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U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
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INTRODUCTION

The Scientific Committee on Epidemiology in Occupational Health of the International Commission on Occupational Health (ICOH) began its activities in 1980 and has, during its short existence, already become an important forum for the exchange of experience in the field of occupational epidemiology. A symposium is held each year (except during the years of the ICOH triennial congress) with the purpose of bringing together active research workers in occupational epidemiology to discuss methodology, findings, and applications of their work.

Previous symposiums were held in Helsinki, Finland (1980), Montreal, Canada (1982), Singapore (1983), Como, Italy (1985), Los Angeles, USA (1986), Stockholm, Sweden (1988), Tokyo, Japan (1989), Paris, France (1991), and Nice, France (1993) and the 10th International Symposium on Epidemiology in Occupational Health will be held in Como, Italy, 1994.

The 9th International Symposium on Epidemiology in Occupational Health was held September 23-25, 1992, at the Omni Netherland Plaza, Cincinnati, Ohio.

The official language of the symposium was English, and was used for all presentations and printed materials.

The 9th International symposium happily continued the outstanding tradition of the earlier meetings on Epidemiology in Occupational Health. Over two hundred and fifty epidemiologists from the United States were joined by over a hundred and fifty of their colleagues from all over the world at this meeting. In preparing for this symposium, we were struck by the growing diversity of occupational epidemiology which is being applied to an increasingly diverse set of problems ranging from work-related psychological disorders to traumatic injuries. This variety is reflected in this book. From the perspective of the three sponsoring organizations, the Scientific Committee on Epidemiology in Occupational Health (ICOH), the National Institute for Occupational Safety and Health, and the Department of Environmental Health at the University of Cincinnati, the meeting was a success because the scientific information

presented at the meeting enhanced our understanding of the causation and prevention of occupational health and safety problems. We would like to express our appreciation to many of our associates from all organizations who have contributed to planning for the symposium and preparation of this book.

Lawrence Fine, Symposium Chair

Andrea Okun, Symposium Vice-Chair

Kathy Masterson, Editorial Assistant

Leo Szilard

"A scientist's aim in a discussion with his colleagues is not to persuade, but to clarify."

recalled on his death, 30 May 64

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THE WORKRELATEDNESS OF AIRWAYS DYSFUNCTION[1]

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Abstract

The syndromes of airways dysfunction include bronchitis, asthma, emphysema and chronic obstructive pulmonary disease. All may be work related with the population attributable fraction reaching 30% for some syndromes in some communities. Evidence both from community based as well as workforce based studies suggests that personal characteristics, related to certain lung function measurements, influence an individual's decision to undertake occupations involving exposure to airborne pollutants; the same characteristics appear to influence an individual's decision to become a smoker. Whether the pertinent measurement of lung function, namely forced expiratory volume in 1 second, is a surrogate for lung size (for which there is no obvious biological hypothesis), or for increased airway reactivity to inhaled environmental agents (a biologically plausible concept) remains to be determined. The Dutch hypothesis of the natural history of airways dysfunction accomodates many of the epidemiologic and clinical features of work related airways dysfunction, with its emphasis on the interaction of environmental exposures with host factors, including inherited

tendencies to develop allergic sensitization and/or bronchial hyperresponsiveness, to evoke the inflammatory process in small airways which eventually leads to airflow limitation. Future research should include better modelling on the response side to accomodate current theories about the mechanisms underlying acute and chronic airflow limitation and their relationship to one another, and better modelling on the exposure side to accomodate the complexity of workplace exposures. Also important is the concept that, because of health selection factors, the community of which working men and women are members is as appropriate target population for the study of the workrelatedness of airways dysfunction as the particular workforce(s) to which they currently belong.

Key words

Community based studies, workforce based studies, health selection, healthy worker and healthy smoker effects, natural history of airflow limitation, Dutch hypothesis

Context and definitions

Establishing the workrelatedness of the agent-specific pulmonary disease of occupations such as the pneumoconioses, though not necessarily always achieved without effort, has nevertheless been reasonably straighforward. The paradigm includes i) developing exposure relationships on the basis of workforce based studies; ii) using these to derive exposure standards, and iii) evaluating whether industries in conformity with these standards have succeeded in reducing disease incidence and/or prevalence within their workforces. By and large, they have (Becklake, 1992a).

Partly for this reason, partly because of the increase in morbidity and mortality attributable to chronic airway disease in the national statistics of several industrialized countries (Murray, 1989), and partly perhaps because of the increase in many jurisdictions of occupational asthma (Malo, 1989; Meredith et al., 1991), conditions associated with airways dysfunction are now some of the most common causes of work related respiratory morbidity. The paradigm for establishing their workrelatedness is less straightforward. Reasons, in addition to those already mentioned, include: i) their multifactorial nature: like coronary artery disease, determinants include host as well as environmental factors; ii)

concurrent exposures, mainly tobacco, and iii) accumulating evidence that both the "healthy" worker and the "healthy" smoker effects lead to an underestimate of the strength of the associations, particularly when using the conventional workforce based study approach (Becklake and Lalloo, 1990b). In addition, because syndromes of airways dysfunction also occur in those not exposed to airborne pollutants at work, it is not possible to assess with certainty the relative contributions of concurrent exposures, occupational and nonoccupational, in the genesis of any of these syndromes in the individual case.

Thus, despite the biological credibility of the concept that airways are at risk for damage by inhaled pollutants, there has been reluctance among those concerned (except those exposed) to accept both the scientific evidence for causality as well as the implications (Becklake, 1992b; Oxman et al., 1993). In this presentation, some of this evidence is reviewed and its implications are considered.

Definitions of the two main concepts embodied in the title are as follows:

Workrelatedness is a term originally used to distinguish work related diseases of multifactorial etiology from agent specific occupational diseases such as the pneumoconioses (World Health Organization, 1985). Nowadays the term is used to embrace the full spectrum of workrelatedness (Hernberg, 1992). To those affected, the distinction is irrelevant. With the exception of IgE mediated asthma induced by a workplace allergen, all the other clinical syndromes associated with airways dysfunction fall into the category of conditions of multifactorial etiology, found in the general population but for which the risk is increased in relation to certain occupational exposures. In the present context, workrelatedness was assessed using the usual criteria for inferring causality from association (Doll, 1984), namely that the associations under scrutiny not be explicable by bias, confounding or chance; that exposure response relationships be demonstrable, including decreased rates following exposure cessation and that they be consistent over time, place, persons, investigators and study designs. Other criteria used include the strength of the associations, time coherence, and biologic credibility.

Airways dysfunction was defined in the broadest sense (Ciba

Symposium, 1959; Pride, 1984) to include asthma (defined clinically as acute episodic airflow limitation, reversible spontaneously or on treatment); chronic bronchitis (defined by the presence of a symptom, mucus hypersecretion); emphysema (defined by pathology or by lung imaging, as permanent enlargement of the terminal airspaces with destruction of alveolar walls); and chronic obstructive pulmonary disease (COPD) (defined clinically and/or by pulmonary function tests as chronic airflow limitation, largely irreversible).

Sources of evidence (see Table 1)

Several reviews (Becklake, 1989b; Higgins, 1973) including two of the Surgeon General's reports (US Public Health Service, 1984, 1985) have recognized the considerable body of published literature prior to those dates, mainly describing cross-sectional workforce based studies which documented the fact that lung function levels, the marker of chronic airways dysfunction most frequently used in survey work, were invariably lower in the occupationally exposed compared to those not so exposed. However, results were inevitably confounded by age and tobacco exposure, both important determinants of lung function level and there was both scepticism that this could be adequately taken into account in analysis by modelling, and reluctance to accept as causal associations demonstrated only in cross-sectional studies with inferred, not demonstrated, appropriate time relationships. Thus in 1984, the Surgeon General's report on Chronic Obstructive Lung Disease implicated only one environmental exposure in its genesis, namely tobacco smoke; occupational exposures were listed together with community air pollution and passive smoking as putative. A similar view is to be found in the 1985 Surgeon General's report.

Since then, a considerable body of evidence has accumulated implicating occupational exposures in the genesis of airways dysfunction. This evidence, broadly based, derives not only from workforce based studies but, somewhat unexpectedly, from community based surveys (Becklake, 1992b), and encompasses a range of outcome measurements, using different designs and study approaches. An exhaustive review is obviously beyond the scope of this presentation and the reader is referred to several recent reviews (Becklake 1989b, 1992b) including one focussing on mineral dusts in which particular attention was paid to methodologic rigor in the evaluation of the published material (Oxman et al., 1993). Some

concept of breadth and variety of the evidence is given in Table 1; footnotes to the Table also identify some of the pertinent publications since those included in the reviews referred to above.

Evidence from workforce based studies

Evidence generated from workforce based studies in the 1970's and early 1980's has been considerably strengthened by results of: i) cohort studies of lung function using multivariate analysis to explore credible biological models, ii) studies using quantitative pathology measurements of emphysema as the outcome variable, and iii) mortality studies.

Examples of the first type of study have been carried out in coal miners, in hardrock miners and in men and women with various non-mining exposures; in many of these studies, a striking feature, and an important one in terms of establishing causality was the comparability between the spirometric lung function losses over time attributable to workplace exposures and those attributable to smoking. For instance, in UK coalminers the excess annual loss of FEV attributable to average exposure in mines was 8 ml/year after accounting for age and smoking, compared to 11 ml/year attributable to smoking after accounting for age and dust exposure (Love and Miller, 1982). Figures for the US coalminers were remarkably similar, 7 and 9 ml/year respectively (Attfield, 1985). Updated figures for US coalminers, incorporating cumulative dust exposure assessments were recently published (Attfield and Hodous 1992) confirming the comparability of smoking and dust effects for exposures in the study period. An earlier study of Paris industrial workers exposed to a variety of workplace pollutants reported similar findings: 8 and 11 ml/year excess loss attributable to exposure and smoking respectively, and French workers smoked heavily during the study period (Kauffmann et al., 1979, 1982). Of interest too in this study was that heat exposure at work was an independant predictor of annual FEV_1 loss, accounting for 13 ml excess loss per annum. Note however that in this study, while 73% of subjects born in France were restudied, the percentage of those born elsewhere who were reexamined was much lower.

Several studies in coalminers, using <u>quantitative pathology measurements</u> of emphysema as the outcome variable, confirmed a relationship between mining exposure, including to dust level, and

the degree of emphysema. Two studies in hardrock miners (Becklake et al., 1987; Hnizdo et al., 1991) exploited the data base of some 33,000 machine readable records of lung pathology at the National Center for Occupational Health, Johannesburg (Hessel et al., 1987). Both sudies took advantage of the high autopsy rate for men who work in the Johannesburg area gold mines; at autopsy, lungs are inflated and whole lung sections made routinely. In the first study (Becklake et al., 1987), a case control design was used, and the predictors of emphysema at autopsy included age, smoking and dust exposure, the odds ratios being 5.6 for 10 years of aging, 5.5 for each 10 cigs/day smoked prior to 1960, and 3.3 for each 10 years of work in a dusty job. The presence of emphysema was not related to silicosis: nor did any of the clinical features recorded at the annual medical examinations 20 years or more earlier predict the outcome, though the number of examinations at which wheezing had been recorded came close to conventional criteria for significance, an observation relevant to the Dutch hypothesis of the natural history of airway disease, discussed later. Missing data may have resulted in overestimation of the odds ratios (de Beer et al., 1992) but not of the role of dust exposure compared to that of smoking (Becklake and Irwig, 1992). In the second study, respirable dust accumulated to age 45 was the strongest predictor of panacinar emphysema at autopsy, silicosis of centrilobular emphysema (Hnizdo et al., 1991). Small airway disease in association with exposure to various mineral dusts, including asbestos, has also been described in several case series (Kennedy et al., 1985; Churg et al., 1985). Animal models suggest that this type of response, essentially a peribronchiolar fibrosis, is evoked by a lower lung dust burden less than that which evokes a diffuse interstitial fibrosis (Bégin et al., 1986).

Mortality studies have been carried out in several occupational cohorts in whom respiratory health status had been evaluated in earlier surveys (Becklake, 1989b). In two of the studies, one in Paris area workers in various industries (Annesi and Kauffmann, 1986) and one in coalminers (Ortmeyer et al., 1974), despite the fact that the outcome measurement was all-cause, not cause-specific mortality, and despite competing effects of smoking, which is causally related not only to chronic lung disease but also to coronary artery disease, a much more powerful killer than lung disease, dust exposure was associated with a significant increase in all-cause SMR. The same was true of a lung function measurement FEV_1/FVC taken

10 years earlier in one instance (Ortmeyer et al., 1974), and over 20 years earlier in the other (Annesi and Kauffmann, 1986). One study, in UK foundry and mine workers, was negative (Foxman et al., 1986). In a study of S African goldminers attributable risks for mortality due to COPD were 5% for dust only, 34% for smoking only, and 59% for their combined effects (Hnizdo et al., 1990b).

Evidence from community based studies

Perhaps the strongest (and certainly the most unexpected) source of evidence implicating occupational exposures in the genesis of airway disease comes from non-workforce based studies, several of which are summarized in Table 2. All were community based, targetted to general population samples. Five were conducted in Europe, 2 in the United States; 5 included men and women, 2 were confined to men; 6 were cross-sectional (Bakke et al., 1991b; Heederik et al., 1990; Lebowitz, 1977; Korn et al., 1987; Krzyzanowski and Kauffmann, 1988; Viegi et al., 1991) and only one, the Cracow study, was longitudinal (Krzyzanowski et al., 1986). Various outcome measures, all based on FEV_1 or its derivatives, were used. In all, occupational exposure was self-reported and thus non-quantitative. In all analyses, smoking was taken into account. Though none of the studies was designed to examine the relationship of occupational exposure to airflow limitation (in 5, the objectives were to assess the ill health effects of community air pollution, in one to describe the natural history of airway disease and one was the Dutch contribution to an international study of chronic diseases), all yielded evidence of such a relationship. For instance, in the Cracow study (Krzyzanowski et al., 1986), men who reported exposure to dusts at work experienced a significant additional loss of 6 ml of FEV_1 per year, over and above the 55 ml/year in those who did not report such exposure; women reporting exposure to variable temperatures at work experienced an additional loss of 6 ml of FEV_1 per year, significantly more than the 38 ml/year in those who did not report such exposures. In the French study of 8692 men and 7772 women, living in 7 cities, FEV_1/FVC% was .78 lower in men reporting any exposure compared to those who did not, even though households in which the head of the house was engaged in a blue collar job with exposure were excluded from the study; in other words, non-intense exposures were implicated (Krzyzanowski and Kauffmann, 1988). In the Italian study (Viegi at al, 1991), although the target population was rural and the percent exposed low,

significant relationships were nevertheless shown. Finally in the Bergen Co. study (Bakke et al., 1991b), though the OR's shown in the Table which were based on spirometry values were not significant, those based on a clinical definition which included spirometry were significant, namely 3.6 for subjects with a high degree of exposure compared to those with none.

"Healthy" worker effect and the concept of health selection

The concept of natural selection is certainly not foreign to human experience: we all recognize the born artist, the born athlete, the born singer. Webster's New International Dictionary (1909) recognizes the dependence of natural selection on "the variability in the characters of different individuals," also its role in favoring "survival of the fittest," referring to Darwins's use of the term. In occupational epidemiology, selection (natural or imposed) on the basis of health-related characteristics is thought to be responsible for the "healthy" worker effect, a term originally coined to describe the usually better than average mortality experience of employed versus non employed individuals, amongst whom are to be found the halt, the lame and the weak. The definition offered in Last's Dictionary of Epidemiology (1988) still refers only to mortality experience. The term is now also used to encompass indices of morbidity and in the context of exposure to airborne pollutants, it appropriately describes the ever increasing evidence of selection into workforces on the basis of health characteristics (Becklake and Lalloo, 1990b). For instance, wheezing and skin test reactivity (reflecting allergic sensitization) have been found to be less frequent among those exposed to potentially allergenic organic dusts at work compared to those not so exposed (Chan-Yeung et al., 1980). Bronchial responsiveness to methacholine has also been shown to decrease not increase with length of service amongst construction insulators in Quebec (Ernst et al., 1989) and the same phenomenon has been described in the short term (over a season) in grain workers in the port of Montreal (Dales et al., 1988). Recently, an analysis of lung function in recruits into the Saskatchewan grain industry revealed that in recruits whose lung function levels were comparable at the time of recruitment, those who quit after their first year exhibited a more severe annual loss of spirometric lung function during their period of employment than those who quit after their second year, and those who quit in their second year exhibited a more severe loss of spirometric lung function during their period of employment than

those who quit after their third year of experience, the inference being that the more sensitive the lung to the effects of dust exposure, the sooner the individual will quit (Zejda et al., 1992).

The first demonstration of the phenomenon of health selection into dusty industries on the basis of lung function level was in a paper already referred to (Kauffmann et al., 1982) describing 12 years followup spirometric measurements in approximately 600 Paris workers aged 30 to 60 when first studied. The phenomenon of health selection was illustrated in the analysis of the subset of individuals exposed to silica dust (see Figure 1). As expected, in the older subjects (40 years and over when first studied), initial FEV level was lower and the loss over time greater in the exposed compared to those not exposed. Note however, that for those aged 30-39 years when first studied, initial levels of FEV were higher, not lower, in the exposed compared to those not so exposed even though their subsequent loss over time was greater.

Is this an isolated phenomenon peculiar to these Paris workers or is it a more general phenomenon, also exhibited by other workforces? The topic was not readily susceptible to research in electronic data bases mainly because the phrase "healthy" worker is not usually cross-indexed to lung function level. However, from a non systematic review carried out recently (Becklake and Lalloo, 1990b), it was apparent that the phenomenon is not rare, and examples were found in studies of UK and Nigerian coal workers, US general smelter workers and Canadian aluminum smelter workers, and there are reports of similar observations in the S African grain industry (Fonn et al., 1993), indicating that the phenomenon respects neither time, place or person. These observations serve as a reminder that a workforce should be regarded as a "biassed sample of the the general population, and inhomogeneous within itself, and that though both bias and inhomogeneity have to be accepted in workforce surveys, they should not be ignored" (Field, 1981). Of interest was that most authors of the papers cited did not comment on the phenomenon.

The "healthy" smoker effect

Tobacco exposure has much in common with many occupational exposures: the pollutants include particles and vapors inhaled under conditions of heat. Exposures are usually experienced first in early

adulthood and are undertaken and/or modified voluntarily. Given the considerable between individual differences in the response to both exposures, it seems unlikely that either exposure is undertaken on a random basis among the individuals who make up the general population.

Evidence of the "healthy" smoker effect has accumulated slowly over the last decade. In our Unit, its presence was first postulated because in a cross-sectional study of young Montreal office workers, ex smokers and sometimes smokers had higher spirometric values compared to never smokers in certain age-gender specific subsets (Leech et al., 1983). The only explanation appeared to be natural selection into the habit on the basis of spirometric level. Coincident in time, a California shopping center study showed that spirometric levels were higher in the teenagers who took up smoking in the following year compared to those who did not (Tashkin et al., 1983). Subsequently Weiss and colleagues, in reviewing the association between smoking on the one hand, and atopy and airway responsiveness on the other, speculated that young persons with these conditions may be intolerant of tobacco smoke and therefore smoke less or not at all, and that this "healthy" smoker effect would obscure any causal relationship (Sparrow and Weiss, 1989).

The term "healthy" smoker related to lung function level proved to be no easier to research in the electronic data bases than the term "healthy" worker. Nevertheless a similar non systematic literature search to that used in connection with the term "healthy" worker yielded similar findings (Becklake and Lalloo, 1990b). An early study documenting the phenomenon was carried out in New Englanders for the purpose of recording the evolution of lung function with age (Ferris et al., 1965). In that study, the highest levels for FEV_1 in the 25 year old age bracket were in the smokers, not the non smokers; the phenomenon did not however attract comment from the authors. Some 15 other studies exhibiting the phenomenon were encountered indicating that the phenomenon respects neither time, place or persons (Becklake and Lalloo, 1990b). At least one study exemplifying the "healthy" smoker effect also exemplified the "healthy" worker effect (Mokoetle, 1990). Additional evidence that the same lung function characteristics are associated with selection into both exposures comes from the community based study of approximately 5000 residents of Bergen

County, Norway (Bakke et al., 1988). In that study the odds ratio of an individual reporting an occupational exposure to dust and gases at work increased with the number of cigarettes smoked daily.

Both the "healthy" worker and the "healthy" smoker effect have important implications for occupational health epidemiology, not the least being that the ill health consequences of both exposures are likely to have been systematically underestimated in younger persons. The fact that the selection phenomenon appears rooted in the characteristics of the target organ is perhaps, on second thought, not surprising. Whether the pertinent feature which appears to be FEV_1 is a surrogate for lung size (for which there is no obvious biologic reason,) or for airway responsiveness to inhaled material (for which there are biologically plausible reasons) remains to be determined.

The natural history of airways dysfunction: the Dutch hypothesis

How do these observations in workforces fit in what is known about the epidemiology (i.e., distribution, determinants and natural history) of airway dysfunction and disease? In the 1960's, two population based studies were launched, one in the UK (Fletcher at al, 1976) and one in the Netherlands (Van der Lende, 1969) and they led to 2 different hypotheses of the natural history of airway disease. The UK study gathered questionnaire and lung function information over a 7 year period in almost 800 men, aged 30-55 at the outset, working in transport and other service industries in West London, employed in nondusty occupations. The objective was to investigate the natural history of what was then considered the British disease, chronic bronchitis, believed to be the consequence of the British climate and heavy urban and industrial pollution which in turn led to recurrent bronchial infection and chronic bronchitis which in turn led to chronic airflow limitation. The results did not support this hypothesis but suggested instead that the main determinant of airway dysfunction was environmental, in the form of exposure to tobacco smoke, resulting in the development of two apparently independent processes, bronchitis with mucus hypersecretion which was reversible when exposure ceased, and chronic airflow limitation which was not. Asthma was considered a separate and unrelated condition.

The Dutch study by contrast was more broadly based, comprising approximately 4500 men and women of all ages including

adolescents, selected from 3 different regions, one rural, one urban, and one urban-industrial. Results were interpreted as supporting the concept of bronchitis and chronic airflow limitation being independent processes but suggested that the main determinant of both was a host factor, described as an asthmatic tendency, with environmental factors including urban air pollution playing little part. Followup observations in both study populations lent support to the other hypothesis, with the British study supplying evidence that a host factor, airway reactivity, was associated with accelerated loss of lung function over time, and the Dutch study implicating environmental determinants including smoking. (Becklake, 1992b).

Dutch researchers recently reviewed their hypothesis for relevance in the 1990's (Sluiter et al., 1991) and reaffirmed the view, expressed originally in 1961 that the three "diseases", emphysema, asthma and chronic bronchitis were in fact expressions of one disease process in which the combination of endogenous (host) and exogenous factors combined to shape the patient's profile. Important features, illustrated in the schema in Figure 2, based on their paper, were i) the hereditary nature, probably independent of each other, of two important features of the condition, allergic sensitization and airway hyperreactivity, with age and gender modulating their expression; ii) diffuse airway obstruction as the common pathophysiologic feature; and iii) complicating factors and other diseases playing a role in the clinical phenotype patient. Tobacco smoking was treated as a separate "pulmonary disease" and occupational exposures did even not receive a mention, despite the persuasive publications of other researchers from the Netherlands (Heederik et al., 1990; Heederik et al., 1992a, 1992b; Post et al., 1992). The advantage of an umbrella term (chronic nonspecific lung disease or CNSLD in Netherlands and chronic obstructive pulmonary disease or COPD in N America), was reaffirmed, provided defining terms were added to ensure adequate treatment of patients and adequate scientific communication.

As the Dutch reseachers point out, the hypothesis has not been proven, and indeed it is complex enough to be almost unprovable except piecemeal. Nor, however, has it been disproven. Like most hypotheses in science, it can therefore stand until disproven at which time it can be modified or updated. To what extent does information from the occupational health field fit into the conceptual framework

of the Dutch hypothesis? To what extent does the Dutch hypothesis assist in the explanation of the health experience of men and women subject to exposure to airborne pollution at work?

Several points are at once obvious:

1. The Dutch hypothesis certainly reflects the clinical experience of occupational health professionals that the clinical syndromes of airways dysfunction form a continuum: COPD is as, if not more, frequently encountered in work exposed individuals as the clinically distinct syndromes of asthma and chronic bronchitis.
2. The Dutch hypothesis provides an explanation for the phenomenon of natural selection given the premise of a hereditary tendency to develop airway hyperreactivity.
3. The Dutch hypothesis recognizes the potential of workplace exposures causing airway hyper-responsiveness through non allergic (i.e., irritant) as well as allergic processes, and provides an explanation as to why airway hyperreactivity induced by occupational allergens or irritants may fail to regress when exposure ceases.
4. In the Johannesburg autopsy study of the hardrock miners referred to above (Becklake et al., 1987,) wheezing in clinical examinations conducted 30 years earlier came close to significance in predicting the presence of emphysema at autopsy. This is consistent with the concept embodied in the Dutch hypothesis that asthma, bronchitis and emphysema are expressions of one disease process, the clinical expression of which depends on both host and environmental factors.
5. The Dutch hypothesis also accomodates the fact that acute airway responses including cross-shift or cross-week changes to several occupational exposures appear to predict long term loss of lung function (Becklake et al., 1988); these relationships could be explained by the maintenance of a chronic inflammatory process. Examples include workplace exposure to isocyanate and to grain dust. In other grain exposed workforces, e.g., in a South African mill, cross shift changes have also been shown to relate to estimated exposure levels (Fonn et al., 1993).
6. The Dutch hypothesis offers an explanation as to why only a percentage of those exposed to inhaled pollutants, tobacco or occupational, are adversely affected.
7. The Dutch hypothesis also accomodates the phenomenon of spirometric "test failure," a phenomenon probably related to

reactivity of the airways (Becklake, 1990a; N'gang'a et al., 1992). Defined as the inability of an individual to generate reproducible results from a forced expiratory manoeuvre, this phenomenon was originally described in workforce based studies (Eisen et al., 1984) and was shown to be a marker of ill health, including being a predictor of future excess lung function loss (Eisen, 1987) and also of mortality (Kellie et 1987). Also, exclusion of subjects on this basis from the analysis of workforce based studies will result in underestimation of the workrelatedness of airways dysfunction (Eisen, 1987).

Attributability, synthesis and conclusions

Given that all the syndromes of airways dysfunction may be work related, what proportion of disease burden in communities is so attributable? Obviously the proportion will be community specific and will depend on the proportion of the population within a community with work exposures, the nature and employment patterns of industries located in a community, on the plants themselves and their salubrity, on employment practices, and on the options and expectations of workers. Obviously attributability will also depend on competing risks of which smoking is the most important.

Table 3 shows estimates of attributability for these syndromes of airways dysfunction, calculated from the results of the community based studies reviewed in Table 2. Mucus hypersecretion was used as a surrogate for chronic bronchitis, wheezing for asthma, and derivatives of the FEV_1 for COPD. Smoking was reported by up to 85% of respondents in some communities, occupational exposures by up to 57% of men respondents and up to 23% of women respondents. Population attributable proportion for bronchitis ranged from 14 to 18%, for asthma from 13 to 29%, and for COPD of the order of 28% in men and less in women. Higher values have been found for agent-specific subgroups such as exposure to solvents in the Tuczon AZ study where the PAR% was over 60% for all 3 syndromes.

Clearly, workplace exposures are responsible for a not inconsiderable proportion of the burden of airways dysfunction in populations. Clearly, because of health selection factors, research into the epidemiology (distribution, determinants, and natural history) of work related airways dysfunction should include community based

as well as workforce based studies. Clearly also, the community of which the worker is a member is as valid a target population for study as the particular workforce in which he or she is currently employed. What at first may appear to be a weakness in community based studies may indeed be one of their strengths, namely that the exposure assessment which though necessarily self reported by the individual (and therefore qualitative rather than quantitative), is nevertheless often closer to an estimate of the individual's total exposure burden than the quantitative measurements of agent specific burden, assiduously gathered in industrial hygiene surveys of the workplace. Another common exposure, to tobacco smoke, is after all also usually expressed in terms of total burden (cigarettes or pipes smoked x time), not in terms of any of the specific components of tobacco smoke. Clearly, therefore, we need ways to synthesize and summarize the lungs' exposure experience in the workplace. In addition, the concept of an "inert" dust becomes less tenable if the process of chronic inflammation in airways (the common pathophysiologic pathway for all the syndromes of airways dysfunction) can be initiated and maintained by continued exposure even to low levels in the workplace.

