has been suggested that even short-term exposure to metal particles can induce systemic inflammation which may display an association with lung function changes and chronic pulmonary diseases (Sobaszek et al. 2000, Fireman et al. 2008) or cardiovascular diseases (Sjögren et al. 2002, Fang et al. 2010). The current understanding of the mechanisms and health effects following particle exposure in welding and in stainless steel production will be described in the following paragraphs.

2.3.1 Oxidative stress and inflammation

Reactive oxygen species, cytokines and exhaled nitric oxide

Inflammation is involved in most of the adverse health effects associated with particle exposure in metal workers. Fumes and aerosols containing metals can induce local inflammation in lung tissue; at the biochemical level, they evoke lipid peroxidation in cell membranes and oxidative damage to the genome (Taylor et al. 2003, Antonini et al. 2005, Leonard at al. 2010). Free radical activity and oxidative stress following generation of reactive oxygen species (ROS) are postulated to have a role in mediating many health effects. Free radicals are species that contain one or more unpaired electrons (Bayr 2005). ROS can be either harmful or beneficial to living organisms. The harmful effects include damage to cellular lipids, proteins, or DNA, leading to an inhibition of their normal function (Valko et al. 2007). The negative effects of ROS have been associated with several diseases, such as asthma (Henricks & Nijkamp 2001), cardiovascular disease (Watson et al. 2008), cancer (Valko et al. 2006) and diabetes (Houstis et al. 2006). On the other hand, at physiological concentrations, ROS are important biological signaling molecules that induce therapeutic and protective effects against diseases (Valko et al. 2007).

Cytokines are low-molecular-weight proteins that regulate the intensity and duration of the immune response and inflammation. Cytokines can be either 1) proinflammatory and act to make a disease worse at the same time while strengthening the body's defense response or 2) anti-inflammatory to reduce inflammation and promote healing (Dinarello 2000). Proinflammatory cytokines, such as interleukin (IL)-1β, IL-6 and TNF-α, are produced mainly by activated macrophages. Selected inflammation markers, which are relevant to this study, and their role in inflammation are listed in Table 4.

Nitric oxide (NO) is a gaseous mediator that regulates many physiological processes including immune responses and inflammation. Exhaled NO (eNO) can be reliably and non-invasively measured as a way of assessing lung inflammation

(Kharitonov & Barnes 2006). Several studies have confirmed that the concentration of eNO is elevated in the airways of patients with asthma (Alving et al. 1993, Kharitonov et al. 1994).

Table 4. Selected cytokines and inflammation markers and their function.

Cytokine/ inflammation marker	Description and function	Reference
8-isoprostane	Marker of oxidative stress formed by free-radical-catalyzed lipid peroxidation of arachidonic acid and cell membrane phospholipids.	Morrow & Roberts 1996
Adiponectin	Hormone of adipocyte origin that is involved in the control of circulating glucose and involved in regulating glucose and lipid levels.	Lee & Shao 2014
Adipsin	An enzyme that is secreted by adipocytes into the bloodstream and is involved in the suppression of infection.	Cook et al. 1987
CRP	C-reactive protein, synthesized by the liver. The CRP levels is largely regulated by circulating levels of IL-6. The concentration of CRP in serum is increased in response to inflammation.	Ridker 2016
E-selectin	An endothelial adhesion molecule that is rapidly induced by inflammatory cytokines such as IL-1 and TNF-α.	Kansas 1996
ET-1	Endothelin-1 is a peptide of 21 amino acids produced by the endothelial cells of arteries. ET-1 has a strong arterial tightening (vasoconstrictor) function. It also induces mitosis in cells.	Davenport et al. 2016
IL-1β	Interleukin 1 beta, a proinflammatory cytokine, important member of IL-1 superfamily. IL-1β is made mainly by macrophages and monocytes but also by nonimmune cells, such as fibroblasts and endothelial cells. IL-1β helps lymphocytes fight infections. It also helps leukocytes pass through blood vessel walls to sites of infection and causes fever by affecting areas of the brain that control body temperature.	Arango Duque & Descoteaux 2014
IL-6	Interleukin 6 is a proinflammatory cytokine, and an important mediator of the acute inflammatory response. IL-6 is secreted mainly by monocytes/macrophages, and T and B cells. IL-6 can induce maturation of megakaryocytes, resulting in an increase in platelets.	Kishimoto et al. 1992
IL-8	Interleukin-8 is synthesized in liver and in lung epithelial cells. IL-8 attracts and activates neutrophils in inflammatory regions.	Bickel 1993
LTB4	Leukotriene B4 is a proinflammatory lipid mediator synthesized in myeloid cells from arachidonic acid. LTB4 induces recruitment and activation of neutrophils, monocytes and eosinophils, and stimulates the production of proinflammatory cytokines and mediators.	Crooks & Stockley 1998
ROS	Free radicals, products of cellular metabolism, that may also be chemicals or particles-induced. ROS defend cells against infectious agents and participate in cellular signaling systems. Overproduction of ROS causes oxidative stress, which may damage DNA, RNA, and proteins, and cause cell death. Types of ROS: superoxide ($\cdot O2^-$), hydrogen peroxide (H_2O_2), hydroxyl radical ($\cdot OH$), hydroxyl ion (OH^-).	Valko et al. 2007
TNF-α	Tumor necrosis factor alpha, a proinflammatory cytokine. Important mediator of the acute inflammatory response. TNF-α stimulates the release of IL-6 and IL-8, and recruitment of neutrophils and monocytes to infection sites. TNF-α is an inducer of endothelial adhesion molecules.	Beutler 1999

Inflammation associated with exposure to metal particles

Local and systemic inflammation is a putative mediator of the adverse health outcomes associated with metal particle exposure. Changes in inflammation markers have been investigated and found both *in vitro* (Pascal & Tessier 2004, Leonard et al. 2010) and *in vivo* (Taylor et al. 2003, Dierschke et al. 2017).

Oxidative stress may be an intermediate step linking the exposure to welding fumes with adverse health outcomes (Li et al. 2004, Han et al. 2005). The *in vitro* exposure study of Leonard et al. (2010) observed intense free radical generation in cells exposed to SS and MS fumes collected one hour prior to exposure. Hydroxyl radical (·OH) generation was much lower when cells were exposed to aged fumes i.e. fumes that had been collected one day or one week before exposure. The study showed that both SS and MS welding fumes were able to generate ROS and ROS-related damage. However, SS fumes had a significantly higher capacity to generate hydroxyl radicals than an equal mass of mild steel fumes (Leonard et al. 2010).

Graczyk et al. (2016) conducted a human exposure study where twenty non-smoking subjects were exposed to TIG welding fumes for 60 minutes. They reported significant increases in oxidative stress biomarkers in urine and plasma samples after three hours of exposure. They also observed that when the exposure to the particle number concentration increased, the level of one oxidative stress biomarker (plasma-8-hydroxy-2'-deoxyguanosine) increased. The study group concluded that additional exposure metrics such as particle number concentration should be recommended for occupational risk assessment in addition to mass measurements (Graczyk et al. 2016).

In a human exposure study conducted by Hartman et al. (2014), inhalation of fumes from MIG brazing of zinc-coated steel caused a significant increase in the levels of high-sensitivity CRP inducing a slight systemic inflammation reaction. Similarly, Markert et al. (2016) exposed healthy male subjects on one day to zinc containing welding fumes, on one day to copper containing welding fumes, and on one day to both zinc and copper containing welding fumes. The concentration of blood CRP was analysed directly after the exposure tests as well as 24 hours thereafter. They found that exposure to zinc as well as copper containing welding fumes were able to increase the CRP level 24 hours after the exposure and there was evidence of asymptomatic inflammation in the exposed subjects. Both zinc and copper containing welding fumes resulted in the same effect (Markert et al. 2016).

In the welding workplace study of Ohlson et al. (2010), blood inflammation markers (IL-6, CRP, fibrinogen) were measured before and after the first work shift after the summer holidays. In addition, two samples were taken after the shift on the following days. It was reported that the levels of IL-6 increased by over 50 % after the first work shift. In contrast, the CRP level did not increase after the first work shift but there was a 17 % elevation after the second shift (Ohlson et al. 2010). In the welding fume exposure study of Baumann et al. (2016), blood IL-6 and CRP levels increased after the 6-hour exposures. The IL-6 level peaked at 10 hours after the exposure while highest CRP levels were measured 29 hours after the fume exposure.

However, contradictory results of welding fume exposure and IL-6 and CRP concentrations have also been reported (Palmer et al, 2006, Scharrer et al. 2007).

