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RESPIRATORY SYMPTOMS AND LUNG FUNCTION IN FOUNDRY WORKERS EXPOSED TO LOW MOLECULAR WEIGHT ISOCYANATES

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ABSTRACT

Background: Some foundries use the Hot Box method, which involves use of a nitrogen-containing binder system to produce cores for hollow castings. During the process, low molecular weight isocyanates such as isocyanic acid (ICA) and methyl isocyanate (MIC) are formed, which are potentially toxic. However, data regarding exposure to these agents, and their health effects, were sparse.

Aims: The objectives of the studies were to characterise levels of exposure to low molecular weight isocyanates in Swedish foundries using Hot Box core binders, and their potential health effects, especially on the upper and lower airways. The specific questions addressed were as follows. What are the exposure levels to ICA and MIC in foundries using Hot Box core binders, and what symptoms are reported by the workers? Are there any signs of acute or residual effects on lung function? Have symptoms and lung function changed over time, and are there any associations between exposure and health parameters?

Material and methods: The four Swedish foundries using Hot Box core binders were invited to participate in four studies. In Study I, individual exposure to ICA, MIC and formaldehyde in 64 foundry workers was assessed. In a parallel study (II), the respiratory symptoms and lung function of the same workers and 134 local referents were evaluated. Four years later, 43 exposed workers and 69 referents participated in a nasal examination. Their exposure to previously described agents complemented with total dust was measured (Study III). Study IV was a four-year follow-up of 70 subjects (25 exposed workers and 55 referents) assessed in Study II, aiming to relate changes in exposure to the prevalence of respiratory symptoms and lung function following improvements to the work environment.

Results: Exposure levels of ICA (GM (geometric mean) 27 $\mu g/m^3$), MIC (GM 5.3 $\mu g/m^3$) and formaldehyde (GM 120 $\mu g/m^3$) at baseline were 50% lower at follow-up. There was a high prevalence of ocular and respiratory symptoms at baseline and nasal symptoms had increased among the exposed workers at follow-up. However, lower airway symptoms were less frequently reported at follow-up. Dry nasal mucosa was observed among exposed workers. FEV_1 (the forced expiratory volume in 1 second) levels pre-shift were slightly reduced in the exposed group both at baseline and follow-up, but the small decrease in lung function over shift in the exposed group at baseline, was not observed at follow-up. However, the effects seemed to be small and not relevant on an individual level. Dose-response relationships were observed between the measured levels of ICA, MIC and formaldehyde and the nasal symptoms, but the nasal signs were only weakly associated with exposure estimates. Lung function findings were not significantly related to current exposure to ICA, MIC or formaldehyde.

Conclusions: The nasal mucosa is a highly sensitive indicator of potentially harmful exposure to air pollution and the high prevalence of nasal symptoms and dry mucosa suggested a link with ICA, MIC and other airway irritants, such as formaldehyde and dust. This may indicate a persistent influence of the working environment, although exposure levels have fallen. The absence of lung function effects over shift and the decline in lower airway symptoms in the exposed group at follow-up indicate positive effects of the remedial measures undertaken since baseline. However, the slightly reduced FEV_1 levels pre-shift in the exposed group at follow-up suggests there may be a residual effect of previous exposure, which would be interesting to address in further studies. The nasal findings indicate that further improvement of the working environment in these foundries is required.

Key words: formaldehyde, foundry, isocyanic acid, methyl isocyanate, lung function, nasal symptoms

SAMMANFATTNING

Bakgrund: Vissa gjuterier använder Hot Box-metoden, som baseras på ett kväveinnehållande bindemedelssystem för att tillverka gjutkärnor för ihåliga gjutgods. Under processen bildas lågmolekylära isocyanater såsom isocyansyra (ICA) och metylisocyanat (MIC), som är potentiellt toxiska. Det fanns få data om exponering för dessa ämnen och deras hälsoeffekter.

Syfte: Målet med studierna var att kartlägga exponeringsnivåerna av lågmolekylära isocyanater i svenska gjuterier, som använder Hot Box-kärnbindemedel, och deras potentiella hälsoeffekter, framför allt i övre och nedre luftvägarna. De specifika frågeställningarna var: Vilka exponeringsnivåer för ICA och MIC förekommer i gjuterier vid användning av Hot Box-kärnbindemedel, och vilka symtom rapporteras av gjuteriarbetarna? Finns det några tecken på akuta eller kvarstående effekter på lungfunktionen? Har symtom och lungfunktion förändrats över tid och finns det något samband mellan exponering och hälsoparametrar?

Material och metoder: De fyra svenska gjuterier, som använder Hot Box-kärnbindemedel inbjöds till fyra studier. I studie I kartlades den individuella exponeringen för ICA, MIC och formaldehyd bland 64 gjuteriarbetare. I en parallell studie (II) undersöktes luftvägssymtom och lungfunktion bland samma gjuteriarbetare och 134 lokala kontroller. Fyra år senare deltog 43 exponerade arbetare och 69 kontroller i en undersökning av näsan. Deras exponering för tidigare beskrivna ämnen, kompletterat med totaldamm, mättes i studie III. Studie IV var en fyraårsuppföljning av 70 personer (25 exponerade och 55 kontroller) från studie II. Syftet var att relatera förändringar i exponering till prevalensen av luftvägssymtom samt lungfunktion efter förbättringar av arbetsmiljön.

Resultat: Den ursprungliga exponeringen för ICA (GM (geometriskt medelvärde) 27 µg/m³), MIC (GM 5.3 µg/m³) and formaldehyd (GM 120 µg/m³) var cirka 50 % lägre vid uppföljningen. Det var initialt en hög prevalens av ögon- och luftvägssymtom. Vid uppföljningen hade nässymtom ökat bland exponerade, men nedre luftvägssymtom rapporterades mindre frekvent vid uppföljningen. Torr slemhinna i näsan observerades bland exponerade. FEV_1-nivåerna (den forcerade expiratoriska volymen på 1 sekund) före skift var något lägre i den exponerade gruppen både initialt och vid uppföljningen, men den lilla minskningen i lungfunktion över skift i den exponerade gruppen vid första undersökningen observerades inte vid uppföljningen. Effekterna föreföll vara små och inte relevanta på individnivå. Dos-responsamband observerades mellan uppmätta nivåer av ICA, MIC och formaldehyd och nässymtom, men de objektiva näsfynden var bara svagt associerade med exponeringsmått. Lungfunktionen var inte signifikant relaterad till aktuell exponering för ICA, MIC eller formaldehyd.

Slutsatser: Nässlemhinnan är en mycket känslig indikator på potentiellt skadlig exponering för luftföroreningar och den höga prevalensen av nässymtom och torr slemhinna tydde på en koppling till ICA, MIC och andra luftvägsirritanter, såsom formaldehyd och damm. Detta skulle kunna indikera en kvarstående påverkan av arbetsmiljön trots att exponeringen minskat. Ingen påverkan av lungfunktionen över skift och minskning av nedre luftvägssymtom i den exponerade gruppen vid

uppföljningen indikerar en positiv effekt av vidtagna åtgärder sedan den inledande studien. De kvarstående något lägre FEV_1-nivåerna före skift i den exponerade gruppen vid uppföljningen skulle kunna tyda på en effekt av tidigare exponering, som skulle vara intressant att följa upp i en senare studie. Effekterna i näsan indikerar att ytterligare förbättring av arbetsmiljön i dessa gjuterier fordras.

Nyckelord: formaldehyd, gjuteri, isocyansyra, lungfunktion, metylisocyanat, nässymtom

LIST OF PUBLICATIONS

The thesis is based on the following papers, which are referred to in the text by the corresponding Roman numerals. For convenience, the studies described in Papers I-IV are referred to as Studies I-IV, respectively.

I. Westberg H., **Löfstedt H.**, Seldén A., Lilja B.G. & Nayström P. (2005) Exposure to low molecular weight isocyanates and formaldehyde in foundries using Hot Box core binders. *Annals of Occupational Hygiene, 49,* 719-725.

II. **Löfstedt H.**, Westberg H., Seldén A.I., Lundholm C. & Svartengren M. (2009) Respiratory symptoms and lung function in foundry workers exposed to low molecular weight isocyanates. *American Journal of Industrial Medicine, 52,* 455-463.

III. **Löfstedt H.**, Westberg H., Seldén A.I., Rudblad S., Bryngelsson I.L., Ngo Y. & Svartengren M. (2011) Nasal and ocular effects in foundry workers using the Hot Box method. *Journal of Occupational and Environmental Medicine, 53,* 43-48.

IV. **Löfstedt H.**, Westberg H., Seldén A.I., Bryngelsson I.L. & Svartengren M. (2011) Respiratory symptoms and lung function in foundry workers using the Hot Box method – a 4-year follow-up. *Journal of Occupational and Environmental Medicine, 53,* 1425-1429.

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CONTENTS

LIST OF ABBREVIATIONS

AM	Arithmetic mean
ATS	American Thoracic Society
BMI	Body mass index
CI	Confidence interval
DL	Detection limit
FEV_1	Forced expiratory volume in 1 second
GM	Geometric mean
GSD	Geometric standard deviation
GSD_B	Between-worker variability
GSD_W	Within-worker variability
HFS	High flow sampling
HPLC	High performance liquid chromatography
ICA	Isocyanic acid
L	Litre
LCMS	Liquid chromatography mass-spectrometry
M	Molar
MDI	Methylene bisphenyl diisocyanate
MIC	Methyl isocyanate
n	Number
NCO	Nitrogen carbon oxygen
NIOSH	National Institute of Occupational Safety and Health
OEL	Occupational exposure limit
OR	Odds ratio
SBACA	Swedish Board of Accreditation and Conformity Assessment
SD	Standard deviation
SRR	Standardized rate ratio
TDI	Toluene diisocyanate
TWA	Time-weighted average
VC	Vital capacity

1 INTRODUCTION

Diverse materials and methods are used in foundries. Some, including four in Sweden (one grey iron and three brass foundries), use the so-called Hot Box method to produce cores, made from resin with a nitrogen-containing binder (Archibald & Smith, 1988), that are used in hollow casting and removed after the metal has solidified. During the process, low molecular weight isocyanates (i.e. isocyanates containing only one NCO group) such as ICA and MIC are formed (Lilja, et al., 2000a, 2000b). Exposure to these monoisocyanates occurs during both core-making and die-casting. This is a source of concern, since isocyanates may have adverse health effects, particularly on the eyes and respiratory system (Criteria Group for Occupational Standards, 2001), which may be compounded by exposure to other substances present in foundries, e.g. formaldehyde and dust. However, prior to the studies this thesis is based upon, exposure levels of monoisocyanates in foundries using the Hot Box method had not been systematically evaluated. Further, no data on health effects of ICA were available, and only sparse data on effects of MIC at considerably higher exposure levels than those measured in Swedish foundries (Criteria Group for Occupational Standards, 2002). Therefore, the four Swedish foundries using Hot Box core binders were invited to participate in four studies to assess the workers' levels of exposure to low molecular weight isocyanates and their health effects (especially respiratory symptoms and lung function).