In conclusion, it is not inappropriate to end this review with a plea echoing one made elsewhere in this symposium, namely that we replace what was called the sometimes mindless search for associations in occupational epidemiology with better modelling, biologically inspired on the response side, and industrial hygiene driven on the exposure side. For instance, dialogue with respiratory physiologists might result in better understanding of the mechanisms underlying variability in the various outcome measurements of airways dysfunction used in occupational epidemiology such as those derived from the forced expiratory volume curve (N'gang'a et al., 1992). Dialogue with immunologists might result in better modelling of some of acute airway responses to inhaled pollutants, such as the components of airway hyperresponsiveness (Gibbons and Macklem, 1992; Sterk and Bel, 1991; Woolcock et al., 1992). Many participants in this symposium have data sets in which the underlying mechanisms for both phenomena could be explored. Hygienists need to develop concepts of exposure burden, encompassing all concurrent exposures, instead of agent specific burden. The model should be tobacco smoke in which all concurrent exposures are considered, instead of individualizing any or some of the estimated 400

constituents. Briefly stated, clinicians, physiologists, toxicologists, hygienists, need to talk to methodologists and vice versa, if we are to move beyond what has been called the "pump handle" era of occupational epidemiology as a means of understanding and so preventing work related airways dysfunction.

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Table 1. The workrelatedness of airways dysfunction: study approaches and sources of evidence*

Target Population(s)	Outcome	Study Design	Comment
Workforce based	Morbidity	Prevalance	Study design most frequently used; many reports prior to 1985[a];
		Cohort	Few before 1985; studies subsequently, in coal and hardrock miners and in asbestos and other dust exposed workers[b]
		Case control	Rarely used
	Pathological features	Case control	Several of emphysema in coal workers, one in hard rock miners[c]
		Case series	Prior to 1985 several of emphysema in coal workers; some recent reports of small airways in Workers exposed to mineral dusts[d]
	Mortality	Cohort	Usually followup of prevalence surveys[e]
Community based	Morbidity	Prevalence	At least 5 since 1985[f]
		Cohort	At least 1 since 1985[g]
		Case control	Rarely used[h]
	Mortality	Cohort	Followup of prevalence survey[i]

* Based on earlier reviews by Becklake (1985, 1989a, 1989b, 1992b) and selected additional references indicated in the footnotes; with few exceptions the studies cited showed significant associations between work exposure and airways dysfunction in the analyses carried out by the authors.

[a] Attfield and Houdos (1992), Becklake (1985, 1992b), Higgins (1973), Cowie and Mabena (1991), Oxman et al., (1993), Seixas et al., (1992);

[b] Becklake (1989b), Ernst and Zejda (1991), Hnizdo et al., (1990a), Oxman et al., (1993);

[c] Becklake et al., (1987);

[d] Becklake (1987), Churg et al., (1985), Kennedy et al., (1985);

[e] Becklake (1989b, 1992b), Hnizdo (1990b);

[f] Becklake (1989b, 1992b), Viegi et al., (1991);

[g] Krzyzanowski et al., (1986);

[h] Kjuus et al., (1981);

[i] Heederik et al., (1992a)

Table 2. The workrelatedness of airflow limitation: evidence from selected community based studies

(continued next page)

Country/area, first author, (year)	Population, age	Outcome measurement			Factors taken into account in analysis	Exposure(s) implicated
		Parameter, (study variable)	Non-exposed	Additional effect attributed to exposure or OR		
Cohort design (continuous outcome measurement)						
Cracow, Poland: Krzyzanowski, (1986)	759 men, 1055 women, 19-70yrs	FEV_1 loss (ml/year)	-55 -38	-6* -1	age, height smoking FEV_1 level	results shown are for dusts: also implicated were chemicals in men, variable temperature in women
Crosssectional design (continuous outcome measurement)						
7 French Cities: Krzyzanowski, (1988)	8692 men, 7772 women 25-59 yrs	FEV/FVC (%)	80.9 81.6	-.78* -.04*	age, height smoking, educational and SE level, air pollution	results shown are for any vs no exposure; in men FVC was also significantly higher with exposure; note households with blue collar workers were excluded from the study
Holland: Heederik, (1990)	668 men 54 ± 12.6	FEV_1 (1)	2.96	-.16*	age, height smoking	results shown are for blue vs white collar workers; also implicated were exposures experienced by textile workers, tailors, construction and transport workers
Crosssectional design (categorical outcome measurement)						
Tucson, AZ: Lebowitz, (1977)	1195 men at work, 18 yrs+	FEV/FVC ≤0.8 or FVC <75% predicted (prevelance %)	1.4*		age, height smoking	results shown are for any vs no exposure: also implicated were exposures to certain specific dusts and fumes

Table 2. The workrelatedness of airflow limitation: evidence from selected community based studies

(continued from previous page)

Country/area, first author, (year)	Population, age	Outcome measurement			Factors taken into account in analysis	Exposures implicated
		Parameter, (study variable)	Non-exposed	Additional effect attributed to exposure or OR		
Cohort design (categorical outcome measurement)						
6 US Cities Korn, (1987)	8515 men and women 25-74 yrs	FEV/FVC < 0.6 (prevalence %)	1.68* (dusts) 1.90 (fumes) 1.57* (both)		age, gender smoking	results shown are for exposure to dusts, to fumes and to both vs no exposure
Po Delta, Italy: Viegi, (1991)	1027 men, 608 women 18-64 yrs	%FEV or FEV/FVC% <.70 (prevalence %)	1.45 (men) NS (women)		age, smoking	results shown for any vs no exposure
Bergen Co, Norway: Bakke, 1991b)	714 men and women 15-70 yrs	FEV_1/FVC <.70 or FEV_1 < 80% predicted (prevalence %)	1.5		age, smoking	results shown are for reported high exposure to asbestos or quartz in the job held longest by the subject vs little or no such exposure

Adapted from Table 31-2, Becklake (1992b) with permission of the publisher (Little, Brown and Company). The Table shows results by design and outcome measurement, which, in all studies, was a derivative of the FEV_1 measurement. In the first 3 studies listed, the test parameter was a continuous variable and the results are shown as the additional effect attributable to exposure. In the other 4 studies, the test parameter was a categorical variable (% of exposed individuals with airways dysfunction) and the results expressed as the Odds Ratio (OR), prevalence OR for the Tucson study, and exposure OR for the last 3 studies. *Copyright by Little, Brown and Company (Becklake, 1992b). Reprinted with permission by the Department of Health and Human Services. Further reproduction prohibited without permission of the copyright holder.*

*Airways dysfunction was significantly related to work exposure in the analysis carried out by the author(s); NS = not significant

Table 3. The workrelatedness of airways dysfunction: population attributable proportion (PAP) % for different syndromes in selected community based studies

City/Country, first author, (year)	Subjects, number age	Exposure %		Bronchitis[a]			Wheezing[b]			COPD[c]			Exposure(s) implicated
		cigs	work	%	OR	PAP	%	OR	PAP	%	OR	PAP	
Tucson, AZ; USA Lebowitz (1977)	1195 M 18+ yr	69	57	13	1.0	-	22	1.1	-	9	1.5*	28	any vs none
7 Cities, France Krzyzanowski (1988)	8692 M 7772 W 25-59 yr	73 28	34 23	6 8	1.5* 2.1*	16 18	17 12	1,6* 1.7*	17 13	na na			any vs none any vs none
6 Cities, USA Korn (1987)	8515 M & W 25-74 yr	58	31	11	1.4*	11	6	1.5*	14	<1	1.5*	14	dust vs none
Bergen, Norway Bakke (1991a, 1991b)	4469 M & W 15-70 yr	43	29	28	1.9*	17	29	1.9*	16	7[d]	1.4	2	dust or gas vs none: for COPD high exposure vs none
Po Delta, Italy Viegi (1991)	1027 M 608 W 18-64 yr	60 38	31 16	19 6	1.6* ns	14	3 4	2.4* 2.9*	29 27	2 <1	2.3* ns	na na	any vs none any vs none

Table shows Odds Ratios (OR's) for exposure for all studies except the Tucson study for which prevalence OR's are shown; also PAP% to indicate the %age by which the prevalence of the condition/syndrome would be reduced in the community if no one had experienced the exposure(s) implicated. In all studies OR's were standardized for age and smoking; other factors taken into account included pack years (Viegi et al., 1991), social and educational level (Krzyzanowski and Kauffman, 1988), city or pollution level (Krzyzanowski and Kauffmann, 1988; Korn et al., 1987), urban/rural differences (Bakke et al., 1991a; Bakke et al., 1991b).

* Results significant in the analyses carried out by the authors; ns = not significant and not reported: na = could not be calculated.

[a] Bronchitis was defined on the basis of phlegm production (Lebowitz, 1977), with cough for 3 months of the year (Bakke et al., 1991a; Bakke et al., 1991b), or persistent for 3 months of the year for at least 2 years (Viegi et al., 1991).

[b] Wheezing was defined as ever or occasional (Bakke et al., 1991a), persistent (Korn et al., 1987), or associated with attacks of shortness of breath (Lebowitz, 1977; Viegi et al., 1991).

[c] COPD was defined variously on the basis of spirometry (see Table 2).

[d] Refers to a subset of 714 men and women who underwent pulmonary function tests in the laboratory; COPD defined using clinical and spirometric criteria.

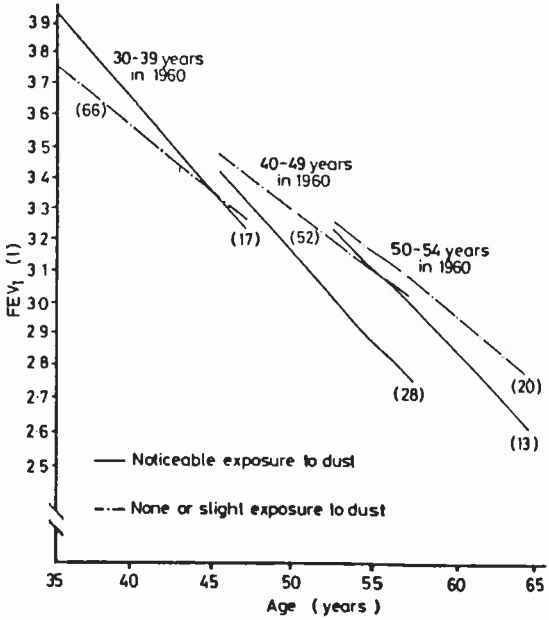

Figure 1. The relationship between FEV_1 and age over a 12 year followup period in 66 men with noticeable exposure to silica dust and abrasives at work compared to 196 men with slight or no exposure. None of the men had changed jobs between studies. Results are shown with men stratified according to age when first studied. ***Copyright by British Journal of Industrial Medicine (Kaufman et al., 1982). Reprinted with permission by the Department of Health and Human Services. Further reproduction prohibited without permission of the copyright holder.***

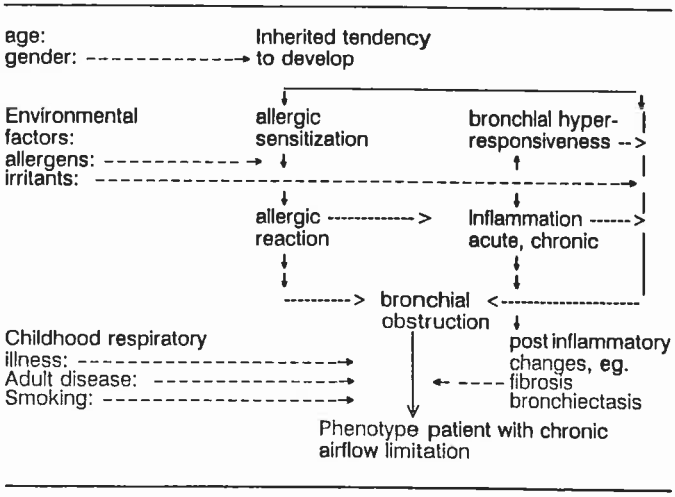

Figure 2. Schema illustrating the Dutch hypothesis of the natural history of chronic nonspecific lung disease (CNSLD), also called COPD: adapted with permission from Sluiter et al., (1991). The dotted lines indicate the areas in which, in the view of the Dutch researchers, knowledge and insights have been added between 1961 and 1990. ***Copyright by European Respiratory Journal (Sluiter et al., 1991). Reprinted with permission by the Department of Health and Human Services. Further reproduction prohibited without permission of the copyright holder.***

OCCUPATIONAL EXPOSURE ASSESSMENT IN EPIDEMIOLOGY - PRINCIPLES IN THE DESIGN OF AN OPTIMAL EXPOSURE ASSESSMENT STRATEGY

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Abstract

A wide variety of approaches to assess occupational exposure in epidemiology have been proposed in recent years. Among these are: job exposure matrices, which translate job histories into qualitative or quantitative exposure estimates, toxico-kinetical modeling, which aims to provide the most biologically reasonable dose estimate, and "time frame modeling," which studies the effects of temporal variations in exposure. However, no clear guidelines exist as to which index of dose is optimal in a specific situation. Multiple comparisons of exposure response relationships based on different indices of exposure have been suggested to avoid this difficulty. However, it is clear that this approach has inherent disadvantages. First, there is no agreement on statistical criteria to discriminate between better and worse performance in the data analysis, and, second, it is to be expected that multiple comparisons will sometimes lead to false conclusions. A preferable alternative is to choose an exposure index on the basis of its validity (sensitivity and specificity) and its reproducibility. For classically discrete measures of exposure this process is straight forward. An analysis of lung cancer and chronic non-specific lung disease incidence data from a Dutch general population cohort with exposure indices generated with two external job exposure matrices and self-reported exposure data illustrates that outcomes of the analysis can roughly be predicted by these indices indicating quality for qualitative and semi-quantitative measures of exposure. For quantitative exposure data, the quality of

the exposure assessment is determined by subjecting the exposure data to an analysis of variance. By this means, intra-individual, inter-individual, intra-group, and inter-group differences in exposure can be calculated, and these parameters used by the researcher to optimize the contrast between individuals or exposure groups, and to make the exposure categories as homogeneous as possible. Data used from a study in the Dutch grain processing and animal feed industry and the U.S. National Coal Workers Pneumoconiosis Study, show that differences in the observed slope of exposure-response relationships can partly be explained by components of exposure variability. This indicates that optimal occupational exposure assessment strategies should be developed *a priori*, or selected before the start of the statistical analysis of the response data, based on information on exposure variability. By doing this, comparison of the results of multiple analysis will avoided.

Key words

Exposure assessment, validity, variance components, misclassification, exposure response modeling.

Introduction

There has been a remarkable growth in interest and activity in occupational exposure assessment in recent years. Job exposure matrices have been developed, and are being used to translate job histories into qualitative exposure information (Heederik et al., 1990; Goldberg et al., 1993). By means of toxico-kinetical studies, researchers are exploring the biological validity of existing indices of exposure. This work is expected to lead to new and better exposure indices which optimally estimate the actual dose at the target organ (Smith 1985, 1987). Epidemiologist have explored new approaches such as; "time frame analysis" to implement effects of temporal patterns in the exposure or peak exposures in occupational cancer epidemiology (Checkoway & Rice, 1992). In respiratory epidemiology, high resolution exposure assessment strategies have been used to characterize peak exposures of short duration and relate these to the development of acute respiratory symptoms (Wegman, 1992).

Another line of research has focused on the optimization of more conventional exposure estimates, such as cumulative exposures. This

work has included the comparison of exposure estimates developed using different strategies, and their validation against medical responses. Misclassification of exposure is a key issue in this area. This paper will be focused on these aspects of exposure assessment and validation.

The best surrogate of exposure?

Occupational epidemiology texts often provide a list of surrogates of exposure (e.g., Vihma, 1981; Checkoway et al., 1987, 1989). Usually, a hierarchy of quality is distinguished, from worst to best, ranging from broad exposure categories based on job titles, departments or sectors of industry derived when actual measurements are not available, to specific numeric estimates for individuals. These rankings reflect the truth, in general. However, as Smith (1992) has shown, pharmacokinetics determine if a specific measure of exposure is a good predictor of dose. Depending on, for instance, the half life of an agent, a cumulative exposure can be an overestimate or underestimate of actual dose. Moreover, the value of an exposure estimate or surrogate is dependent on both its bias and its variability. While qualitative measures may be subject to biases, quantitative estimates may be unreliable because of excessive variability. For instance, it is well known that day to day and worker to worker variability in exposures can be quite large (Heederik et al., 1991a; Kromhout et al., 1993; Rappaport et al., 1993). For these reasons, it is to be expected that what one might call the conventional or classical measures of exposure might, in some cases, be poor predictors of dose. As a result, these limitations in the exposure estimate could lead to a poor correlation with response.

In many epidemiologic studies no one exposure index stands out as being the obvious and overwhelming choice for correlation with response. Consequently, researchers are forced to use and compare different indices of exposure (Blair & Stewart 1992; Smith, 1992). This is unsatisfactory because it may lead to more chance findings. Moreover, differences in the findings arising from different exposure indices make for difficulties in interpretation of the results, and in coming to overall conclusions (Lee-Feldstein, 1989). These problems point to the real need for a better understanding of the validity and reliability of various approaches to exposure estimation, and for the necessity for criteria for optimal exposure indices. The

availability of such information would enable researchers to optimize their exposure estimation strategy based on the nature of the exposure data and the biologic processes, before attempting correlation with the response. By having the resources to enable researchers to make their choice regarding exposure indices independent of the final correlation with the response, the results would be substantially strengthened in terms of validity, and the likelihood of chance findings minimized. In conclusion, the performance of a measure of exposure in the analysis depends on its biological plausibility, and its validity and precision. Lacking information on these aspects, it is difficult to account for a poor observed relationship between exposure and response in any given situation. In this paper, the effect of misclassification of exposure is explored further as a key issue in choosing a specific index of exposure. Aspects of validity and precision will be discussed for various exposure assessment strategies, both qualitative (or semi-quantitative) and quantitative. Based on our experiences, and those of others, some general guidelines will be formulated. Most emphasis will be given to quantitative exposure assessment strategies.

The influence of misclassification of exposure

Misclassification of exposure may introduce a bias in the estimate of the magnitude of the relationship between exposure and effect. If the misclassification is due to random error in a continuous exposure variable, the bias is towards zero and referred to in the statistical literature as "attenuation." In general, this type of error also reduces the power of a study to detect an association between exposure and disease (Armstrong, 1990).

Basically, statistical theory on "misclassification error" has been described for several types of exposure measures. Effects on non-differential or random misclassification has been well described for situations in which two or more distinct exposure categories exist. The influence of non-differential misclassification is less well understood when quantitative exposure assessment strategies are being used. This is remarkable, because especially quantitative exposure assessment is an approach which has been advocated by many researchers, and its application shows considerable growth. Understanding the influence of misclassification error for several types of exposure assessment becomes especially important because it has been suggested that multiple comparisons of exposure response

analyses with different exposure measures is important in order to understand the performance of different exposure indices.

Qualitative information on exposure

Lacking complete measured exposure information on individuals it is often necessary to employ qualitative methods to estimate the missing data. Qualitative information about occupational exposures is often gathered using questionnaires. However, despite their widespread application, the reproducibility and validity of the information elicited by questionnaire has been established in a limited number of studies.

Generally, occupational questionnaires are designed to obtain a full occupational history based on a categorization by job titles and industry. Several studies have found good agreement between self-reported occupational histories and employer records or governmental records of such information (Jonathan et al., 1957; Keating et al., 1950: Mosel & Cozan, 1952; Goldstein et al., 1971; Pershagen & Axelson, 1982; Siemiatycki et al., 1981; Baumgarten et al., 1983). In most of these studies, there was 50-80% agreement between the different sources of information, although the maximum time period involved was only 13 years. One specific problem involves the coding of the occupational and industrial titles. The number of different occupations and industries is large, the information often vague, and differences between industries and occupations often seem unclear. Therefore, coding has to be done by instructed personnel following strict written guidelines. Although there is limited information on the performance of coding personnel, validity and precision are probably moderate to poor. In a recent study in eight European Community countries, it was shown that the percentage of agreement for repeatedly coding the occupational status (comparable to the socio-economic status) was 70% (Cohens Kappa 0.65), and somewhat higher for coding a specific industrial occupational (Cohens Kappa 0.70). For coding the industrial occupation there appeared to be specific clusters of disagreement in occupations involved in handling metal goods, engineering and vehicle industry. The validity of coding occupational status was poor to moderate if a shortened set of instructions were used compared to a standard version (Cohens Kappa 0.37-0.52) (Rona & Mosbech, 1988, 1989).

Although categorizations of the occupational history can be useful, information on the exposures received in the various occupations cannot usually be obtained from them. Several researchers have therefore developed questionnaires, which ask about specific exposures, or contain questions referring to known health hazards in the workplace that can simply be confirmed or denied (ALA, 1983; Rosenstock et al., 1984). Rosenstock et al., 1984, showed that occupational exposures assessed with a self-completed questionnaire had 75% sensitivity and 70% specifically and a positive predictive value of 83% when the exposures obtained with the questionnaire were compared to the estimates of an occupational hygienist for the different jobs. However, Bond et al., 1988, showed that in a retrospective study, respondents recalled only approximately 3% of the chemicals they had ever worked with during their employment period in a chemical plant. This suggests that in certain situations recall of the past experience can be poor.

Semi-quantitative measures of exposure

Semi-quantitative exposure estimation is the process of estimating a subject's exposure on an ordinal scale by ranking the degree of exposure based on knowledge of the tasks performed and the nature of the work process. This method is often applied because it is simple, comprehensive and efficient, and because it leads to cost savings when applied in combination with strategies in which the exposure is actually measured (Kromhout et al., 1987). Typically, the principle behind this approach is to divide a population into a number of more or less homogeneous groups on the basis of the level, duration, and frequency of exposure.

Woitowitz et al., 1970, were probably the first to explicitly describe a qualitative ranking of jobs and tasks in three so called "danger classes" of workers in an asbestos cement producing industry and compare the semi-quantitative estimate with exposure measurements. They showed that what they called "danger class" ("Gefahren klasse 1") had a lower level of dust exposure than danger class G3 while G2 had an arithmetic average exposure in between. The procedure and criteria which lead to these estimates was not described, however. Since then, a number of attempts have been made to assess exposures using workers (DoPico, 1982; Rom et al., 1983; Kromhout et al., 1987; Hertzman et al., 1988; Teschke et al., 1989), occupational hygienists (Blum et al., 1980; Rosenstock et al., 1984;

Kromhout et al., 1987; Hawkins & Evans, 1989; Post et al., 1991), plant supervisors (DeFonso & Kelton, 1976; Wald et al., 1984), and chemists (Gerin et al., 1985).

Further studies have studied the reliability and validity of estimates generated by different raters. Overall, these have shown it is possible to identify workers with the highest exposure, without recourse to any exposure measurements. The procedure is not without its problems. Kromhout et al., 1987, showed that although hygienists were able to rank welders in two industries, actual exposure levels of corresponding exposure categories in the two industries differed considerably. This indicates hygienists are able to rank exposures within industries, but have trouble in successfully equating exposures across different industries (Figure 1).

Hawkins & Evans (1989) evaluated the ability of occupational hygienists to assess actual exposure risk (Table 1). Twenty four hygienists familiar with batch processes, predicted toluene exposures of a group of workers in a chemical processing plant. After limited historical data were presented, the procedure was repeated. The authors concluded that, experienced hygienists provided subjective estimates which could be used for retrospective or prospective epidemiological studies and hazard evaluation. However, results of the first estimation round showed that a difference of almost a factor three existed with empirical estimates of the arithmetic mean exposure. Estimates improved considerably after the limited information was given. Results of the study by Post et al., 1991, confirmed these findings to some extent. They showed hygienists are able to rank occupational titles by level of exposure. However, the success of the hygienists depended on the chemical considered. Hygienists were able to rank occupational group by methylene chloride exposure which was used intermittently, during cleaning activities. Results of ranking was poor for styrene, which was constantly present in the work environment at levels above the odor threshold. In their experience the ability of hygienists to give an absolute estimate of the exposure without some quantitative exposure information was limited and dependent on the type of process (bath/continuous) or the agent (odor threshold). However, the above mentioned problems imply that some exposure monitoring is necessary to calibrate the estimation process and estimate an actual exposure risk.

Some insight into the performance of qualitative and semi-quantitative exposure estimates in an exposure-response analysis is given by two studies, which describe the performance of general Job Exposure Matrices in occupational cancer studies. In a paper by Hoar et al. 1980, a job exposure matrix was described in which job titles, by industry, were linked to specific occupational exposures. It was this feature that was seen as an advantage for general population and case-control studies, because it is especially difficult to derive valid and reproducible exposure estimates for these types of epidemiologic studies. Other job exposure matrices have been developed since, of which the one created in the UK (Pannet et al., 1985), probably is widely applied (Heederik et al., 1990; Kauppinen et al., 1992). In job exposure matrices, the information on which the exposure estimates are based is derived from various sources such as expert opinions, hygiene handbooks, questionnaire data, exposure surveillance data, or if possible, actual measurements. This makes if difficult to generalize on the validity of Job Exposure Matrices. Kauppenin et al., 1992 concluded, the job exposure matrix described by Pannett et al., 1985, performed well in comparison with an assessment by hygienists if the exposure prevalence was above 10%. Kromhout et al., 1992, also showed that the performance of the job exposure matrices described by Pannett et al., 1985, and Hoar et al., 1980, was dependent on the relative number of persons actually exposed. This observation is directly related to the sensitivity and specificity of a job exposure matrix to identify workers with exposure. When the number of true exposed persons is relatively low it is better to have a matrix with a high specificity and a low sensitivity than the other way around. In this case the matrix generates as few as possible false positives. In case of a situation of a high exposure prevalence this becomes less critical. They also showed that by changing the cut-off point for deciding who is considered (high) or not exposed one can change the sensitivity and specificity of the job exposure matrix and optimize its performance for a specific situation (Figure 2). It is evident these different cut-off points do have a strong impact on risk ratios found (Figure 3). This illustrates that it will be difficult to make a generalization about the criteria that should be used to optimize the performance of a job exposure matrix. The performance required depends on the exposure prevalence, and thus indirectly on the study design and endpoint under investigation. Optimizing the validity of

a matrix is clearly preferred. Certainly, optimizing its performance in the analysis is a second best choice.

Quantitative exposure assessment on the individual level

Quantitative estimates of exposure are usually considered to be superior to other types. However, detailed guidelines on how to achieve optimal quantitative estimates in general do not exist, although various strategies have been proposed (Oldham & Roach, 1952, Ashford, 1958, Prais & Aitchison, 1954, Heederik et al., 1991b, Rappaport, 1991).

Air pollution levels are measured on a continuous scale, and exposure levels vary considerably over time and in space. Suppose we want to quantify the exposure of all workers in a population by monitoring each worker. If there is a large day-to-day (or intraindividual) variability of exposure, several measurements will be necessary to obtain a precise estimate of a worker's long-term exposure.

By taking only one measurement per individual, a poor approximation of an individual's exposure will be obtained. By taking repeated measurements on the same individual, the influence of the day-to-day variability is diminished and the estimate of the worker's long-term exposure improves with the number of measurements taken. Statistical equations to calculate the optimal measurement effort for this type of strategy have been described, for a given bias in the exposure-response regression coefficient, and for certain levels of intraindividual and interindividual variability in exposure (Liu et al., 1987). In a practical example, Brunekreef et al., 1987, have shown how intensification of the measurement effort resulted in stronger relationships between health effects and exposures being demonstrated. A clear illustration of this phenomenon is given in the following table which is based on data from the U.S. National Coal Workers Pneumoconiois Study as earlier analyzed by Attfield, 1985 (Table 2). Per worker, an average number of 34 dust exposure measurements was available. By randomly sampling a subset of all measurements per worker, exposure-response analyses could be performed using fewer measurements. The bottom line of the table gives the relationship between lung function change (FEV_1) over an eleven year period and dust exposure if all available measurements were used to calculate an

average dust exposure over the period. The regression coefficients between lung function and exposure were corrected for age and smoking habits. The other lines give results of similar analyses using fewer exposure measurements per worker.