2.3.2 Pulmonary effects

The pulmonary health effects of welding fume exposure have been studied and reviewed extensively (Sferlazza & Beckett 1991, Martin et al. 1997, Antonini 2003, Antonini et al. 2003, Antonini et al. 2004, Cosgrove 2015). Metal fume fever (MFF) is the most frequent acute respiratory outcome encountered in welders (Antonini 2003). MFF is an influenza-like reaction consisting of fever, chills, dyspnea, headache, myalgia and malaise (Mueller & Seger 1985, Nemery 1990, Kaye et al. 2002, Rehman 2013). Other features include cough, thirst, a metallic taste, salivation, and a neutrophil leukocytosis. The illness is most commonly induced by inhalation of zinc oxide fumes from galvanised (zink coated) steel or brass welding (Gordon & Fine 1993, Barceloux 1999, Kaye et al. 2002).

Early experiments conducted a few decades ago have detected a small acute decline in lung function during welding work (Akbar-Khanzadeh 1993, Keimig et al. 1983), although that effect has not been observed in all studies (Akesson & Skerfving 1985). In longitudinal studies of welders, a decline in lung function has been observed (Chinn et al. 1990, Wolf et al. 1997), and this effect was also found in nonsmoking welders (Hjortberg et al. 1992, Meo et al. 2003). Furthermore, several studies have indicated that welders have an increased risk of developing several respiratory diseases, such as rhinitis (Castano & Suarthana 2014), bronchitis (Sferlazza & Beckett 1991, Contreras & Chan-Yeaung 1997, Bradshaw et al. 1998, Erkinjuntti-Pekkanen et al. 1999, Lillienberg et al. 2008), and asthma (Wang et al. 1994). In addition, pneumococcal pneumonia (Coggon et al. 1994, Palmer at al. 2009, Wong et al. 2010) has been reported among welders, but the mechanism for this association is not totally understood. A recent *in vitro* study suggested that pneumonia would in part be mediated by the capacity of welding fumes to increase platelet-activating factor receptor dependent pneumococcal adhesion and infection of lower airway cells (Suri et al. 2016). In England, the Department of Health has recommended that welders should receive a single dose of the pneumococcal vaccine to prevent pneumonia (Palmer & Cosgove 2012). In addition to many respiratory diseases, there is growing evidence that there is an association between steel welding fume exposure and fibrosis (Cosgrove 2015).

The increased risk of welders to develop asthma has been described in population based studies (Karjalainen et al. 2002, Storaas et. al 2015) as well as in epidemiological settings (Wang et al. 1994, Beach et al. 1996) and in case studies. The case studies have indicated that occupational asthma (OA) would be related principally to SS welding (Keskinen et al. 1980, Hannu et al. 2005, Hannu et al. 2007), although OA following MS welding has also been reported (Vandenplas et al. 1995).

Furthermore, there is evidence that welding of other metals, such as aluminium, can also cause OA (Vandenplas et al. 1998).

Long-term respiratory health effects have not been observed in previous studies investigating Finnish ferrochromium and stainless steel production (Huvinen et al. 1996, Huvinen et al. 2002). An American longitudinal study showed that pulmonary function in steelworkers, as measured by FEV_1, decreased over the working years but particle exposure did not alone explain the FEV_1 decline. A history of allergy, trauma and pneumonia as well as aging and weight gain were reported to contribute to the decline in the workers' lung function values (Banks et al. 1999).

2.3.3 Cardiovascular effects

The term cardiovascular refers to the heart and blood circulation. Blood inflammation markers have been discussed mainly in paragraph 2.3.1. Welders have an increased risk of morbidity and mortality from ischemic heart disease (IHD) (Moulin et al. 1993, Hilt et al. 1999, Sjögren et al. 2002). An increased cardiovascular mortality has also been reported among stainless steel production workers (Cappeletti et al. 2016), although the evidence is not as consistent as among welders. An epidemiologic study of Finnish ferrochromium and stainless steel workers' cause-specific mortality revealed that mortality from diseases of the circulatory system, in particular from IHD, was significantly decreased compared to population mortality rates of the same region (Huvinen & Pukkala 2016).

Oxidative stress has been implicated as one of the possible mechanisms for the cardiovascular effects of particle exposure since this kind of stress can induce endothelial dysfunction and systemic inflammation (Utell et al. 2002, Lee et al. 2014). An association has been observed between short-term occupational particle exposure and the effect on endothelial cell activation and function in circulation in welders (Fang et al. 2010). Heart rate variability (HRV) is a marker of autonomic nervous system and adverse cardiovascular effects; HRV measures the variation of beat to beat intervals (Tsuji et al. 1996). A reduction in HRV has been associated with particle exposure in metal workplaces as well as in environmental settings (Magari et al. 2001, Cavallari et al. 2008, Fang et al. 2009, Han et al. 2016).

2.3.4 Cancer

The International Agency for Research on Cancer (IARC) has categorized welding fumes into group 2B (possibly carcinogenic to humans) in 1990 (IARC 1990). However, a re-evaluation of the carcinogenicity of welding fumes is in progress and the results of the assessment will be published later in volume 118 of the IARC Monographs. According to preliminary information, welding fumes will classified into category Group 1 (carcinogen) (Guha et al. 2017).

Hexavalent chromium (Cr^{6+}) is categorized in group 1 (carcinogenic to humans) (IARC 2012) and trivalent chromium (Cr^{3+}) in group 3 (not classifiable as to its carcinogenicity to humans) (IARC 1990). Both welders and stainless steel production workers are exposed to Cr^{6+}.

Epidemiological studies have revealed an association between welding and an increased risk of lung cancer (Moulin 1997, Kendzia et al. 2013, Matrat et al. 2016). Matrat and her colleagues (2016) identified a clear dose–response relationship between welding and lung cancer. There are results indicating that gas welding is more harmful than arc welding, and the risk of lung cancer increases when the workpiece is covered by paint, grease or other substances. Previously, also 't Mannetje et al. (2012) found a stronger association between the risk of lung cancer and gas welding than for arc welding. The study of Sorensen et al. (2007) reported a relationship between lung cancer and SS welding but not MS welding. Positive associations were observed in all three studies (Matrat 2016, 't Mannetje et al. 2012, Sorensen et al. 2007) after adjusting the results for smoking and combined exposure to asbestos.

There is some evidence that welding of MS can also increase the cancer risk (Hansen et al. 1996, Ambroise et al. 2006). In a Canadian study, the lung cancer risk was not linked to the welding method but was associated with smoking habits (Vallières et al. 2012). Interestingly, the group of Vallières observed an increased lung cancer risk among light smokers but not among heavy smokers.

Few studies have investigated the mortality attributable to cancer and cancer incidence among stainless steel workers but there do not seem to be any consistent relationships between occupational exposure and cancer (Axelsson et al. 1980, Långård et al. 1980, Moulin et al. 1990, Moulin et al. 2000). Huvinen & Pukkala (2013) reported that as compared to the population of the same region, the overall cancer incidence among Finnish ferrochomium and stainless steel workers was not elevated and in fact, the lung cancer risk was decreased by about 20 %.

3 AIMS OF THE STUDY

The aims of this study were

1) to measure occupational exposure to particles and acute pulmonary and systemic health effects in two large metal construction plants where arc welding and sheet metal working of MS were being undertaken (Paper I),
2) to determine the inflammatory responses following welding inhalation tests in subjects with suspected occupational asthma (Paper II),
3) to assess workers' particle exposure during the ferrochromium and stainless steel production chain in terms of particle mass and number concentrations (Paper III), and
4) to study the association between stainless steel workers' particle exposure and levels of systemic and pulmonary inflammation markers (Paper IV).

4 MATERIALS AND METHODS

4.1 OCCUPATIONAL EXPOSURE IN WELDING SHOPS

The first part of the study (Paper I), a workplace survey among MS welders, was carried out in two large metal plants located in southwest Finland. Altogether, twenty workers from a shipyard company and an offshore construction company were recruited to participate in the study. Metal inert gas (MIG), metal active gas (MAG), and flux cored arc (FCAW) welding processes were being carried out in the plants. Five of the subjects used modern fresh air face shields during the exposure measurements. Particle measurements were conducted during the work shift. Inhalable dust samples were collected from the workers' breathing zones using an IOM (Institute of Occupational Medicine) sampler. The sampling time varied from one to three hours, representing the average total exposure by workers while performing a particular task. Dust samples were analyzed gravimetrically according to the Finnish standard (SFS, 1988).