In Study I the exposure to ICA, MIC and formaldehyde in the Swedish foundries was assessed.

In parallel to the exposure investigation, to further elucidate the possible respiratory health effects of monoisocyanates, a study of the respiratory symptoms and lung function of the foundry workers were evaluated in Study II.

Four years later, in Study III the acquired data were complemented with dust exposure measurements in the foundries and nasal examination of exposed workers and referents. The objectives were to elucidate further the possible effects of monoisocyanates, formaldehyde and total dust, with particular reference to ocular and nasal symptoms.

Study IV was a four year follow-up of foundry workers who participated in Study II. The objective was to relate changes in exposure to the prevalence of respiratory and ocular symptoms, and lung function, following improvements to the work environment.

The studies were approved by the Human Research Ethics Committee of Örebro County Council (Decision no. 1013/00) and the Regional Ethical Review Board in Uppsala (Decision no. 2004:M-471). Informed consent was obtained from each subject.

2 BACKGROUND

2.1 THE SWEDISH FOUNDRY INDUSTRY

The foundry industry is a key sector of the industrialized world that has a long tradition and is highly technically developed in Sweden. There are three main types of foundries in Sweden (iron, steel and non-ferrous metal), which are managed by a few large companies and numerous small companies. However, the numbers of small companies have declined in recent decades due to structural changes resulting in a series of mergers and closures.

In 2010, almost 270,000 tonnes of foundry products (ferrous, steel and non-ferrous metal castings) were produced in Sweden, pre-dominantly by iron foundries (Table 1). This was approximately 2% of the amount produced in Europe, excluding Russia (Peter Nayström, personal communication, 2012). Two important markets for the products of Swedish foundries are the automobile and telecommunications industries.

Table 1. Overview of the Swedish foundry industry in 2010 (Peter Nayström, personal communication, 2012)

Type of foundry	Number of foundries	Employees	Production 1,000 tonnes
Iron foundries	32	2,600	201.2
Steel foundries	13	950	18.1
Metal foundries	73	2,750	47.3
Total	**118**	**6,300**	**266.6**

2.2 WORK OPERATIONS IN THE FOUNDRY INDUSTRY

Sector-specific work operations in the foundry industry include melting, sand-mixing, core-making, moulding, casting, shaking-out and fettling (Figure 1). Other, general activities include transportation, cleaning and maintenance (although the furnaces and ladles are very robust and usually require relatively little maintenance).

Various casting methods, involving use of permanent or disposable moulds are used, depending on the raw material. For brass alloys and aluminium, static die-casting using permanent moulds may be suitable. In the simplest form, a mould consists of two halves, but often the product needs a more sophisticated mould with several assembled components. The moulds are made of iron or steel, while the cores are usually made of steel, but sometimes cores of sand and a binder system are required (Svensson & Svensson, 2004).

There has been a general improvement of the foundry work environment in recent decades. Administration and dusty transports have been built-in. Better ventilation and dust filtering systems have been installed. Hygiene in the work premises has improved, technical developments have eliminated high-exposure work operations and the use of respirators has improved (Peter Nayström, personal communication, 2012).

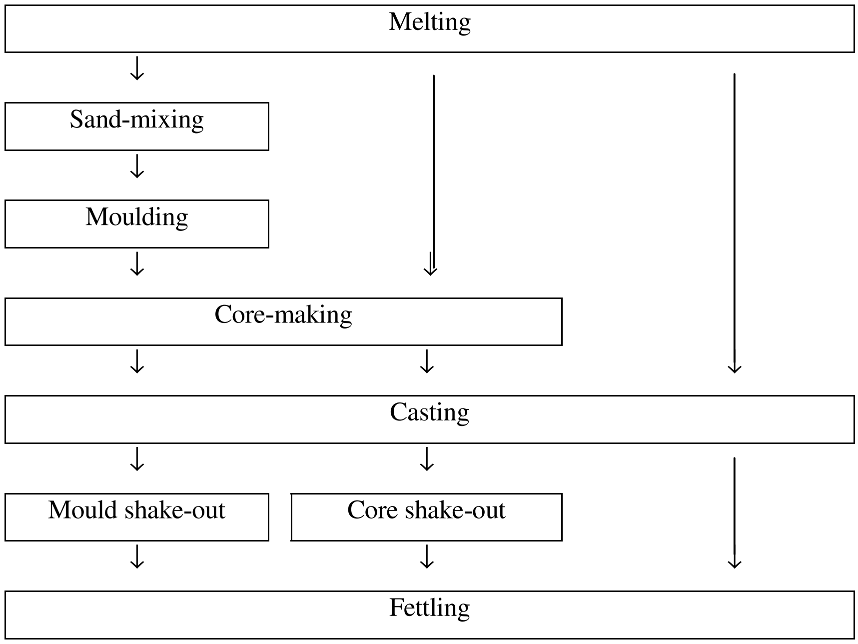

Figure 1. Key work operations in foundries

2.3 THE HOT BOX METHOD

Some foundries use the so-called Hot Box method, introduced 50 years ago in the foundry industry, to make cores for hollow castings. In this method, a liquid binder based on a furfuryl alcohol or phenol resin is mixed with a curing agent that contains nitrate or chloride and dry sand. All conventional Hot Box binders also contain urea and formaldehyde. The mixture is blown into a heated core box, then acid is released upon heating, usually to temperatures of 230 ºC to 290 ºC, which induces rapid curing. The cores are used in casting and removed after the metal has solidified (Archibald & Smith, 1988).

Exposure to isocyanates in foundries has historically been associated with the use of isocyanate-based chemical binders for core production, most commonly MDI used to generate polyurethanes in the Cold Box method (Archibald & Smith, 1988). During the thermal degradation of polyurethane binders (which contain isocyanate functional groups), both mono- and di-isocyanates may be released. Accordingly, increased air concentrations of MDI, phenyl isocyanate and aromatic amines (in particular aniline), arising from the thermal degradation of urethane binders during casting have been detected (Renman, et al., 1986). This also applies to nitrogen-containing binders. Hence, monoisocyanates have been detected in numerous new exposure situations, including casting where Hot Box core binders are used (Lilja, et al., 2000a). The Hot Box method has been shown to generate low molecular weight isocyanates such as ICA and MIC; notably ICA levels up to 190 µg/m³ and MIC levels up to 29 µg/m³ were measured in a study of two brass foundries by Lilja, et al., (2000b).

2.4 ISOCYANATES

Isocyanates are a group of highly chemically reactive agents, and both di- and pre-polymerised isocyanates are used to form polyurethane. They are commonly used in soft and hard foam plastics, insulation materials, two-component adhesives, foam rubber, and various types of paints and hardeners, e.g. in the automobile industry. Health effects of diisocyanates have been evaluated, and their main reported adverse effects are respiratory disorders, such as asthma, and irritative effects on the mucous membranes and skin (Criteria Group for Occupational Standards, 2001).

2.5 LOW MOLECULAR WEIGHT ISOCYANATES

The text in this section is essentially based on a document from a Swedish criteria group (Criteria Group for Occupational Standards, 2002). At temperatures above 0 ºC ICA is an unstable liquid with a boiling point at 23.5 ºC. Various reactions have been described, for instance ICA has a tendency to polymerize into cyanuric acid. It is soluble in water, but disintegrates both via ionization and by hydrolysis into ammonia and carbon dioxide (Belson & Strachan, 1982). ICA is not commercially available due to its instability. It is usually found together with MIC in welding plumes and around castings, often in concentrations up to 10 times higher.

MIC is a clear liquid at room temperature with a boiling point at 39 ºC. It is sparingly soluble in water, but reacts violently on contact with water, massively releasing heat. The odour threshold is above 5 mg/m³. MIC is used in the production of carbamate pesticides (Bucher, 1987) and in manufacture of polymers and coatings (Anonymous, 1984). Photolytic breakdown of sodium methyldithiocarbamate releases some MIC, thus it can occur in the air around application points of the pesticide (Geddes et al, 1995). The Swedish Chemicals Agency has received no reports of the substance's use for any commercial purposes in Sweden (Åsa Almkvist, personal communication, 2012). MIC is found in tobacco smoke; measured contents in the main stream from cigarettes range from 1.5 to 5 µg per cigarette (IARC, 1986). In the laboratory, MIC has also been identified in emissions arising from the thermal breakdown or chemical transformation of carbamide resin binder present in some mixtures of core sand and mineral wool (Karlsson, et al., 1998b; Lilja et al., 2000a). Thermal degradation of polyurethane-based core binders is a further important source of low molecular weight isocyanates. Exposure measurements in foundries indicate that MIC occurs primarily where Hot Box cores are used in die-casting (Lilja, et al., 2000b). In addition, monoisocyanates may be formed and emitted when polyurethane paints, glues or lacquers are thermally degraded in processes such as welding, cutting or grinding operations in automobile repair shops (Antonsson, et al., 2000). An estimated 7,500 individuals are occupationally exposed to ICA and MIC in Sweden, mainly in the automobile industry (SWEA, 2005d). Due to their prevalence and potential health effects, analytical methods for determining low molecular weight isocyanates, like ICA and MIC, at low concentrations have been developed (Karlsson, et al., 1998b, Spanne, et al., 1999).