When fewer measurements have been used, a weaker relationship was observed between lung function and exposure. Slopes of exposure response relationships could differ by a factor of three when the result of using three exposure measurements is compared to using all available measurements. One should realize that in the latter case, still more than three thousand measurements are required. Few examples of epidemiological studies exist in which anything close to such a measurement effort was realized. This sample clearly demonstrates the so called attenuation effect. Formulas presented in the literature allow calculation of the optimal number of measurements given the intraindividual variability (day-to-day) and interindivdual variability in exposure (Liu et al., 1978).

Quantitative exposure assessment using groups

For grouping strategies the theory is slightly different, being less well described, though analogous. The performance of a grouping strategy in an epidemiological study is determined by the intragroup variance (the homogeneity), the intergroup variance (the contrast), and the number of measurements in a category (the precision) (Prais & Aitchison, 1954). This is illustrated by Figure 4. The Figure shows the exposure distribution of two groups. In Figure 4B, overlap between the groups is considerable because large differences between workers within both groups exists. This implies the difference in exposure between the two groups (signal) is small in comparison to the differences between the workers within the groups (noise). The relative heterogeneity in the two groups leads to overlap in exposure distributions. This illustrates that some workers seem to be misclassified in relation to their actual exposure.

The situation depicted in Figure 4A is more favorable for accurate exposure assignment to workers. The difference in exposure between the groups is greater in relation to the differences between the workers within the groups, resulting in less overlap of the exposure distributions. One would expect that an analysis of the relationship between a health outcome and exposure would be more successful in situation B than A, because of the lower

misclassification. This concept is illustrated by a reanalysis of data from Dutch grain processing and animal feed workers (Heederik et al., 1991b; Simd et al., 1992). The workers were grouped into various numbers of categories (three and eight for endotoxin, and two, three, and eight for dust exposure). The group mean exposure levels were calculated and used for further analysis. Table 3 shows the regression coefficients of FEV_1, on average dust exposure, based on different groupings, and corrected for confounding variables. The Table also shows the ratios of intergroup and intragroup variability of exposure as calculated with an analysis of variance as described in Heederik et al., 1991b. This number essentially measures the ratio of the amount of "signal" relative to the amount of "noise" in the exposure data. For endotoxin, the ratio changed little as the number of groups was increased from three to eight. The actual slopes of the exposure response relationships of lung function on endotoxin exposure confirm what was seen in the signal:noise ratios, in that, the slopes changed little when the number of groups was increased from three to eight. For dust exposure, a different picture emerges. There, the regression analysis shows a factor of two in the slope, depending on the grouping used. The ratio of intragroup and intergroup variance reduces with increasing slope, which indicates that grouping by eight categories leads to more contrast between more homogeneous exposure groups.

In contrast to exposures derived for individuals from data collected on them, those derived from grouping strategies are less subject to attenuation effects in exposure-response modeling. Even if the average exposure for a category will systematically over- or underestimate the true exposure for some individuals assigned to the group (assuming pure homogeneity was not attained), attenuation will not occur for that reason, because this type of error is of the Berkson type (Durbin, 1954; Prais & Aitchison, 1954; Armstrong, 1990). However, bias of a regression coefficient can still be present because of misclassification of workers between categories, or because of a poor estimate of the average exposure caused by a limited number of measurements per exposure category. When only few measurements are available, attenuation can occur even in case of a group strategy (Armstrong, 1990). Little information exists about the latter problem, but results of a simulation in the same study of grain dust exposed animal feed workers showed that if considerably fewer exposure measurements were used than the 530 gathered for the original

analysis to calculate the average exposure of an occupational title group, relationships between cumulative endotoxin exposures and lung function level became attenuated (Table 4). When all exposure measurements were used, stronger exposure response relationships were obtained than when, for instance, only 75 measurements (approximately 9 per exposure category) were used. Slopes of the exposure response relationships (Table 4) are the average of 50 simulations, and differed by more than a factor 1.5.

These examples show that researchers have the potential to optimize the use of exposure data in the data analysis phase of a project by changing the grouping structure of the population. The same principles can, of course, be used to improve exposure assessment during the data collection phase. After information about variance components has been gathered during the pilot phase of a study, the design, in terms of measurement effort (number of measurements per worker), and in the choice of grouping structure, can be optimized. However, until now, only limited experience exists with these indices which characterize the quality of an exposure assessment strategy, and with theoretical models for exposure optimization. The absence of sufficient experience can be explained by a few reasons. Equations presented in the statistical literature have been developed for fairly ideal situations, and assume balanced designs which require equal numbers of measurements for each worker. In occupational epidemiology the measurement effort is often limited and this requirement is only seldom fulfilled. Another reason is that very studies exist that have sufficient information for reliable study and contrast of various strategies. Because of these reasons, very limited insight exists in the performance of different exposure assessment strategies relative to each other.

Conclusions

Results of comparative studies of two general population job exposure matrices with self-reported exposure information, as well as results from validation studies from qualitative and semi quantitative exposure estimates suggest that reliability, in terms of inter-rater agreement and validity are not always sufficient for useful application to exposure-response determination. Well controlled semi-quantitative exposure assessment studies show that overlap between exposure categories can be considerable, suggesting frequent worker misclassification. Comparison of ranking of the exposure

with actual measurements in different but comparable industries suggest that misclassification of exposure is likely to occur. Poor performance of semi-quantitative estimates might be related to some characteristics of the agent under study as well (odor threshold, use in the process).

Quantitative exposure assessment strategies based on individual estimates are relatively inefficient, and require a considerable measurement effort. Grouping strategies may be more efficient, and improve in usefulness as the heterogeneity between groups declines, as the contrast between categories increases, and as the number of measurements per category increases. However, designing a strategy does involve some compromises, given a limited budget for sampling. Making categories as homogeneous as possible will generally lead to a large number of small groups containing few workers who have similar occupations or who perform similar tasks. This in its turn reduces the number of measurements per exposure category, and thus the precision of the estimate of the average exposure. In contrast, choosing fewer groups will maximize the precision within a group, but diminish the contrast between groups and increase intra-group heterogeneity.

Results presented in this review illustrates that hierarchies in measures of exposure as presented in many occupational epidemiology textbooks are a simplification of reality. In the near future more emphasis should be given to determining the validity and precision of exposure measures used for epidemiological purposes. This should be done in advance, in a pilot study, to optimize the exposure assessment strategy. The alternative, consisting of optimizing the use of exposure data during analysis of exposure response, is considered a second best approach.

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Table 1. Comparison of subjective and empirical exposures estimates made by 24 experienced occupational hygienists (from: Hawkins and Evans, 1989).

	subjective estimates		
parameter	with	without data	measurements
median (ppm)	8.9	3.0	0.37
mean (ppm)	14	4.4	4.6
90th	41	21	16

Table 2. Regression analysis of the relationship between individual mean exposure to coal dust and eleven year change of lung function (FEV_1) for 1105 coal miners corrected for age, standing height and pack years of tobacco smoked with different numbers of samples per worker.

	Coefficient FEV_1	$^{s.e.}$
Samples/worker	[ml per mg/m^3]	
3	-18	11
6	-25	13
9	-32	13
12	-36	14
15	-38	14
all samples	-45	15

Table 3. Slope of exposure response relationship (ß) of present dust or endotoxin level and lung function (FEV_1) for different categorizations of the exposure corrected for age, standing height and pack years of tobacco smoked. Ratio of intragroup and intergroup (λ) variances in exposure is given as well.

# Exposure Categories	$^{\beta}$endotoxin	$^{\lambda}$endotoxin	$^{\beta}$dust	$^{\lambda}$dust
8	-0.0049	1.02	-0.0081	1.28
3	-0.0041	1.02	-	-
2			-0.0042	1.57

Table 4. Underestimation of exposure-response relationship between cumulative endotoxin exposure among grain and animal feed workers dependeing on the number of exposure measurements used in the exposure-response analysis. Estimates of the slope of the exposure-response relationship are an average of 50 simulations.

exposure measurements used [n]	slope in FEV_1 [L per yr/g/m^3]
25	0.58
50	0.51
75	0.63
100	0.62
125	0.64
225	0.77
325	0.80
425	0.82

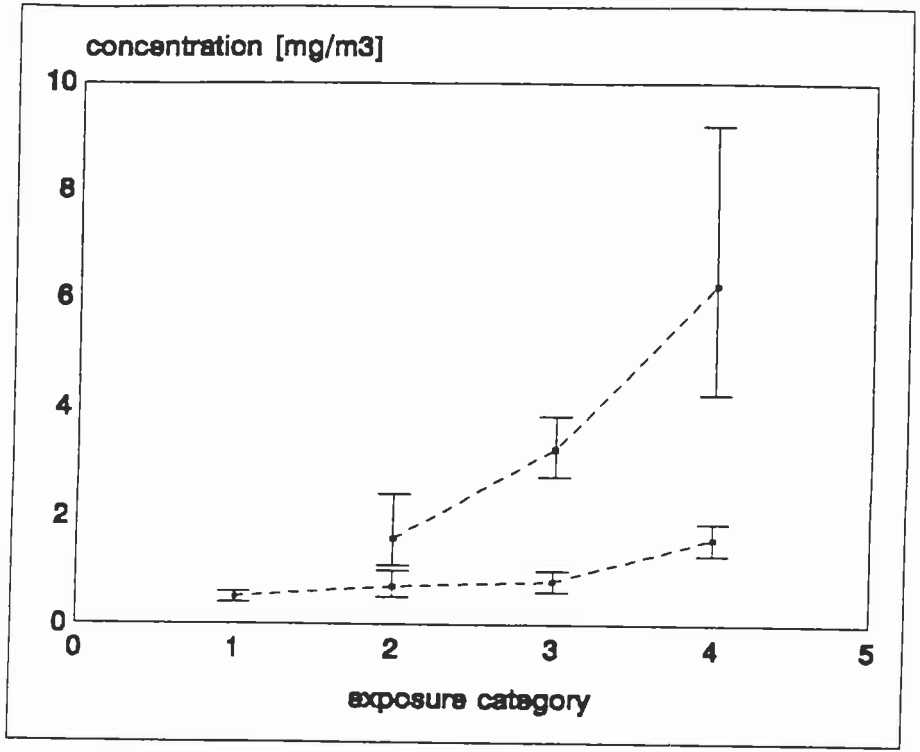

Figure 1. Estimates of welding fume exposure by an occupational hygienist in two industries compared to measured exposure levels (arithmetic mean plus confidence intervals) (from Kromhout et al., 1987).

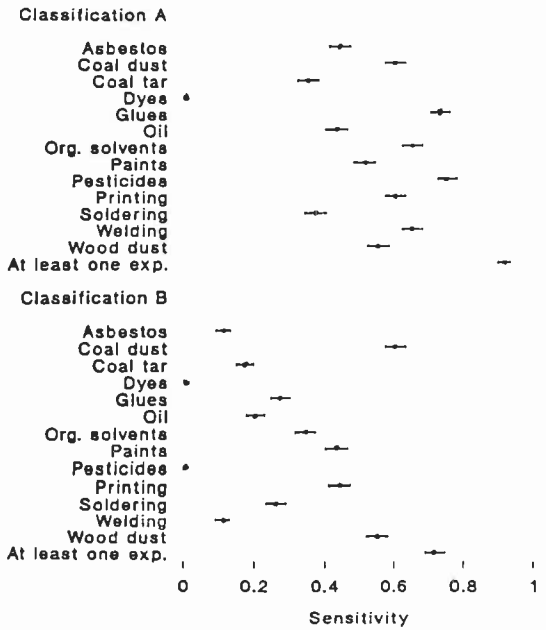

Figure 2a. Sensitivity of the Medical Research Council matrix, considering both low and high exposure subjects exposed (A classification) and considering only high exposure subjects as exposed (B classification): The Zutphen Study, 1977/1978. Org., organic; exp., exposure

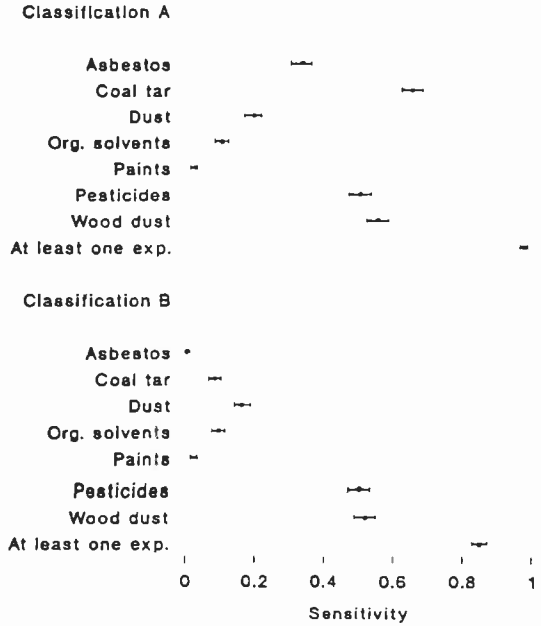

Figure 2b. Sensitivity of the Harvard matrix, considering both low and high exposure subjects as exposed (A classification) and considering only high exposure subjects as exposed (B classification): The Zutphen Study, 1977/1978. Org., organic; exp., exposure

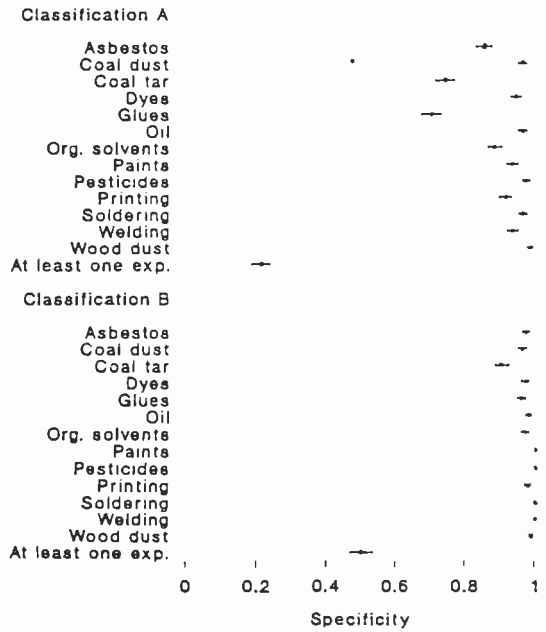

Figure 2a. Specificity of Medical Research Council matrix, considering both low and high exposure subjects exposed (A classification) and considering only high exposed subjects exposed (B classification): The Zutphen Study, 1977/1978. Org., Organic; exp., exposure.

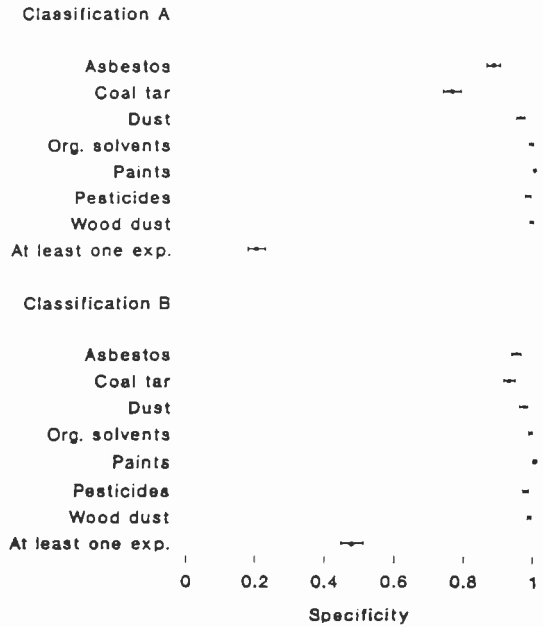

Figure 2b. Specificity of the Harvard matrix, considering both low and high exposure subjects as exposed (A classification) and considering only high exposure subjects as exposed (B classification): The Zutphen Study, 1977/1978. Org., organic; exp., exposure.

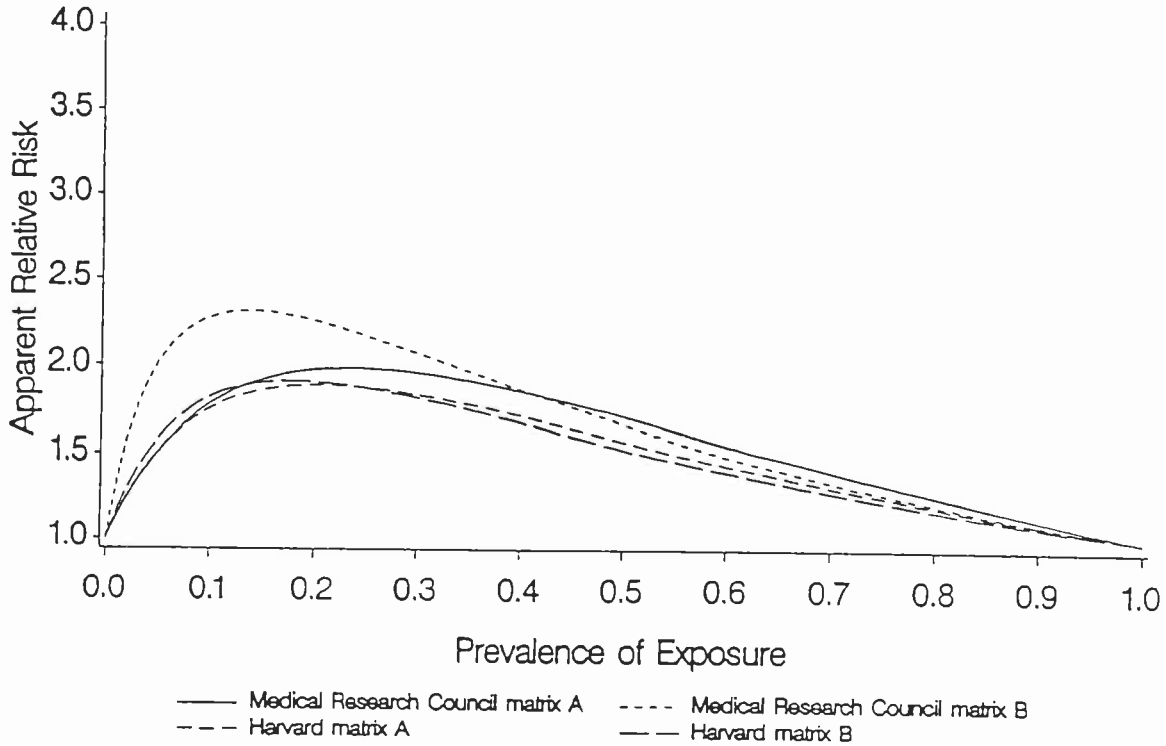

Figure 3. Prevelance of exposure and apparent relative risk

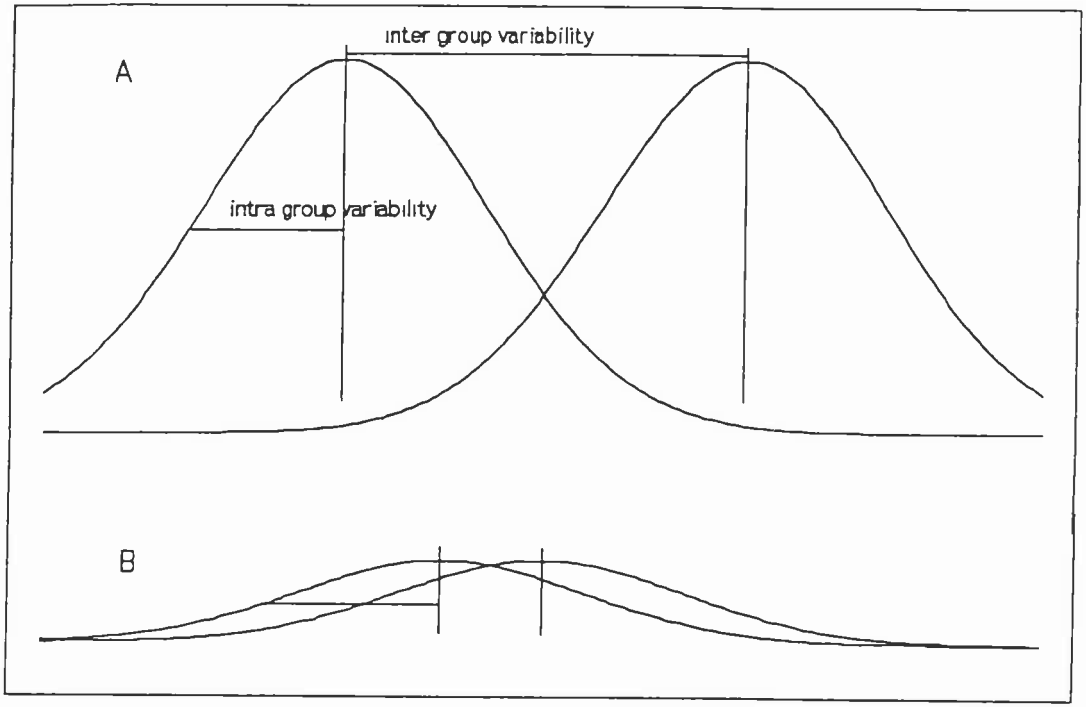

Figure 4. Exposure distributions for two occupational groups with A) large inter-group and small intra-group viriability in exposure; B) small inter-group and large intra-group variability in exposure.

BIOMARKERS AND MOLECULAR EPIDEMIOLOGY OF CANCER

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Introduction

By combining biologic markers with epidemiologic methods, molecular epidemiology offers a potentially powerful tool in cancer prevention. Indeed, the vast majority of cancer deaths (500,000 in the U.S. and 5 million worldwide each year) is in theory preventable, believed to result from environmental factors. Therefore, environmental carcinogenesis, broadly defined to include both lifestyle (smoking, diet) and non-lifestyle factors (workplace and ambient exposure to industrial or man-made chemicals) represents a challenging and important area of cancer prevention.

Traditionally, the two major tools in identifying and assessing carcinogenic risks from workplace exposures have been epidemiology and quantitative risk assessment (QRA). Epidemiology has been severely handicapped by the long latency of the disease, problems in estimating past exposure, and insensitivity to modest increases in common cancers. Joined with molecular epidemiologic studies, biologic markers have the potential to provide quantitative human data on the biologically effective dose of carcinogens, resultant molecular effects and genetic/acquired factors that modulate these effects.

There is the expectation that biologic markers can be incorporated into analytic epidemiologic studies (cohort and case-control) in such a way as to increase the power of such studies to identify causal relationships between exposure to specific agents and increased risk of cancer. For example, carcinogen-DNA adducts provide information on the interacted or biologically effective dose of carcinogens. As such, they can serve to assign subjects to "exposed" and "unexposed" groups on a more meaningful basis than self-reported exposure, job history or environmental monitoring, thereby

increasing the power of a study by reducing random exposure misclassification. Moreover, certain biologic markers of preclinical response or biologic effect (those correlated with cancer and occurring before progression to malignancy were inevitable) might ultimately replace clinical disease as an endpoint. Possible candidates include specific alterations of specific oncogenes or tumor suppressor genes and signal chromosomal aberrations. By providing an earlier and a more commonly occurring outcome, such markers would mitigate the latency problem in cancer epidemiology, increase study power, and allow effective intervention. Finally, a combination of such biologic measures of molecular dose and effect with biomarkers of susceptibility could identify subgroups of the population at highest potential risk for epidemiologic follow-up and intervention.

With its general reliance on extrapolation from results of chronic bioassays in rodents, QRA for carcinogens is an uncertain exercise, involving a number of assumptions about interspecies relationships and the nature of the carcinogenic process itself. The expectation by risk assessors is that biologic markers will not only permit early identification of potential risks (hazards) to humans but will provide comparative data on molecular dose, response and susceptibility in experimental animals and humans, facilitating quantitative extrapolation between species. Another potential contribution is the molecular documentation of human interindividual variation in the biologic response and susceptibility to carcinogens, which could then be explicitly factored into QRA (Perera et al., 1991a).

By expanding our knowledge of the mechanisms or stage at which individual carcinogens exert their effects in humans, biomarkers could permit us to design more effective intervention and prevention strategies, and to monitor their efficacy. For example, biomarkers may be used to identify previously exposed workers who would benefit most from chemoprevention and to provide intermediate endpoints in clinical trials of chemopreventive agents (Reynolds, 1991 and Lippman et al., 1990).

Despite this potential, most biomarkers are in the validation stage. For example, there exist numerous biomonitoring studies where persons with known (usually high) exposures to genotoxic compounds have been sampled. However, there are relatively few

examples of studies in which a hypothesis regarding cancer causation has been tested within a well-designed "molecular epidemiologic" study. There are still fewer well-developed applications of molecular epidemiology to QRA. And there is a dearth of methods to detect important environmental carcinogens, such as dioxin and other chlorinated organics, that do not interact efficiently with the genetic material.

On the other hand, the feasibility of biomonitoring and molecular epidemiology has been demonstrated. The diversity of methods now being validated and the increasing interest in seriously addressing problems posed by the union of experimental technology and epidemiology are both highly encouraging. For review please see Perera, 1987; IARC, 1988; Schulte, 1989; Vineis et al., 1990; Harris, 1991; Hulka, 1991; Perera 1993; and Sugimura et al., 1991.

An Example: Recent Research on Polycyclic Aromatic Hydrocarbons (PAH)

Iron foundry workers who have well characterized exposure to carcinogenic PAH and who are considered to be at increased risk of lung cancer (Perera et al., submitted) constitute a model population for validating biologic markers. In a recent study, we evaluated the internal dose of PAH (1-hydroxypyrene in urine), as well as the relationship between the biologically effective dose of PAH (PAH-DNA adducts in white blood cells) and two biomarkers of biologic effect (mutation in peripheral blood cells at the hypoxanthine guanine phosphoribosyl tranferase (HPRT) and glycophorine A (GPA) loci (Perera et al., submitted; Santella et al., in press). In particular, the relationship between current external PAH exposure (based on personal and ambient monitoring) and levels of these biomarkers was evaluated to determine whether PAH-DNA adducts, which can reflect individual differences in metabolic handling of PAH, are better predictors of mutation than external exposure.

The worker cohort was ethnically homogeneous and comprised 48 workers in a Finnish iron foundry. Subjects were interviewed at enrollment using a standardized questionnaire to elicit occupational, smoking, health and environmental histories.

Personal monitoring was carried out on the day of sampling or on the day before. In addition, stationary samples were collected from

seven points in the foundry and four points in the control areas on two separate days. Analysis was carried out for total particulate and PAH concentrations. Based on benzo[α]pyrene (BP) data from personal sampling, the workers were exposed to a range of 2 - 60 ng/m^3 of BP. This level is approximately 30 fold lower than previous measurements in this plant (150 - 200 ng/m^3).

Workers were divided into three exposure categories: low (<50 ng BP/m^3), medium (50 - 200 ng/m^3) and high (>200 ng/m^3). Mean levels of urinary 1-hydroxypyrene in the three groups were 2.7, 1.8, and 3.6 umol/mol creatinine respectively. Mean PAH-DNA adduct levels increased with exposure from 5.2 (low exposure group) to 6.1 (medium exposure group) to 9.6 adducts/10^8 nucleotides (high exposure group) ($r=0.28$; $p=0.08$). The two markers were positively but not significantly correlated ($p=0.37$). Levels of HPRT mutant frequency (Mf) (adjusted for age and cloning efficiency) also increased gradually with BP exposure from 1.04/10^6 cells in the low exposure group (<5ng/m^3) to 1.13/10^6 cells in the medium exposure group (5 - 12 ng/m^3), to 1.82/10^6 cells in the high exposure group (>12 ng/m^3) ($r=0.46$; $p=0.06$). As evidenced by the large standard deviation and the range of values within each of these groups (1.5 - 4.5 fold), workers with comparable levels of external exposure showed a variable molecular response in terms of mutation induction. HPRT Mf was highly correlated with PAH-DNA adducts ($r=.67$, $p=0.004$).