Venous blood samples were taken before and at the end of the work shift. The concentrations of IL-1β, IL-6, IL-8, tumor necrosis factor alpha (TNF-α), soluble endothelin-1 (ET-1), and E-selectin in plasma samples were determined by enzyme immunoassay (EIA), using commercial reagents. In addition, platelet count, leukocytes and their differential count, hemoglobin, hematocrit, levels of sensitive C-reactive protein (CRP), lipids, glucose as well the levels of fibrinogen were analyzed using established methods.

Baseline peak expiratory flow (PEF) and measurements of forced expiratory volume in one second (FEV_1) and the exhaled nitric oxide (eNO) level were assessed before the work shift and approximately 24 hours after baseline measurements using a portable pocket-sized spirometer and an inert plastic bag, respectively. Figure 3 shows the procedure of clinical tests during the workplace study.

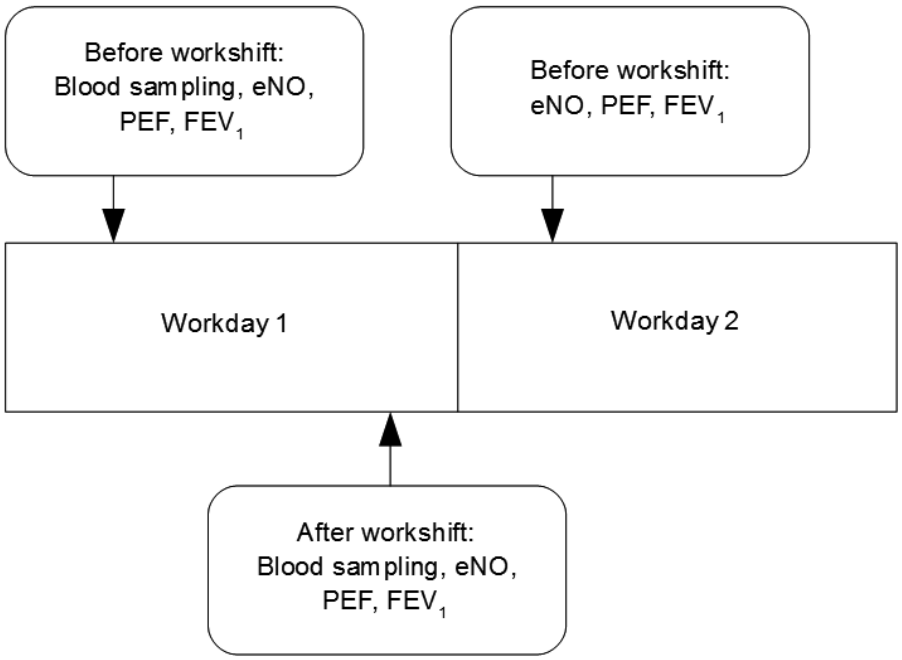

Fig. 3. Study protocol of clinical tests during the workplace study.

4.2 WELDING INHALATION CHALLENGE TESTS

The welding challenge tests (Paper II) in patients with suspected occupational asthma were performed in the special welding chamber at FIOH, Helsinki. The exposure challenge test protocol has been described earlier by Hannu et al. (2007). Fifteen subjects were exposed to mild steel (MS) (control test) and stainless steel (SS) welding fumes on consecutive days. One subject was exposed only to MS welding fumes. The manual metal arc welding (MMAW) exposure time was 30 minutes. During the exposure, five rods were consumed in the MS control test and 11 rods in the SS welding test. Inhalable particle mass measurements were performed during the tests using an IOM sampler. The samples were analyzed gravimetrically. Particle number size distributions from 30 nm to 10 μm were measured with ELPI during exposure tests of three subjects.

Study participants were monitored for 24 hours after each challenge. Altogether, five venous blood samples (one blood sample before each of the challenge tests and one blood sample after each of the challenge tests with the fifth sample on the next day after the tests) were taken from each of the subjects (see Fig. 4). The concentrations of IL-1β, IL-6, IL-8, TNF-α, endothelin-1, and E-selectin in the plasma samples were determined by EIA using commercial reagents. Platelet count, leukocytes and their differential count, hemoglobin, haematocrit, concentrations of sensitive CRP, lipids, glucose, and levels of fibrinogen were analyzed using

established methods. Baseline measurements of PEF, FEV_1, and eNO were performed before MS exposure, and approximately 22 h after the MS and SS exposure. Figure 4 shows the procedure of clinical tests during the inhalation challenge study.

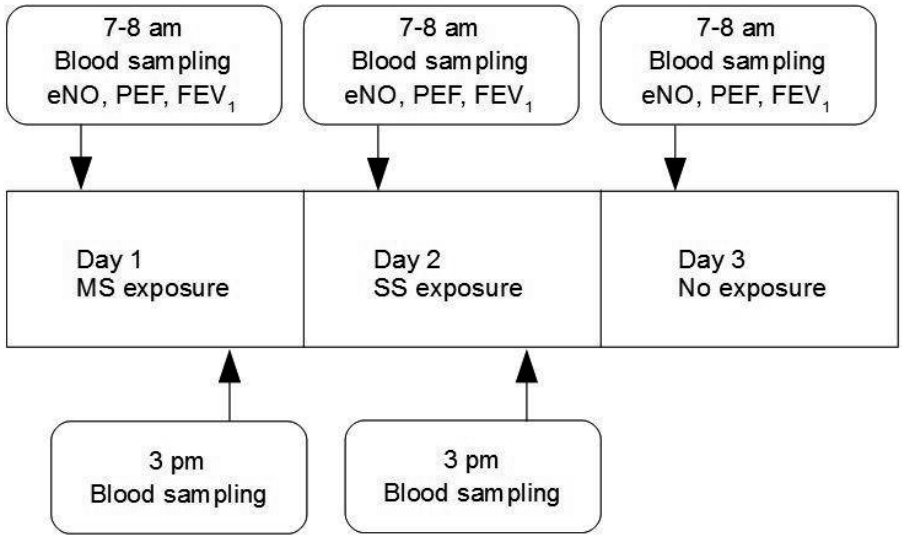

Fig. 4. Study protocol of clinical tests during inhalation challenges.

4.3 OCCUPATIONAL EXPOSURE IN FERROCHROMIUM AND STAINLESS STEEL PRODUCTION

This study (Paper III) was conducted in an integrated ferrochromium and stainless steel plant in Northern Finland. Personal exposure to inhalable dust was measured with an IOM sampler from the breathing zones of 23 workers. The average sampling time was 6.5 hours. Dust samples were analyzed gravimetrically according to the Finnish standard (SFS, 1988).

Particle mass area sampling was carried out in a total of 40 sites around the mill. Inhalable and total dust measurements were performed concurrently with an IOM sampler and a Millipore 37 mm cassette and filter.

Total particle number concentrations from 10 to 1000 nm were measured with hand-held CPC in 24 locations. Total particle number concentrations and size distributions were measured using Grimm SMPS+C with long DMA to obtain a size range from 11 to 1083 nm. The measurement cycle was 208 seconds. Sampling was performed in 17 locations, where sampling times varied according to the process operation from 1.8 to 17 hours. The longest measurements were conducted in control rooms during the night shifts. Particle size distributions were determined from

SMPS+C measurement data by averaging the entire measurement period. Measured particle concentrations were assumed to represent the workers' exposure in the process site.

4.4 INFLAMMATION MARKERS IN FERROCHROMIUM AND STAINLESS STEEL WORKERS

A cross-sectional study (Paper IV) was conducted in an integrated ferrochromium and stainless steel plant in Northern Finland. Altogether 333 workers participated in the study. Participants were divided into three exposure groups 1) Cr^{6+} (n=84), 2) Cr^{3+} (n=146), and 3) control group (n=103) according to data on their occupational exposure to these chromium species obtained from earlier measurements conducted on site. The Cr^{6+} group consisted of steel melting shop workers, the Cr^{3+} group of ferrochromium workers (sintering and crushing) and controls were cold rolling mill workers. For each worker, a personal daily exposure assessment was calculated based on the exposure data collected over the years by the occupational hygienist of the steel plant and the particle mass and number measurement results reported in Paper III. Exposure data was linked to the data for the time spent in the process area and in the control rooms retrieved from the workplace surveys conducted by occupational health professionals.

Respiratory health was examined by questionnaire and spirometry. Exhaled NO concentration, and levels of inflammatory markers in exhaled breath condensate (EBC) (8-isoprostane and leukotriene B4; LTB4) and in serum samples (adiponectins, adipsins, IL-6, IL-8, and CRP) were analysed.