2.6 HEALTH EFFECTS

Apart from the strongly acidic liquid ICA, which reportedly causes painful blisters on the skin (Belson & Strachan, 1982), there are no data regarding toxic effects of ICA on humans or animals (Criteria Group for Occupational Standards, 2002).

Human data regarding MIC are also sparse. A study on dose-response relationships in four individuals found health effects at considerably higher exposure levels than those measured in Swedish foundries. In the cited short-term exposure study, no effects were detected at 1 mg/m³, but exposure to 4.8 mg/m³ for up to 5 minutes provoked ocular and mucous membrane irritation, the symptoms increased at 9.6 mg/m³ and were reportedly intolerable at 100 mg/m³ (Kimmerle & Eben, 1964). A chamber study by the Mellon Institute, USA (Mellon Institute, 1970), cited in a report from a European scientific committee (SCOEL, 2006), also exposed subjects (eight volunteers) for short periods; all reported ocular symptoms at 4.2 mg/m³ and several reported respiratory symptoms. However, the effects disappeared within 10 minutes after the exposure, except in one woman who reported "having something in her eyes" for 45 min. At 1.2 mg/m³, all reported ocular irritation after 10 minutes. Throat irritation was less evident (Table 2).

A study of workers with long-term, low-level exposure to MIC at a chemical facility found no detrimental effects on lung function (Avashia, et al., 1996). However, massive exposure to MIC following accidental emission in Bhopal, India, in 1984 resulted in ca. 2,500 people dying within a week, and survivors displayed dyspnea as well as injuries to the eyes and respiratory tract. Exposure levels to MIC were subsequently estimated to have reached 200 mg/m³ (Dhara & Dhara, 1995), and a study of chronic health effects after the Bhopal accident found a higher prevalence of respiratory symptoms and a lower mean mid expiratory flow rate associated with residence close to the site of release (Cullinan, et al., 1997).

Irritation of the upper and lower airways is the most commonly reported effect in animal experiments, and permanent lung damage at higher doses, as illustrated by the following findings. Exposure to 7.2 mg/m³ MIC for 6 hours/day for four days led to bronchial fibrosis in mice examined by Hong, et al. (1987). Ferguson, et al. (1987) and James, et al. (1986) observed 50 % decreases in respiratory rates (RD50), indicating sensory irritation, in mice exposed to 4.6 mg/m³ MIC for 90 minutes and 7.0 mg/m³ for 30 minutes, respectively. Stevens, et al. (1987) registered no changes in the lung function of rats exposed to 7.2 mg/m³ for two hours, but exposure to 24 mg/m³ depressed their diffusing capacity. Dodd, et al. (1987) recorded no respiratory effects in rats of the substance at 1.4 mg/m³, but exposure to 7.4 mg/m³ for 6 hours/day for 4+4 days resulted in lesions in the respiratory tract.

MIC-specific immunoglobulin antibodies (IgE, IgG and IgM) were observed in a limited number of Bhopal victims during the Indian disaster (Karol & Kamat, 1988).

Table 2. Effects in volunteers of short-term controlled exposure to MIC (SCOEL, 2006).

Exposure level (mg/m³)	**Exposure duration (minutes)**	**Effects**	**Reference**
100	1-5	Unendurable irritation	Kimmerle and Eben, 1964
9.6	1-5	Severe irritation of mucous membranes	Kimmerle and Eben, 1964
4.8	1-5	Tearing, irritation of eyes, nose and throat	Kimmerle and Eben, 1964
4.2	1	Eye irritation in all of 8 subjects Tearing in 7 subjects Nose or throat irritation in 3 subjects Odour perception by none	Mellon Institute, 1970 cited in SCOEL 2006
1.2	5	Eye (5 of 6 subjects), nose (5) and throat (3) irritation, tearing (5) subjects	Mellon Institute, 1970 cited in SCOEL 2006
	2	Eye (3 of 6 subjects) and throat (1) irritation	
	1	No irritation	
1.0	1-5	No irritation	Kimmerle and Eben, 1964

2.7 FORMALDEHYDE

A criteria document concluded that 0.3 mg/m³ formaldehyde is the lowest level at which human sensory irritation may occur in a low, but significant, percentage of exposed workers (Wibowo, 2003). Irritation to formaldehyde is first experienced in the eyes. For most people, irritation does not occur until they are exposed to at least 1.2 mg/m³ (Paustenbach, et al., 1997). Mild, reversible changes in lung function have been reported in sensitized individuals at levels approaching 2.4 mg/m³ (Bender, 2002).

Antibodies against formaldehyde, due to exposure in the respiratory tract, have also been found (rarely), and the relationship between sensitization and occurrence of symptoms is uncertain (Bardana & Montanaro, 1991; Wantke, et al., 2000).

2.8 OCCUPATIONAL LUNG DISEASES

Silicosis is a well-known occupational lung disease caused by exposure to quartz dust, in foundries for example (Muldon, et al., 1996). In recent decades, the incidence of silicosis in Sweden has declined dramatically, but new cases still occur occasionally. Other forms of lung damage are commonly observed in people who work in dusty environments (Becklake, 1985), but the precise cause of this damage is unclear. Workers may be exposed to complex mixtures of substances under diverse conditions, including various air pollutants in addition to large quantities of dust in such working environments. Several studies have found impaired lung function in foundry workers (Gomes, et al., 2000; Johnson, et al, 1985; Kuo, et al., 1999; Mikov, 1974) and workers in other trades (Mwaiselage, et al., 2004; Wu, et al., 2004), and both the size and chemical properties of dust particles may influence effects on the respiratory system in these (and other) environments (Schlesinger et al, 2006). Occupational asthma is associated with TDI exposure. However, there is no consistent evidence of decreased FEV_1 from exposure to mean levels up to 36 µg/m³ of TDI (Ott, 2002).

2.9 OCCUPATIONAL RHINITIS

Occupational rhinitis is two to four times more prevalent than occupational asthma, and various studies have found that it precedes the development of asthma in 20-78% of affected subjects (EAACI, 2008). In a study of painters exposed to toluene-diisocyanate, 42% were found to be suffering from occupational rhinitis (Ucgun et al, 1998). Similarly, a questionnaire-based study of workers exposed to methylene bisphenyl-diisocyanate in a moulding plant found that 36% had occupational rhinitis (Bernstein, et al., 1993), and Finnish metal foundry workers reported occupational rhinitis more often than a population-based cohort of all employees (SRR 4.3, 95% CI 1.6-11.0; Hytönen, et al., 1997). On the other hand, a European multi-centre follow-up study of workers engaged in manufacturing and treating metal found the risk of occupational rhinitis to be low, with ORs of 0.9 and 0.5 for new incidences of allergic rhinitis and perennial rhinitis, compared to office workers (Radon, et al., 2008). In a study of rhinitis symptoms in German adolescents early in their working life, metal workers were found to have an OR of 1.8 (95% CI, 0.8-3.9) compared to unexposed individuals. The OR for physician-diagnosed rhinitis in the exposed group was 0.6 (Riu, et al., 2007).

2.10 OCCUPATIONAL EXPOSURE LIMITS AND LEGAL ASPECTS

An OEL is the highest exposure level of a given substance allowed in work environments by the pertinent authority (in Sweden the Swedish Work Environment Authority**,** SWEA). A threshold 8-hour time-weighted average (TWA) is intended to protect almost all workers from health effects, even if they are exposed at that level for 8 hours every day during their working life (Table 3) (SWEA, 2005b).

Table 3. Present Swedish OELs (8-hour TWA) and year of introduction for selected substances in the work environment of foundries using the Hot Box method (SWEA, 2005b).

Substance	8 hour TWA ($\mu g/m^3$)	Introduced (year)
ICA	18	2004
MIC	24	2004
Formaldehyde	600	1987
Inhalable dust	10,000	2004

Before 2004, there were no specific Swedish OELs for ICA and MIC. The OEL for isocyanates from 1993 was also used for ICA and MIC, but this was not the initial intention, because these substances were not recognised in the work environment when the OEL was established.

From 1974 to 2004, there was a Swedish OEL for inorganic total dust (10,000 $\mu g/m^3$), but it was rejected as an OEL for inhalable dust.

If exposure to ICA or MIC occurs in the work environment, the employer is obliged to allow the employee to have a medical examination, including spirometry, before employment begins or if respiratory symptoms occur during employment (SWEA 2005a, 2005c).

3 AIMS OF THE STUDIES

The objectives of the studies this thesis is based upon were to elucidate the exposure to low molecular weight isocyanates of workers in Swedish foundries using Hot Box core binders and their health, especially respiratory symptoms and lung function.

The specific questions addressed were:

What are the exposure levels to low molecular weight isocyanates in Swedish foundries using Hot Box core binders?

What respiratory symptoms are reported by foundry workers using Hot Box core binders?

Are there any signs of acute or residual effects on lung function in this work environment?

Have symptoms and lung function changed over time, and if so how?

Is there any association between exposure to these substances and health parameters?

4 MATERIAL AND METHODS

4.1 SURVEYED POPULATIONS IN STUDIES I AND II

The first studies were based on foundry workers in the four Swedish foundries (three brass foundries and one grey iron foundry) producing cores with the Hot Box method. The binder in use at all foundries was based on a carbamide-formaldehyde resin (<1% formaldehyde) and a curing agent containing ammonium nitrate (10-15%), urea and sodium hydroxide or water. The brass foundries were producing water taps, and the grey iron foundry spare parts for the automobile industry. During core production, both manual and enclosed automatic core machines were used, similarly during die-casting both manually operated and enclosed robots were used.