The level of GPA NN phenotype variant frequency (Vf), which predominantly reflects large-scale chromosomal damage, showed no increase by exposure group; nor was NN Vf positively correlated with PAH-DNA adducts. GPA NO phenotype Vf, which would be anticipated to respond to the induction of point mutations by BP and other PAH increased slightly but not significantly from the low to medium to high exposure group from 8.21 to 10.67 to 11.75/10^6 cells respectively ($r=0.25$; $p=0.32$). However, this endpoint was not significantly correlated with PAH-DNA binding. Nor were GPA and HPRT correlated. This result indicates that neither measure of GPA mutation accurately reflects the interindividual variation in biologic response in the erythroid bone marrow cells that are the targets for mutation.

A significant finding is the increasing trend with exposure in HPRT

Mf in parallel with PAH-DNA binding. Although worker exposure to cyclophosphamide and ethylene oxide has been linked to HPRT mutation and/or hemoglobin adducts (Huttner et al., 1990 and Tates et al., 1991), to our knowledge this is not only the first report of increased HPRT mutation in PAH exposed workers but is the first report of an association between DNA binding of an industrial carcinogen and induction of somatic mutation in humans.

It is noteworthy that current PAH levels in the plant are approximately 30-fold lower than those which were previously shown to increase PAH-DNA binding (Perera et al., submitted). Thus, this report extends the "dose-response" curve for PAH-DNA adducts downward, at the same time linking them to increased mutation.

Another significant finding is the marked interindividual variation in all biomarkers evaluated, consistent with that seen in other molecular epidemiologic and biomonitoring studies in populations with occupational or environmental exposure to mutagens/carcinogens (MacLeod et al., 1988). As mentioned, the observed variation probably reflects differences in processes such as activation, detoxification and DNA repair which are partially under genetic control.

Finally, a parallel study in a non-worker population also exposed to PAH and related air pollution from fossil fuel combustion in Eastern Europe has observed the same substantial interindividual variation (2-75 fold) in all biomarkers evaluated (Perera et al., in press). All the biomarkers evidenced an effect of air pollution exposure: PAH-DNA by immunoassay, DNA adducts by P32 postlabeling, chromosomal aberrations, sister chromatid exchanges and ras P21 oncoprotein overexpression. Adducts were correlated with chromosomal aberration ($p=0.05$) providing further evidence of a link between the biologically effective dose of carcinogen and an irreversible biologic effect relevant to cancer induction. There was no apparent threshold for formation of any of the biomarkers studied. This is the first report of clear increases in multiple biomarkers in an environmentally (non-occupationally) exposed population. Potential markers of susceptibility (vitamins, P450, glutathione transferase) are being analyzed jointly to determine whether they modulate the molecular effects of exposure.

Conclusion

The field of biomarkers and molecular epidemiology of cancer has made significant progress in the past 5 - 10 years. As illustrated above, research has demonstrated the sensitivity of multiple markers to low levels of environmental exposure as well as the potential of molecular epidemiology to elucidate the complex nature of interindividual variation in cancer risk -- the central issue in cancer prevention. In conclusion, it appears that the potential of this interdisciplinary approach to prevent cancer justifies a serious commitment to validating this approach.

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Table 1. Internal dose

Compound Analyzed	Exposure/Source	Biologic Sample	Population	References
CFA*	Occupational exposure	Urine	Workers	Eadsforth et al., 1988
1-Hydroxy-pyrene	Coal tar products	Urine	Workers	Jongeneelen et al., 1989
Mutagens	Various occupational exposures	Urine	Workers	Vainio et al., 1984
Mandelic Acid	Styrene	Urine	Workers	Brenner et al., 1991

*CFA, 3-Chloro-4-fluoroaniline

Table 2. Biologically effective dose - protein adducts

Endpoint	Exposure/Source	Biologic Sample	Population	References
Alkylated Hb	Propylene oxide	RBC	Workers	Osterman-Golkar et al., 1984
Hydroxy-ethylhistidine, Hydroxyethyl-valine	Ethylene oxide	RBC	Workers	Calleman et al., 1978; van Sittert et al., 1985; Farmer et al., 1986; Tornqvist et al., 1986; Mayer et al., 1991
PAH-albumin	PAH in workplace	Plasma	Workers	Sherson et al., 1990

Hb, hemoglobin
PAH, polycyclic aromatic hydrocarbons

Table 3. Biologically effective dose - DNA adducts

Endpoint	Exposure/Source	Biologic Sample	Population	References
PAH-DNA	PAH	WBC	Workers	reviewed in Santella, 1991
Spectrum of DNA adducts	Various industrial exposures	WBC	Workers	reviewed in Santella, 1991

Table 4. Early biologic effect or response

Endpoint	Exposure/Source	Biologic Sample	Population	References
Chromosomal aberrations	Industrial chemicals radiation	WBC	Workers	van Sittert et al., 1985; Sarto et al., 1984; Galloway et al., 1986, Evans,1982, for review
DNA hyperploidy	Aromatic amines	Bladder and lung cells	Workers	Hemstreet et al., in press; Hemstreet, 1988
HPRT mutation	Radiation	WBC	Workers	Messing et al., 1986
Micronuclei	Organic solvents, heavy metals	WBC	Workers	Hogstedt et al., 1983
Oncogene activation	PAH	Serum	Workers	Perera et al., 1988b
Single strand breaks	Styrene	WBC	Workers	Walles et al., 1988; Brenner et al., 1991
Single chromatid exchange	Industrial chemical exposure, radiation	WBC	Workers	Carrano and Moore, 1982; Wilcosky and Rynard, 1990
Unscheduled DNA synthesis	Propylene oxide	WBC	Workers	Pero et al., 1982

HPRT, hypoxanthine guanine phosphoribosyl transferase
PAH, polycyclic aromatic hydrocarbons
WBC, white blood cells

Table 5. Examples of genetic factors influencing susceptibility

Gene	Population	Reference
CYP 2D6	Lung cancer cases and controls	Ayesh et al., 1984; Caporaso et al., 1989; Caporaso et al., 1990
CYP 1A1	Lung cancer cases and controls	Kawajiri et al., 1990
CYP 2E1	Lung cancer cases and controls	Uematsu et al., 1991
GST 1 (μ)	Lung, stomach, colon cancer	Seidegard et al., 1986; Seidegard et al., 1990; Strange et al., 1991
NAT	Smokers, colon	Cartwright et al., 1982; Vineis et al., 1990
DNA Repair Genes		reviewed in Freidberg, 1985
Tumor suppressor genes, Rb, p53	Retinoblastoma, Li-Fraumeni syndrome	reviewed in Li, 1990

CYP, cytochrome P450
GST, glutathione-s-transferase
NAT, N-acetyltransferase
Rb, retinoblastoma

EPIDEMIOLOGY AS A TOOL FOR OCCUPATIONAL STANDARD SETTING

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Introduction

Occupational standards in a broad sense include qualitative classification of hazardous agents into several specific categories such as carcinogenicity and hypersensitivity, as well as quantitative standards such as threshold limit values. Epidemiological method has certainly contributed to both these categories. However, my impression is that more emphasis has been placed by occupational epidemiologists on the epidemiology of cancer than on any other facets of occupational health. As a result, a number of chemicals have been classified as human carcinogens. But even for carcinogenicity, quantitative aspects have been far less studied mainly because of the difficulty of exposure assessment. For the purpose of determining occupational exposure limit, epidemiological studies on the quantitative relationship between exposure and effect are undoubtedly most desirable. It is the purpose of this paper to clarify how much epidemiological studies have contributed to the recommendation of current occupational exposure limits and consider a strategy for further research.

Analysis of the Documentation of Occupational Exposure Limit

A meta-analysis was made on the published documentation of the occupational exposure limits recommended by Japan Association of Industrial Health (JAIH).[1] The first recommendation of occupational exposure limits by JAIH appeared 1961. The list has been annually revised and enlarged and the current list[2] of 1992 includes 166 chemicals except for dusts and physical agents. All newly recommended or revised exposure limits have been accompanied by the published statement of reasons of the decision.[1] By analyzing the content of the document, it is possible to know what kind of critical data were used as bases of the recommendations. The philosophy underlying the exposure limit by JAIH is essentially the same as that

of most other exposure limits including TLV by ACGIH[3] and MAK by DFG.[4]

A comparison of the current lists of JAIH and ACGIH shows that, out of 158 substances which are listed in both, 100 have the same values, 36 are given lower values by JAIH than by ACGIH, and 22 are assigned higher values by JAIH. The discrepancy reflects the difference in the recentness of recommendation or revision, different interpretation of the same data, and the difference of information source. However, these gaps are not large as a whole. The method of determining the recommended values by JAIH is considered to be a typical sample of the ways employed by most occupational standard setting organizations.

Table 1 is a summary of information which was used for determining occupational exposure limits for acetone.[1,5,6] It indicates that no-observed effect level (NOEL) for irritative action of acetone has not been established. From this information JAIH recommended 200 ppm while most other countries adopted higher values as shown in Table 2 on the basis of essentially the same data. This is an example of substances for which exposure limits were set at levels causing some effect on humans. A review of JAIH documentation[1] disclosed that such levels causing tolerable effects were selected as the exposure limit for 24 chemicals. For 10 substances, maximum NOELs themselves or nearby values were adopted and the values around minimum observed effect levels (OELs) or values between OELs and NOELs were adopted for 20 substances. For these 54 chemicals there seems to be little margin of safety.

Table 3 shows the ratios between adopted exposure limits and OELs and NOELs. The ratio of 1 means that the exposure limits are set at levels where some tolerable effects are observed as in the case of acetone or are set at NOELs.

Table 4 is the summary of the effects of tetraethoxy silane (or ethyl silicate) on animals.[1,5] There is no information on the effect on humans. Both ACGIH and JAIH recommended 10 ppm which is one fifth of NOEL (50 ppm). So, this substance is classified in the ratio of 0.2-0.25 category in Table 3. Table 3 demonstrates that the limits for 92 chemicals among 121 (76%) have ratios of 0.5 or larger and

that occupational exposure limits generally have a very limited margin of safety.

In order to clarify the extent of contributions by epidemiology, a study that served as the source of critical information in setting the exposure limit for each chemical was identified and classified into three categories; namely, epidemiology, non-epidemiological human observation, and animal experiment.

The conditions of classifying as epidemiology were: (1) sound statistical comparison between 2 or more groups of workers with different exposure levels, (2) reasonable comparability of the observed groups except for the exposure, and (3) satisfactorily accurate measurement or estimation of the exposure. It was not easy in some cases to distinguish between epidemiology and non-epidemiological human observation, but the result of the classification shown in Table 5 is considered to reasonably reflect the actual situation. Epidemiological studies were used for the standard setting of only 19 out of 121 chemicals (16%), while non-epidemiological human observations amounted to 54% and animal experiments 30%. Table 5 also shows that mean ratios between adopted exposure limits and OELs or NOELs are 0.88 for epidemiological studies, 0.77 for non-epidemiological human observations and 0.38 for animal experiments. This result indicates that quantitatively reliable epidemiological studies are fewer than expected from the standpoint of occupational standard setting. It is also clear that the quality of standards needs to be much improved. Another interesting and obvious point suggested by this analysis was that more epidemiological data have been obtained for chemicals withlong history of industrial use. A long history of use means the presence of stronger social counteraction against the improvement of working environment. As a result, exposure limits recommended on the basis of epidemiology tended to stick to the borderline between safe and unsafe exposure. Furthermore, it must be admitted that exposure limits for some long-existing chemicals such as several heavy metals are considerably higher than no-effect levels in most countries. For these substances, gradual lowering of exposure limits along with the socially acceptable improvement of working condition seems to be a future practical solution. Anyway good epidemiological data provide the most reliable basis for all sorts of decision.

Application of epidemiological method to test the hyperthesis that a current exposure limit is correct.

It cannot be denied that epidemiology is not predictive in essence. Animal experiment will be much more relied on in the future as the basis of the standard setting. Epidemiology should be used to test the validity of such standards of tentative nature. Epidemiological method is most efficient when the study is designed to test the hypothesis that a current exposure limit is correct. Groups of workers with different levels of exposure around the current exposure limit of a chemical and, most preferably, a group without exposure are to be observed according to a well-designed epidemiological protocol.

I would like to present some data on toluene diisocyanate and acetone which hopefully serve as the examples of epidemiological study aiming at the test of the validity of existing exposure limits.

Table 6 shows exposure limits for toluene diisocyanates (TDI). JAIH's value were 20 ppb since 1965. However, in view of number of reports suggesting much lower threshold limit values, a cohort study of TDI workers in 7 polyurethane foam (PF) manufacturing factories were conducted from 1981 through 1985.[7,8] Fifty-seven TDI-exposed workers and 24 reference workers were followed for 4 years to clarify the relationship between exposure and pulmonary effects. The exposure concentration of TDI was measured by personal monitors (MCM 4000, MDA Sci.) designed to give continuous TDI exposure profiles on paper tape. The monitor was worn on the chest of each TDI worker throughout the working time. Figure 1 shows a typical example of the TDI exposure profiles of the workers in slab-type PF manufacturing factories. In 3 out of 7 factories, huge slabs of urethane foam were produced by the batch and workers were exposed to intermittent high concentration of TDI as shown in Figure 1. Other factories called mold-type factories were mainly producing seat cushions and headrests for automobiles in a continuous manner.

One hundred and fifty-nine personal exposure data were obtained for 57 workers during the study period. The PF workers were classified into 2 groups. Group L consisted of 28 PF workers whose exposure levels were very low. All PF workers in group L were working in the mold-type PF manufacturing process and were continuously

exposed to a low level of TDI with little variation in the exposure levels. Group H consisted of the remaining 29 PF workers mostly in the slab-type factories. In addition, it was interesting to note that group H could be further divided into 2 groups according to the levels of peak exposure. Fifteen workers whose TDI exposure profile indicated that they and repeatedly experienced one or more short-term high exposure to TDI exceeding 20 ppb were classified into H1. The occasional short-term peak exposure was up to 30 ppb or more. Group H2 consisted of 14 PF workers whose peak exposure levels were 3-14 ppb. No significant age differences were found among groups H, L and reference workers. Mean duration of working in the PF factories was 13.8 years in H1, 19.4 years in H2 and 17.4 years in L. The smoking rate was lower in group H than in group L and the slight difference between group H1 and H2 was not statistically significant.

Pulmonary function with special reference to airway obstruction was assessed by the forced maximal expiratory flow-volume test using an electronic spirometer (ASC-1000, Asahi Medical). Table 7 shows that time-weighted average concentration of TDI was 8.2 ppb in group H1, 1.7 ppb in group H2, and 0.1 ppb in group L. Peak exposures were 30-80 ppb in H1, 3-14 ppb in H2 and less than 1 ppb in L. Peak exposures were 30-80 ppb in H1, 4 ppb in H2 and 1 ppb in L. Table 8 shows the age- and height-adjusted flow-volume indices measured in 1981 and the average annual loss (AAL) in groups H, L and the reference workers.

Age- and height-adjustment was done by using a prediction equation which was derived from the result of the same pulmonary function test conducted on additional 100 males workers with no known exposure to hazardous chemicals. In Table 8 there were no noteworthy differences. However, when group H was divided into H1 and H2, the results were different. Table 9 shows the age- and height-adjusted flow-volume indices measured in 1981 and the AALs in group H1 and H2. There were no significant differences in the cross-sectional comparison in 1981. However, average annual loss of pulmonary functions was significantly larger in group H1.

The fact that only the workers with repeated short-term high exposure to TDI exceeding 20 ppb shows a relatively large pulmonary functionloss suggests that the short-term high exposure

levels are more relevant to the induction of pulmonary effects than the average exposure. The longitudinal change in the pulmonary function in TDI-exposed workers was reported by Peters et al.,[9] Adams,[10] Wegman et al.,[11] Diem et al.,[12] and Omae.[13] The relationship between exposure and effect was reported by them but the role played by peak TDI exposure had not been studied. On the basis of our observation, JAIH proposed 20 ppb as the ceiling value and 5 ppb as the TWA for TDI in 1992. This recommendation may apparently resemble the exposure limits of TDI proposed by other organizations. However, its peak limitation of 20 ppb as the ceiling value is slightly more stringent than STEL by ACGIH,[3,5] peak limitation by German Research Association[4] and others. It is also emphasized that JAIH's peak limitation was provided with an epidemiological basis by our study which had intentionally included the continuous 8-hour measurement of personal exposure in the study protocol. Although current exposure limits of TDI might not be completely protective or some workers with higher sensitivity, a progress is certainly being made by epidemiological studies.

Another topic which seems relevant to the discussion of epidemiology as a tool of standard setting is acetone, a very common organic solvent. As shown in Table 2, the exposure limits for acetone differ greatly. JAIH recommended 200 ppm mainly on the basis of human exposure experiments in 1972.[14,15] This experiment was 1-week exposure study and the reported irritative symptoms might have occurred because of the lack of adaptation. In view of the discrepancy of the recommended values, Japanese industries using acetone have not decided to control the exposure in conformity to JAIH recommendation. Preliminary survey of several acetate fiber manufacturing factories in Japan suggested that the exposure concentration of acetone was less than 750 ppm, the most widely accepted exposure limits, but higher than 200 ppm.

In order to test the validity of the value of 750 ppm, we performed a cross-sectional study on 110 male acetone-exposed workers and 67 male reference workers in 3 factories producing acetate fibers.[16] The acetone-exposed men were not exposed to any other hazardous chemicals and the mean length of acetone exposure was 14.9 years. The assessment of the exposure was made by the measurement of acetone in breathing zone by personal samplers (n=288), acetone in alveolar air (n=293), acetone in blood (n=108) and acetone in urine

(n=275). As shown in Table 10, the acetone concentration in the breathing zone air was about 350 ppm on the average and there were not much differences among 3 factories and days of measurements.

The items for health effect assessment are listed in Table 11. As the results of this study, we found significantly more prevalence of subjective complaints such as irritation of the eyes, light inflammation of the eyes, tearing, acetone odor, heavy feeling in the head, nausea, faint feeling in the head, palpitation, loss of weight, slow healing of the external wound and phlegm in the winter or at night. In order to analyze the exposure-response relationship, the acetone workers were classified into 3 groups, namely, higher-, middle-, and lower-exposed groups according to the acetone concentration in breathing zone air and other biological specimen. Figure 2 is a typical finding of exposure-response-relationship for a subjective symptom suggesting the light narcosis or irritation. AC-A, AC-B, AC-E, and AC-U denote acetone in alveolar air, in blood, in breathing zone air, and in urine used for classifying the workers into 3 exposure groups. To test the reliability of the subjective complaint of weight loss, we obtained the past record of body weight measured in the periodical health checks conducted at 6-month interval. Table 12 shows that the average body weight change of the exposed workers in the last 3 years was significantly smaller than the reference workers. Among the neurobehavioral tests in Table 11, were found statistically significant reduction in simple reaction time and digit span, that is the numbers of figure recollection. Manifest anxiety scale, self-rating depression scale, variation of RR interval and blood or serum determinations did not show acetone-related changes.

Thus, the outcome of this cross-sectional study indicate that, at exposure concentration around 350 ppm, acetone caused irritative and anesthetic effects as expressed by significantly higher prevalence of subjective symptoms with good exposure-response relationships and significantly reduced simple reaction time and digit span in workers with long-extended exposure. Although this study was a cross-sectional observation, the assessment of exposure was very accurately performed.[17] It may be reasonably concluded that the current exposure limit of 500-750 ppm in many countries are not adequate if such irritative and anesthetic effects as observed in this study are to be prevented.

Conclusions

The analysis of the published document of occupational exposure limits recommended by Japan Association of Industrial Hygiene disclosed that: 1) exposure limits for a majority of chemicals have very limited margins of safety, 2) results of epidemiological studies have been used for the standard setting of only 15% of the chemicals, and 3) the apparent margin of safety was smallest when epidemiological data were used, while it was second smallest for non-epidemiological human observation and largest for animal experiments. However, it was discussed that good epidemiological data provide the most reliable basis for all sorts of decision. Furthermore, it was pointed out that the epidemiological method is most efficient when the study is designed to test the validity of a current exposure limit. Since the animal experiment is expected to be the main source of toxicity information in the future, and the nature of epidemiology is not predictive, the role of epidemiology as a tool for standard setting will lie in the test of the validity of existing standards. Two examples of the test of existing standards by epidemiology were presented using the data on toluene diisocyanate and acetone.

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Table 1. Effect of acetone on humans

Concentration (ppm)	Exposure duration	Effect	Author
950-1060	Long-term	Eye and resp. irritation	Raleigh and McGee (1972)
700	Long-term	Respiratory irritation. Giddiness, Loss of strength	Vigliani and Zurlo (1955)
307-918	Long-term	Eye and throat irritation	Parmeggiani & Sassi (1954)
500	6hs x 6 days	Irritation, Reduced simple reaction time	Matsushita et al. (1969)15
250	6hs x 6 days	Headache, Tiredness next morning. Slightly reduced reaction time	
100	6hs	Slight irritation	

Table 2. Regulated or recommended occupational exposure limits of acetone

1000ppm	Germany
750ppm	ACGIH, OSHA, Belgium, France, U.K.
500ppm	Australia, Finland
250ppm	NIOSH, Denmark, Sweden
200ppm	JAIH

JAIH: Japan Association of Industrial Health

Table 3. Ratio between adopted exposure limit to minimum observed effect level or maximum no-observed effect level

(JAIH, 1992)

Ratio	Number of chemicals
1	54
0.66-0.75	10
0.5	28
0.2-0.25	18
0.1-0.125	9
0.05	2
	121

Table 4. Effect of tetraethoxy silane on animals

Concentration (ppm)	Exposure duration	Effect	Author
1060-2350	4 hours	Death	Kasper et al.
164	8hrs x 17days	Loss of body weight	
125	7hrsx5~30days	Kidney injury	Row et al.
400	30 days	Kidney and liver injury	Pozzani &
88	90 days	Decrease of kidney weight	Carpenter
50*	90 days	No effect	
23	90 days	No effect	

* Maximum no-observed effect level

Table 5. Distribution of ratio by type of study

Ratio	Human observation (except epidemiology)	Epidemiology	Animal experiment	Total
1	38	13	3	54
0.75 (0.66-0.75)	4	3	3	10
0.5	15	3	10	28
0.25 (0.2 -0.25)	6	0	12	18
0.1 (0.1-0.125)	2	0	7	9
0.05	0	0	2	2
	65	19	37	121
Mean ratio	0.77	0.88	0.38	0.67

Table 6. Occupational exposure limit for TDI (ppb)

		TWA	Peak Limitation	
JAIH	(1965)	20	–	
JAIH	(1990)*	2	20	Ceiling
JAIH	(1992)	5	20	Ceiling
ACGIH	(1991)	5	20	STEL
DFG	(1991)	10	20	Peak category I

*Tentative recommendation

Table 7. TDI exposure concentration (ppb)

	GROUP H			GROUP H1			GROUP H2			GROUP L		
Exposure concentration during the follow-up study periods												
Number of samples	125			77			48			34		
Peak exposure level (range)	3-80*			30-80*			3-14			<1		
Time-weighted average (TWA) (mean)	5.7			8.2			1.7			0.1		
Exposure concentration (TWA) by study year												
Study year	1981	1983	1985	1981	1983	1985	1981	1983	1985	1981	1983	1985
Number of samples	43	44	38	24	27	26	19	17	12	16	4	14
Arithmetic mean	6.0	5.3	5.8	9.3	7.3	8.1	1.9	2.1	0.8	0.2	0.0	0.2
Maximal concentration	22	20	30	22	20	30	3	4	3	1	0	1

*Upper limit of TDI concentration measured by MCM 4000/4100 system was 80 ppb

Table 8. Age- and height-adjusted flow-volume indices in 1981 and average annual loss of the indices in groups H and L, and reference workers (mean and SD)

	GROUP H (n=29)	GROUP L (n=28)	References workers (n = 24)
Age- and height-adjusted flow-volume indices in 1981			
%FVC	103.9 ± 11.0	100.3 ± 7.9	104.2 ± 12.8
%FEV_1	102.5 ± 9.7	99.4 ± 9.7	103.5 ± 11.9
%MMF	95.5 ± 20.9	93.4 ± 19.6	101.9 ± 27.7
%FEV_1%	99.0 ± 5.7	99.2 ± 4.7	99.8 ± 4.8
%MEF_{50}	96.0 ± 27.4	95.3 ± 24.2	102.8 ± 30.0
%MEF_{25}	95.8 ± 21.6	90.4 ± 20.9	102.8 ± 33.3
%PEF	100.2 ± 15.2	97.6 ± 12.4**	109.6 ± 15.4
Average annual loss (AAL)			
%FVC	-0.19 ± 1.40	-0.22 ± 0.92	-0.02 ± 1.06
%FEV_1	-0.56 ± 1.52	-0.38 ± 0.80*	-0.34 ± 1.06
%MMF	-0.32 ± 4.23	0.11 ± 2.96	-0.30 ± 2.39
%FEV_1%	-0.37 ± 0.99	-0.10 ± 0.94	-0.29 ± 0.88
%MEF_{50}	-0.64 ± 4.63	-0.58 ± 2.86	-0.93 ± 2.47
%MEF_{25}	-0.06 ± 6.07	1.01 ± 4.37	-0.50 ± 5.49
%PEF	0.12 ± 1.72	0.61 ± 1.61	0.72 ± 1.66

* $P < 0.05$ against expected value of AAL (=0);
** $P < 0.01$ against reference workers

FVC, forced vital capacity;
FEV_1, forced expiratory volume in 1 s;
MMF, maximal mid-expiratory flow;
FEV_1%, FEV_1/FVC x 100;
MEF, forced expiratory flow at 50% and 25% of FVC;
PEF, peak expiratory flow

Table 9. Age- and height-adjusted flow-volume indices in 1981 and average annual loss of the indices in groups H1 and H2 (mean ± SD)

	Group H1 (n = 15)	Group H2 (n = 14)
Age- and height-adjusted flow-volume indices in 1981		
%FVC	104.6 ± 8.2	103.2 ± 13.6
%FEV_1	102.6 ± 7.7	102.4 ± 11.8
%MMF	93.4 ±22.1	97.9 ± 20.1
%FEV_1%	98.3 ± 6.1	99.9 ± 5.3
%MEF_{50}	93.9 ±31.6	98.2 ± 23.0
%MEF_{25}	93.9 ±20.2	97.8 ± 23.6
%PEF	101.7 ±15.2	98.6 ± 15.6[3*]
Average annual loss (AAL)		
%FVC	0.10 ± 1.51	-0.49 ± 1.17
%FEV_1	-0.81 ± 1.76	-0.28 ± 1.13
%MMF	-2.39 ± 4.13[1*, 4*]	1.91 ± 3.02[1*]
%FEV_1%	-0.89 ± 0.96[2*, 4*]	0.19 ± 0.63
%MEF_{50}	-2.42 ± 5.10	1.27 ± 3.07
%MEF_{25}	-3.28 ± 5.64[1*, 4*]	3.38 ± 4.39[1*]
%PEF	-0.38 ± 1.46[3*]	0.66 ± 1.79

[1*] $P < 0.05$
[2*] $P < 0.01$ against expected value of AAL (=0)
[3*] $P < 0.05$ against reference workers (see Table 3)
[4*] $P < 0.05$ against group L (see Table 3)

Table 10. Acetone exposure concentration

1st day of day shift	Plant A	Plant B	Plant C	All Plants
No. of samples	65	20	25	110
Mean (ppm)	379.3	356.9	276.8	351.9
Range (ppm)	40-957	19-574	5-511	5-957
2nd day of day shift				
No. of samples	64	20	25	109
Mean (ppm)	413.7	314.7	261.0	360.5
Range (ppm)	26-1212	19-488	5-580	5-1212

Table 11. Items for health effect assessment

- QUESTIONNAIRES (SELF-ADMINISTERED)
  - Q1. Symptoms in the last 6 months
  - Q2. Manifest Anxiety Scale (MAS)
  - Q3. Self-rating Depression Scale (SDS)
  - Q4. Symptoms before work
  - Q5. Symptoms during or after work
- NEUROBEHAVIORAL TEST ITEMS EXAMINED
  1. Finger Tapping (dominant, non-dominant)
  2. Simple Reaction Time
  3. Choice Reaction Time
  4. Digit Span (forward, backward)
  5. Benton Visual Retention Test (4 figures)
- AUTONOMIC NERVOUS SYSTEM
  1. R-R interval variation of ECG
- BLOOD EXAMS
  1. GOT, GPT, GGT, ALP, TC
  2. RBC, Hb, Ht, WBC, Phagocytic function