4.5 STATISTICAL ANALYSES

In study I, all response variables were continuous but not all were normally distributed. Therefore one-sample Wilcoxon test was applied when comparing clinical data measured before and after the work shift.

In study II, inflammatory response variables were continuous and mostly normally distributed. Data before and after a challenge test was compared using the paired t-test. The Wilcoxon one sample test was used if the variable was non-normally distributed.

In study IV, the means of the variables in exposed and non-exposed group were compared using the t-test or ANOVA in the comparison of the three groups with respect to their chromium exposure. The association of inflammatory markers with particle exposure was analysed in all subjects together. The association of exposure to different dust concentration was assessed by applying linear regression analysis.

In studies I, II and IV, statistical significance was met when $p < 0.05$. Studies I and II analyses were performed using the Statistical Analysis System, SAS Version 9.1. In study IV, statistical analyses were performed using the SPSS 15.0 software package.

5 RESULTS

5.1 EXPOSURE TO PARTICLES IN WELDING SHOPS

The workers' 8-hour weighed average exposure to inhalable particles in two large welding shops (Paper I) was 9.4 mg/m^3 (Table 5). The job title was welder in 35 % of the study subjects and sheet metal worker in the rest. Welders' exposures, as measured in the breathing zone, was clearly higher than the sheet metal workers exposure. However, five out of seven welders were wearing fresh air respirators and thus the exposure levels in those workers is overestimated. None of the sheet metal workers were using fresh air or other kinds of respiratory protection on the study day.

Table 5. Workers exposure to particles by job title in welding shops measured with IOM sampler.

Job title	N	Inhalable particle mass, average [mg/m^3]	Min	Max	SD
Welder	7	18	4.0	35	13
Sheet metal worker	13	4.6	1.5	9.2	2.1
All workers	20	9.4	1.5	35	10

Manual inert gas/active gas (MIG/MAG) welding generated higher particle exposure as compared to manual metal arc (MMA) welding (Table 6). Five of the welders and two of the sheet metal workers operated MIG or MAG welding during the exposure study. Two welders and eight sheet metal workers were using the MMA welding technique. Three of the study subjects did not provide information about the welding method they had used during the exposure measurements. The exposure data subdivided according to the welding technique being used is presented in Table 6.

Table 6. Workers' exposure to particles by welding technique in welding shops measured with the IOM sampler.

Welding method	N	Inhalable particle mass, average [mg/m^3]	Min	Max	SD
MMA	10	8.2	2.9	34	9.3
MIG/MAG	7	14	3.5	35	12

5.2 PARTICLE EXPOSURE IN WELDING CHALLENGE TESTS

This chapter presents the results of the particle exposure measurements conducted during a 30-min welding challenge test in 14 patients with suspected occupational asthma (Paper II). The average particle mass exposure was higher in SS welding test as compared to MS welding, 40.2 and 31.6 mg/m^3, respectively. Significant variation in particle exposure between the study subjects was observed among MS and SS welding groups (Table 7). The calculated 8-hour weighted average exposure was 50 % lower than the Finnish OEL (5 mg/m^3) for inorganic dust in SS and 40 % in MS welding. OEL was exceeded in one SS welding test, where the 8-hour weighted exposure was 6.3 mg/m^3 (data not shown).

Table 7. Study subjects' average exposure to inhalable particles (mg/m^3) measured with IOM sampler during controlled MS and SS welding challenge tests.

Challenge test	N	Particle mass, measured	Range	SD	Particle mass, 8-hour weighted
MS	14	31.6	12.7-79.4	16.5	1.98
SS	14	40.2	15.9-100	19.8	2.51

Particle number concentration and size distribution were measured in MS exposure tests in two subjects and SS exposure tests using ELPI in three others. The total particle number concentration varied from 1.68×10^6 to 1.88×10^6 cm^{-3} in MS and from 1.76×10^6 to 3.18×10^6 cm^{-3} in SS welding tests. SS welding generated a higher particle concentration, presumably due to the higher number of rods (11 rods) consumed in the 30-minute tests compared to MS (5 rods). The particle size distribution was rather similar in all five welding challenge tests (Figure 5). Particle size distribution was unimodal, with the mode being around 430 nm in all exposures.

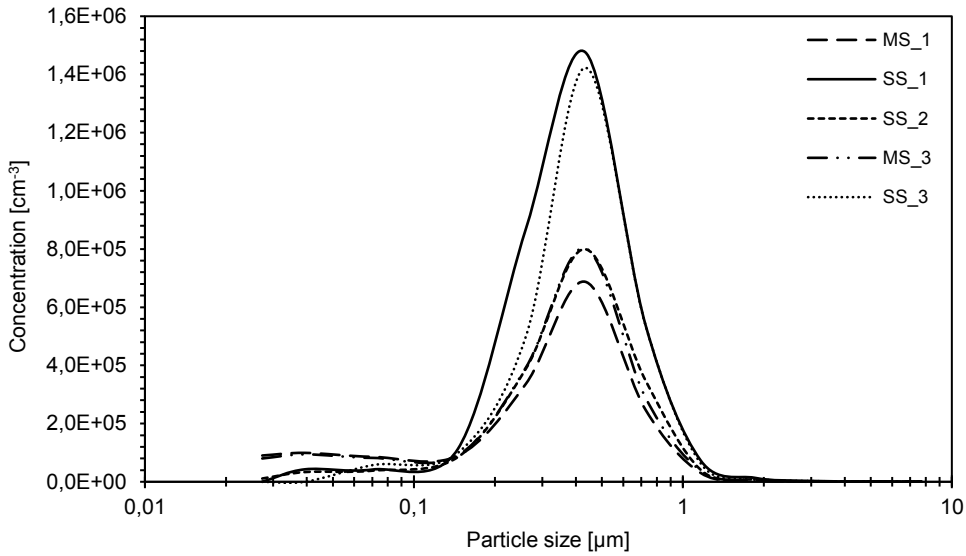

Figure 5. Particle number size distribution in two MS and three SS welding challenge tests.

5.3 EXPOSURE TO PARTICLES IN FERROCHROMIUM AND STAINLESS STEEL PRODUCTION

In this chapter, particle mass and number measurement results of ferrochromium and stainless steel production phases are presented (Papers III and IV). The workers' personal particle exposure was at its highest in the sintering plant and in the stainless steel melting shop, and at its lowest at the end of the production chain in the cold rolling mill. The highest geometric mean exposure (1.95 mg/m^3) was measured in the stainless steel melting shop. The personal dust exposure ranged from 0.80 to 5.70 mg/m^3 (Table 8).

Table 8. Workers' personal particle exposure (mg/m^3) in ferrochromium and SS production phases measured with IOM.

Process area	N	GM (GSD)	Percentile (GM) 5 %	Percentile (GM) 95 %	Range
Sintering plant	3	1.86 (1.12)	1.31	2.61	1.60-2.10
Ferrochromium smelting	4	1.27 (1.54)	0.57	2.84	0.70-2.40
Stainless steel melting	11	1.95 (1.82)	1.28	2.98	0.80-5.70
Hot rolling mill	2	0.22 (2.24)	N/A	N/A	0.10-0.50
Cold rolling mill	3	0.14 (1.68)	0.03	0.70	0.10-0.30

GM: geometric mean; GSD: geometric standard distribution; N/A: not available due to the small number of measurements

Generally, particle number concentrations were higher at the beginning of the production chain. The average total particle number concentrations in the production areas measured with SMPS+C and CPC3007 varied from 58 × 10^3 to 662 × 10^3 cm^{-3} and from 25 × 10^3 to 295 × 10^3 cm^{-3}, respectively (Table 9). The SMPS+C results were consistently higher than the CPC3007. The same distinction between the instruments has been reported previously (Asbach et al. 2012, Leskinen et al. 2012). Nevertheless, in all measurement locations, the CPC3007 results followed the same trend as SMPS+C, although the measurements were not conducted at the same time.

The highest particle number concentrations were measured in the ferrochromium smelter, where the average concentration in three SMPS+C measurements was 662 × 10^3 cm^{-3}. In the cold rolling process, particle number concentrations were an order of magnitude lower than in the previous process phases. The total particle number concentration obtained with SMPS+C ranged from 9.8 × 10^3 to 332 × 10^3 cm^{-3} (Table 9).

Particle number concentrations were lower in the control rooms than in the production areas during all the phases. However, in the control room of the sintering plant, the particle number concentration was considerably higher as compared to the other control rooms studied. The average total particle number concentration measured with SMPS+C was 243 × 10^3 cm^{-3}, which was one order of magnitude higher than the levels in the other control rooms studied, and only roughly half of the process room concentration. The same result was achieved using CPC3007.