In Study I the surveyed population comprised a group of workers who were exposed to emissions arising from the thermal degradation of the chemical binders used in the Hot Box method, and in study II both these and a second group of workers who were not exposed (as defined by officials from the participating companies and the local occupational health services) participated. The exposed group consisted of all 74 individuals who worked with the Hot Box method in the foundries, and thus monoisocyanates were potentially their main occupational exposure. Ten workers (14%) in the exposed group declined to participate. In the brass foundries, core-makers, die-casters and fettlers were included (in total 40 workers) and in the grey iron foundry 24 core-makers. The exposed workers did not wear respiratory protection.

At each foundry, employees working outside the core-production and die-casting halls, such as assembly workers and storage workers with no significant chemical exposure, were recruited as referents. The referents did not work in areas of core production or die casting and were assumed not to be exposed to ICA, MIC, formaldehyde, dust, or other harmful chemical agents. They were working on assembling, polishing, surface coating, and product-testing, in areas well separated from the foundries.

The assumption that referents were unexposed was supported by the observation that only low levels of oil mist (<20% of the Swedish OELs of 1 mg/m^3) were measured in the areas where they worked in one of the foundries.

The intention was to match referents to those exposed by gender and age. When someone declined to participate, a new person was invited to take part in the study as a referent. The target was to include twice as many referents as exposed subjects. One hundred and ninety-three individuals were invited and 59 (31%) of these declined to participate.

4.2 SURVEYED POPULATION IN STUDY III

The three Swedish brass foundries included in Studies I and II also participated in Study III, but the iron foundry declined to participate. The study population comprised exposed workers and referents according to the criteria applied in Studies I and II. The exposed group consisted of all 48 individuals who worked with the Hot Box method in the three included foundries. Eighty-four individuals were identified and asked to participate as referents. Seventy-two per cent of all the subjects in this study also participated in the initial study four years earlier. Forty-three (90%) of the exposed individuals and 82 (98%) of the referents participated in the study.

The assumption that referents were unexposed was supported by the observation that only low levels of total dust (<20% of the Swedish OELs of 10 mg/m³) were measured in the areas where they worked in all foundries.

4.3 SURVEYED POPULATION IN STUDY IV

At follow-up four years after the base-line study, one of the foundries declined to participate, which considerably reduced the study base. Among the remaining subjects from Study II, 14 exposed workers and 25 referents were unavailable for the follow-up due to changes in their work tasks (six exposed and 10 referents), retirement (two exposed and four referents), health problems (three exposed and one referent) or new work elsewhere (three exposed and 10 referents). Accordingly, at follow-up the exposed group consisted of 26 workers still involved with the Hot Box method and 56 referents still working outside the core-production and die-casting halls. One worker in each group chose not to participate, leaving 25 exposed workers and 55 referents for the study.

4.4 METHODS APPLIED IN STUDY I

Individual exposure to ICA, and MIC was measured over four or five sampling periods of 5 minutes duration, randomly distributed over the course of a single shift in the foundry. Exposure to formaldehyde and total dust was measured over a single 8-hour sampling period. The measurements were considered to reflect individual exposure during a shift, and 8-hour averages were calculated for ICA and MIC.

Isocyanates were sampled by liquid chemosorption using impinger bottles, containing 0.01 M dibutylamine dissolved in toluene (Karlsson, et al., 1998b; Tinnerberg, et al., 1997), and formaldehyde was sampled with diffusive samplers (GMD Systems, Inc.), which exploit a reaction between aldehydes and dinitrophenylhydrazine (Levin, et al., 1988).

The monoisocyanates and formaldehyde were analysed with LCMS and HPLC techniques, respectively (Karlsson, et al., 1998a). All analyses were performed by the SBACA-accredited laboratory at the Department of Occupational and Environmental Medicine, Örebro University Hospital.

4.5 METHODS APPLIED IN STUDY II

Individual exposure to ICA, MIC and formaldehyde was measured as described in Paper I. Exposure variables such as mean levels of ICA, MIC and formaldehyde were used in the analyses of the impact on lung function. In addition, the lung function of the workers was evaluated, and a week before spirometric measurements a questionnaire was distributed to the participants by a company official. The questionnaire was originally in English, but was translated into Swedish for use in studies of workers exposed to organic acid anhydrides (Nielsen, et al., 2001). It covered work tasks, exposure during work and leisure, tobacco habits and health status with particular reference to respiratory symptoms. A short questionnaire regarding tobacco habits during the day and respiratory symptoms was also administered to the workers after their shifts on the days of spirometric measurements.

The exposed workers were categorised into groups (core-makers, die-casters and other exposed) based on their answers to questions regarding work activities in the questionnaire. In unclear cases, the information regarding profession was evaluated by an occupational hygienist. Lung function was investigated using a dry-wedge bellows spirometer (Vitalograph, Buckingham, United Kingdom) according to ATS guidelines (ATS, 1995). Spirometry was performed immediately before and after a day shift; for the exposed group this was done after an unexposed period of at least two days. The results were expressed as percentages of predicted VC and FEV_1, using gender-specific Swedish reference materials. (Hedenström, et al., 1985, 1986). For each individual, the exposure measurements were taken on the same day as the lung function tests. Exposure variables such as present work category, time in present job, and mean levels of MIC and formaldehyde were used in the analyses of the substances' impact on lung function.

4.6 METHODS APPLIED IN STUDY III

Individual exposure to ICA, MIC and formaldehyde was sampled and analyzed as described in Papers I and II. Exposure to total dust was measured over a single 8-hour sampling period, and the measurements were considered to reflect individual exposure during a shift. Exposure variables such as mean levels of ICA, MIC, formaldehyde and total dust were used in the analyses of the substances' impact on nasal signs and symptoms and ocular symptoms. Total dust was sampled using personal HFS-pumps with flow rates varying between 1-5 L/min. The aerosol was adsorbed on cellulose ester filters with a pore size of 0.3 µm; these were connected to impinger bottles and subjected to a sampling flow of 1 L/min. Total dust was sampled using a modified version of NIOSH method 0500 for "Particulates, not otherwise regulated" (NBOSH, 1979; NIOSH, 1994).

Individuals in the exposed group were classified into subgroups according to their individual exposure to ICA, MIC and dust: individuals exposed to quantities greater than the median of the group were placed in one subgroup, while those with exposures below the median were placed in another. In the case of formaldehyde, a similar classification was applied, but in this case the threshold was the limit of detection of formaldehyde: highly exposed individuals were those exposed to any detectable quantity of formaldehyde. The referent group was used as an unexposed standard.

A week before the investigation, the questionnaire used in study II was distributed to the participants by a company official. In addition, the participants were subjected to nasal examinations, after completing a short additional questionnaire regarding their nasal and ocular symptoms during the preceding week. The questions concerning nasal symptoms had been used in an earlier study (Wålinder, et al., 1998).

Both the exposed subjects and the referents were examined by an experienced rhinologist, who was not informed of the examinees' exposure status. He documented the examinees' nasal status including mucosal dryness, crusts, dampness, swelling and redness. Participants were judged to exhibit nasal signs if there was evidence of harm or irritation in at least one of their nostrils.

To assess the 'total pollutant level' to which an individual was exposed, an integrated metric was devised; the measured concentration of each pollutant was divided by its OEL to give a ratio, the ratios of each pollutant examined were then summed, and this sum was used as an integrated measure of the total exposure of workers to airborne irritants.

4.7 METHODS APPLIED IN STUDY IV

The self-administered questionnaire on respiratory and ocular symptoms used in study II and III was redistributed to the participants by a company official.

Lung function was investigated before and after a day shift in the same manner as in study II.

Serum samples originally collected in 2001 and kept frozen were thawed and analysed at follow-up using ImmunoCAP Phadiatop assays (Phadia AB, Uppsala, Sweden) to obtain immunological indications of atopy (Vidal, et al., 2005).

Each subject's individual exposure to ICA, MIC and formaldehyde was measured as previously reported. Briefly, the exposure over a work shift to monoisocyanates was calculated from the mean level obtained from four to five short-term (5 minutes) samples, whereas formaldehyde levels were obtained from full-shift samples. To investigate the association of current lung function with the work environment, individual mean exposure levels in 2001 and 2005 were calculated.

The jobs held by the referents in both 2001 and 2005 were considered to not involve exposure to ICA, MIC or formaldehyde.

4.8 STATISTICAL METHODS APPLIED IN STUDY I

Air concentrations were characterized from results of analyses of the individual ICA, MIC and formaldehyde samples, and TWAs were calculated for the total number of measurements, different jobs and foundries. As the air concentrations were approximately log-normally distributed, they were expressed as the GMs and corresponding GSDs. In addition, for some statistical analyses, following Seixas, et al. (1988), parameters of the normally distributed air concentrations were also applied. Univariate analysis of variance, with Tukey post hoc tests, was applied to the ICA and MIC concentrations, with the different foundries and job titles as explaining variables. The within- and between worker variability was assessed using variance component estimation.

4.9 STATISTICAL METHODS APPLIED IN STUDY II

Differences in the mean age between exposed and referent subjects were analysed using Student's t-test, the median number of symptoms with the Wilcoxon rank sum test, and the prevalence of individual symptoms with the χ^2-test. In the analysis using the Wilcoxon rank sum test non-responses to individual questions were interpreted as the respondents not having symptoms, while in the analyses with the χ^2-test, they were treated as missing values. Differences between lung function before shift and expected values were evaluated with Student's t-test. Linear regression analysis was used to estimate differences between work categories in lung function before shift and changes over shift. Multiple regression was used to study the relationship between lung function before shift and the following explanatory variables: time in present job for core-makers, die-casters and other exposed subjects; BMI; and smoking habits (pack-years). Multiple regression was also used to analyse the relation between changes in lung function over shift and mean levels of monoisocyanates and formaldehyde, as well as smoking, during the day of investigation. The high correlation between ICA and MIC made it difficult to separate their effects from each other. Consequently, the means obtained from analyses of the short-term samples of ICA and MIC were used as independent variables in separate regression analyses of changes in lung function over shift. Logarithmic transformation was used for ICA, MIC and formaldehyde in the analyses.