Table 12. Average body weight changes (kg/year)

	n	last 1 year	last 3 years
Reference workers	51	0.48 + 1.68	0.11 + 0.56
AC workers	85	0.16 + 2.66	-0.24 + 0.99*
AC-E level			
Lower	19	0.73 + 2.15	-0.06 + 0.61
Middle	50	0.04 + 2.79	-0.24 + 0.93
Higher	16	-0.13 + 2.70	-0.49 + 1.38

Mean + S.D. *: $p < 0.01$ compared to reference workers

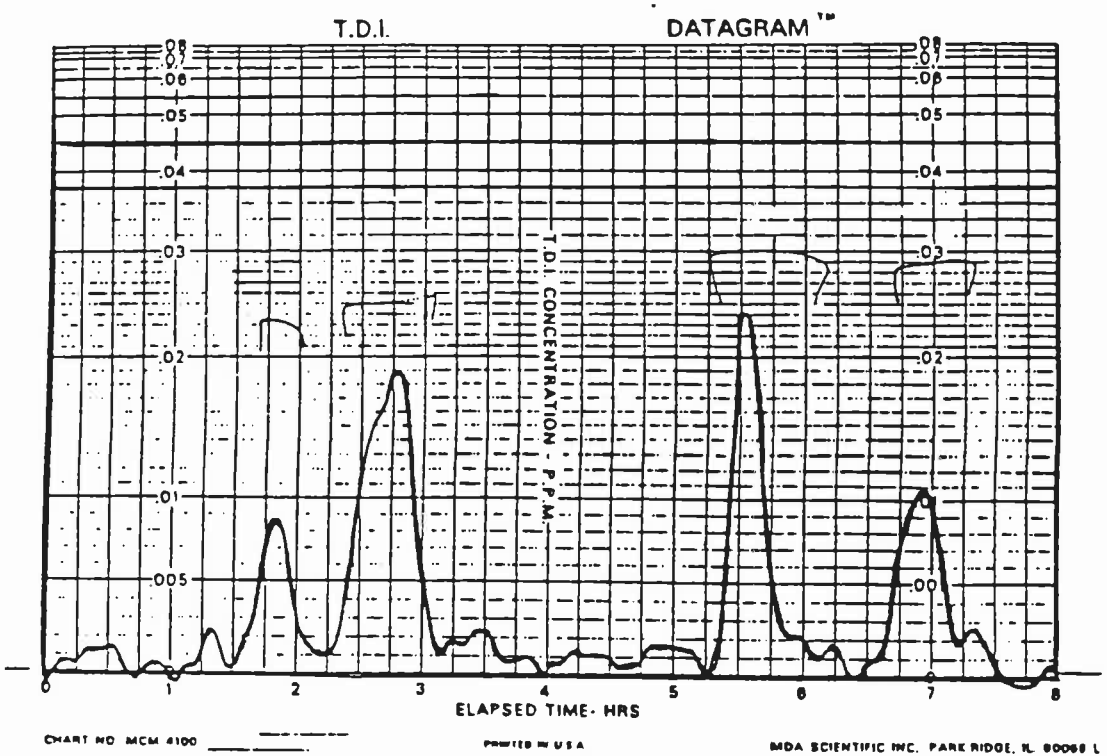
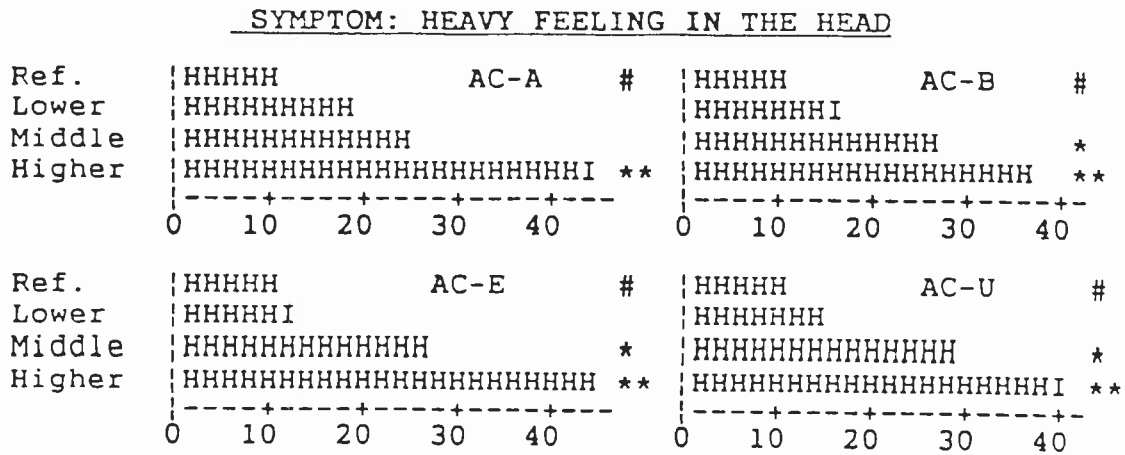


Figure 1. Typical exposure profile to toluene diisocyanate (TDI) in slab-type PF manufacturing factory



*, **: $p < 0.05$, 0.01 compared to reference workers.
#: $p < 0.05$ by 2 x 4 contingency table analysis.

Figure 2. Prevalence (%) of subjective symptom by biological and environmental monitoring levels of acetone

ON THE ESTABLISHMENT OF ASSOCIATIONS BETWEEN PSYCHOSOCIAL WORK ENVIRONMENT AND CORONARY HEART DISEASE

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The relationship between the psychosocial environment and cardiovascular illness risk has attracted considerable attention during recent years. In the modern Western societies this seems to be logical since physical demands are diminishing and the increasing complexity of a modern society increases the demands upon psychosocial interaction. In several countries an increasing number of employers' unions and trade unions have realized that a functioning psychosocial work environment is depending heavily on good work organization.

Another reason why the development in this field is accelerating is that methods for monitoring physiological and endocrinological processes that are consequences of a bad psychosocial work environment have become cheap and practically feasible. When mechanisms in the interplay between the environment and bodily function become known, the medical occupation may accept these relationships more willingly.

In the 1960's systematic studies of work conditions were made. For instance, Kornitzer and his collaborators observed in a retrospective study of two bank groups in Belgium (1) that employees in one of them, the private one, had a higher incidence of coronary heart disease than employees in the other one, state owned banks. This could not be explained by biomedical risk factors (2). This group has later discussed the complex relationships between stress, biomedical risk factors and cardiovascular risk (3). This study was one of the first ones which indicated a possible relationship between a certain kind of work conditions, work demands (which were higher in the private banks), and risk of myocardial infarction. Other cross-sectional studies during this period (4-7) indicated that there may be

a relationship between excessive overtime work and cardiovascular illness risk, and Hinkle's study of "night college" men in the Bell Telephone Company was the first prospective indication in this direction (8). During the same period there were also studies which indicated a higher incidence of myocardial infarction among lower level employees in large companies (9). This of course related to the social class observation discussed above and raised for the first time suspicion that psychosocial stress may not primarily be a problem for people with a lot of responsibility, as researchers had tended to believe previously.

During this phase of confusion and lack of theoretical models, sociologists entered the field. Karasek introduced his demand - control model which was an architect's synthesis of the demand (="stress") and the "lack of control" (sociological) research traditions (10). In generating the concept "lack of control," or "lack of decision latitude" as Karasek labelled it, sociologists had been following traditions from Marx. The question was: Is the worker alienated from the work process? It was assumed that the possibility to utilize and develop skills (skill utilization), a concept developed in work psychology, was closely related to authority over decisions. In factor analysis of responses to questions about work content these two factors mostly go together, and accordingly they have been added to one-another to constitute decision latitude (11). The other dimension, psychological demands, included qualitative as well as quantitative demands.

Karasek's original hypothesis, that excessive psychological demands interact with lack of decision latitude in generating increased risk of cardiovascular disease, was tested in a number of epidemiological studies in the 1980's (11-19). There have been many published prospective or cross-sectional studies. The methodology has varied considerably. The most important distinction is that some studies were using the victims' own descriptions of their work situations, whereas others have used aggregated job descriptive data, based on representative workers in the occupations in the population. Both methods have advantages and problems. However, individual traits may be associated with systematically distorted work descriptions, and this systematic distortion may be related to illness risk - with both overestimation and underestimation as possible result. The use of aggregated data gives an opportunity to avoid individual distortion

(although of course collective distortion may still take place). On the other hand, the use of aggregated data does not allow for variations between work sites. This may lead to substantial underestimation of true associations (12). The underestimation problem in the use of aggregated data is probably a more pronounced problem in estimating the importance of psychological demands, since this variable shows relatively small variance between occupations. Decision latitude, on the other hand, shows considerable variance between occupations (11). Even the aggregated methodology has varied across studies. In some studies, the classifications have been based on means for each one of the dimensions from employees in the different occupations in the working population. In others single questions have been representing the dimensions, and several combinations (demand/skill utilization and skill/authority over decisions) have been tested.

A recent epidemiological study in Sweden (19) using one of the aggregated methodologies merits some interest. In this case a large number of cases of myocardial infarction were identified by means of the nation-wide Swedish death register and by means of county registers including hospitalizations. Controls stratified with regard to gender, age and geographical area were selected randomly from the population. Analyses were confined to "occupationally stable" subjects who stayed in the same occupation during the two most recent censuses (which were five years apart) and to those who had a first myocardial infarction (in contract to subsequent infarctions). Figure 1 shows the results for men below age 65 and Figure 2 the results for men below age 55. Each one of the available questions that are usually included in the demand and control scores has been displayed separately. The results are typical for this kind of study, with stronger age-adjusted relative risks among the younger men. The expected pattern with the strongest relative risk in the strain quadrant is observed. The results for women were not as clearly in line with the job strain hypothesis, and it should be pointed out that the job strain hypothesis has been less well documented for women than for men.

True (multiplicative) interactions between psychological demands and decision latitude have only been observed in two studies (13, 14), whereas in the others additive interactions were seen. There is no doubt, however, that the use of the two dimensions together have

provided better predictions than either one of them alone.

The summary of relative risks indicates, as expected, that studies utilizing self-reported work descriptions have shown higher relative risks (2.0-4.0 versus 1.3-2.0). Demands have been shown to be relatively more important in studies utilizing self-reported data than in studies utilizing aggregated data. Some of the studies have covered other risk factors and one of them also type A behavior (15). In general the adjustment for standard risk factors for cardiovascular disease does not eliminate the association between the high demand/low decision latitude combination and cardiovascular (in most studies clinically verified myocardial infarction and in three studies CHD) disease risk. In one case, the Framingham study (15), the adjustment for other risk factors strengthened the association.

Only one study, the Hawaii cardiovascular survey (16), showed no association at all between high demand/low decision latitude and cardiovascular illness risk. Interestingly the participants in this study were above 55 years of age at the start of the follow-up period. Studies of participants younger than 55 years of age in general have shown stronger associations than those including older subjects. Another observation is that the high demand/low decision latitude has proven to be a more powerful predictor of cardiovascular illness risk in blue-collar than in white-collar men. For instance, a Finnish study (17) included mainly blue-collar workers and showed a strong association. The study by Johnson and Hall (13) includes separate analyses of blue-collar and white-collar men which illustrate this point. For further discussion see Marmot and Theorell (20).

A small clinical five-year follow-up study of men in Stockholm below age 45 who had suffered a myocardial infarction indicated that returning to a job perceived as psychologically demanding and with low decision latitude may be associated with increased risk of re-infarction death (21). This was true even after adjustment for biomedical risk factors, degree of coronary atherosclerosis, type A behavior and education. This finding emphasized the potential importance of this research to cardiovascular rehabilitation.

There are two recent developments in this field. First of all, Johnson has included social support in the theoretical models. A study of cardiovascular disease prevalence in a large random sample

of Swedish men and women indicated that the joint action of high demands and lack of control (decision latitude) is of particular importance to blue-collar men whereas the joint action of lack of control and lack of support is more important for women and white-collar men. The multiplicative interaction between all the three of them (iso-strain) was tested in a nine-year prospective study of 7000 randomly selected Swedish working men. Interestingly, for the most favored 20% men (low demands, good support, good decision latitude) the progression of cardiovascular mortality with increasing age was slow and equally so in the three social classes. In blue-collar workers, however, the age progression was much steeper in the worst iso-strain group than it was in the corresponding iso-strain group in white-collar workers (22).

Secondly, attempts are now being made to use the occupational classification systems in order to describe the "psychosocial work career." Researchers have pointed out (23) that an estimate of work conditions only at one point of time may provide a very imprecise estimation of the total exposure to adverse conditions. Descriptions of all the occupations during the whole work career are obtained for the participants. Occupational scores are subsequently used for a calculation of the "total lifetime exposure". The "total job control exposure" in relation to nine-year age-adjusted cardiovascular mortality in working Swedish men was studied. It was observed for both men and women that the cardiovascular mortality differences between the lowest and highest quartiles of control were three-fold both for men and women (24). It should be pointed out, however, that these age-specific differences were unadjusted for biomedical risk factors. Analyses adjusting for conventional cardiovascular risk factors are currently underway.

A few notes on psychometric properties of some of the demand-control-support measures should also be made since they may be of more general interest in the field of psychosocial methodology. We have noticed that the scales measuring the two aspects of decision latitude, namely intellectual discretion and authority over decisions (which together constitute the decision latitude scale), show wide differences between occupational groups (25). Furthermore, analyses of internal consistency show that Cronbach alfa coefficients are high when mixed working populations are studied but considerably lower when homogenous occupation groups are studied. One possible

reason for this may be that decision latitude is determined to a great extent by the content of work in the occupation, whereas demands and social support are reflecting local work site conditions and individual perception to a greater extent. Table 1 shows the results of a comparison between one random sample of working men and women and two samples of occupations (medical secretaries and furniture movers) with regard to the internal consistency (Cronbach alfa) and the indices of psychological demands, intellectual discretion, decision latitude and social support at work (25). For intellectual discretion it is obvious that the internal consistency is low for both the homogenous groups. For the total decision latitude scale the internal consistency is good in the population groups but low in the male furniture mover group. In the group of medical secretaries the internal consistency of the decision latitude index is high. However, in a group of female caring personnel it was observed to be low, 0.6, and this was the only group which also showed a low Cronbach alfa coefficient for the psychological demands index - 0.5 (26). For social support the internal consistency was good in all groups.

Table 1. Internal consistency (Cronbach alfa) of the indices (Swedish version) of psychological demands, intellectual discretion, decision latitude (sum of authority over decisions and intellectual discretion) and social support ("positive factors") at work in male and female working population group (random samples) and male furniture movers and female medical secretaries, respectively.

Index	Furniture movers	Medical secr.	Male pop.	Female pop.
Psychological demands	0.70	0.70	0.75	0.80
Intellectual discretion	0.37	0.35	0.54	0.70
Decision latitude	0.48	0.80	0.76	0.77
Social support = "positive factor"	0.83	0.86	0.89	0.89

Two different forms of the demand-control-support questionnaires are presently used. The first one is an expansion of Karasek's original questionnaire which was originally based upon the American QES studies (27). This has been extensively tested and used

particularly in the United States but also in central Europe and in Japan. Not only is the decision latitude scale based upon a slightly larger number of questions than the original one, in addition other scales have been included such as social support, physical demands and personal insecurity. The second one has been used mainly in Sweden. It is shorter and does not have as many dimensions as the American one. It also uses only four response categories for each question and a frequency based rather than intensity based grading. The tests of internal consistency in Table 1 refer to the Swedish version which has five questions dealing with (mainly quantitative) psychological demands and six questions dealing with decision latitude (four about intellectual discretion and two about authority over decisions).

A model similar to the demand-control model has been developed and tested by Siegrist and his co-workers (28). Their model uses "effort" and "social reward" as the crucial dimensions, the hypothesis to be tested being that high effort without social reward is pathogenetic. The social reward dimension has elements both of decision latitude and of social support. In a recently published study of industry workers it was shown that combinations of high effort and lack of reward predicted increased myocardial infarction risk independently of biomedical risk factors. The relative risk was in the order of 4.0.

Another important area in work organization that has been studied during the period is working hours. Although previously no relationship was believed to exist between exposure to shift work and risk of myocardial infarction several new studies support the hypothesis that there is a relationship. For example, a study of a cohort of paper-pulp factory workers in Northern Sweden showed that there was such a relationship that became successively stronger with longer duration of exposure - up to 20 years of exposure when the relationship was attenuated and even reversed (29). The authors speculated that the attenuated effect after the longest exposure periods could be a "selection" effect - only the most healthy workers remained till the end. "Aggregated" studies of typical shift work occupations have also shown increased myocardial infarction risk in them compared to other occupations (30). There have been speculations regrading mechanisms underlying these relationships. Both direct (catecholamine) and indirect mechanisms - via, for

instance, unhealthy diet during night work hours - have been discussed (31). There is also an indication that improved shift work schedules may be associated with improved cardiovascular risk profiles (32).

Long working hours have also been studied. The classical study by Hinkle and co-workers (8) in the Bell Telephone Company indicated that men who worked full time and also went to night college had an increased age-adjusted cardiovascular death risk. The study of working men and women in five counties in Sweden provided an analysis of the one-year incidence of hospitalization for myocardial infarction (33). The results indicated a pronounced difference between men and women. Men in occupations classified as "overtime occupations" in the national surveys had a lower age-adjusted hospitalization incidence than other working men, even after adjustment for a number of possible social confounders. For women the opposite was true - "overtime work" occupations had higher hospitalization incidence than others. An "overtime occupation" was defined as an occupation in which at least ten hours of overtime work per week was "frequently" (occupations with above median frequency) reported. It should be emphasized that this is a relatively modest cut-off point. The level of overtime work in the study by Hinkle, for instance, is much higher. The gender difference is most likely due to the double roll of women. Since women, in Sweden as well as in other countries, have more responsibility for home and children, it is more difficult for them to handle overtime work. The interactive effects between home work and paid work on psychosomatic symptoms are more pronounced for women than for men (34). Another possible explanation may have to do with the fact that men perceive that they have a higher level of skill utilization and authority over decisions than do women (35). Accordingly, overtime work could be less rewarding for women than for men. And correspondingly a modest level of overtime work for a man is more frequently associated with stimulating work. Studies in this area are difficult to interpret, however, and it should be pointed out that the most recent study (19) did not confirm this differential effect of long working hours on women and men respectively.

One area which has developed more specifically than other research endeavors in this field is the study of bus drivers. There is now overwhelming evidence that bus drivers, particularly those driving

in inner city areas, have an excess risk of developing myocardial infarction (36-38) at an early age compared to other workers. Possible reasons for this excess risk have been explored. It has been shown that standard risk factors cannot explain all of it (39). It has previously been suspected that exposure to carbon monoxide may be of importance, but this seems most unlikely to be of importance (39). Other toxicological exposure may be of importance, for instance combustion products (40). However, it has been emphasized in recent research that job strain may be a very important factor (41) and some physiological consequences of job strain in bus drivers have been explored. Catecholamine (42) have been shown to be elevated in bus drivers when job strain increases, for instance. However, more specific hypotheses have also been developed. Belkic and her collaborators have found that bus drivers seem to develop more rapidly than others an aroused electrophysiological response to "the glare pressor test" particularly when instructions simulate a traffic situation (43). It is possible that professional drivers have an accumulated experience of dangerous situations associated with sudden "glares" particularly at night and that this may be a potent factor explaining why bus drivers develop an excess risk for myocardial infarction after some years of driving - they become constantly hyperalert during driving and this may be of importance to several of the risk factors. Accordingly it seems important to diminish number of driving hours and to try to improve external conditions for bus driving, for instance by creating special bus routes, by educating pedestrians and by reinventing the conductor!

In the area of work organization and cardiovascular disease there has been considerable activity. The concepts and theoretical models that have been used are relatively simple, and it has turned out that they are also robust in the sense that they have been testable by means of widely different methodologies. Still, theoretical analysis of the concepts demand control, and support will be necessary since there is no universal agreement about definitions. As expected, the models are not universally applicable to all kinds of studied populations. The demand-control model, for instance, is highly useful for blue-collar men below age 55, butless useful for other groups. The total demand-control-support model, on the other hand, may be more universally applicable. And alternative models, such as the effort-reward model proposed by Siegrist (44), will be further developed

in the near future.

Further notes on social support at work

As mentioned earlier social support at work has been shown to be of importance at least to development of cardiovascular symptoms (18,45). It has also been shown recently that continuously monitored heart rate is associated with job social support - the poorer support the higher heart rate (46). And one study has shown that spontaneous variations in social support at work are associated with variations in mean systolic blood pressure during a working day. During periods of poor support the systolic blood pressure is higher and vice versa. This observation was based upon working men and women in six occupations who were observed on four different days three-four months apart. Blood pressure was measured once every hour on each of these days (47). Also in this area there has recently been methodological development. By means of a series of factor analyses Unden (48) has developed scales for measuring instrumental, emotional and other basically different kinds of social support at work.

Physiological measurements

The physiological basis for the associations between psychosocial factors and coronary heart disease has been a lively research field during the period. Catecholamines have been suspected of mediating some of the relationship, and during the period it has become possible not only to study urinary excretion (which is still a good way of collecting data on sympathoadrenal activity during integrated periods of time) but also the small concentrations that exist during rest in venous plasma. A study by our group has recently shown that poor social network and support as well as a job "classified" as boring all contribute to an elevated venous plasma adrenaline at rest in the studied 28-year-old men (49). On the whole, however, the main endeavor has been the study of urinary catecholamine excretion (50). Recently, epidemiological studies have shown a correlation between poor social network and high urinary excretion of catecholamine (51) and also between poor decision latitude and high catecholamine excretion (52). On the other hand, it has also been found that sympathoadrenal reactions in different organs may be specific and generalizations should accordingly not be made in all instances (53).

The possibilities to monitor physiological functions continuously have induced a revolution in this field. For instance, since we can now study heart rate and blood pressure during activity and sleep, we have started to explore how psychosocial factors relate to development of coronary atherosclerosis, for instance. The lowest heart rate during sleep correlates with degree and progression of coronary atherosclerosis (54,55). It could be that inability to relax is associated with a high heart rate during sleep as well as with progression of coronary atherosclerosis. Similarly, Undén and Orth-Gomér have shown that poor social support at work is associated with a high heart rate through day and night (48). The interpretations of these associations are not clear, but it is possible that feelings of loneliness may activate the sympatho-adrenal system.

A growing field that relates to catecholamines is also coagulation. For instance, a boring job (or job strain) has been related to high plasma fibrinogen levels (56) and recently lack of reward was shown to be associated with high plasma fibrinogen levels among middle managers (57). The question that arises could be formulated in the following way: To what extent do psychosocial clots and psychosocial atherosclerosis exist? Certainly the common themes in lack of social support in life in general and lack of possibilities to learn and to influence decision at work may be - boredom and lack of reward.

Conclusion

The research in cardiovascular psychosocial epidemiology has not provided any final answers, but several very useful concepts have been developed and utilized, and many empirical results point at possible interventions, for instance, in work organization and social networks. When we relate the findings to the question about the contribution of psychosocial work factors to the association between social class and cardiovascular morbidity/mortality we find that some of the relevant psychosocial risk factors, in particular psychological demands, are more common in the upper social classes which is quite contrary to the expectations. On the other hand most of the relevant ones, namely lack of decision latitude, lack of social support, lack of social reward and shift work, are all more common in the lower classes. Therefore we would expect, on balance, that psychosocial work factors would contribute to the association between low social class and cardiovascular risk. The few efforts

that had been made to analyze this empirically have indeed verified that some of the variance in cardiovascular illness risk between social classes can be explained by means of psychosocial job conditions (18).

Future research goals

It is obvious from what I have said that research in this field has established a few possible general models for studying the relationship between the psychosocial work environment and risk of cardiovascular illness development. These general models, however, are far from applicable to practical preventive work. One has to devote energy to the formulation of more specific models that are applicable to care givers, bus drivers, industry workers, teachers, etc.

Very few studies have evaluated the effects of work organization changes in line with the theoretical models that have been used. A strict evaluation has turned out to be difficult since attention to individual risk factors and individual counselling concerning them has turned out to be a necessary motivational factor in work organization change processes (58). In line with the quality of working life research, the changes that have been tried are focussing on improved social support and increased decision latitude. One example is to increase the number of structured staff meetings, which enables increased social support as well as improved democracy in decision making in the work site. Very few studies have tried such changes and evaluated them in relation to cardiovascular disease. One example has been a Swedish study which showed a program which included individual counselling as well as exploration of the work organization and subsequent initiation of changes (59). This study showed that an improved lipoprotein pattern was found in the experimental work sites but not in the control sites. It is impossible to know whether this favorable change was due to the individual counselling or to work organizations initiated by the program. Interestingly the program was taken up differently in the four work sites that participated in the experimental program. In one work site ('active"), the employees were more used to organizational work and the supervisors more inclined to be actively engaged in such work than in the other work sites ("passive"). Figure 3 shows that the plasma cortisol levels developed differently in these groups. In both groups there was a tendency for the cortisol levels to increase

initially during the process, but subsequently they diminished in the active group and increased in the passive group. There was also a tendency for plasma testosterone levels to rise more in the active group (in women particularly) than in the passive group, and this increase was still observed at the time of follow-up four months after the end of the program (60). We shall need more research of this kind in the future in which controlled interventions are explored by means of psychological as well as physiological methods.

It has become obvious that physical and psychosocial work environment factors could interact in complex ways and that this has been neglected in previous research. A large-scale multidisciplinary case-control study, SHEEP, of all myocardial infarctions in the greater Stockholm area during a two-year period has the goal of filling this gap. In the same vein, a large scale longitudinal study of several thousand working men and women is just starting in Stockholm. The goal of this study, WOLF, is to follow the development of biomedical and psychosocial risk factors in different occupations and work sites in Stockholm.

One criticism against the use of the demand-control model has been that there is a relationship between low social class and high risk of developing cardiovascular illness and that this in itself may explain the association between job strain and cardiovascular illness risk (61). In several studies, however, social class or education have been factors that have been adjusted for, and despite this, the relationships have remained significant (11). There is a possibility that the relationship between low social class and elevated cardiovascular illness risk may be partly explained by the fact that adverse job conditions are more common in lower socioeconomic strata than in other groups of the population. This should be explored more in detail in future research.