Table 9. Particle number concentrations (cm^{-3}) in ferrochromium and SS production phases measured with SMPS+C and CPC3007.

Location and instrument	N	N_{tot}	sdN_{tot}	N_{tot} range
Sintering plant				
SMPS+C				
Production area	2	529 000	53 400	383 000-670 000
Control room	1	243 000	28 300	170 000-316 000
CPC3007				
Production area	2	201 000	16 100	85 200-281 000
Control room	2	96 900	10 200	39 600-132 000
Ferrochromium smelter				
SMPS+C				
Production area	3	662 000	321 000	101 000-2 740 000
Control room	1	24 200	14 700	6 200-124 000
CPC3007				
Production area	1	139 000	39 000	84 800-360 000
Control room	2*	50 500	29 900	9 800-299 000
Stainless steel melting shop				
SMPS+C				
Production area	4	450 000	306 000	70 400-2 480 000
Control room	1	25 000	10 600	8 610-43 700
CPC3007				
Production area	5	180 000	59 100	6 000-556 000
Control room	6	6 970	2 060	1 070-294 000
Hot rolling mill				
SMPS+C				
Production area	2	528 000	93 500	84 600-1 340 000
Control room	0	N/A	N/A	N/A
CPC3007				
Production area	1	295 000	73 200	193 000-492 000
Control room	2	5 090	1 640	1 000-13 000
Cold rolling mill				
SMPS+C				
Production area	3	57 700	36 100	9 770-332 000
Control room	0	N/A	N/A	N/A
CPC3007				
Production area	2	25 300	9 030	10 200-139 000
Control room	1	7 590	2 120	3 590-14 900

N/A: not available; *not comparable to the other control rooms measured

The mode of the particle number distribution was below the measuring range of SMPS+C (10 nm) in the sintering, ferrochromium smelting and stainless steel melting processes. In the hot and cold rolling mills, the first mode was below 10 nm and the middle point of the second mode was in the size range of 20-40 nm (Fig 6d-e). Similarly, the mode of the particle number distribution was below the measuring

range in the control rooms of the ferrochromium smelter and stainless steel melting shops (Fig. 6f). The particle distribution in the sintering plant control room was multimodal (Fig. 6f solid line).

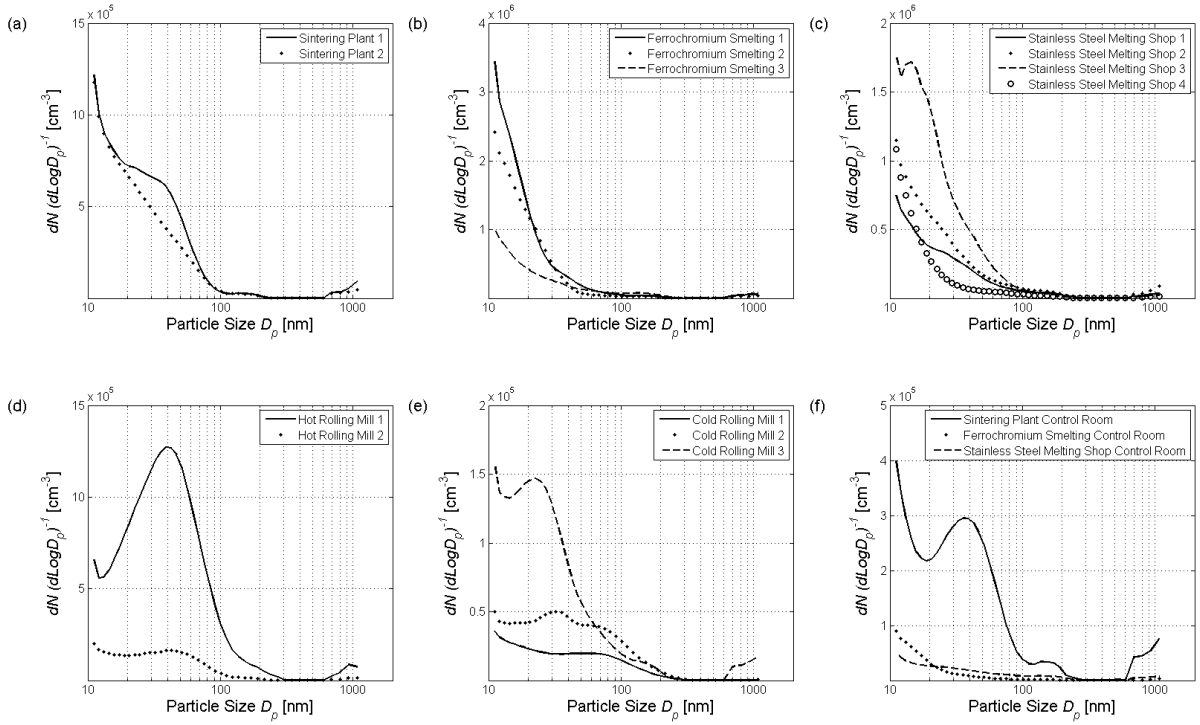

Figure 6. Averaged particle number concentrations in stainless steel production phases. Distributions have been determined by averaging the individual distributions over the whole measurement period. The Y-axis is different in A-F.

Stainless steel workers' daily personal particle mass and number exposure were calculated according to the measurement data and time spent in the process area (Paper IV). The evaluated exposure in three study groups (Cr^{3+}, Cr^{6+}, control group) is presented in Table 10. Irrespective of the measurement method, the highest evaluated mass concentration was present in the Cr^{6+} group. However, the particle number concentration was higher in the Cr^{3+} group as compared to Cr^{6+} group.

Table 10. Evaluated personal particle exposure in study groups.

Measurement metrics, unit; instrument	**Cr^{3+} group n=84** median (Q_{25}-Q_{75})	**Cr^{6+} group n=146** median (Q_{25}-Q_{75})	**Control group n=103** median (Q_{25}-Q_{75})
Inhalable mass, mg/m^3; Grimm dust monitor*	0.13 (0.03-0.60)	0.56 (0.38-1.1)	0.04 (0.02-0.07)
Thoracic mass, mg/m^3; Grimm dust monitor*	0.10 (0.03-0.30)	0.31 (0.23-0.55)	0.04 (0.02-0.05)
Alveolic mass, mg/m^3; Grimm dust monitor*	0.05 (0.02-0.11)	0.10 (0.08-0.17)	0.02 (0.01-0.03)
Inhalable dust, mg/m^3; IOM	0.24 (0.17-0.43)	0.63 (0.31-0.96)	0.05 (0.05-0.05)
Total dust, mg/m^3; Millipore 37mm	0.18 (0.14-0.37)	0.36 (0.29-0.73)	0.05 (0.05-0.20)
Particle number conc., cm^{3-}; CPC3007	103 000 (39 000-149 000)	80 000 (30 000-296 000)	23 000 (NA)
Total dust**, mg/m^3; Millipore 37mm	0.28 (0.14-0.81)	0.40 (0.25-0.57)	0.12 (0.10-0.20)

*Gravimetric factor 1 was used; **Earlier measurements in stainless steel plant; NA: not analyzed

5.4 INFLAMMATION EFFECTS CAUSED BY EXPOSURE TO METAL PARTICLES

This chapter presents the main inflammation and pulmonary results from Papers I and II (section 5.4.1) and from Paper IV (section 5.4.2).

5.4.1 Systemic inflammation and pulmonary effects after welding fume exposure

Welding fume exposure induced a significant decrease in the hemoglobin level and in the number of erythrocytes in the workplace study subjects and in welding exposure challenge participants after MS and SS exposure (Table 11); in contrast, the number of leukocytes and neutrophils increased significantly in both study groups. In addition, the number of platelets increased after both welding challenge test.

With respect to the systemic immune parameters, the concentration of IL-1β and soluble E-selectin decreased significantly during the working day. A decrease in the E-selectin level was also observed among welding challenge test participants, but only after MS exposure test.

The baseline level of eNO was elevated (>30 ppb) in three workplace study subjects and in five welding challenge test participants (data not shown). No statistically significant changes were found after the work shift nor between the welding exposure tests (Table 11). However, the eNO concentration increased by over 30 % in five exposure study participants after the MS exposure test, and in two participants after the SS exposure test as compared to the baseline level measured before the first exposure.