4.10 STATISTICAL METHODS APPLIED IN STUDY III

The characteristics of the study population were analysed using χ^2 and Student´s t-tests, while the prevalence of nasal signs and individual symptoms in relation to exposures were analysed using logistic regression. The mean concentrations of ICA and MIC to which each worker was exposed over the course of a shift were calculated. Spearman's rank correlation coefficient analysis was used to calculate correlations between exposures to different substances. A first set of analyses encompassed all of the subjects, but in addition some analyses of subgroups of the subjects were conducted. In order to study the effects of asthma and allergies on the results, a set of analyses was also performed in which asthmatic and allergic subjects were excluded. The composition of the exposed group differed somewhat from that of the referents, notably in terms of gender distribution and smoking habits. Consequently, further analyses were performed in which only male subjects were considered or smokers were excluded.

4.11 STATISTICAL METHODS APPLIED IN STUDY IV

Spearman's rank correlation coefficient analysis was used to assess the correlations between the investigated chemical agents. Differences in the characteristics of the study populations were analysed using χ^2 or Student´s t-tests, as appropriate. Differences in symptom prevalence were compared using χ^2-tests and Odds Ratios. Effects on lung function were analysed using Student´s t-test, Spearman's rank correlation coefficient analysis and multiple linear regression.

In all studies levels of ICA, MIC and formaldehyde below the DL in individual samples were assigned a value of $DL/\sqrt{2}$ (Hornung & Reed, 1990).

P-values <0.05 were regarded as statistically significant, and 95% CIs were calculated for the regression parameters.

5 RESULTS

5.1 RESULTS FROM STUDY I

For each individual, 4-5 short-term air samples of low molecular weight isocyanates, in total 298 samples, were taken and analysed. Sixty-four individual 8 h TWAs were calculated, representing the exposure of 15 die-casters, 39 core-makers and 10 other exposed subjects. In addition, one full shift sample of formaldehyde was acquired (Table 4).

Table 4. Measurements of the exposure of foundry workers (individual 8 h TWAs) to ICA, MIC and formaldehyde.

Chemical agent	Air concentration (µg/m³)					
	n	GM	GSD	AM	SD	Range
ICA	64	27	2.3	38	34	<4-190
MIC	64	5.3	2.1	7.3	7.1	<4-31
Formaldehyde	64	120	2.8	190	250	14-1,600

The exposures to ICA and MIC in the grey iron and three brass foundries were similar, although the cores and casting techniques in the two classes of foundry differed, but the exposure pattern differed between the work categories. However, high levels of formaldehyde were attributed to one particular foundry.

Notably, die-casters were exposed to the highest TWA levels of monoisocyanates, and core-makers were exposed to higher air concentrations of formaldehyde than die-casters. A comparison between foundries revealed that core-makers and die-casters in one of the foundries were exposed to ca. 2 or 3 times higher air concentrations of both ICA and MIC than their counterparts in the other foundries.

An analysis of variance designed to identify factors affecting air concentrations of ICA and MIC showed that workers' exposure to the substances was significantly affected by both their job title ($F=54.14$ and 41.40) and, to a lesser extent, the foundry they worked in ($F=17.11$and 7.50).

The total GSD_B and GSD_W varied from 1.5 to 2.3, and the GSD_B for ICA (but not MIC) was slightly higher than the GSD_W. The variance ratio (λ) of the two variability measures ranged from 0.77 to 0.89, and the ratio of the 2.5% and 97.5% (the 95% CI limits) for the between-worker variability (R_{95B}) for all workers was higher or equal to those of the job titles.

5.2 RESULTS FROM STUDY II

There were strong correlations between peaks and means of air concentrations obtained from short-term samples for both ICA (r=0.97) and MIC (r=0.96), and between means obtained from analyses of short-term samples of ICA and MIC (r=0.78), but their correlations with formaldehyde were very low (r=0.09 and r=-0.20).

The exposed group reported a higher prevalence for most symptoms in the previous year than the referents (Table 5). Dripping or blocked nose during the preceding year was the most prevalent symptom among both exposed and referent subjects, but the proportion of affected workers was similar in both groups. Lower airway symptoms (wheezing, breathlessness or tightness in the chest) during the previous year were most frequently reported by core-makers, and none of the die-casters reported these symptoms. Ocular irritation and coughing without infection were significantly more prevalent among exposed workers, especially core-makers. These were also the most common work-related symptoms reported by exposed workers, who reported them significantly more often than referents. The total incidences of ocular and respiratory symptoms (median 2 vs. 1; not in table), and work-related symptoms, were also higher among the exposed workers than referents. Excluding asthmatic subjects from the analysis did not change the results.

Lung function (VC and FEV_1) before shift was significantly lower than predicted for both exposed workers and referents, but particularly for core-makers (Table 6). BMI was significantly negatively associated with both VC and FEV_1 before shift, according to multiple regression analysis. FEV_1 also decreased with smoking, expressed as number of pack-years. Time in present job for core-makers, die-casters, and other exposed workers, did not influence lung function significantly before shift. However, when those with asthma were excluded, significant negative effects of time spent as core-maker on both VC and FEV_1 were detected, while the effect of smoking on FEV_1 became non-significant.

The decreases over shift of VC and FEV_1 were limited, but significantly greater among exposed foundry workers compared to referents, and the change was most pronounced among core-makers (Table 6). This pattern was similar in each of the foundries. With regard to changes in lung function, there were no significant effects of ICA, MIC, formaldehyde, or smoking during the day of investigation. Excluding subjects reporting asthma did not change the results.

Reanalysing the study data after excluding 12 former foundry workers among referents did not substantially change the results either. Only a negative effect of time spent as core-maker on VC (p=0.044) arised.

Table 5. Frequencies of symptoms and their relation to work as reported by exposed foundry workers (n=64) and referents (n=134).

	Exposed		Referents	
	n	**%**	**n**	**%**
During the last year, have you experienced:				
- whistling or wheezing in your chest?				
Yes	12	19	22	17
- related to work?	4	7	2	2
No	52	81	111	83
- waking up with tightness in your chest?				
Yes	8	13	6	5
No	53	87	115	95
- attacks of breathlessness?				
Yes	6	10	10	8
- related to work?	3	5	1	1
No	57	90	123	92
- attacks of cough without infection?				
Yes	19	30*	21	16
- related to work?	10	16*	5	4
No	45	70	112	84
- fever attacks?				
Yes	5	8	13	10
- related to work?	1	2	0	0
No	59	92	121	90
- running, itchy eyes?				
Yes	25	39*	32	24
- related to work?	19	30*	6	5
No	39	61	102	76
- dripping or blocked nose?				
Yes	28	44	61	46
- related to work?	7	11*	3	2
No	36	56	71	54
- nose bleeding?				
Yes	19	31	29	22
- related to work?	6	10*	3	2
No	43	69	104	78

* Significant difference versus referents ($p<0.05$)

Table 6. Pre-shift lung function (VC and FEV_1) and changes in lung function over shift among exposed foundry workers and referents.

	Exposed								Referents	
	Core-makers n=39		Die-casters n=15		Other exposed n=10		All n=64		n=134	
VC	%	SD	%	SD	%	SD	%	SD	%	SD
Before	90.7*	10.2	97.2	12.7	97.5	15.8	93.3*	12.1	93.9*	10.8
After	88.5	9.9	95.7	11.7	95.5	16.3	91.3	11.8	93.2	10.5
Difference	-2.2**	3.0	-1.5	2.8	-2.0	2.3	-2.0**	2.8	-0.7	3.0
FEV_1										
Before	92.4*	10.3	96.6	11.5	98.6	15.7	94.4*	11.6	96.3*	11.6
After	90.4	11.0	96.9	11.1	97.5	17.8	93.0	12.5	96.4	11.7
Difference	-2.0**	4.8	0.3	3.0	-1.1	3.0	-1.4**	4.3	0.1	3.8

* Significant difference versus predicted value (reference material; p<0.05).
** Significant difference versus referents (p<0.05).

5.3 RESULTS FROM STUDY III

The GMs of the measured ICA, MIC, formaldehyde and total dust exposure levels were 12, 3.1, 37 and 360 µg/m³, respectively. All measurements of MIC, formaldehyde and total dust were below the Swedish OELs and 64% of ICA measurements.
The correlations between the peak exposure levels of ICA and MIC (r=0.87), and those between the mean exposure levels over short periods to ICA and MIC (r=0.92), were higher than all other correlations between ICA, MIC, formaldehyde and total dust exposure levels (r=-0.08-0.65). In general, the results obtained using peak levels of ICA and MIC mirrored those obtained using the mean levels.

All subjects classified as being highly exposed to ICA were also highly exposed according to an integrated measure of exposure based on the summed ratios of the measured exposure levels to the OELs for each substance monitored.

High proportions of both groups reported having experienced nasal symptoms at some point during the preceding year (53% of all the exposed workers vs. 46% of the referents), but the percentage of individuals reporting either any nasal symptom or nose bleeding did not differ significantly between the groups, and these events were not significantly associated with exposure. The prevalence of nasal symptoms among individuals exposed to the foundry environment for more than five years was lower (43%) than that for the exposed group as a whole. Ocular symptoms were reported by 33% of all the exposed workers and the referents. Work-related nasal symptoms during the preceding year were more prevalent among (all) members of the exposed group (OR 5.8, 95% CI 1.5-22.9). The symptoms were associated with exposure to all of the agents examined, and dose-response relationships between symptoms and the measured levels of ICA and MIC were detected when the exposed individuals were divided into low and high exposure groups. Work-related nose bleeding and ocular symptoms were not significantly associated with exposure.