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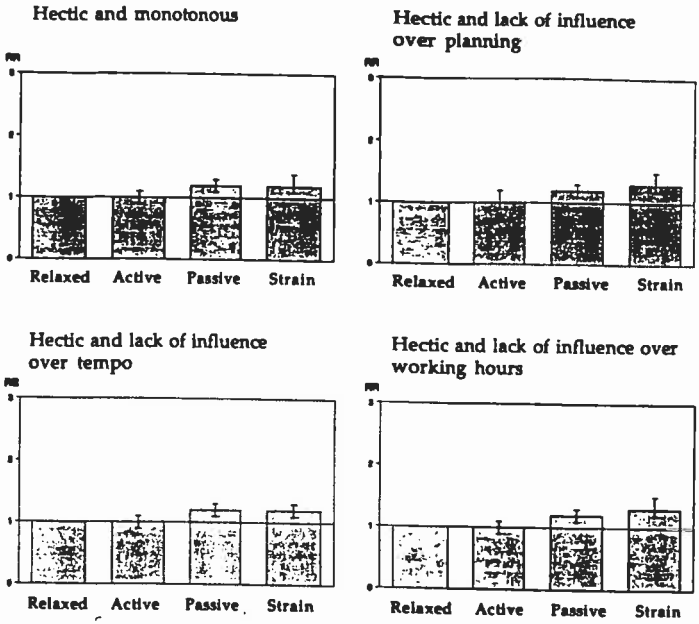


Figure 1a. Age-adjusted relative risk (and 95% CI) of developing myocardial infarction in relation to occupation characteristics among men ("stable employment") 30-64 years of age. (n ≈ 6800 cases and 15000 controls)

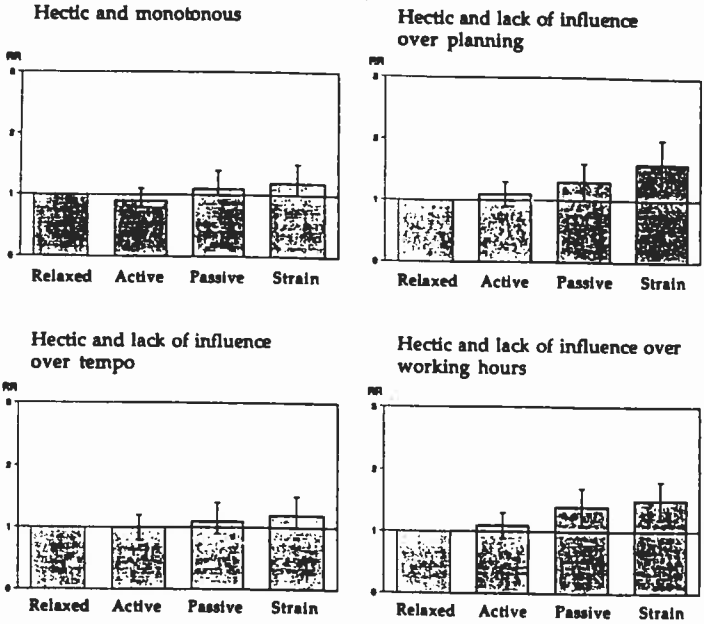
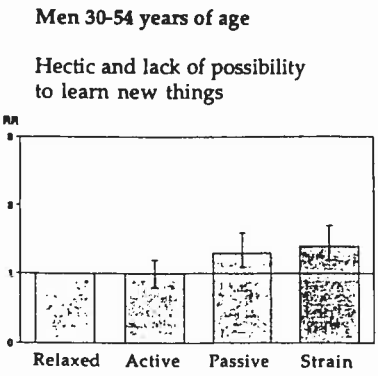


Figure 2a. Age-adjusted relative risk (and 95% CI) of developing myocardial infarction in relation to occupation characteristics among men ("stable employment") 30-54 years of age. (n ≈ 6800 cases and 15000 controls)



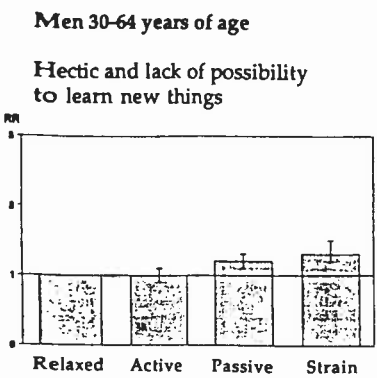


Figure 2b. **Figure 1b.**

Age-adjusted relative risk (and 95% CI) of developing myocardial infarction in relation to occupation characteristics among men ("stable employment"). (n = 6800 cases and 15000 controls)

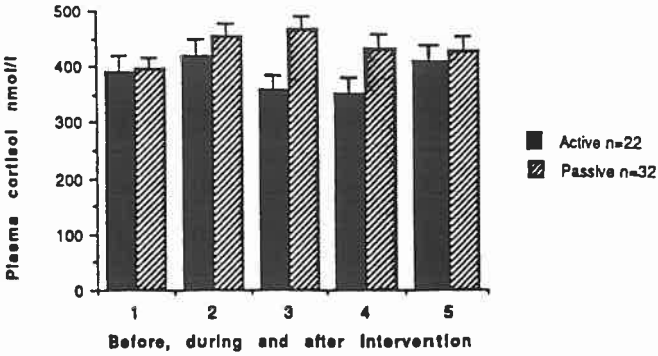


Figure 3. Total group plasma cortisol

CASE-COHORT STUDY DESIGNS IN OCCUPATIONAL EPIDEMIOLOGY

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In a case-cohort study, researchers obtain exposure and confounder histories for all cases occurring in a cohort over a follow-up period, and for a random sample ("sub-cohort") of the cohort. The random sample will include some persons who become cases, and many who do not. Like the "nested" case-control design ("case-control within cohort"), this provides an inexpensive way to obtain relative risk estimates with more detailed exposure and confounder information than would be possible for the whole cohort. Our experience and a review of the small amount of literature on the case-cohort design suggests the following advantages over the nested case-control design for occupational studies: (i) from the person years at risk in the random sample, we can obtain approximate SMRs using external rates, as well as "internal" rate ratio estimates; (ii) we may study more than one disease using the same random sample; (iii) we may select and collect data on the random sample prior to identifying cases; (iv) if cases can be identified by other means, such as linkage to a cancer registry, we need ascertain mortality only for the random sample, rather than the entire cohort; and (v) under some circumstances relative risk estimates are more precise for the same sample size. However, there are also disadvantages: (i) the analysis is more complicated, especially for correct confidence intervals, which are slow to compute, and only currently available from one software package (EPICURE); (ii) for efficiency, we must usually stratify the random sample, choosing separate sampling fractions to provide a similar ratio of cases: sample in each stratum; (iii) we must calculate indices (e.g., cumulative) of exposure for each year during which a sampled subject was in the cohort, not just up to the age of diagnosis of the matched case, as in a nested case-control study; and (iv) likelihood ratio significance tests are not strictly valid. We illustrated these conclusions with reference to two occupational case-cohort studies currently nearing completion.

VARIABILITY OF EXPOSURE TO POSTURAL LOAD ON THE BACK IN OCCUPATIONAL POPULATIONS

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Introduction

Postural load has been recognized as an important occupational risk factor for low-back pain. Several epidemiologic studies have shown that postural load on the back, that is nonneutral postures of the trunk like bending and twisting, is significantly related to the risk of low-back pain.

When conducting an epidemiologic study on disorders of the back among occupational populations, often exposure to postural load has to be assessed. Since measurement of nonneutral trunk postures is time-consuming and labour intensive, a common approach is to monitor a random sample of workers of each occupational group under study. Subsequently, the average values of the parameters measured are being used to characterize the postural load of the workers within each occupational group.

In epidemiologic studies based on a comparison of occupations with clearly distinguishable levels of exposure this approach warrants that differences in exposure among occupations are substantially larger than differences among workers within the occupation; that is, that the exposure variability within occupational groups is small compared to differences between occupational groups. This usually implies exposure groups with workers more or less uniformly exposed, often referred to as homogeneous exposure groups. The concept of homogeneous exposure groups can be evaluated by several criteria. A fairly simple approach is to calculate the range ratio, being the ratio of the 97.5th percentile to the 2.5th percentile of the distribution of worker's mean exposure. A more sophisticated measure is the variance ratio λ, the ratio of the within-worker and the between-worker variance. The variance ratio takes into account that not only workers of groups are sampled but also specific parts of worker's exposure experience. To calculate the within-worker

variance repeated measurements are necessary. An extension is to partitioning of the total exposure variability into the between-group variance, the between-worker variance and the within-worker variance (1). Since variability of exposure can be regarded as a specific type of information bias, assessment of these components may enable the investigator to evaluate the attenuation of associations between exposure and health outcome (2).

Subjects and methods

Workers were randomly selected from five occupational groups in three different companies (see Table 1). The first three occupational groups worked at a terminal in the Port of Rotterdam, involved in transport of freight container from the ship to the quay, and from the quay to the stack. The fourth group consisted of woodworking machinists in a woodworking company. These workers operated various woodcutting machines. The fifth group consisted of 50 packers in a large auction of flowers.

The assessment of the postural load on the back was focused on nonneutral postures of the trunk in the sagittal plane (flexion) and the transversal plane (axial rotation). Observations were made at the workplace every 20 seconds during two periods of 30 minutes, thus collecting 90 observations of each worker during each measurement. In most occupational groups this will cover at least 15 complete work cycles. The exposure measure presented is the percentage of the total working time spent with the trunk in flexion or rotation.

Results and discussion

The results of the measurements of percentage of worktime with trunk flexion and rotation are presented in Table 1. Since the distribution of exposure measurements in each occupational group was best described by a log-normal distribution, the data were log-transformed. For each occupational group the geometric mean (GM) and the geometric standard deviation (GSD) are presented. Within each occupational group large differences were observed between the measurements of worker's exposure to trunk flexion and rotation. Although the differences in mean exposure to trunk flexion among the occupational groups were large, the large GSDs indicate that some overlap in distributions will be present.

Table 2 shows large values of the $R_{0.95}$ for almost every group. Rappaport (3) has advocated a rather strict definition of a homogeneous exposure group, characterized by a range ratio $R_{0.95}$ of two or less. The presented range ratios in Table 2 indicate that workers within the same job can be differently exposed. The interindividual variability in postural load may be explained by variations in the tasks performed and the subjects' anthropometry and work methods. However, the consequence for misclassification of exposure of substantial between-worker variance in epidemiologic surveys depends on the relative magnitude of the other sources of variability.

Therefore, the variance ratio is of importance. In case of $\lambda > 1$, the within-worker variance is larger than the between-worker variance. This was found for 4 out of 10 distributions. The within-worker variance may be partly explained by differences in the tasks performed. The averaging time of the measurements and the number of repeated measurements can also account for the observed variability of exposure to postural load within one shift. The poor agreement between the variance ratio and the range ratio points out that a large variance ratio can still imply large differences in exposure to postural load among workers of the same occupational group.

Another way of investigating differences in exposure status between occupational groups is the partitioning the total exposure variability into its main elements. It was found that the use of occupational groups could explain the variability of exposure to postural load due to trunk flexion and rotation for 47% and 72%, respectively. The between-group variance was the most important source of variability of exposure in this survey. In case of trunk flexion, the between-worker variance and the within-worker variance were 24% and 29%, for trunk rotation 12% and 16%.

This type of analysis may guide the investigator to the appropriate selection of occupational groups and exposure measurement strategy. Often, a random sample of workers of the occupational groups under study is monitored. Such approach warrants that the between-group variance is the principal source of variability of exposure. The within-group variance (i.e., the between-worker and within-worker variance) can be reduced by selecting occupational groups with

maximal contrast in exposure. For example, by excluding occupational groups with an intermediate exposure. When confronted with a large within-worker variance, the workers of the population under study have to be monitored repeatedly, or alternatively, be monitored with increased averaging time of measurement. In case of individuals as most important source of differences in exposure to postural load the most appropriate approach would be to monitor each subject under study in order to estimate postural at individual level. Some study designs will require extensive measurement programs.

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Table 1. Measurements of percentage worktime with trunk flexion and rotation by occupational title group (log-transformed data)

Occupational title group	Flexion GM	GSD	Rotation GM	GSD
Straddle carrier drivers (21)	3.0	3.9	35.9	1.6
Crane operators (20)	26.8	2.2	1.8	3.0
Office workers (10)	22.0	1.7	4.7	2.4
Woodworking machinists (14)	8.0	3.0	6.6	2.7
Packers (12)	10.6	1.6	25.3	1.5

Table 2. Range ration ($R_{0.95}$) and variance ratio (λ) for the distributions of percentage worktime with trunk flexion and rotation by occupational title group (log-transformed data)

Occupational title group	Flexion $R_{0.95}$	λ	Rotation $R_{0.95}$	λ
Straddle-carrier drivers (21)	14.7	3.0	5.1	0.2
Crane operators (20)	16.9	0.3	7.4	3.6
Office workers (10)	4.6	1.0	17.7	0.5
Woodworking machinists (14)	35.9	0.5	18.8	0.8
Packers (12)	2.5	2.8	1.8	7.1

MORTALITY STUDIES OF MACHINING FLUIDS; AN EXPOSURE-RESPONSE ANALYSIS OF RESPIRATORY AND DIGESTIVE CANCERS

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This cohort mortality study was designed to examine whether long term exposure to specific types of machining fluids is associated with excess risk of specific causes of mortality. Machining fluids (MF) are widely used in a variety of common industrial metalworking operations to lubricate and cool both the tool and the working surfaces. Based on previous studies of MF-exposed populations, particular interest was focused on respiratory cancers (lung and larynx) and digestive cancers (stomach and colorectal).

The design was a retrospective cohort mortality study of more than 45,000 hourly workers who worked at least three years prior to 1.1.85 at one of three automobile manufacturing plants in the midwestern U.S.(1). The cohort was predominately white male, although it included 7,750 blacks and 4,680 females. By the end of follow-up in 1984, 10,159 (22%) of the study population were deceased.

Methods

The measures of exposure were quantitative estimates of cumulative exposure to specific types of machining fluids, i.e., mg/m^3 - years exposure to straight mineral oil, soluble MF and synthetic fluids, used in machining or grinding operations. Type of MF used was assigned to each job-department-plant-calendar year combination after review of plant purchasing and industrial hygiene records, and interviews with plant personnel. Estimates of total MF aerosol were based on current measurements of total aerosol collected by the investigators in assembly, machining and grinding operations in the three study plants and historical air sampling data collected by the company, as well as extensive interviews with plant personnel.

Follow-up extended from 1940 to 1984 and included over 1 million years of follow-up. Most of the cohort had been exposed to soluble MF, whereas only 23% had worked with straight mineral oils, and 14% with synthetic MF. The average duration of exposure was close to 10 years for soluble MF and 5-6 years for straight or synthetic MF. Exposure levels had decreased by approximately 5-fold during the follow-up period for all types of MF. In 1980, the average levels of exposure were 0.1 mg/m^3 for straight, 0.4 mg/m^3 for soluble, and 0.1 mg/m^3 for synthetic fluids.

Relative risks were estimated in Poisson regression models for each cancer of interest, based on the 33,619 subjects in Plants I and II. (For technical reasons, Plant III was not included at this time.) Separate models were fit to estimate associations between each cancer and cumulative exposure to each of the three types of MF and grinding. In each model, the following covariates were included along with the primary exposure variables; gender, race, plant, age at risk, year at risk, and length of follow-up. Cumulative exposure to a specific type of fluid was categorized by choosing cut-offs that equalized the number of total deaths in each category. The cut-offs were fixed for each type of exposure.

Results

Respiratory Cancers: In the analysis of **larynx cancer**, an exposure-response trend was found in the model containing straight MF exposure. In that model, the rate ratio (RR) increased from 1.0 (by definition) in the unexposed internal reference category up to 2.1 (95% confidence interval (CI):0.9-4.7) in the highest category. The cut-off for the highest category of exposure to straight MF was >2.5 mg/m^3-years.

For **lung cancer**, no increasing risk was observed with increasing exposure to any type of MF. In fact, the rate ratios for lung cancer were often less than 1.0, suggesting that exposed subjects had lower risk than unexposed subjects. For soluble MF, there was a decreasing risk with increasing exposure. In the highest category of soluble MF exposure, > 50.0 mg/m^3-years, the RR was 0.6 (95%CI: 0.5-0.9).

Gastrointestinal Cancers: Elevated relative risks were observed for **esophageal cancer** and each of three types of MF, when type of

operation (machining or grinding) was not considered. In these models, however, exposure-response trends were not evident. Stronger evidence for an association was observed when exposure was limited to grinding operations. As seen in the Table below, there was a monotonic pattern of increasing risk as cumulative exposure increased across all but the highest category. The relative risk estimate reached 3.7 before it decreased to 2.3. The highest RRs were statistically significant.

Table 1. Poisson regression model esophageal cancer and grinding exposure in cohort of auto workers

Level (mg/m^3 -yrs)	N Deaths due to COD*	Rate Ratio	95% CI
0	5	1.0	
>0 - 2.49	10	1.8	0.6 - 5.4
2.50 - 9.99	15	2.8	1.0 - 7.5
10.0 - 24.9	15	3.7	1.3 - 10.3
> 25.0	8	2.3	0.7 - 7.1

*Cause of death

There was no evidence of an association between stomach cancer and any type of MF. Based on previous studies, we anticipated an association between **stomach cancer** and grinding. Our results, however, suggested only a minimal elevation in risk, which did not increase with exposure. As grinding MF exposure increased, the RR increased to 1.5, and then decreased to 1.2 and remained constant.

In contrast to stomach cancer, stronger evidence was observed for an association between straight MF and **rectal cancer**. The rate ratio increased in a monotonic fashion up to 2.9 (95%CI:1.3-5.0) in the highest exposure category. No excess risks were observed for rectal cancer in relation to other types of MF.

Discussion

In summary, evidence of an association was documented between grinding and esophageal cancer and between straight MF and both larynx and rectal cancers. If one concludes that these associations are causal, then possible reasons for the excesses at these sites need

to be considered. With regard to straight MF, either the polyaromatic hydrocarbons (PAH), one of the several common additives, or perhaps even the oil itself may be the principal carcinogenic agent in this environment.

Although the aerosol generated in grinding operations was almost entirely MF, there are several distinctions between MF use in machining versus grinding that are relevant to interpreting the results. First, the particle size distribution produced by grinding is larger than that found in machining operations, which has implications for differential deposition. Secondly, whereas all three types of MF are used in machining operations, straight MFs are only rarely used for high speed grinding due to high viscosity. Finally, the higher speeds used in grinding operations may alter the chemical composition of the MF.

The most puzzling finding in this analysis was the apparent negative risk for lung cancer. One possible explanation for this finding concerns the endotoxin that is present in MF, primarily in soluble MF. Deficits of lung cancer have been observed in other populations exposed to endotoxin, e.g., cotton textile workers. The endotoxin present in these automobile production plants is currently being explored further.

NIOSH has estimated that 1.2 million workers in the U.S. engaged in metal grinding or machining operations are exposed to these fluids, while over 6 million workers are more generally exposed to the various components of the fluids. Machining fluids have typically been studied as if they were homogeneous agents. They are, however, complex mixtures, and many of their components and common additives are known or suspect carcinogens, tumor promoters, or co-carcinogens. Better specification of the causal agent(s) in this work environment is essential for an assessment of risk associated with metal working fluids in use today.

A series of nested case-control studies are currently underway to further examine the associations identified in the Poisson analysis. For the cancers of most interest, i.e., cancer of the larynx, esophagus, stomach, and rectum, cases and matched controls have been selected. In each nested analysis, the relative risk associated with exposure to specific components will be evaluated, including various metals (e.g., chromium, nickel, cobalt, lead, iron, and steel), sulfur compounds, chlorinated compounds, and biocides.

JOB STRESS AND CARDIOVASCULAR RISK FACTORS IN A JAPANESE WORKING POPULATION

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To examine the effects of job stress on risk factors for cardiovascular disease in Japan, a cross-sectional study was conducted of male employees in two factories of a Japanese electrical corporation in 1984. The subjects were asked to complete questionnaires concerning job stress and other covariates. Their medical history was assessed through interviews by trained nurses. In addition, the nurses measured height, weight and blood pressure, and collected blood samples from each subject. Obesity was calculated using the Body Mass Index. The overall response rate was 88%. A total of 2,672 male respondents, excluding 158 with a medical history of hypertension, cardiovascular disease or diabetes mellitus, were subjected to the present analysis. Four job stressors were assessed: 1) hours of overtime, 2) job overload, 3) control over workpace, and 4) human relations at work. Four cardiovascular risk factors were examined in the physical check-up: 1) systolic blood pressure (SBP), 2) diastolic blood pressure (DBP), 3) total serum cholesterol, and 4) number of cigarettes smoked per day. Covariates were age, education, martial status, major occupational categories, rotating shift work, alcohol consumption, caffeine consumption, exercise, obesity, family history of heart disease, and type A behavior. Analysis of covariance controlling for these eleven covariates was employed to assess the effects of the job stressors and their interactions on the risk factors SBP and DBP were significantly higher in those working 51 or more hours of overtime per month than those working 50 or less hours ($p<0.05$). SBP and DBP were significantly higher in those with lower control over workpace than those with higher control ($p<0.01$). The interactive effects between overtime and control over workpace on SBP and DBP were significant ($p<0.01$), showing the highest blood pressure in the group with more overtime and lower control over workpace. None of the job stressors were

significantly related with total serum cholesterol or number of cigarettes smoked ($p > 0.95$). It is suggested that long working hours and little control over workpace are related to high blood pressure in Japanese male workers. The present study supported, in part, the job demand-control model, but failed to indicate the stress-buffering effects of human relations in the workplace.

STUDY OF MORTALITY IN THE UK NATIONAL REGISTRY FOR RADIATION WORKERS

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Estimates of the risks associated with exposure to ionizing radiation are based mainly on studies of the survivors of the atomic bombings of Hiroshima and Nagasaki and on groups irradiated for medical reasons. Many of these individuals were exposed to higher doses than would arise in an occupational context, and their doses were incurred almost instantaneously. To use these data to predict risks associated with occupational exposures therefore requires additional information on how to extrapolate risks to low doses and low dose rates. As an alternative, direct evidence on the effects of occupational exposure may be obtained from epidemiological studies of radiation workers. For reasons of statistical power, it is important that such a study be based on a large cohort. Consequently, after extensive consultations with interested parties, the National Radiological Protection Board set up the National Registry for Radiation Workers (NRRW)[1,2] in 1976 to provide the largest possible study of UK radiation workers. The results of the first analysis of the NRRW, are summarized here; further details are given elsewhere.[3,4]

The study population comprised 95,217 individuals employed in five major organizations in the nuclear industry. Of these workers, just over 40,000 had been included in several smaller studies published previously.[5-8] The NRRW, as well as having a longer period of follow-up for those previously-studied workers who were in employment during or since 1976, also contained large groups not studied previously, such as nuclear power plant workers and workers covered by the Defence Radiological Protection Service (DRPS). The mean cumulative external recorded dose was 33.6 mSv. The distribution of cumulative dose was skew; 62% of the workers had a dose less than 10 mSv, whereas 9% had a dose in excess of 100 mSv. Whilst just over half of the workers in the latter category worked for British Nuclear Fuels, there were also large numbers in

this dose category from other organizations such as the UK Atomic Energy Authority and DRPS. Just under 95% of the workers had only one period of radiation work. For the remaining workers who had two or more such employments, a unified dose and employment history was set up.

The cohort of workers was followed-up principally via the National Health Service Central Registers for England and Wales and for Scotland. Use was also made of tracing facilities at the Department of Social Security and various other organizations.[4] Of the 95,217 workers, 69 could not be traced satisfactorily, 1,850 were recorded as having emigrated, and 6,660 were recorded as having died by the end of follow-up, which was the end of 1988 in most instances.

Standardized Mortality Ratios (SMRs) were calculated[9] using the general population of England and Wales as a comparison, and excluding the first 10 years following the start of radiation work (2 years in the case of leukemia) so as to allow for latency in any radiation effect. As expected, there was a Healthy Worker Effect; the SMRs for all causes (85, based on 4884 deaths) and all malignant neoplasms (86, based on 1363 deaths) were both significantly less than 100, indicating that mortality rates in the NRRW cohort overall were less than those in the general population. An important contributor to the result for all cancers was the low SMR for lung cancer (76, based on 478 deaths) which, along with the reduced SMR for non-malignant diseases related to smoking (89, based on 2085 deaths), suggests differences in smoking habits compared with the general population. The SMRs for leukemia excluding chronic lymphatic leukemia (CLL) (93, based on 44 deaths) and multiple myeloma (65, based on 12 deaths) were both less than 100, although neither was statistically significant ($p > 0.05$). The only disease grouping with a significantly raised SMR was thyroid cancer (SMR 303, $p < 0.01$, based on 9 deaths). Further investigations did not reveal any relationships between the thyroid cancer risk and either external recorded dose or the individual's workplace.

In view of the potential for confounding inherent in the use of an external control group, greater emphasis is placed on analyses internal to the NRRW cohort. Tests for trend in mortality with external recorded dose were performed,[10-11] with adjustment for age, sex, calendar period, industrial classification (a surrogate for social

class), and first employer/site. For all known causes other than malignant neoplasms, the estimated excess relative risk (RR) per unit dose was very close to zero (0.01 Sv^{-1}, 90% confidence interval (CI) (<-0.30, 0.36)), whereas for the grouping of all malignant neoplasms there was weak evidence of an increasing trend (one-sided p=0.10). In contrast to two earlier studies that are included within the NRRW database, there was no significant trend in prostrate cancer risk with dose (p=0.28). The trend with dose in the risk of multiple myeloma approached statistical significance (excess RR 6.9 Sv^{-1}, 90% CI (-0.03,46), p=0.06), although this finding was influenced largely by individuals in the previously published Sellafield study.[6] There was an increasing trend in leukemia risk with dose which attained statistical significance when CLL (which does not appear to be radiation-inducible) was excluded (p=0.03). Subsidiary analyses showed that, for example, excluding those workers monitored for internal exposure or removing corrections made to dose histories had little qualitative influence on these results.

Table 1 compares the cancer risk estimates from the NRRW with those from the study of mortality among the Japanese atomic bomb survivors[12] and from a combined study of about 36,000 U.S. workers.[13] As well as the excess relative risk per unit dose, lifetime risks based on appropriate projection models[4] are presented. While the central estimates from the NRRW are about twice those recommended by the International Commission on Radiological Protection (ICRP),[14] which were based on applying a DDREF (dose and dose rate effectiveness factor) of 2 to the Japanese data, it can be seen from Table 1 that the 90% confidence intervals (CI) from the NRRW are very wide and contain the ICRP values. Furthermore, the central estimates of risk from the U.S. study are negative, both for all malignant neoplasms and for leukemia. When the U.S. results are combined with those from the NRRW, the central lifetime risk estimates, namely 4.9% Sv^{-1} (90% CI <0,18) for all malignant neoplasms and 0.30% Sv^{-1} (90% CI <0,1.04) for leukemia, are close to those of ICRP (namely 4% Sv^{-1} and 0.4% Sv^{-1} respectively). Although the confidence intervals are wide, they encompass the ICRP risk estimates. The results from the worker studies do not, therefore, provide evidence that the ICRP estimates are materially in error. Nevertheless, the first analysis of the NRRW does provide valuable information, particularly on leukemia risks.

The next analysis, which will include further groups of workers and will have a longer follow-up, should produce more powerful evidence on the risks of occupational radiation exposure.

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Table 1. Comparison of Risk Estimates from Studies of the Japanese Atomic Bomb Survivors, NRRW and the Combined Cohort of U.S. Nuclear Workers

	Atomic bomb survivors[a]		NRRW	U.S. Nuclear Workers[b]
Cohort size	75991		95217	35933
Person years (thousands)	2185		1218	705
Collective dose (man Sv)	10000		3198	1140
Dose range (Sv)	0-4+	0-0.5[a]	0-0.5+	0-0.5+
Excess relative risk, Sv^{-1} (90% CI)				
All malignant neoplasms	0.41[c] (0.32, 0.52)	0-38[c]	0.47 (-0.12, 1.20)	-0.99 (<-1.6, 0.38)
Leukemia	5.2[d] (3.8, 7.1)	2.4[d]	4.3 (0.40, 13.6)	<-1.5 (<-1.5, 3.4)
Lifetime risk, $\%Sv^{-1}$ (90% CI)	ICRP			
All malignant neoplasms	4[e] (3, 5)[f]		10 (<0, 26)	<0 (<0, 8.2)
Leukemia	0.4[e] (0.3, 0.5)[f]		0.76 (0.07, 2.4)	<0 (<0, 0.60)

Notes

(a) Results are presented both for the entire cohort of atomic bomb survivors and also for those with doses of 0.5 Sv or less.[12]

(b) Workers at Hanford, Oak Ridge and Rocky Flats.[13]

(c) Value for all malignant neoplasms excluding leukemia, based on all ages at exposure.[12]

(d) Value for all ages at exposure.[12]

(e) Derived by ICRP,[14] based on applying a DDREF of 2 to the Japanese data.

(f) Approximate values based on the Japanese data.

Adapted from articles owned by the National Radiological Protection Board, Chilton Didcot, Oxon OX11 ORQ, United Kingdom.

LUNG FUNCTION AMONG INSULATION WORKERS A CROSS-SECTIONAL AND LONGITUDINAL STUDY

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The use of asbestos as an insulation material was banned in Denmark in 1972, but despite the increasing extent to which insulation workers were able to protect themselves against the negative effects of asbestos, a suspicion remained that insulation workers were still at risk of lung disease because of the exposure to other types of dust, e.g., mineral wool.

Exposure data

Measurements of exposure to asbestos before 1972 are not available in Denmark. However, the Danish National Institute of Occupational Health has measurements of mineral wool and total dust concentrations from the late 1970s. Two hundred measurements were taken at 32 worksites where mineral and glass wool were used as insulation. The highest concentrations of fiber were found in the insulation of district heating pipes and of cramped spaces in old buildings. These concentrations were up to 3 fiber/ml.