With respect to the lung function tests, there were no statistically significant FEV_1 or PEF changes (Table 12) and no asthmatic responses after the work shift, compared to the results before the work shift. Among welding challenge participants, there were slight reductions in the FEV_1 and PEF values after both MS and SS tests. Only FEV_1 decrease after MS exposure was not statistically significant.

Table 11. Hematological and inflammatory parameters before and after exposure to welding fumes.

Parameter	Workplace exposure			Welding challenge tests							
				Day 1			Day 2			Day 3	
	Before work shift	After work shift	p	Before MS	After MS	p	Before SS	After SS	p	Day after SS	p*
Hemoglobin, g/l	159±10	152±11	<0.01	157±13	154±12	0.02	158±12	155±12	0.02	157±11	
Leukocytes, 10^9 cells l^{-1}	8.6±2.3	10±2.7	0.01	6.5±1.2	7.4±1.5	<0.01	6.7±1.0	7.8±1.6	<0.01	6.7±0.9	
Neutrophils, 10^9 cells l^{-1}	5.0±1.9	6.1±2.2	0.04	3.7±1.2	4.4±1.3	<0.01	3.8±0.9	4.8±1.4	<0.01	3.9±1.0	
Lymphocytes, 10^9 cells l^{-1}	2.7±0.80	2.9±0.90		2.2±0.66	2.2±0.45		2.3±0.6	2.3±0.5		2.1±0.64	
Eosinophils, 10^9 cells l^{-1}	0.32±0.21	0.27±0.16		0.20±0.09	0.16±0.09	0.01	0.25±0.09	0.20±0.09	0.02	0.23±0.11	0.03
Erythrocytes, 10^{12} cells l^{-1}	5.1±0.30	4.9±0.30	<0.01	5.0±0.38	4.9±0.34	0.01	5.0±0.34	4.9±0.31	<0.01	4.9±0.32	
Monocytes, 10^9 cells l^{-1}	0.49±0.14	0.56±0.19	0.04	0.40±0.11	0.51±0.15	0.01	0.38±0.08	0.56±0.20	<0.01	0.37±0.13	
Basophils, 10^9 cells l^{-1}	0.10±0.04	0.09±0.04		0.03±0.05	0.06±0.05		0.04±0.05	0.06±0.05		0.04±0.05	
Platelet count, 10^9 cells l^{-1}	284±76	279±77		273±63	291±62	<0.01	282±57	293 ±60	<0.01	278±52	
Sensitive CRP	2.0±3.5	2.0±3.9		1.5±2.2	1.5±2.2		1.6±2.2	1.6±2.1		1.5±2.2	
P-fibrinogen, g/l	3.4±1.1	3.3±1.1		3.4±0.98	3.1±0.93		3.4±0.91	3.5±1.1		3.6±1.01	
IL-1β, pg/ml	0.49±0.30	0.29±0.14	0.01	0.57±0.43	0.45±0.30		0.65±0.86	0.65±0.76		0.46±0.30	
IL-6, pg/ml	3.6±2.3	4.1±2.4		2.7±1.6	2.5±1.6		2.5±1.4	2.4±1.1		2.6±1.4	
IL-8, pg/ml	5.9±3.6	4.4±1.5		7.7±2.8	7.2±3.6		8.3±4.8	7.4±2.7		7.4±3.3	
TNF-α, pg/ml	1.3±0.50	1.1±0.40		2.0±0.68	2.0±0.83		2.1±1.1	1.8±0.53		1.8±0.6	
Endothelin -1, pg/ml	1.2±0.96	1.2±0.61		0.92±0.23	0.86±0.22		0.87±0.21	0.88±0.35		0.90±0.26	
E-selectin, ng/ml	60±23	58±23	0.03	49±21	46±19	0.04	47±19	47±20		46±20	

*comparison of blood test 5 on day 3, and of blood test 1 on day 1

Table 12. Exhaled nitric oxide and lung function parameters before and after exposure to welding fumes.

	eNO, ppb	p	FEV_1, l	p	PEF, l/min	p
Workplace exposure study						
Before work shift	20.0±12.5		3.90±0.70		578±67	
After work shift	19.4±14.8	0.21	3.90±0.70	0.12	581±64	0.88
Welding challenge tests						
Before exposure tests	25±22		3.74±0.47		566±92	
After MS exposure	25±24		3.65±0.46	0.03	543±79	0.02
After SS exposure	28±27		3.59±0.48	0.26	529±87	0.02

5.4.2 Inflammation markers in ferrochromium and stainless steel workers

Differences of inflammation marker levels between Cr^{3+}, Cr^{6+} and control study groups are presented in Table 13 and in Table 14. The p-values indicate whether there are significant differences between the Cr-study groups and the control group.

With respect to the systemic immune parameters, the concentration IL-8 was significantly higher in the Cr^{3+} group than in the control group. However, the CRP level tended to be higher in the control group than in the Cr-exposed groups but these differences were not statistically significant.

Table 13. Blood inflammation markers in study groups.

Inflammation marker	Cr^{3+} group	Cr^{6+} group	Control group	p-value
IL-6, pg/ml				
mean (sd)	5.7 (6.7)	4.6 (4.6)	5.3 (4.8)	0.077
range	0.20-41	0.3-24	1.0-28	
IL-8, pg/ml				
mean (sd)	10 (9.7)	8.9 (3.8)	7.9 (2.9)	0.001
range	3.3-92	2.5-42	2.7-17	
Adiponectin, µg/ml				
mean (sd)	2.0 (0.80)	2.2 (0.85)	2.2 (0.83)	0.300
range	0.90-6.1	0.90-6.0	0.70-4.7	
Adipsin, µg/ml				
mean (sd)	899 (180)	917 (165)	933 (167)	0.473
range	457-1350	352-1360	571-1450	
CRP, µg/ml				
mean (sd)	1.5 (1.4)	1.6 (2.2)	1.9 (2.3)	0.056
range	0.20-8.2	0.20-14	0.20-15	

With respect to the pulmonary inflammation markers, the level of 8-isoprostane in EBC was significantly higher in the Cr^{6+} group as compared to the Cr^{3+} and control groups. In addition, the concentrations of eNO and alveolar eNO were higher in the

Cr^{3+} group than in the other study groups, although the differences in the eNO level were not statistically significant ($p<0,05$).

Table 14. Exhaled nitric oxide concentrations and pulmonary inflammation markers in exhaled breath condensate in study groups.

Inflammation marker	Cr^{3+} group	Cr^{6+} group	Control group	p-value
8-isoprostane, pg/ml				
mean (sd)	16.1 (12)	17.9 (12)	14 (9.9)	0.008
range	0.4-52	0.24-72	0.02-63	
LTB4, pg/ml				
mean (sd)	17 (9.3)	18 (8.9)	18 (10)	0.827
range	2.0-44	3.0-45	3.3-45	
eNO, ppb				
mean (sd)	19 (21)	16 (9.8)	17 (13)	0.960
range	(3.0-137)	3.8-56	2.7-84	
eNO, alveolar, ppb				
mean (sd)	2.1 (0.64)	1.9 (0.66)	1.9 (0.58)	0.039
range	0.65-3.4	0.40-5.2	0.65-3.8	
eNO, bronchial, ppb				
mean (sd)	0.63 (0.54)	0.66 (0.45)	0.71 (0.61)	0.644
range	0.01-3.8	0.07-2.3	0.04-4.0	

6 DISCUSSION

6.1 OCCUPATIONAL EXPOSURE TO METAL PARTICLES

The particle mass concentrations of welding fume particles were clearly higher among welders as compared to those of sheet metal workers. The average mass concentrations were 18 and 4.6 mg/m^3, which are 180 % and 46 % of Finnish OEL for inorganic dust (10 mg/m^3), respectively. The results are in line with earlier publications (Cena et al. 2016, Antonini 2003). However, sheet metal workers' actual exposure may be greater than that of welders' because of the difference in the use of respiratory protection while they are working. The sheet metal workers did not use respiratory protection while welders wore efficient fresh air respiratory protection. Extensive variations in exposure within the workers in both occupation groups in the workplace study are likely due to different working postures and the distance from the arc (Cena et al. 2016). Work tasks, techniques, ventilation, and working practices can also explain the non-uniform exposures in these workers (Rappaport et al. 1999, Liu et al. 2011). It should be stressed that extensive variation does not necessarily mean unacceptable working conditions, instead it can be an indication of a workplace where health protection actions have succeeded in minimizing exposures (Wambach 2002). MIG/MAG welders' average particle exposure (14 mg/m^3) was 59 % higher than MMA welders' exposure (8.2 mg/m^3). Both workplaces that participated in the study had good general ventilation and several local exhaust ventilation units in use. However, some of the welders had to work in confined spaces, where local exhaust could not be applied, and the measured exposure reached the Finnish OEL for inorganic dust.