Compared to the referents, a greater proportion of all members of the exposed group experienced nasal symptoms during the week immediately preceding their nasal examination (74% vs 39%; OR 4.6, 95% CI 2.0-10.7). Specific symptoms such as nasal discharge (OR 3.0, 95% CI 1.3-7.2) and sneezing (OR 3.1, 95% CI 1.2-7.8) were more prevalent among the exposed individuals than the referents. Significant associations between most exposures and symptoms were detected when the exposed individuals were divided into low and high exposure groups. A dose-response relationship between the prevalence of any nasal symptom and exposure to ICA, MIC and formaldehyde was also observed (Table 7). The prevalence of irritated eyes in the week immediately preceding testing correlated with high exposure to formaldehyde (OR 6.3, 95% CI 1.4-28.4), but no significant relationship was detected between six other ocular symptoms and exposure to any of the agents investigated in this study (data not tabulated). However, the affected individuals did not offer any clear opinions as to whether their nasal and ocular symptoms were work-related and declined to answer questions about any such potential relationships.

Table 7. Prevalence of nasal symptoms during the week before the examination in brass foundry workers exposed to air pollutants and referents.

Exposure	**Any nasal symptom**	
	OR	**95% CI**
ICA		
unexposed (n=67)	1	
low exposed (n=21)	**3.9**	**1.4-11.5**
high exposed (n=21)	**5.0**	**1.6-15.4**
MIC		
unexposed (n=67)	1	
low exposed (n=21)	**3.9**	**1.4-11.5**
high exposed (n=21)	**5.0**	**1.6-15.4**
Formaldehyde		
unexposed (n=67)	1	
low exposed (n=30)	**4.3**	**1.7-11.2**
high exposed (n=12)	**4.7**	**1.2-19.1**
Total dust		
unexposed (n=67)	1	
low exposed (n=21)	**6.7**	**2.0-22.1**
high exposed (n=20)	2.9	1.0-8.3

Significant results in **bold.**

The incidence of at least one clinical sign was significantly more common among the exposed workers (88%) than among the referents (67%) (OR 3.7, 95% CI 1.3-10.8). Dry mucosa with or without crusts was also more prevalent among the exposed individuals than the referents (OR 2.6, 95% CI 1.2-5.7). However, when the exposed individuals were divided into low and high exposure groups, significant associations between dry mucosa and all exposures (with weak indications of a dose-response relationship for dust) were detected (Table 8). There were no significant associations between exposure and other nasal signs.

Excluding subjects suffering from asthma or allergies, females, or smokers did not change the results substantially.

Table 8. Prevalence of nasal signs in brass foundry workers exposed to air pollutants and referents.

Exposure	**Dry mucosa with or without crusts**	
	OR	**95% CI**
ICA		
unexposed (n=67)	1	
low exposure (n=21)	**4.5**	**1.5-13.6**
high exposure (n=21)	1.9	0.7-5.0
MIC		
unexposed (n=67)	1	
low exposure (n=21)	**4.5**	**1.5-13.6**
high exposure (n=21)	1.9	0.7-5.0
Formaldehyde		
unexposed (n=67)	1	
low exposure (n=30)	**2.8**	**1.1-6.9**
high exposure (n=12)	2.8	0.8-10.2
Total dust		
unexposed (n=67)	1	
low exposure (n=21)	2.3	0.8-6.2
high exposure (n=20)	**4.2**	**1.4-12.8**

Significant results shown in **bold.**

5.4 RESULTS FROM STUDY IV

The GMs of ICA, MIC and formaldehyde concentrations at follow-up were substantially lower (by approximately 50%) than those recorded in 2001 in the same foundries. In accordance with the previous findings, a significant correlation between ICA and MIC was observed (r=0.85 and 0.80 in 2001 and 2005, respectively). The variation in individual exposure levels between different years was characterised by lower but significant correlation coefficients for ICA (r=0.50) and MIC (r=0.32). The correlation between formaldehyde levels in different years was not significant (r=0.31; p=0.13).

A dripping or blocked nose was the most common symptom in both groups in 2001 and at follow-up, but the prevalence had increased among the exposed workers at follow-up. However, nose bleeding was less frequently reported at follow-up (Table 9). At least one nasal symptom was reported by 57% of the exposed workers compared to 47% of the referents at follow-up (data not shown), similar to the proportions obtained in 2001. Thirty-two percent of the exposed group reported a dripping or blocked nose in 2001 and at follow-up, compared to 22% of the referents in both years. In correspondence with the higher overall prevalence of dripping or blocked nose, work-related dripping or blocked nose in exposed workers had increased from 8% in 2001 to 17% at follow-up. A dripping or blocked nose at baseline was more common among subjects no longer in exposed jobs at follow-up compared to subjects that were still exposed (OR 1.9, 95% CI 0.4-8.6).

Lower airway symptoms were less frequent in both groups at follow-up than in 2001 (Table 9). Cough without simultaneous infection was reported only by smokers or former smokers. Ocular symptoms had decreased among the exposed subjects at follow-up compared to 2001, but they were still common in both exposed workers and referents. For the exposed group, the incidence of work-related ocular symptoms decreased between 2001 and 2005 from 24% to 8%, but remained similar for the referents (6% vs 4%; data not shown). Ocular symptoms at baseline were more common among subjects no longer in exposed jobs at follow-up compared to subjects that were still exposed (OR 1.7, 95% CI 0.4-7.9).

Table 9. Prevalence of mucous membrane and respiratory symptoms in exposed foundry workers and referents participating in both 2001 and 2005.

Symptom	**Exposed n=25**		**Referents n=55**	
	2001	**2005**	**2001**	**2005**
	%		%	
Did you during the last year experience:				
- Whistling or wheezing in your chest	12	4	11	5
- Awakenings by tightness in your chest[1]	13	4	4	2
- Attacks of breathlessness[1]	8	4	2	0
- Attacks of cough without infection	20	16*	11	2
- Fever attacks	0	4	4	2
- Ocular irritation	32	24	29	27
- Dripping or blocked nose	40	52	38	38
- Nose bleeding[1]	30	22	18	22

[1] Based on responses on both occasions: Awakenings by tightness in chest (Exposed n=23 and Referents n=47), Attacks of breathlessness (Exposed n=24) and Nose bleeding (Exposed n=23). * p<0.05 (exposed vs referents)

Both the exposed group and the referents had a slightly lower lung function pre-shift than predicted (Table 10). Values for VC were similar for both groups, but FEV_1 was lower for the exposed workers than referents, and this difference was larger at follow-up than in 2001. However, over a whole shift, no significant changes at follow-up were observed in either group (data not shown). Non-smoking exposed workers had significantly lower lung function compared to non-smoking referents at follow-up (FEV_1 89.8% vs 99.4%), although there was no significant difference in this respect between exposed smokers and referent smokers (data not shown).

Table 10. Lung function (VC and FEV_1 in percent of predicted values) pre-shift in foundry workers and referents participating in both 2001 and 2005 and the change (Δ) between the years.

	Exposed n=25			**Referents n=51[1]**		
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**
VC						
2001	93.1	11.8	69.9-119.6	93.9	11.8	68.1-113.6
2005	92.3	13.0	69.3-125.8	93.5	11.4	68.8-114.1
Δ (2005-2001)	-0.8	4.2	-11.2-6.5	-0.4	3.8	-11.0-5.9
FEV_1						
2001	95.1	10.9	79.8-124.5	96.4	13.3	59.7-117.3
2005	93.8	11.5	77.8-125.2	96.7	13.5	65.2-121.7
Δ (2005-2001)	-1.3	5.5	-14.0-8.8	0.3	5.3	-13.8-10.3

[1] Data missing for four referents

The decreased lung function of the exposed workers over the whole shift in 2001 correlated significantly with a decrease in lung function pre-shift from 2001 to 2005 (VC r=0.51 and FEV1 r=0.57). Multiple regression analysis, did not reveal any significant association between changes in lung function at follow-up and: exposure to MIC and formaldehyde, smoking habits (pack-years) or childhood allergy.

6 DISCUSSION

The exposure levels to ICA and MIC observed in Study I were of the same magnitude as those found in an earlier survey of Swedish foundries environments (Lilja, et al., 2000a; 2000b). In general, the die-casters were more exposed to ICA and MIC than the core-makers, but the core-makers were exposed to higher concentrations of formaldehyde.

In Study II exposed foundry workers more frequently reported ocular and airway symptoms during the preceding year than the referents, and the differences were significant for the prevalence of ocular irritation and coughing. Both groups had reduced lung function before shift compared with reference values. BMI and smoking habits, but not time in the present job, were negatively associated with lung function before shift. Among exposed workers, especially coremakers, both VC and FEV_1 decreased significantly more over shift than for referents, but the changes were not related to monoisocyanate or formaldehyde exposure estimates.

Study III focused on upper airways with reference to the results in Study II. The key findings were that nasal signs and symptoms were substantially more common in exposed workers than in the referents. The percentages of exposed foundry workers exhibiting clinical signs in the nasal mucosa (particularly dry mucosa) and reporting symptoms were significantly greater than those among the referents. Moreover, the prevalence of nasal symptoms in the week immediately preceding the examination was related dose-dependently to individual exposures to ICA, MIC and formaldehyde.

The prospective Study (IV) found that exposure to all the investigated chemical agents had decreased by about 50% compared to four years earlier. Nevertheless, the prevalence of nasal symptoms had increased in the exposed group and a high prevalence of ocular and nasal symptoms among both exposed workers and referents was still reported at follow-up, although both groups had a lower prevalence of lower airway symptoms than in 2001. In contrast with 2001, no significant change in lung function over a whole shift was observed at follow-up, but FEV_1 pre-shift was slightly lower for the exposed workers than the referents.

6.1 STUDY POPULATION AND METHODS

Participants in both the exposed and referent groups were blue-collar workers recruited from the same companies, and they also shared other background characteristics, suggesting that the data had good internal validity.

The non-participation rate was higher among referents in Study II, which may have led to overrepresentation of referents with symptoms and underestimation of the risks associated with the investigated chemical agents. However, there was a high participation rate among those exposed, which is important for validity.