Individual measurements exist from 1988 which were taken by the occupational health service of the building industry. These measurements, particularly during the clean-up phase, showed fiber concentrations up to 10 fiber/ml. Most often the level was between 0.03 and 1 fiber/ml when personal exposure was measured. The level of total dust concentration with regard to normal insulation work was between 1 and 10 mg/m.^{3}

Materials and methods

All members of the Copenhagen Union of Insulation Workers were invited to participate in the study. Three hundred and forty men accepted, corresponding to 74% of the men invited. One hundred and sixty-six bus drivers (83% of the 200 randomly selected) were used as control group. Six years prior to the present study 114 of

the insulation workers had participated in a similar study. Furthermore, eight years after the initial study, 59 of the bus drivers took part in a similar study. These 59 men represented 80% of the Copenhagen group of the 166 bus drivers who had taken part in the original lung function study. These two groups of men were the study population and control group, respectively, in the prospective part of the study.

A lung function test was then carried out according to international recommendations. FVC and FEV_1 were measured. The students t-test and analysis of variance were used, and the level of significance was 5%.

Results

The mean values of FVC were approximately the same in the two groups. With regard to FEV_1, the insulation workers had significantly lower values than bus drivers, regardless of smoking category. Non-smokers had better lung function than the other groups and the exsmokers among the insulation workers had reduced FVC as well as FEV_1.

The distribution of FVC values among the insulation workers and bus drivers was quite similar, but there were relatively more insulation workers with low FVC values. However, there was a marked difference with regard to FEV_1. Only 3 bus drivers had values below 2 liters, whereas 62 insulation workers had values below that level.

Table 1. Mean values of FVC and FEV_1

	FVC (1)			FEV_1 (1)		
Smoking	Insul. worker	Controls	p	Insul. worker	Controls	p
Current	3.99	4.09	NS	2.50	3.35	***
Previous	3.44	4.32	**	2.11	3.57	***
Never	4.35	4.37	NS	2.80	3.71	***
All	4.01	4.15	NS	2.50	3.42	***

**: $p < 0.01$, ***: $p < 0.001$

Table 2. Average decline in lung function in insulation workers and controls

	FVC (cl/year)			FEV_1 (cl/year)		
Smoking	Insul. worker	Controls	p	Insul. worker	Controls	p
Current	9.2	2.8	***	17.5	2.2	***
Previous	6.0	3.5	*	16.9	3.1	**
Never	3.6	3.8	NS	15.4	5.6	**
All	7.7	3.1	**	17.0	2.9	**

*:$p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$

The longitudinal observation of decrease in lung function values per year showed that the decrease was greater among insulation workers than among bus drivers. There was a moderate difference between insulation workers and bus drivers with regard to FVC. However, the difference was found only between previous and current smokers. The decrease among insulation workers was far greater with respect to FEV_1, due to the fact that relatively many insulation workers whose FEV_1 dropped significantly. The modest effect of smoking on FEV_1 in comparison with doing insulation work is noteworthy, but consistent with results from the cross-sectional study.

Discussion

Our findings suggest that an obstructive reduction of lung function is more pronounced among insulation workers, since the FEV_1 was generally lower and a great many had pathologically low values compared with bus drivers. The difference in vital capacity was relatively smaller, most likely because relatively few insulation workers with diagnosed asbestosis participated in the study. Selection among insulation workers could well have caused a certain bias in the study. In the first study, there were 6 cases of asbestosis among the 144 insulation workers; 3 of these men died during the follow-up period and 2 did not show up for the follow-up study. This source of error created a negative bias.

On the other hand, there were presumably a many people with healthy lungs among the 26% non-respondents in the cross-sectional study, considering that most of the non-respondents were younger people. Similarly, there was a relatively strong health-related

selection among the control group as a consequence of their jobs as bus drivers. This selection, however, is not especially related to lung disease. Nonetheless, these selection factors can hardly explain why so many of the insulation workers had low values of FEV_1.

Furthermore, differences in the circumstances surrounding the studies could have played a role as well. Even though the same equipment was used, different people carried out the tests, which could have had an influence on the lung function results. However, the almost identical mean values for FVC in the two groups and the consistence between the results of the cross-sectional and the prospective studies does not suggest such a bias.

The contribution of smoking to the reduction of lung function in insulation workers was relatively modest in relation to the effect of the job. This could be because the pathological reaction in the air passages, caused by occupational exposure to dust, was so strong that the effect of tobacco smoke was obscured. This is borne out, for instance, by the fact that the reduced FEV_1 in exsmokers among the insulation workers did not appear to improve, as would otherwise normally have been the case and which was the case for the bus drivers.

Conclusion

A cross-sectional and longitudinal study of members of the Copenhagen Union of Insulation Workers showed that there was a markedly lower lung function in the study population than in the control group, which consisted of bus drivers. The reduction in lung function was mostly of an obstructive type, as the FEV_1 in insulation workers averaged nearly one liter lower than in bus drivers. This difference was particularly due to the low values among relatively more insulation workers. The effect of tobacco smoking on lung function was almost negligible in relation to the effect of working with insulation materials.

CHILDHOOD CANCERS AND PATERNAL EXPOSURE TO IONIZING RADIATION: FINDINGS FROM THE OXFORD SURVEY OF CHILDHOOD CANCERS (OSCC)

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In 1990, Gardner et al. published the results of a case-control study of leukemia and Lymphoma among young people near the Sellafield nuclear plant in West Cumbria. Excess risks of leukemia and non-Hodgkin's Lymphoma (particularly leukemia) were associated with paternal employment and recorded external dose of whole body penetrating radiation during work at the plant before conception. The present study has sought additional information on the general topic of childhood cancers and paternal exposure to ionizing radiation from the records of the Oxford Survey of Childhood Cancers (OSCC).

Subjects for this analysis comprise 15,279 childhood cancer deaths occurring in children aged 0-15 years in England, Scotland and Wales during the period 1953-81. Each case child was individually matched with a healthy control child; controls were matched for sex and date of birth, and the residence of death for the case child was the same as the residence of birth for the control child. The parents of each case-control pair were interviewed by a single interviewer. Paternal occupations were abstracted from the original interview folders and input, in text form, to computer files. An alphabetical list of all 13,604 unique job titles (job dictionary) was then supplied, devoid of any information on case/control status, to a medical physicist (P.J.R.), who selected those job titles with a potential for exposure to man-made external ionizing radiation at work. The relevant folders were then reviewed for additional information. Finally, the medical physicist classified the likely average external radiation exposure associated with each selected job title for the six month period before the birth of the relevant child, according the same dose groupings used by Gardner et al. A classification was

also made for whether or not there was potential exposure to radionuclides.

For all childhood cancers, of the 8 fathers placed in the highest exposure group (10 or more mSv), 4 were case fathers and 4 were control fathers (RR=1.00 95% C.I.=0.25-4.00). Corresponding figures for the 5-9 mSv group were 8 and 4 respectively (RR=2.00, 95% C.I.=0.60-6.64), and corresponding figures for the lowest exposed group (1.4 mSv) were 55 and 42 respectively (RR=1.31, 95% C.I.=0.88-1.96). There were 27 case fathers with the potential for exposure to radionuclides and only 10 control fathers (RR=2.70, 95% C.I.=1.31-5.58). When these two radiation variables were analyzed jointly, the external radiation relative risks were reduced to 1.03, 0.93 and 0.59, whilst that for potential exposure to radionuclides was increased to 2.87 (95% C.I.=1.15-7.13). Findings from this study suggest that paternal exposure to radionuclides is a risk factor for childhood cancer, rather than exposure to external ionizing radiation, and that this risk is expressed for the overall grouping of all childhood cancers. Clearly research on other populations is required.

USE OF MULTIPLE-CAUSE MORTALITY DATA IN EPIDEMIOLOGIC ANALYSES

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Epidemiologists studying mortality have usually confined themselves to analysis by underlying cause of death. However, a typical death certificate also lists contributory causes, and may list other diseases (not related to the underlying cause) as "other significant conditions." The underlying cause is chosen by nosologists according standard guidelines provided by the World Health Organization, which are based on the order of all diseases listed on the death certificate and on their causal relation. The information on contributory causes and other significant conditions is usually ignored, but can provide useful epidemiologic information.

The U.S. National Center for Health Statistics makes available multiple cause-of-death data tapes, beginning in 1968 and continually updated. These tapes have a record for each U.S. death, which includes age, race, sex, date of death, underlying cause of death, contributory causes of death, and other significant conditions. Up to 14 separate entries (20 after 1978) may be coded for causes of death and significant conditions. Causes of death and significant conditions are coded according to the International Classification of Diseases (ICD) coding system which was in effect at the time of death. To date there have been few etiologic analyses conducted using the National Center for Health Statistics multiple cause data.

We have created U.S. mortality rates (age, sex, race, and calendar-time specific) and proportions using multiple cause-of-death data, for the years 1960-1989 (data from 1960-1967 were imputed). U.S. multiple cause rates and proportions enable the user to calculate expected occurrences of disease on the death certificates of a cohort under study. There are an average of 2.66 causes/contributory conditions listed on U.S. death certificates, increasing over time from 2.54 in the 1960's to 2.76 in the 1980's. The ratio of multiple cause listings to underlying cause listings varies by disease, from low

ratios for cancers to high ratios for diseases such as diabetes, arthritis, prostate disease, hypertension, pneumoconiosis, and renal disease.

Use of these data is illustrated with two cohorts. Multiple cause analysis (but not underlying cause analysis) revealed two-fold significant excesses of renal disease and arthritis among granite cutters. For workers exposed to dioxin, neither multiple cause nor underlying cause analysis indicated any excess of diabetes, an outcome of a priori interest.

The use of multiple cause-of-death data potentially provides a new tool for epidemiologic analysis of mortality data. For many causes of deaths, the ratio of observed to expected deaths using multiple cause will be similar to that ratio using underlying cause (this was the case for our example with dioxin-exposed workers). That is, multiple cause analysis may not reveal any new association between exposure and disease. However, even if the point estimate of effect (e.g., the standardized mortality ratio or proportionate mortality ratio) remains the same, for many causes of death the sample size of observed deaths and expected deaths is increased using multiple cause data, and confidence intervals for the ratio of observed to expected are correspondingly narrowed. Furthermore, in some instances the use of multiple cause data may give different point estimates, revealing an associations not seen using underlying cause data.

Multiple cause data reflects the prevalence of specific diseases at death. Diseases which have a high ratio of multiple cause listings versus underlying cause listings on the death certificate are candidates for multiple cause analysis. Diseases which have a long course and are often not the cause of death, but are serious enough to be noted by the physician on the death certificate, are the best candidates.

MEASUREMENT AND EVALUATION OF SYMPTOM INTENSITY TO IMPROVE UNDERSTANDING OF ACUTE RESPIRATORY HEALTH EFFECTS

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Background

The study of respiratory irritants in the workplace can prove important both because these agents cause acute discomfort and because they may serve as precursors of chronic disease. Since irritant events are not fatal, some consideration needs to be given to the intensity of the response or its severity. Furthermore, since irritant events are generally reversible, their study should also include consideration of the frequency. Few reports have considered either the frequency of irritant events or the severity in other than semiquantitative ways.

Results of a short-term prospective study of workers exposed to sodium borate particulate, an acute respiratory irritant, have recently been reported.[1] The study was undertaken to evaluate dose response relationships between five irritant symptoms and acute exposures to particulates present during processing of boron containing ores. Data were collected on both the frequency and severity of the five symptoms.

The published findings report significant associations between both daily and 15-minute short-term exposure profiles and frequency of the five symptoms, without regard to symptom severity. Acute incidence rates for each of the individual irritant symptoms were found to be associated with increased exposure levels regardless of whether daily or short-term exposures were used. The exposure-response slopes, however, were steeper when short-term exposure levels were used. Results from multivariate logistic regression analysis suggested that current smokers were somewhat less sensitive to the airborne sodium borate dust exposure. Presence of a current

cold was also significantly associated with throat irritation, cough and breathlessness.

Here we present an evaluation of the psychophysical measurement scale used by subjects to scale the intensity of each irritant symptom.

Methods

Overall the design was as a short term prospective cohort study in which a pre-shift baseline health survey was followed by a continuous measure of exposure and hourly interviews for irritant symptoms. All employees with direct exposure to refined sodium borate dusts were invited to participate along with all current non-office hourly employees without routine exposure to these dusts. The same full study protocol was applied to each group. Subjects were tested on each of four (generally consecutive) workdays.

At each interview subjects were queried about whether any of the symptoms had occurred in the previous hour. If they responded affirmatively, they were asked to estimate the time of onset within one of the four previous 15-minute intervals. They were also asked to characterize the severity of each symptom recorded. To measure symptom severity, the subject was shown a scale developed for the study (Figure 1). This instrument was adapted from a psychophysical scale with ratio properties which has been used to study physical exertion and pain.[2] The subjects identified the severity of each reported symptom using this ten point scale. The interview was administered and responses recorded by a technician assigned to attend the study subject throughout the work day.

A personal direct reading aerosol monitor (the Miniram) was used in conjunction with a datalogger system which allowed continuous measurement of airborne particulate matter throughout the work shift. Since this aerosol monitor is most sensitive to aerosols in respirable size range and to high humidity, it was calibrated so that the real-time reading from the datalogger could be interpreted as total particulate concentration.[3]

As an alternative means for recording symptoms, an electronic "event marker button" was inserted into the datalogger attached to each personal exposure monitoring device. By pushing the button, subjects were able to indicate the onset of an irritant symptom at any

time during the workshift. Intensity of "marked" symptoms was not recorded. This allowed a comparison between prompted (by interview) and unprompted (marked) symptoms.

Results

The study population was surveyed over the course of approximately one year, during which the 106 participants were successfully tested hourly for six consecutive hours on four consecutive days (a total of over 2500 survey hours). Since there were only three females and five non-white subjects, sex and race could not be evaluated in the subsequent analysis.

In the evaluation of severity, symptoms reported at the pre-shift survey were considered typical of the background experience of this population (including the common cold). The severity of these pre-shift symptoms was compared to the severity of symptoms that developed over the course of the work day. Average symptom severity varied somewhat by type: nasal irritation 2.1, eye irritation 2.5, throat irritation 1.1 , cough 1.9 , and breathlessness 2.0. Those with colds reported slightly higher severity for cough, but otherwise a common cold did not appear to affect the pre-shift symptom severity.

During work, almost half of all symptom reports had a severity of 1 or less, while fewer than ten percent were scored 5 or greater. Nasal symptoms were the most common, reported 2, 3 and 9 times more frequently than cough, throat irritation and breathlessness, respectively. The severity scores assigned to nasal irritation ranged from 0.5 to 7 (Figure 2). This frequency distribution has a mode of 3.0 and is somewhat skewed toward the lower scores. The shape of this distribution contrasted most with that for eye irritation which had the same mode (3), but almost no variance around the mode was observed.

During work, each type of symptom was reported more often during periods of higher exposure. The exposure-response relationships were statistically significant and consistent across all symptom intensity levels with enough events to be evaluated.

Without regard to severity score, nasal symptoms showed a monotonic increase with exposure ranging from 0.1 events/15

minutes at exposures < 1 mg/m^3 up to 0.32 events/15 minutes at exposures < 10 mg/m^3. Figure 3 shows the exposure-response relationships for nasal irritation by increasing severity scores. Frequency increased with increasing exposure for all severity groups. Within exposure categories, the frequency of irritation decreased with higher severity. Also when frequency was ignored, the average severity of nasal symptoms increased with exposure level. Finally, the frequency of symptoms recorded by the event marker was seen to increase with exposure at rates closest to those prompted symptoms with a severity score of $\geq$ 3.

Discussion

These results suggest that it is possible to quantify the intensity of irritant symptoms in an internally consistent manner. The findings further indicate that information on severity can be used to refine our understanding of exposure response relationships. Just as continuous measures of more objectively measured physiologic functions (e.g., pulmonary function) have allowed examination of effects of low level environmental exposures, more detailed knowledge about irritant symptoms may also allow better understanding of these common, everyday experiences.

Since the responses to the questionnaire were "prompted," the lower scored symptoms may well have been symptoms which would not have been noted in the absence of the intense scrutiny associated with the study. In this regard, the events marked by the subject using the button attached to the datalogger were considered "unprompted" symptoms. The exposure-response pattern of these marked responses suggested that symptoms that might be volunteered in the absence of a study would be of score 3 or higher.

Further work is necessary to validate the severity scaling system for irritant exposures. Use of such a scaling system to study a number of different irritants, including ones that produce irritation severe enough to prompt self-protective actions on the part of the exposed, may allow irritant agents to be assigned potency scores as well. Studies with the severity scale could as well provide information relevant to control efforts by focusing on the intensity as well as the frequency of respiratory irritant symptoms. If the event marker proves to identify symptoms of moderate or greater severity

consistently, the ease of its use may allow much more detailed study of acute irritant events in actual work environments.

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	SYMPTOM SEVERITY SCALE	
0	Not at all	
0.5	Very, very little	(Just Noticeable)
1	Very little	
2	Fairly little	
3	Moderate	
4	Pretty much	
5	A lot	(Strong)
6		
7	Very much	
8		
9		
10	Very, very much	(Almost maximal)
•	Maximal	

Figure 1. Severity scale

Severity Score	Percent of Nasal Symptoms Reported
0.5	10%
1	18%
2	22%
3	37%
4	8%
5	3%
>5	2%

Figure 2. Distribution of scores

Dust Exposure (mg/m^3)	Severity Scores						Marks
	≥0.5	≥1	≥2	≥3	≥4	≥5	
< 1	.01	.01	.01	.01	.00	.00	.01
1-4	.04	.03	.02	.02	.00	.00	.02
5-9	.17	.15	.13	.07	.00	.00	.06
> 10	.32	.30	.24	.17	.05	.02	.12

*Events per 15-minute interval

Figure 3. Nasal symptom frequency* by exposure and severity

PHYSICAL JOB DEMANDS, JOB CONTROL AND PREGNANCY OUTCOME

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Aim of study

Strenuous working conditions have been associated with preterm delivery and low birth weight, but studies are inconsistent. For preventive intervention in the antenatal clinic, it is important to identify selfreported factors which alone or in combination are risk indicators. The aim of the present study was to investigate the effect of physical job demands in pregnancy on the frequency of low birth weight (<2500 g) and preterm delivery (<259 days).

Analytical model

Several studies support the view that lack of job control combined with high psychological job demands can have negative effects on health. Assuming that job control may also modify the effects of physical workload, we employed a two-dimensional model (Figure 1) similar to the Demand Control Model (Karasek and Theorell 1990) employed in stress research.

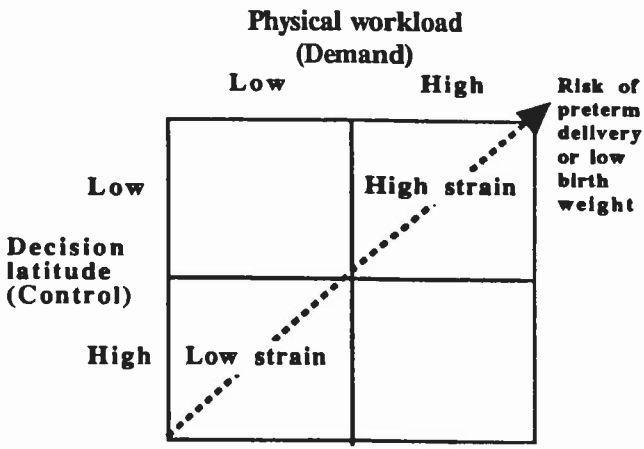

Figure 1. A two-dimensional model for the combined effects of physical workload and lack of job control on pregnancy

Material

Data were collected through a national survey with a self-administered questionnaire to all women giving birth in Norway during a six weeks period in 1989. Of 6235 women registered by the Central Bureau of Statistics in Norway as giving birth in the actual period, 5438 (87.2%) responded. We report some results on low birth weight (non-smoking mothers only) and preterm birth in Nordic nullipara with single births, age 20-29, employed beyond the first trimester.

Results

Physical job demands had less effects alone than in combination with lack of job control (control with work pace). Appendix Table 1. A two by two table combining levels of demand and control identified subgroups of high and low risk better than dichotomization according to level of either demand or control alone. For instance, in jobs requiring daily twisting or bending several times per hour, RR for low birth weight was 1.8 (0.7-4.5) compared to jobs without this type of physical demand (Figure 2).

		Daily twisting/bending several times per hour: No	Daily twisting/bending several times per hour: Yes	
Daily deciding work pace	No	Percent of population: 19.3 % RR 3.8 11.4*	Percent of population: 45.4 % RR 4.3 13.0*	Percent of population: 64.7 % RR 4.2 6.0*
	Yes	Percent of population: 18.3 % RR 0.3 1.0	Percent of population: 17.0 % RR 1.5 4.4	Percent of population: 35.3 % RR 0.7 1.0
		Percent of population: 37.6 % RR 1.9 1.0	Percent of population: 62.4 % RR 3.5 1.8	Total population 823=100% % 2.9

*95% confidence interval did not include 1.

Figure 2. Low birth weight (<2500 g) single births, first born, Norway 1989. Non-smoking mothers age 20-29, working beyond 1st trimester (N=823).

For jobs with lack of daily control with work pace, RR was 6.0 (1.4, 25.2) compared to jobs with such control. For daily twisting or bending several times per hour combined with lack of control with work pace, RR was 13.0 (1.8, 94.5), compared to the risk in jobs without this physical demand and with control with work pace. For preterm delivery, corresponding RRs were 1.2 (0.7, 2.2) for daily twisting or bending several times per hour, and 1.7 (0.8, 3.7) for daily twisting or bending combined with lack of control with work pace (Figure 3).

Daily deciding work pace	Daily twisting/bending several times per hour: No	Daily twisting/bending several times per hour: Yes	
No	Percent of population: 18.5 % RR 4.2 1.2	Percent of population: 48.5 % RR 5.7 1.7	Percent of population: 67.0 % RR 5.2 1.8
Yes	Percent of population: 16.2 % RR 3.4 1.0	Percent of population: 16.8 % RR 2.3 0.7	Percent of population: 33.0 % RR 2.9 1.0
	Percent of population: 34.7 % RR 3.8 1.0	Percent of population: 65.3 % RR 4.8 1.2	Total population 1381=100% % 4.5

Figure 3. Preterm delivery (<259 days) single births, first born, Norway 1989. Mothers age 20-29, working beyond 1st trimester (N=1381).

For physical workload defined as daily standing/walking, the pattern differs, implying highest risk in particular for LBW in sedentary jobs combined with lack of control (Figure 4).

Daily deciding work pace	Daily working standing/walking: No	Daily working standing/walking: Yes	
No	Percent of population: 18.5 % RR 6.7 21.4*	Percent of population: 46.2 % RR 3.2 10.2*	Percent of population: 64.7 % RR 4.2 6.0*
Yes	Percent of population: 19.7 % RR 0.3 1.0	Percent of population: 15.6 % RR 1.6 5.1	Percent of population: 35.3 % RR 0.7 1.0
	Percent of population: 38.2 % RR 3.2 1.0	Percent of population: 61.8 % RR 2.8 0.9	Total population 823=100% % 2.9

* 95% confidence interval did not include 1.

Figure 4. Low birthweight (<2500g) single births, first born, Norway 1989. Non-smoking mothers age 20-29, working beyond 1st trimester (N=823).

Conclusion

Physical job demands like lifting heavy loads or frequent twisting or bending tend to increase the risk of LBW and preterm delivery. Lack of control with work pace is a strong risk indicator, and increases the adverse effect of physical job demands. Combination of different levels of physical demands and job control distinguish better between low and high risk subgroups than each factor alone.

Reference

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Table 1. Frequency (%) of preterm delivery (> 259 days) and low birth weight (< 2500 g) by physical work load and job control in single births, first born, of Nordic parents in Norway 1989. Mothers age 20-29, working outside home beyond 1st trimester of pregnancy (N = 1381). For birth weight, the population is restricted to non-smoking mothers (N = 823). (R) indicates groups used as references for relative risk (RR) estimates.

	% of population	Preterm delivery < 259 d %	RR	(95% CI)	Low birth weight (Non-smoking mothers) < 2500 g %	RR	(95 % CI)
Daily standing or walking							
No (R)	34.2	4.1			3.2		
Yes	65.8	4.7	1.1	(0.7 - 2.0)	2.8	0.9	(0.4 - 1.9)
By **Control** with work pace							
No load/Control (R)	16.9	2.3			0.3		
Load/Control	16.1	3.4	1.5	(0.5 - 4.6)	1.6	5.1	(0.6 - 45.3)
No load/no control	17.3	5.9	2.6	(0.9 - 7.1)	6.7	21.4	(2.9 - 15.8)*
Load/No control	49.7	5.0	2.2	(0.9 - 5.5)	3.2	10.2	(1.4 - 75.4)*
Lifting 10-20 kg loads > **20 times weekly**							
No (R)	76.4	4.2			2.2		
Yes	23.6	5.1	1.2	(0.7 - 2.1)	4.8	2.2	(0.9 - 5.2)
By **Control** with work pace							
No load/Control (R)	27.5	3.1			0.4		
Load/Control	5.5	1.4	0.5	(0.1 - 3.5)	2.6	6.5	(0.4 - 102.0)
No load/No control	48.9	4.7	1.5	(0.8 - 3.0)	3.3	8.2	(1.1 - 62.0)*
Load/No control	18.1	6.2	2.0	(0.9 - 4.3)	5.5	13.6	(1.7 -109.0)*
Daily twisting or bending several times per hour							
No (R)	34.7	3.8			1.9		
Yes	65.3	4.8	1.2	(0.7 - 2.2)	3.5	1.8	(0.7 - 4.5)
By **Control** with work pace							
No load/Control (R)	16.2	3.4			0.3		
Load/Control	16.8	2.3	0.7	(0.2 - 2.1)	1.5	4.4	(0.5 - 38.8)
No load/No control	18.5	4.2	1.2	(0.5 - 3.2)	3.8	11.4	(1.5 - 87.3)*
Load/No control	48.5	5.7	1.7	(0.8 - 3.7)	4.3	13.0	(1.8 - 94.5)*
Daily decide work pace							
Yes (R)	33.0	2.9			0.7		
No	67.0	5.2	1.8	(1.0 - 3.4)	4.2	6.0	(1.4 - 25.2)*

*95% Confidence interval did not include 1.

LARYNX CANCER AND OCCUPATION: PRELIMINARY RESULTS FROM THE IARC MULTICENTRIC CASE-CONTROL STUDY

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During 1979-1982, a multicentric population based case-control study on cancer of the larynx and hypopharynx has been conducted in Calvados (France), Turin and Varese (Italy), Zaragoza and Navarra (Spain), and Geneva (Switzerland). Among males, over 1100 cases and 3000 controls were enrolled in the study. Details on the study design and results according to alcohol drinking and tobacco smoking have been published (1). Subjects were asked about their occupational history since 1945 and were classified as ever employed in 156 occupations and 70 industries. Odds ratios (OR) and 95% confidence intervals (CI) were calculated via logistic regression controlling for centre, age, alcohol drinking, tobacco smoking and socioeconomic class. Among the occupations at higher risk in this preliminary analysis were butchers (OR, 2.6; 95% CI, 1.2-5.4), wood machine operators (OR, 2.9; 95% CI, 0.9-9.8), blacksmiths (OR, 1.9; 95% CI, 1.0-3.8), mechanics (OR, 1.3; 95% CI, 0.8-2.2), potters (OR, 5.5; 95% CI, 1.3-22), reinforced concrete workers (OR, 2.4; 95% CI, 0.9-6.1), housebuilders (OR, 1.7; 95% CI, 0.9-3.2), plasterers (OR, 3.0; 95% CI, 0.6-14). Among the industries at higher risk were boot and shoe manufacture (OR, 1.4; 95% CI, 0.8-2.6), wood industries other than furniture making (OR, 2.3; 95% CI, 0.7-7.0), non ferrous metal production (OR, 2.6; 95% CI, 1.0-6.9), radio equipment manufacture (OR, 1.9; 95% CI, 0.7-5.6), shipbuilding (OR, 1.9; 95% CI, 0.8-4.7), hotels (OR, 2.0; 95% CI, 0.9-4.7), railroads (OR, 1.5; 95% CI, 1.0-2.4), and hairdressing (OR, 2.3; 95% CI, 1.0-5.3). For selected categories, duration of employment and time since beginning of employment were also investigated. The possible confounding effect of other factors, such

as use of filter, color of tobacco and dietary factors was not taken into account. The problem of multiple comparison has been addressed by applying the empirical Bayes ranking methodology proposed by Thomas and coworkers (2). In addition, a job-exposure matrix (3) for 16 chemicals or groups of chemicals has been applied to the occupational histories of cases and controls.