Particle exposure in the welding challenge test varied between the study subjects although the study protocol, ventilation and welding technique and materials were identical. During the test, some participants were bent over very close to the object being welded, and therefore their breathing zone particle concentrations were higher than those participants who kept a longer working distance to the object being welded. The average 30-min particle mass concentration in MS and SS exposures were 32 mg/m^3 and 40 mg/m^3, respectively. High particle exposures can occur in workplace conditions, for example Hedmer and her colleagues (2014) reported maximun workplace exposure to welding fumes of 38 mg/m^3. Although welding fume exposure was high in this study, the calculated 8-hour weighted average exposure remained 50 % lower than the Finnish OEL for inorganic dust.

The particle number size distribution was very similar in all welding challenge tests. Most of the particles were smaller than 1 μm, and the number mode was around 0.4 μm. This kind of particle distribution is in line with those measured in workplace conditions (Elihn et al. 2011). SS welding generated a higher total particle concentration (variation from 1.76×10^6 to 3.18×10^6 cm^{-3}) compared to MS welding (from 1.68×10^6 to 1.88×10^6 cm^{-3}), presumably due to the difference in the welding

test protocols. In the SS exposure tests, a higher number of rods were consumed than in the MS tests. The welding test protocol is standardized and is applied when investigating whether welders are suffering from occupational asthma in Finland (Hannu et al. 2007), and it was not changed in this study.

In stainless steel production, the exposure to inhalable dust was highest at the beginning of the production chain in the sintering, ferrochromium smelter and stainless steel melting shop i.e. the geometric mean values of measured concentrations were 1.86, 1.27 and 1.95 mg/m^3, respectively. Workers' exposures in hot rolling and cold rolling were clearly lower, 0.22 and 0.14 mg/m^3, respectively, due to the fact that workers spend most of their time in control rooms, and furthermore, there are no hot processes in the cold rolling mill, thus the formation of the particles is negligible compared to that in the earlier production phases which require high process temperatures. Workers' personal occupational exposure levels to total dust reported earlier in the same plant were 1.5 mg/m^3 in the ferrochromium smelter, 1.8 mg/m^3 in the stainless steel melting shop and 0.3–0.5 mg/m^3 in cold rolling (Huvinen et al. 1993). Workers spent on average 85 % of their working time in the control rooms, which substantially affected their exposure. With one exception, personal exposure levels in this study were below 50 % of the Finnish eight-hour OEL for inorganic dust (10 mg/m^3). The highest personal exposure (5.7 mg/m^3) was measured in the stainless steel melting shop, where a worker was operating the process control and undertaking maintenance tasks near the electric arc furnace and argon-oxygen decarbonization converter.

Similar to mass concentrations, particle number concentrations were higher in the early stages of the stainless steel production chain. Total particle number concentrations measured with SMPS+C in the sintering plant, ferrochromium smelter, stainless steel melting shop and hot rolling mill were 670 × 10^3, 2740 × 10^3, 2480 × 10^3, and 1340 × 10^3 particles/cm^3, respectively. The lowest total particle number concentration, 332 × 10^3 particles/cm^3, was measured in the cold rolling mill. Particle number concentrations have not been reported previously in the stainless steel production chain. However, similar results have been reported in other industrial environments, such as foundries and welding shops (Chen et al. 2008, Evans et al. 2008, Heitbrink et al. 2009).

Particle number concentrations were lower in the control rooms than in the measured production areas, except in the sintering plant control room where the particle number concentration was higher than in the other studied control rooms. Changes in the sintering process were seen in control room measurements, which suggests that particles were originating from the process via air leakage points. No differences were observed in particle concentrations between the sintering plant control room and other control rooms in the particle mass measurements (data shown in Paper III). Thus, without real-time particle number measurements, these leakages would not have been identified. However, particle number measurements with SMPS and ELPI can challenging in large scale industrial environments when conducting an occupational exposure assessment due to the large size, complex

operation, and high costs of the instruments. In addition to stationary sampling, real-time personal exposure assessment to particle number concentrations and lung deposited surface area measurements can be conducted nowadays with instruments such as DiscMini (Testo SE & Co, USA). Stationary sampling results are usually more crude estimates of personal exposure. If one wishes to obtain more accurate information about workers' exposure to hazardous substances, then the exposure assessment should be based on personal measurements. Environmental studies have shown that personal measurements give higher results compared to static sampling (Harrison et al. 2012). However, static measurements conducted at the emission source are similar to the levels reported for personal samples (Corn 1983, Lange 1999).

Controlling the exposure to metal particles should follow the commonly used control measures and hierarchy to prevent exposure to hazardous materials (Figure 7). In general, the most effective ways to control exposures include elimination or substitution of the hazard. In welding shops, robot welding can prevent exposure and at the same time increase productivity. If elimination or substitution is not possible, which is often the case in welding shops and the metal prosessing industry, then engineering controls such as improvements in general ventilation or adding local exhaust ventilation or enclosures should be considered to limit exposure, even though these may require large investments. Furthermore, particle exposure can be reduced with administrative controls; these may include training, working procedures and instructions. The final way to control particle exposure is using personal protection equipment (PPE; e.g. respirators, gloves, safety glasses). In welding work, protection of eyes and face from ultraviolet and infrared radiation, heat and splash is always needed.

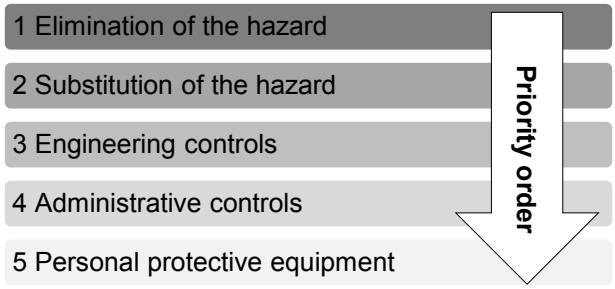

Figure 7. The hierarchy of control; steps for exposure reduction (adapted from NIOSH).

6.2 HEMATOLOGICAL AND SYSTEMIC INFLAMMATION MARKERS

6.2.1 Welding

Exposure to welding fume particles caused a mild systemic inflammatory response; this was observed as statistically significant changes in blood hematological and systemic inflammation markers. Changes were detected in hemoglobin, leukocytes, neutrophils, platelets, IL-1β and E-selectin levels. Similar changes were found in workers after the work shift and in study subjects after the welding exposure tests. Exposure induced a significant decrease in the hemoglobin level as well as in the number of erythrocytes in both study groups. This finding has not been observed in other studies dealing with acute effects of welding fumes (Kim et al. 2005, Palmer et al. 2006, Scharrer et al. 2007), even though not all basic hematological markers have been investigated in studies investigating systemic inflammation after metal particle exposure. However, a significant negative association between the concentration of ambient particulate matter and blood hemoglobin levels has been reported (Seaton et al. 1999). The effect is especially apparent in the elderly (Gong et al. 2004, Honda et al. 2017). In this thesis, the differences in metabolic intensity and fluid shifts during moderate or low level physical work could have caused the decrease in the hemoglobin levels (Harrison et al. 1985).

The number of leukocytes and neutrophils increased significantly in both welding study groups. Kim et al. (2005) have reported similar findings. They found a significant increase in white blood cell and neutrophil counts in non-smokers after exposure to welding fumes.

An increase in the level of CRP is considered as a risk factor for cardiovascular diseases (Calabro et al. 2003, Lind et al. 2003). No changes in CRP concentrations were found in this study, but an increase in this parameter has been reported after welding fume exposure by Kim et al. (2005). In the cross-over study of Hartman et al. (2013), increases in the high sensitive CRP levels and neutrophil counts were detected after MIG welding of zinc coated steel. In the controlled welding fume exposure study of Markert et al. (2016), male volunteers were exposed to either zinc or copper or zinc and copper and all of these exposures signifigantly increased blood CRP levels (Markert et al. 2016). In line with this thesis, neither Scharrer et al. (2007) nor Palmer et al. (2006) observed any changes in CRP levels after exposure to welding fumes.

Platelets are important determinants of acute cardiovascular events. In the welding exposure study, the number of platelets increased after both welding challenge tests. Conversely in the workplace study, the platelet count tended to decrease, although the change was not statistically significant (Table 10). An elevated platelet count in peripheral blood has previously been reported after inhalation of diesel exhaust particles (Krishnan et al. 2013). Reactive thrombocytosis due to

increased inflammation or bone marrow stimulation could have caused the increase in platelet count.