The self-reported life-time incidences of asthma did not differ significantly between exposed workers and referents, and were similar to recent domestic findings in men (8.2%) and women (9.1%) (Pallasaho, et al., 2002). Swedish legislation may lead to asthmatics being selectively excluded from certain work tasks and, thus, fewer asthmatics in the exposed population. Accordingly, only one of the referents who had previously worked in the foundry was asthmatic and another reported coughing. There may also have been individuals with undiagnosed asthma or mild airway obstruction, but the proportions are unknown. For these reasons, the effect of the substances on lung function may have been larger than we found, and we also carried out analyses with all asthmatic subjects excluded.

The rate of participation was high in both groups in Study III, but the relatively small number of subjects involved in this study rendered it difficult to detect subtle effects and to identify possible dose-response relationships. The wide confidence intervals reflect the limited precision of the results due to the small number of subjects.

Swedish legislation regarding isocyanate exposure may cause employers to avoid assigning asthmatic employees to certain duties that would result in exposure. As mentioned above, this might be expected to reduce the number of asthmatics, and consequently reduce the number of subjects with rhinitis, in the exposed group. The influence of this possibility was assessed by performing secondary analyses, examining only non-asthmatic and non-allergic subjects, but the overall results remained stable. Some individuals with undiagnosed asthma or mild airway obstruction may not have been excluded from these analyses, but the numbers of such individuals cannot be known.

The loss of information caused by the non-participation of one of the original foundries in the follow-up illustrates an inherent problem of prospective studies. The loss of almost 40% of the participants in the original study reduced the statistical power of this already small study group. Other changes of exposure status in the original study group augmented this effect, resulting in only about 40% of the original participants being available for the follow-up. However, the paucity of epidemiological data on the potential effects of occupational monoisocyanate exposure was considered sufficient reason to continue this study.

As well as reducing the statistical power, the reduction of the study base also raised concerns regarding the internal validity of the remaining data. However, in a comparison of the data for the follow-up study group with data for the entire study group of exposed subjects and referents in 2001, both exposure levels and results of medical investigations were strikingly similar. These observations suggest that the follow-up data were sufficiently valid for a prospective investigation.

The same subjects were reinvestigated after four years to elucidate differences in respiratory symptoms and lung function in relation to the work environment in general, and to selected chemical agents in particular. Ideally, the results using this approach should not be affected by individual variations, but due to the small number of subjects at follow-up there were high levels of uncertainty for many of the explored relationships.

Excluding data pertaining to smokers, females or asthmatic and allergic subjects from the analysis did not substantially change the findings of this study, thus excluding such individuals from the subject pool was not necessary.

6.2 EXPOSURE MEASUREMENTS

The exposures to ICA, MIC, formaldehyde and total dust of workers with several job titles in Swedish foundries using the Hot Box core binder system were thoroughly characterized. All Swedish foundries using the system were included and their total work forces were included in the study, except for die-casters in the grey iron foundry. In the casting station in the grey iron foundry various kinds of cores and binders were used, including Cold Box, epoxy-sulphur dioxide and Hot Box cores, as well as green sand moulding. Measurements during the casting process would almost certainly have detected thermal degradation products, including isocyanates, emanating from other binders than the binder under study, thus die-casters in this foundry were excluded.

The core-making and casting equipment and techniques used in the foundries included both old and new core machines (and processes), the cores varied substantially in size and shape, and both manual and automatic die-casting techniques were used in all of the brass foundries. However, most (80-90 %) of the core- and die-casting machines were used, and in each of the foundries work proceeded as normal, during the course of the studies. Thus, it seems reasonable to assume that the study was conducted under representative conditions for the industry, and that the exposures measured reflect those experienced under ordinary working, production conditions in terms of the type of products manufactured, production rates, core sizes and ventilation systems used.

The sampling programme was initially based on measurements of selected mono- and di-isocyanates, in particular ICA and MIC. Partly for practical and cost reasons, other potentially significant agents - e.g. total dust (including potentially respirable quartz), phenol and mineral oil mist - were not sampled. The measurement campaign was intended to provide complementary information to a parallel medical study on respiratory symptoms and lung function impairments. However, due to its potential effects in the respiratory tract, formaldehyde was included. The sampling strategies for the short- and long-term samples as well as the number of samples for each job title followed established theory and practice (Leidel, et al., 1977).

For sampling isocyanates (in particular ICA and MIC) we used the most recently developed analytical methods, enabling the determination of several isocyanates in each sample. No other isocyanates than ICA and MIC were determined (Karlsson, et al., 1998b; Levin, et al., 1988) and during the course of this project, several inter-laboratory method controls were performed. Formaldehyde was sampled and analysed using standard methods (Levin, et al., 1988) at an SBACA-accredited laboratory.

The results of the exposure measurements in Study I were consistent with earlier measurements of monoisocyanates during work with Hot Box core binders. Our survey was preceded by measurements carried out by the Swedish Foundry Association of emissions during the thermal degradation of different nitrogen-containing binders for cores and moulds. Among core-makers using the Hot Box method in two of the brass foundries in this study, levels of ICA up to 62 µg/m³ and MIC up to 8 µg/m³ were measured in an earlier study. Corresponding values for die-casters were 190 µg/m³ and 17 µg/m³, respectively (Lilja, et al., 2000b). These figures were in the same order of magnitude, and the exposure patterns were the same, as those recorded in Study I. The overall within- and between-worker variability expressed as GSD observed in Study I also reflected well the normal variability in industrial settings (Rappaport, 1991).

Analysis of the variation between foundries and job titles indicated that no sole foundry or job title alone could represent the distribution of air concentrations for the whole group regarding compliance or epidemiology.

The chemical measurements were performed during the winter season, when air concentrations are likely to be higher than average, thus representing a worst-case seasonal sampling scenario. All Swedish foundries using the Hot Box core method participated in the survey, hence there were no external validity problems. A previous analysis of formaldehyde in the grey iron foundry found air concentrations ranging from 200 to 1,800 µg/m³, and similar levels were recorded in this study. Historically, dust and phenol measurements have been performed by the company health services and safety engineers at the three brass foundries, and the total dust concentrations in the working environments of the die-casters and core-makers have varied between 100-3,000 µg/m³ and 100-1,500 µg/m³, respectively, while in the grey iron foundry the corresponding respirable dust concentrations have varied between 200 and 600 µg/m³. Historically, the air concentrations of phenol were equally low, ranging from 90 to 170 µg/m³.

The strong correlations between peak and mean concentrations of both ICA and MIC obtained from the analyses of short-term samples suggested there was no need to assess the effects of both peaks and means. There was also a strong correlation between mean concentrations of ICA and MIC obtained from short-term samples, which hindered attempts to separate the effects of ICA and MIC. Consequently, the means obtained from the short-term samples of ICA and MIC were used as independent variables in separate regression analyses of changes in lung function over shift.

The monoisocyanate and formaldehyde levels observed in Studies III and IV were about 50% lower than those observed four years earlier. All measurements of MIC, formaldehyde and total dust were below the Swedish OELs and 64% of ICA measurements. The reduction of exposure levels at follow-up was probably due to systematic efforts on the part of the foundries to improve the working environment over the course of the preceding decade, in particular the installation of better exhaust ventilation systems and reductions of the nitrogen content of binders used in the Hot Box system (Nayström & Lilja, 2003).

The generally low exposure levels observed in Study III yielded small differences between subjects exposed to high and low levels of the analytes, complicating attempts to determine dose-response relationships, although nasal symptoms and signs were significantly more prevalent among all the exposed individuals than the referents in Study III.

It was assumed that all of the agents monitored contributed, to some extent, to irritative effects in the exposed group. Hence, an integrated exposure variable was designed to measure the total exposure of subjects to all of the pollutants examined, but it was found that all of the subjects classified as being highly exposed by this metric could also be thus classified simply by examining their exposure to ICA alone.

6.3 OCULAR SYMPTOMS

The prevalence of ocular irritation in the week immediately preceding testing was found to be correlated with high formaldehyde exposure. No other such correlations were found. Irritation of the eyes is one of the first symptoms of formaldehyde exposure and may vary rapidly in response to changes of exposure levels. Therefore, questions regarding ocular symptoms in the preceding week may be more valid than questions regarding symptoms during the preceding month or year. The formaldehyde levels observed for all subjects in this study were below the proposed threshold of 0.3 mg/m^3 (Wibowo, 2003). However, the formaldehyde limits in non-industrial environments are somewhat lower: 0.1 mg/m^3 in Norway and WHO recommendations, 0.15 mg/m^3 in Denmark (NBHW, 2006; WHO, 2000). Several of the exposure measurements in this study exceeded these limits. Therefore, the observed prevalence of eye irritation may have been a consequence of simultaneous exposure to several irritant compounds; this suggestion would need to be corroborated by further research. The similar prevalence of ocular symptoms in exposed workers compared to the referents in the follow-up study (IV) and reduction in prevalence of work-related ocular symptoms in exposed workers between 2001 and 2005 may have been due to improvements in the work environment in recent years; in Study II, the prevalence of ocular symptoms in the exposed group was significantly higher than in the referents.

6.4 NASAL SYMPTOMS

An unusually high prevalence of nasal symptoms was noted in both the exposed group and the referents in Study II. However, nasal symptoms are also common among people who are not subject to industrial exposure. For example, the prevalence of nasal symptoms in the week prior to testing in a sample of primary school personnel examined by Wålinder ,et al. (1998), 50%, was intermediate between that observed in the exposed and referent groups in Study III. Exposed workers exhibited an elevated prevalence of work-related nasal symptoms and there was a dose-response relationship between nasal symptoms during the week preceding the examination and exposure to ICA, MIC, and formaldehyde. Although the exposure levels observed were lower than those that have previously been reported in these foundry environments, the results described in Study III clearly indicate that the nasal mucosa, which is highly exposed to airborne contaminants, is sensitive to exposure and acts as a leading indicator of the nature of the work environment.