The association between welding fume exposure and IL-1β or soluble E-selectin levels has not been studied before. E-selectin is an endothelial cell surface marker; in its soluble, circulating form, it is considered to be a marker of activation of vascular endothelium by TNF-α and IL-1β. The concentration of IL-1β decreased in this study significantly during the work shift, but these changes were not seen in subjects who participated in the welding exposure tests. In addition, the E-selectin level declined in the workplace study subjects. A decrease in the E-selecting level was also observed among welding challenge test participants, but only after the MS exposure test. Previously, E-selectin has been associated with acute myocardial infarction (Suefuji et al. 2000) and coronary artery disease (Fang et al. 2004).

No statistical differences were found here in the concentrations of acute-phase inflammation mediators such as TNF-α, IL-6 and IL-8. Statistical significant changes in TNF-α and IL-8 have not been reported in humans following exposure to welding fumes (Scharrer et al. 2007, Umukoro 2016), although in the publication of Ohlson et al. (2010), an increase in the IL-6 level was observed after occupational particle exposure in different industrial work environments. Furthermore, increases in TNF-α, IL-6 and IL-8 levels have been detected in bronchoalveolar lavage (BAL) after zinc oxide fume exposure (Blanc et al. 1993, Kuschner et al. 1997, Fine et al. 2000).

6.2.2 Ferrochromium and stainless steel production

The associations between particle exposure, different chromium compounds and systemic inflammation have not been studied previously in stainless steel production workers. Some associations in the Cr-exposed groups in relation to blood inflammation markers were found but these differences could not be explained with any specific evaluated particle concentrations.

Blood IL-6 and IL-8 levels were highest in the Cr^{3+} group. The evaluated particle number concentration was also highest in the Cr^{3+} group. However, statistical analyses did not reveal any significant association between the evaluated particle number exposure and IL-6 and IL-8 levels.

Interestingly, the CRP level was the highest in the control group. This is in line with the study of Kim et al. (2005), who reported the same trend in CRP levels before welding fume exposure. In the non-exposed control group, the baseline CRP level was higher before undertaking the exposure test to welding fumes as compared to the welder group, however the difference was not statistically significant (Kim et al. 2005).

Adipokines, such as adiponectin and adipsin, have been shown to regulate inflammatory responses, also in the lungs (Sood 2010). No differences between the study groups' adiponectin and adipsin levels were found in this study. Sauni et al. (2012) examined the associations between silica exposure and blood inflammation

markers; they reported that silica exposure was associated significantly with increased adiponectin and adipsin levels.

6.3 LUNG FUNCTION AND PULMONARY INFLAMMATION MARKERS

6.3.1 Welding

Exposure to welding fumes has been associated with reduced pulmonary function and asthma as described in paragraph 2.3.2. However, this study did not detect amy statistically significant FEV_1 or PEF changes in workers' lung function test results compared to their levels before the work shift. In the participants undergoing the welding challenge, there were slight reductions in the FEV_1 and PEF values after both MS and SS tests and only the FEV_1 decrease after MS exposure was not statistically significant. In the study of Akbar-Khanzadeh (1993), the reductions in the lung function parameters measured before and after the work shift were approximately four times greater among welders than among the non-exposed controls. In this study, the differences in lung function results between workplace and exposure test groups could be explained by the fact that 89 % of subjects who participated in the welding challenge test had asthma. In contrast, in the workplace study subjects, there were only two (10 %) who had physician diagnosed asthma.

It has been postulated that changes in welders' lung function are transient, occurring at the time of exposure and returning to normal during non-exposure periods (Donoghue et al. 1994, Sobaszek et al. 2000, Zeidler-Erdely et al. 2014). However, little is known about the long term significance of the acute declines in welders' lung function.

No statistically significant changes in welders' eNO levels were found either in the workplace study subjects after the work shift or in the subjects who participated in the welding exposure tests.

Due to the small number of study subjects in both welding study groups, it was not possible to assess the role of lifestyle markers, e.g. smoking, blood glucose and lipid levels (Papers I and II). However, the average blood glucose baseline level was elevated in the workplace study group (Paper I) and in both study groups, the lipid levels were higher than the Finnish reference value. There are some air pollution studies which have suggested that oxidative stress following particle exposure may be linked with impaired metabolism of glucose and lipids (Chuang et al. 2010, Yitshak Sade et al. 2016). Furthermore, several studies have reported a negative interaction between smoking and increased risk of adverse health outcomes related exposure to welding fumes (Chinn et al. 1990, Vallières et al. 2012, Haluza et al. 2014, Wong et al. 2017).

6.3.2 Ferrochromium and stainless steel production

The associations between particle exposure, different chromium compounds and pulmonary inflammation have not been studied previously in stainless steel production workers. The concentration of alveolar eNO was higher in the Cr^{3+} group as compared to the control group. In addition, the 8-isoprostane level in EBC was higher in the Cr-exposed groups than in the control group. The concentration of the leukotriene, LTB4, in EBC was in the same range in all study groups. Previously, increased EBC LTB4 levels have been observed by Dierschke et al. (2017) when welders with and without work-related symptoms in the lower airways and non-welders without symptoms, were exposed to welding fumes (1 mg/m^3) and to filtered air. In that work, the LTB4 concentration decreased significantly in all participants after welding exposure as compared to when they were breathing filtered air.

There was no evidence for any consistent association between pulmonary inflammation markers and any of the evaluated particle exposure concentrations in the statistical analyses.

7 CONCLUSIONS

According to this study, workers' particle mass exposure was higher in welding shops than in a stainless steel plant. Particle number exposure was not measured in welding shops, but welding exposure challenge tests indicated that most of the particles generated in welding and in stainless steel production phases are 10-40 nm in size.

This study revealed that metal workers' particle exposure can be considerable in welding shops, especially among sheet metal workers. Sheet metal workers did not use personal respiratory protective equipment or they used less efficient respirators than welders. Thus, sheet metal workers' exposure to the particles generated from sheet metal and welding processess can be higher than that of welders.

In stainless steel production work, both particle mass and number exposure are highest at the beginning of the production chain in the sintering, ferrochromium smelting and stainless steel melting processes. The lowest particle levels were present in the cold rolling mill. Workers' particle exposure in stainless steel production phases may be low or moderate when measured as the mass concentration but not as the number concentration. Process workers spent most (approximately 85 %) of their working time in the control rooms breathing filtered air which reduced their personal exposure. However, particle number measurements in the control rooms revealed leakages from the process area leading to some exposure to particles also in these rooms. Good general ventilation is important in all workplaces where there are airborne metal particles. In confined spaces and in areas with poor ventilation, and in tasks where molten metals are present, it may be necessary to utilize personal respiratory protective equipment if no other occupational hygiene control measures can be applied.

Welding fume exposure induced a mild systemic inflammatory response following the work shift and welding fume challenge tests. During the work shift and exposure tests, the numbers of peripheral blood leukocytes and neutrophils increased whereas the hemoglobin level and the number of erythrocytes decreased significantly. In addition, the concentration of IL-1β and E-selectin decreased statistically significantly during the working day. A statistically significant decrease in the E-selectin level was also observed after MS welding challenge test.

No changes were observed in pulmonary function in the welding workplace participants. However, there were slight reductions in the FEV_1 and PEF values after both welding exposure tests. Furthermore, no statistically significant changes of eNO were found after the work shift nor in the welding exposure tests.

During stainless steel production, particle exposure did not affect on peripheral blood or pulmonary inflammation markers in a manner that would be predicted from industrial hygienic measurements. Personal exposure levels are rather low in comparison to the particle concentrations measured in the production areas of the plant; this was attributable to the relatively long time that the workers spend in the

control rooms. In addition, SS production workers use efficient personal respiratory protection while performing the most dusty tasks.

The long term significance of the acute systemic inflammation and acute lung function decline is not clear. Inflammatory processes may be important triggering steps in mediating adverse cardiovascular events or even cancer associated with metal particle exposure. Thus, factors affecting particle generation, exposure and deposition, such as the type of particles generated, the particle size and concentration, are significant factors that should be considered when developing workplace protective strategies.

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MERJA JÄRVELÄ

This thesis reports occupational exposure to particles in welding workplaces and in a ferrochromium and stainless steel production. Systemic and pulmonary inflammation response and pulmonary function were analyzed. Changes in workers´ blood inflammation markers were found in welding workplaces. Exposure should be reduced by using control measures that improve occupational hygiene in all working environments where exposure to metal particles is likely.

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