Nasal signs and questions regarding symptoms in the preceding week may be more valid than questions regarding symptoms during the preceding months or year, due to habituation and subjects' difficulties to remember symptoms. The highest levels of exposure to formaldehyde observed in this study were comparable to those (0.073 and 0.174 mg/m^3) found to induce swelling of the nasal mucosa in a previous experimental study (Falk, et al., 1994). Dust exposure might also play a causative role in the nasal symptoms described in this study; in a climate chamber experiment on the influence of dust on respiratory health, it was found that nasal irritation was induced when the level of total suspended particulates in the form of office dust exceeded 136 µg/m³ (Mølhave, et al., 2000).

A high prevalence of dripping or blocked nose was reported by the exposed group at follow-up, and a higher proportion of the exposed workers reported those symptoms in both years compared to the referents, suggesting the problems were persistent.

The higher prevalence of nasal symptoms among workers exposed in 2001 (but not 2005) compared to workers still exposed at follow-up is not surprising. Recently it has been shown that subjects with rhinitis tend to avoid jobs that entail exposure to irritants (Wiebert, et al., 2008). This effect can be a possible explanation of the low incidence of occupational rhinitis reported by Radon, et al. (1998). There may have been a selection out of exposed job among workers with rhinitis in this study, which can cause underestimation of the prevalence of symptoms among exposed workers. While there was no indication of an unusually high turnover of the workforce at the plants studied, the possibility of a healthy worker effect cannot be excluded (McMichael, et al., 1974).

In Study II in 2001, nose bleeding was found to be common among exposed workers, but this was not the case at follow-up. The lower prevalence of nose bleeding reported at follow-up may be attributable to decreased exposure of the subjects compared to those in the previous study.

No previous reports of health effects of ICA were found in a literature review, and the exposure levels of MIC observed in this study have not been associated with health effects. Generally, the formaldehyde exposure observed in Study II was lower than the level at which mucous membrane symptoms are usually reported (Wibowo, 2003). Exposure to inorganic dust and formaldehyde (aerosol) might be of importance, but was not measured in this study. The higher prevalence of work-related symptoms among those who were exposed represents an important fraction of the difference in total symptom prevalence between exposed workers and referents. To some extent, this may be explained by awareness of perceived exposure risks among those exposed and, thus, a tendency to over-report symptoms.

It is also possible that irritative effects might arise from the combined effects of exposure to multiple pollutants.

A selective loss of exposed symptomatic individuals before the cross-sectional sample was taken would decrease the possibility of detecting any possible effect of exposure. However, the over shift lung function effect detected supports the hypothesis that exposure was the most probable cause of the over-represented symptoms in the exposed workers.

6.5 NASAL SIGNS

There are numerous potential causes of dry nasal mucosa, which can arise from constitutional vulnerability of the mucosa, or in response to acute or chronic occupational exposure to irritants and other pollutants. The constitution and nature of the mucosa reflects its exposure to irritants and other airborne species over extended periods, and are not solely functions of the individual's symptoms over the week immediately prior to a nasal examination. The dry mucosa and crusts observed in exposed individuals might reasonably be attributed to the conditions in the foundry working environment, in which the nasal mucosa is exposed to a complex mixture of air pollutants. Although no dose-response relationship between estimated exposure and nasal signs was observed in this study, the results obtained are indicative of the existence of some sort of impact of the working environment in the foundries on the nasal mucosa.

6.6 LUNG FUNCTION

In Study II, no evidence of a relationship between exposure to ICA, MIC or formaldehyde and reduced lung function was observed. A possible explanation for the absence of a difference in lung function before shift between the exposed and referent groups in this study may be the so-called healthy worker effect (McMichael, et al,, 1974). However, there were no indications of high turnover in the workforce at the plants. Nonetheless, this does not exclude the possibility of a healthy worker effect. More highly exposed individuals with airway obstruction and airway symptoms may leave employment or move to jobs with lower exposure due to worsening of symptoms, thus being selectively removed from the cross-sectional sample. Thus, selection bias due to the cross-sectional study design remains a potential confounder for results in this study.

Although no association between exposure and lung function appeared in this study, air pollutants such as dust may be abundant in foundries, and previous studies have found impaired lung function in foundry workers (Gomes, et al., 2000; Johnson, et al., 1985; Mikov, 1974). Occupational asthma is associated with toluene diisocyanate exposure. However, there is no consistent evidence of decreased FEV_1 from exposure to mean levels up to 36 µg/m³ of toluene diisocyanate (Ott, 2002).

A possible reason for the low lung function among both the exposed workers and the referents could be the overweight observed in these groups, since BMI was the factor with the clearest negative correlation with lung function. Theoretically, this relationship could be due to BMI either causing or being an effect of impaired lung function or respiratory symptoms. However, a high BMI is known to have negative effects on lung function (Jones & Nzekwu, 2006; Morgan & Reger, 2000), and obesity has been described as a risk factor for asthma in several studies (Bråbäck, et al,, 2005; Rönmark, et al., 2005). The decrease in FEV_1 before shift associated with smoking was expected, given the well-known obstructive effect of long-term smoking. In contrast, the finding that time spent as a core-maker negatively affected lung function, solely from the analysis with asthmatic subjects excluded, is difficult to interpret since asthmatics should, intuitively, be a sensitive group.

An over shift effect was seen among the exposed, above all core-makers, compared to the unexposed subjects. Different cross-shift changes in FEV_1 among workers in other trades have been reported. For instance, Meijer, et al., (1998) and Skogstad, et al. (2006) found cross-shift increases in FEV_1 among rubber workers exposed to dust and fumes of 79 ml and reductions in FEV_1 among non-smoking bar and restaurant workers (before the implementation of a smoking ban) of 3.1%, respectively. This is an acute effect and may be an early sign of disease development, but it is weak, and thus in itself is of limited importance for health. There was no correlation between change of lung function over shift and the measured exposure level to monoisocyanates. This was expected because human and animal MIC toxicity data indicate that it only has health effects at higher exposure levels than those measured in this study. With regard to ICA, there was no earlier investigation to compare with the study data. The absence of any detected impact of formaldehyde on lung function over shift seems reasonable, with reference to earlier studies of its health effects (Wibowo, 2003). Smoking during the day of investigation did not have any acute effects on lung function.

In the follow-up Study (IV), which involved a fraction of the participants in the previous study, no such difference in lung function was observed over a similar shift, but a difference before shift was detected. Initially no significant relationship between exposure to monoisocyanates or formaldehyde and a reduction of lung function was detected, but the updated lung function data in the follow-up study are compatible with a general improvement in the work environment in the foundry areas of interest.

The reductions in lung function over a shift observed in 2001 may have been early indications of susceptibility; a hypothesis supported by the correlation between over shift lung function in 2001 and pre-shift lung function at follow-up. Care should be taken to avoid over-interpreting the increasing, but not statistically significant, reduction in pre-shift lung function (notably FEV_1) over time, from 2001 to 2005, in the exposed workers compared to the referents. However, these findings may indicate a small but persistent effect on the major airways of the exposed workers, which would be interesting to follow-up in further study.

Non-smoking exposed workers had a significantly lower FEV_1 pre-shift than non-smoking referents. These results are difficult to explain and must be interpreted with caution because of the small number of individuals studied and the fact that no significant association with exposure was revealed by the analyses. Additional occupational exposure for workers who were still smoking did not seem to be significant.

6.7 IMMUNOLOGY

Although MIC-specific immunoglobulin antibodies have been observed in a limited number of Bhopal victims (Karol & Kamat, 1988), this was not investigated in the present study because the workers were exposed to considerably lower levels of monoisocyanates than encountered during the Indian disaster. Antibodies against formaldehyde, due to exposure in the respiratory tract, have also rarely been found, and the relationship between sensitization and occurrence of symptoms is uncertain (Bardana & Montanaro, 1991; Wantke, et al., 2000). Hence, it remains unclear whether the observed correlation of respiratory symptoms and signs with the foundry environment arose because of an irritant or immunological response. However, the latter is unlikely because reports of sensitization at low levels of chemical exposure are scarce (Arts, et al., 2006).

6.8 FURTHER RESEARCH

The effect on lung function before shift would be interesting to follow-up with spirometry to elucidate the further progression in the exposed foundry workers.

The still high prevalence of nasal symptoms implies that repeated exploration of these symptoms in parallel with the continuing improvement of the working environment in these foundries is warranted.

7 CONCLUSIONS

In Swedish foundry environments during core-making with the Hot Box method and die-casting, low molecular weight isocyanates (in particular ICA and MIC), formaldehyde and dust were identified. Exposure levels were 50% lower at follow-up four years later.

A high prevalence of ocular and respiratory symptoms was observed among exposed workers at baseline and nasal symptoms had increased among the exposed workers at follow-up. However, lower airway symptoms were less frequently reported at follow-up.

Dry nasal mucosa was observed among exposed workers. FEV_1 levels pre-shift were slightly reduced in the exposed group both at baseline and follow-up, but the small decrease in lung function over shift in the exposed group at baseline, was not observed at follow-up. The effects seemed to be small and not relevant on an individual level. A specific group of workers, core-makers, exhibited a lower lung function than other categories.

Dose-response relationships were observed between the nasal symptoms and the measured levels of ICA, MIC and formaldehyde, but the objective nasal signs were only weakly associated with exposure estimates. Lung function findings were not significantly related to current exposure to monoisocyanates or formaldehyde.

The high prevalence of nasal symptoms and signs suggested a link with monoisocyanates and other airway irritants, such as formaldehyde and dust, in the foundry environment and may indicate a persistent influence of the working environment in the foundries despite recent reductions in exposure levels of the chemical agents.

The absence of lung function effects over shift and the decline in lower airway symptoms in the exposed group at follow-up indicate positive effects of the remedial measures undertaken since baseline. The slightly reduced FEV_1 levels pre-shift in the exposed group at follow-up suggests there may be a residual effect from previous exposure, which would be interesting to follow-up in further study.

The nasal mucosa is a highly sensitive indicator of potentially harmful exposure to air pollution and these findings indicate that further improvement of the working environment in these foundries is required.

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