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THE OCCUPATIONAL CANCER INCIDENCE SURVEILLANCE STUDY (OCISS): RISK OF LUNG CANCER BY LENGTH OF EMPLOYMENT FOR WHITE AND BLACK MALES

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Introduction

The risk of lung cancer in the Occupational Cancer Incidence Surveillance Study (OCISS) was studied previously looking at usual occupation and industry.[1] In continuing analyses, we analyzed lung cancer risk by length of employment among those ever employed in selected occupations and industries. Lung cancer risk was assessed by increasing years of employment to determine whether a dose-response relationship existed between lung cancer risk and length of employment. In addition to comparing the results from this study to the previous study looking at usual occupation and industry, we examined whether lung cancer risk differed by race.

Methods

The OCISS has been described in detail elsewhere.[1] Briefly, the OCISS is a population-based study of occupational risk factors for selected cancers occurring among residents of the Detroit metropolitan area. Incident lung, colon and rectum cancer cases diagnosed among black and white men between the ages of 40 and 84 are included in this report. This case-control study included 3792 lung cancer cases and 1966 colon and rectum controls.

Data were gathered by telephone interview with the subject or his surrogate. The interview obtained a complete lifetime occupational history, smoking history, medical history, demographics and residential history. Occupation and industry data obtained by interview were coded using the 1980 U.S. Census Bureau codes.[2] Individual codes for occupations and industries with similar exposures were grouped together for analysis. In addition, we

selected occupations and industries with little or no exposure to carcinogens and defined them as an unexposed group.[1]

The risk of lung cancer among "exposed" occupations and industries was estimated relative to those who only had unexposed occupations and industries during their lifetime. Odds ratios for occupations and industries were estimated using a logistic regression model controlling for age at diagnosis and cigarette smoking.[3] The Chi-square test for trend was used to determine whether there was a linear association between years of employment and lung cancer.[4]

Results

White males show significant increases in risk with increasing years of employment for agricultural workers, personal service workers, driver sales, metal finishers, furnace workers, drivers, and food preparation workers (Table 1). Black males had a significant trend in elevated risk for mechanics.

Similar tables were produced looking at the risk of lung cancer by number of years employed in grouped industries (Table 2). White males had significant trends in elevated odds ratios in the railroad and oil and gas sales industries. Farming, ferrous primary metal manufacturing, automobile repair, hospitals and odd jobs increased significantly with increasing years of employment for black males.

Black and white males, for many of the same occupations and industries, show increased lung cancer risk with increasing years of employment. However, the risk estimates for black males are often two to three times higher.

Conclusion

In conclusion, we were able to detect a dose-response relationship for several occupations and industries when using length of employment as a surrogate for exposure. Lung cancer risk was found to differ by race for many of the same occupations and industries examined. Specifically, black males appear to have a greater risk of lung cancer due to exposure in the workplace after adjusting for cigarette smoking and age at diagnosis. Further research is needed to determine if blacks have been given jobs with heavier exposure historically or whether there are some other factors at work that have

yet to be identified. Overall these results signify the need to include blacks in studies of occupational exposures and to analyze workplace risks separately among whites and blacks.

This study produced some results that were similar to those observed in a previous analysis of usual occupation and industry. However, the demonstration of a dose-response pattern of association between lung cancer and certain occupations and industries strengthens the probability that these are biologically meaningful results. This pattern of association also enables us to target specific employment groups that may provide the best opportunities for further research.

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Table 1. Occupational cancer incidence surveillance study (OCISS): Risk of lung cancer by number of years employed in grouped occupations

		WHITE MALES			BLACK MALES		
Occupation Groups	Number of Years Employed	Lung Cancer Cases	Colon/ Rectum Cancer Controls	OR	Lung Cancer Cases	Colon/ Rectum Cancer Controls	OR
Agricultural workers	0	88	81	1.0*	12	10	1.0
	1-9	129	65	1.6**	49	23	2.6
	10+	114	56	1.7**	70	28	3.3**
Personal service workers	0	88	81	1.0*	12	10	1.0
	1-9	35	18	1.7	10	7	1.8
	10+	7	1	7.1	4	2	2.4
Driver sales	0	88	81	1.0*	12	10	1.0
	1-9	56	24	2.1**	11	7	2.4
	10+	64	18	2.7**	6	2	5.3
Mechanics	0	88	81	1.0	12	10	1.0*
	1-9	98	44	1.6	21	10	2.2
	10+	127	63	1.5	43	10	5.0**
Production inspectors	0	88	81	1.0	12	10	1.0
	1-9	81	67	0.8	17	13	1.6
	10+	121	58	1.6**	39	14	3.1
Metal finishers	0	88	81	1.0*	12	10	1.0
	1-9	135	80	1.1	56	31	2.7
	10+	199	84	1.8**	46	28	2.1
Furnace workers	0	88	81	1.0*	12	10	1.0
	1-9	35	22	1.3	29	12	3.9**
	10+	53	13	2.9**	34	15	3.3
Drivers	0	88	81	1.0*	12	10	1.0
	1-9	153	73	1.5**	50	29	2.3
	10+	225	73	1.9**	62	38	1.9
Welders	0	88	81	1.0	12	10	1.0
	1-9	41	27	1.1	34	9	5.0**
	10+	85	39	1.4	37	19	2.5
Armed services personnel	0	88	81	1.0	12	10	1.0
	1-9	1502	746	1.3	366	149	3.0**
	10+	39	18	1.5	11	4	4.9
Health technicians	0	88	81	1.0	12	10	1.0
	1-9	12	8	1.3	14	3	5.3
	10+	6	2	2.3	11	1	15.4**
Food preparation workers	0	88	81	1.0*	12	10	1.0
	1-9	52	33	1.3	33	16	2.8
	10+	50	22	1.9**	23	8	3.1

*Chi-square test for trend significant at $p \leq .05$

**Confidence interval significant at $p \leq .05$

Table 2. Occupational cancer incidence surveillance study (OCISS): Risk of lung cancer by number of years employed in grouped industries

		WHITE MALES			BLACK MALES		
Industry Groups	Number of Years Employed	Lung Cancer Cases	Colon/ Rectum Cancer Controls	OR	Lung Cancer Cases	Colon/ Rectum Cancer Controls	OR
Farming	0	73	70	1.0	15	14	1.0*
	1-9	132	60	1.6	49	23	3.2
	10+	103	48	1.7	70	28	3.6
Ferrous primary metal mfg.	0	73	70	1.0	15	14	1.0*
	1-9	61	42	0.8	44	25	2.6
	10+	125	37	2.5	49	13	6.1
Auto-mobile mfg.	0	73	70	1.0	15	14	1.0
	1-9	359	191	1.4	143	49	4.3**
	10+	999	552	1.3	419	160	3.8**
Food mfg.	0	73	70	1.0	15	14	1.0
	1-9	62	33	1.4	28	13	3.8**
	10+	77	33	1.5	18	8	4.1**
Other transport -ation mfg.	0	73	70	1.0	15	14	1.0
	1-9	21	13	1.4	9	1	11.4**
	10+	20	4	3.7**	4	2	2.3
Railroads	0	73	70	1.0*	15	14	1.0
	1-9	27	14	1.2	22	13	2.6
	10+	40	15	2.4**	9	6	2.7
Oil and gas sales	0	73	70	1.0*	15	14	1.0
	1-9	95	37	1.5	17	14	1.4
	10+	51	18	2.3**	13	3	3.7
Automobile repair	0	73	70	1.0	15	14	1.0*
	1-9	38	26	1.1	26	6	5.9**
	10+	42	17	1.6	28	5	8.1**
Hospitals	0	73	70	1.0	15	14	1.0*
	1-9	38	12	2.7*	26	4	6.7**
	10+	15	10	0.9	23	5	6.8**
Odd jobs	0	73	70	1.0	15	14	1.0*
	1-9	34	19	1.4	20	11	2.4
	10+	9	7	0.7	13	2	8.9**

*Chi-square test for trend significant at $p \leq .05$

**Confidence interval significant at $p \leq .05$

LUNG CANCER MORTALITY AND AIRWAY OBSTRUCTION AMONG METAL MINERS EXPOSED TO SILICA AND LOW LEVELS OF RADON DAUGHTERS

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Introduction

The International Agency for research on Cancer (IARC,1987) classified the evidence for carcinogenesis of crystalline silica as limited in humans but sufficient in animals. Goldsmith (1982,1986) suggested several mechanisms in the relationship between exposure to silica, silicosis and lung cancer. Maillard (1980) and Heppleston (1985) came to opposite conclusions suggesting, as McDonald (1989) did, smoking and other occupational exposures (polycyclic aromatic hydrocarbons (PAHs), radon) as confounding factors. More recently, further conflicting results have been published on this issue. Pairon et al. (1991) concluded that studies published to date were not sufficient to consider occupational exposure to silica per se an independent cause of lung cancer, particularly in absence of silicosis. A number of epidemiological studies reported a significant association between impaired lung function and lung cancer, even after adjusting for smoking and age, among respiratory patients, large community based cohorts and pneumoconiotic workers. (Tockman et al., 1987; Kuller et al., 1990; Nomura et al., 1991; Harber et al., 1986). These results suggest that combining initial poor lung function and smoking history may identify subjects at an unusually high risk of lung cancer in follow-up studies.

Subjects and Methods

The present study concerns the lung cancer mortality among miners employed in two lead and zinc mines in Sardinia. We looked at the effect of silica and radon daughters exposures, taking into account the smoking habit and lung function of cohort members. In both mines the ore consists mostly of blende and galena. The wall-rocks differ between mine A and B: dolomite and limestone, which matrix is mainly carbonate, in mine A and methamorphic schist, which

matrix is quartz and syderite, in mine B. The sub-level stoping technique was the main mining method. Diesel engines were introduced only since the 70's. Data on respirable dusts, by gravimetric method, and percent free silica content, by x-ray difractometry, were available since the 60's from several static and personal air samplings. A limited number of radon measurements in both mines was available only since the 1979.

We followedup to December 31, 1988, 1741 male underground and surface workers, with at least 1 year of employment, who underwent a cross-sectional survey on respiratory function in 1973. Each cohort consisted of more than 98% of the total workforce at that time, 906 from mine A and 835 from mine B. Information on previous jobs, length of employment in mine, retirement and migration were checked through personnel records and union registers. No migration between mines was noticed until 1985. The 1973 survey included a standardized questionnaire for occupational history and smoking habit. The (1973) x-ray chest films were reviewed and classified according to the ILO scale. An acceptable spirometry according to the American Thoracic Society criteria was available for 99% of cohort members. Airways obstruction was established when FEV1/VC ratios were lower than the limits predicted from the ECSC references. The vital status was ascertained by the residence town registers where a copy of the death certificate was available for all deceased subjects. The expected numbers of deaths were calculated from the regional rates, specific for 5-year age group and each calendar year of follow-up. Standardized mortality ratios and the 95% confidence intervals were calculated according to Rothman. In the nested case-control study the adjusted ORs were calculated by the logistic regression.

Results

The respirable dust from mine A contained a maximum of 2% quartz whilst in mine B it ranged between 6.5 and 29%. The respirable dust concentrations were comparable between the two mines by calendar periods; in underground workplaces they averaged respectively 2.6 and 2.5 mg/m^3 during 1962-70,1.8 and 1.6 mg/m^3 during 1971-80, and 1.7 and 1.6 mg/m^3 during 1981-88. The mean concentration of respirable free silica was about 0.02 mg/m^3 in mine A and ten fold higher in mine B, suggesting a significant silica exposure and risk of silicosis only in this mine. The in-air radon

short-time decay products were very low in mine B. Measurements from mine A showed a general mean annual exposure of 1.4 working level months (WLM), the highest value being 3.5. The mean cumulative exposure of miners from mine A who spent 25 years in underground was estimated about 31 WLM, with highest values not exceeding 120 WLM. However because of limited data, no careful individual estimate could be calculated.

The workforce of the two cohorts were comparable to each other by age and length of employment in mine. Only about 4% of all workers had experienced other jobs (rural or building) before being hired at the mine. More than 68% of Monteponi's workers and 81.1% of Montevecchio's were lifelong underground miners. Smoking was comparable between mines with more than 72% ever smokers. About 20% of workers from mine A and 15% from mine B had a spirometric airways obstruction. As expected the prevalence of silicosis was significantly higher among miners from mine B; (38 films [4.6%] were classified as 1/1 or more in the ILO scale). In mine A, where the quartz exposure was much less relevant, it was only 0.6%.

Among the whole cohort the mortality for all causes and cardiovascular diseases was slightly lower than expected. Nonmalignant chronic respiratory diseases showed a significant twofold increased mortality. All cancer mortality was not different from expected: 24 subjects (5 never smokers and 19 smokers) died of lung cancer, yielding an SMR close to 100 (12% excess). Other specific cancers showed an increased but not significantly higher SMR.

The mortality for all causes and all cancers was similar between the two cohorts. However, lung cancer showed a 28% excess in mine A and a slight deficit in mine B (SMR 85) where a stronger increase of the SMR for respiratory diseases can be also noticed (SMR 351). The SMR for lung cancer was highest among underground miners from mine A with a significant upward trend by duration of employment in underground jobs. Mine B underground workers showed lung cancer SMRs close to 100 without significant trend by years of exposure. Surface workers experienced a lung cancer mortality lower or not different from expected (Table 1).

Table 1.

				Years in Underground		
		Surface	Underground	1-9	10-19	20+
Mine A	Obs	6	1	1	3	7
	SMR	101	148	107	134	163*
	CI	37-220	74-265	2-598	27-393	65-336
Mine B	Obs	1	6	1	3	2
	SMR	145	99	98	97	104
	CIs	1-251	36-214	1-545	19-376	12-376

* Chi square trend for years in underground statistically significant at 5% level.

Among underground workers with airways obstruction, those from mine A showed the highest SMR (SMR:316) with a lung cancer mortality more than three-fold higher than expected and about two-fold higher than that found among obstructive miners from mine B (SMR:167). On the contrary, among miners with normal spirometry the SMRs were close to 100 or less (Table 2).

Table 2.

		Airway Obstruction			Normal Spirometry		
		Obs	SMR	95% CIs	Obs	SMR	95% CIs
Under ground	Mine A	6	316	116-687*	5	106	34-247
	Mine B	2	167	19-603	4	85	23-219
Surface	Both Mines	1	91	1-507	6	84	31-183

* Statistically significant at 5% level.

The confounding by age and smoking on the association between working underground, airways obstruction and lung cancer was explored in a nested case-control study by logistic regression. Four living controls for each case, matched by year of birth and smoking

category, were randomly selected from cohort A. The results confirm the independent effect of airways obstruction on lung cancer risk: the adjusted OR was 2.58 for airway obstruction (Table 3).

Table 3.

Mine A		Cases	Controls
Sample size	N	17	68
Age	Mean (SD)	49.8 (5)	50.2 (4)
Ever Smokers	N (%)	14 (82.3)	56 (82.3)
Pack-Years	Mean (SD)	25.6 (9)	23.1 (15)
Underground miners	N (%)	11 (64.7)	33 (48.5)
Airway Obstruction	N (%)	07 (41.2)	15 (22.0)

Adjusted ORs:			
	Working Underground	OR: 1.79	CIs: 0.67-478
	Airways Obstruction	OR: 2.58	CIs: 1.00-6.86

Eight deaths occurred among the silicotics of both mines, one in mine A and seven in mine B. Five were cancers and within them only one was a lung cancer; two stomach cancers were also noticed in mine B. However, because of small numbers we were not able to get any other information about the association between lung cancer and silicosis.

Conclusions

Similar results were reported in our previous follow-up study of 724 silicotic miners. In that cohort we did not find an increased risk of lung cancer in association with either the degree of exposure to silica dust or silicosis, but patients with airway obstruction had a SMR for lung cancer two- to three-fold higher than expected, the excess growing with the degree of the airways impairment. The smoking adjusted risk estimate by the Mantel-Haenszel analysis was 2.86 for moderate airflow obstruction and 7.23 for severe airflow obstruction. (Carta et al., 1991)

The present study has several limitations: small sample size and short follow-up time, but we are now checking the reliability of

death certificate by analysis of clinical and necropsy records and collecting information on smoking changes, lung function data and further silicosis evidence during the follow-up. However, despite the lack of statistical significance of single SMRs, the different trends of the SMR for lung cancer between the two mines are strongly suggestive, and that associated with the exposure to radon daughters and airway obstruction is statistically significant. According to the present and our previous results among Sardinian metal miners, crystalline silica, per se, does not appear to independently affect lung cancer mortality. The slight lung cancer excess found in mine A, mainly concentrated among miners with the longest employment in underground jobs and with airways obstruction, might be explained by the exposure to radon daughters in underground, though estimated as within relatively low levels. Smoking and radon exposure seem to share the role of initiating the carcinogenic process; airways obstruction might enhance the risk of exposed workers or it may be a significant marker for an enhanced risk of lung cancer. Airborne dust, probably independently from quartz content, might cooperate in the carcinogenic process as carrier of lung carcinogens (alpha-particles from radon daughters, PAHs); at the same time, concurrently with smoking, it might cause airways obstruction and lung clearing impairment which can enhance the potential effectiveness of inhaled carcinogens on bronchial and lung tissue. These reflections suggest the need for more aggressive advice for smoking cessation and indication that periodical lung function tests for early detection of subjects at risk must flank the improvement of ventilation and other technical interventions for further reducing both radon-progeny and dust exposure in the mining environment.

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OCCUPATIONAL RISKS OF BLADDER CANCER IN FRANCE: A MULTICENTRIC CASE-CONTROL STUDY

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Relationships between occupational risk factors in France and bladder cancer were assessed from a hospital-based case-control study conducted between 1984 and 1987 in five regions representing different industrial activities (such as mines, textile, metal work, rubber and chemical industry). 765 cases (658 men, 107 women) and an equal number of controls were included in the study. Odds ratios adjusted on matching variables (age, residence, hospital), tobacco smoking and coffee consumption were estimated by unconditional logistic regression. A significantly increased risk of bladder cancer among men was observed in coal mining (OR = 3.46 95% CI 1.62-7.41), chemical industry (OR = 2.41 95% CI 1.18-4.91), and car manufacture (OR=1.89 95% CI 1.02-3.48). Aircraft and ship officers (OR=11.74 95% CI 1.44-95.41), managers (OR=1.78 95% CI 1.18-2.69), street vendors (OR=4.04 95% CI 1.08-15.10), miners (OR=2.30 95% CI 1.0-5.30) and machinery fitters (OR=1.53 95% CI 1.03-2.29), also presented an increased risk. Among women, working in the clothing industry was associated with an elevated odds ratio (OR=3.29 95% CI 1.22-8.91). Some occupational exposures, as assessed by expert evaluation, were significantly more frequent among cases: organic solvents (OR=1.43), industrial oils and greases (OR=1.50), welding fumes (OR=1.54) and coal dust (OR=2.07). Variations in risk associated with these exposures according to time period, duration and level, and their joint effects, will be presented. Also high risks observed in coal mining, petroleum refining, glass industry, chemical industry, steel foundry, car manufacture and mechanics are consistent with a role of exposure to polycyclic aromatic hydrocarbons and this relationship will be studied further.

CANCER IN WELDERS AND OTHER WORKERS IN A NORWEGIAN SHIPYARD

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This study is conducted to investigate a possible relation between exposure to welding fumes and cancer, especially lung cancer. 4,571 male shipyard workers, including 623 welders, were followed in a historical cohort study.

The workers had their first employment at the shipyard between January 1, 1940, and December 31, 1979. The incidence of cancer was observed from January 1953 through 1990. The mean length of follow-up was 24.0 years for the total cohort and 21.5 years for the welders. Loss to follow-up was 1.1%.

The shipyard was established in 1900 as a local service yard and expanded after World War II due to repair and rebuilding works. Shipbuilding on a larger scale began in the 1950's. Until 1977, when the yard started constructing for the offshore oil-industry, the welding was mainly performed on mild steel.

There were 408 cases of cancer in the total cohort vs. 361 cases expected based on the Norwegian national age adjusted rates for men. Among the welders 38 cases of cancer were observed vs. 26 expected. An increased incidence of lung cancer with 9 cases compared with 3.5 expected were observed among the welders.

Smoking and exposure to asbestos are possible confounders in this study. Smoking data from the work-force in 1984 showed more smokers among the workers as compared with the Norwegian male population. A difference in smoking habits are likely to account for a fraction of the elevated lung cancer rates. There were 4 cases of mesotheliomas in the cohort vs. 1.2 expected. Asbestos was used in the yard until the early 1970's. No cases were found among the welders (0.1 expected).

In the present study, a cohort of shipyard workers including welders was followed for up to 50 years since first exposure. The results show a possible relationship between exposure to mild steel welding fumes and lung cancer--even when considering the effect of smoking and asbestos as confounders.

NON-MALIGNANT PLEURO-PULMONARY DISEASE AND THE DEVELOPMENT OF MALIGNANT MESOTHELIOMA IN WESTERN AUSTRALIAN CROCIDOLITE WORKERS

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Introduction

Minor pleural changes are common in subjects exposed to asbestos especially when CT scanning is used in diagnosis or when post mortem studies are conducted (1). In the Wittenoom cohort (2), plain chest radiological evidence of diffuse or pleural thickening or localized plaques has been commonly seen (3), and malignant pleural mesothelioma has been a major problem (2,4). The finding of pleural plaques may simply be an indicator of past exposure but is often associated with the presence of other asbestos related disease and can be a cause of fear of additional disorders, particularly malignant mesothelioma. This possible association has been of great personal as well as medico-legal and scientific concern.

Previous studies of the significance of pleural plaques have not been helpful and have yielded conflicting results through being hampered by a shortage of cases of malignant mesothelioma, unconventional X-ray reading methods, unconventional statistics, and also by the absence of information on relative degrees of asbestos exposure of the workers (5-8).

One previous study (3) raised the possibility that employment groups who tend to exhibit diffuse benign pleural disease rather than localized benign pleural disease are at greater risk of developing malignant mesothelioma. No previous studies have been able to examine the effects of degree and duration and time since asbestos exposure on the relationship between benign pleural disease and malignant mesothelioma.

Crocidolite was mined in Western Australia by the Australian Blue Asbestos Company between 1943 and 1966. The employment records of the Australian Blue Asbestos Company have formed the basis of an ongoing prospective study of mortality in this cohort (2,4) in which there were 104 cases of malignant mesothelioma to December 1991.

The aims of the current study were to determine whether diffuse pleural thickening or pleural plaques are associated with the subsequent development of malignant mesothelioma and to examine the possible effects of other radiographic signs on subsequent development of malignant mesothelioma taking into account the independent effects of degree and duration of exposure and time since exposure.

Subjects

The subjects included in this study were drawn from the cohort of 6,910 former Wittenoom crocidolite workers on whom details of employment and past exposure to crocidolite were available from employment records of the defunct Australian Blue Asbestos Company and a survey of levels of airborne fibers > 5 microns in length conducted throughout the industry in 1966 (2). The cases consisted of 102 male ex-employees who had developed malignant mesothelioma to December 1987, and the controls were 707 disease free subjects from the industry who were matched for age (within 1 year), sex, and calendar period of diagnosis of malignant mesothelioma in the cases.

Methods

Plain chest radiographs were sought for all cases and controls from the Perth Chest Clinic, which is responsible for the statutory periodic radiographic surveillance of all subjects in the mining industry in Western Australia and which retains these films in perpetuity, and also from teaching hospitals in Western Australia. The presence of parenchymal and pleural disease were determined according to the ILO classification for the pneumoconioses (9). The median reading of three independent trained readers was taken for each radiograph. Films taken within 1 year of the diagnosis of malignant mesothelioma for each case and their controls were excluded from analysis because changes may have represented early signs of

mesothelioma in the cases. The date of diagnosis of malignant mesothelioma was obtained from Cancer Registries in all states of Australia, the WA Mesothelioma Registry, the WA Mesothelioma Pathology Survey (10), and from the records of the Australian Mesothelioma Surveillance Programme (11).

X-ray scores were grouped according to the period of time before the diagnosis of the case. Each time period before the diagnosis of each case was analyzed separately. To determine if the presence of any radiographic abnormality recorded in the ILO classification was associated with the development of malignant mesothelioma, conditional logistic regression analysis was performed using cumulative asbestos exposure (and intensity and duration of exposure separately), time since first exposure, and the level of radiographic abnormality as covariates.

Results

Radiographic abnormality was fairly common in all subject in this study. The average prevalence of profusion of small opacities > 1/0 on the ILO scale was 20% for the most recent film for all controls. This compares with the prevalence of 16% for radiographic abnormality in randomly selected subjects from Wittenoom in 1983 (12).

For the 102 cases of malignant mesothelioma 80, radiographs taken 2 or more years prior to the diagnosis of mesothelioma were obtained. X-rays for the same period were obtained for 420 of the controls. Both duration and intensity of exposure (and therefore also cumulative exposure) were greater in the cases than the controls, but the time since first exposure was similar.

For any time period prior to the diagnosis of malignant mesothelioma, the presence of diffuse or localized pleural thickening was similar in cases and controls. For any time period prior to diagnosis, the presence of small opacities in the lung was also similar in cases and controls.

Multivariate analysis indicated significant differences between the cases and controls for duration and intensity of exposure as well as time since first exposure but no effect of any radiological abnormality included in the ILO classification. The relative risk of

malignant mesothelioma with time from first exposure per loge (year) was 2.3. This compares with previous estimates of 3.45 (13), suggesting that the slope of the risk of mesothelioma with time since first exposure may have declined.

Discussion

Although radiographic abnormality was fairly common in all groups, there was no radiographic sign included in the ILO classification that significantly affected the risk of mesothelioma after adjustment for exposure variables. Asbestosis (as measured by ILO category 1/0 or more) had no effect and is therefore not a marker for the development of malignant mesothelioma after allowing for the effect of exposure variables in this group of subjects exposed to crocidolite. Diffuse or localized pleural thickening also had no effect and was also therefore not a marker for the development of malignant mesothelioma in this group. No other radiological sign included in the ILO classification had any effect on mesothelioma incidence in these subjects.

There is some evidence from this study that the increase in the incidence of mesothelioma with time from first exposure in this cohort of Wittenoom workers is decreasing as the exponent for the effect of time from first exposure on the relative risk of mesothelioma was lower than in previous analyses for earlier data.

The current study has the marked advantage of being able to take exposure levels of subject with benign pleural disease into account in considering their risks of malignant mesothelioma. It demonstrates that, after allowing for exposure variables, there is no additional effect of the presence of benign pleural disease on the occurrence of malignant mesothelioma.

Acknowledgements

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A CASE-CONTROL STUDY OF MULTIPLE MYELOMA AND OCCUPATION

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A number of epidemiologic studies have examined the association between multiple myeloma and employment in particular occupations or industries. Elevated relative risks have been observed for employment in agricultural occupations, painting or paint manufacturing, and wood-related occupations. However, results have been inconsistent across studies and considerable uncertainty remains concerning the role of work-related exposures in the etiology of multiple myeloma (Riedel et al., 1991).

Life-time job histories from a population-based, case-control study were analyzed to investigate the relationship between multiple myeloma and employment in various occupations and industries. Cases were under the age of 80 years, newly diagnosed with multiple myeloma between July 1, 1977, and June 30, 1981, and residents of four geographic areas (King and Pierce counties in Washington state; Davis, Salt Lake, Utah, and Weber counties in Utah; five counties of metropolitan Atlanta; and the three metropolitan Detroit counties) were identified using population-based tumor registries. Controls were selected to be similar in age and sex to the cases, but otherwise representative of the population in the regions. In three of the regions, random digit dialing methods were used while in the fourth, Washington state, a geographical sampling technique was used. Data on cases and controls were collected as part of a collaborative study of risk factors for multiple myeloma and chronic lymphocytic leukemia (Koepsell et al., 1987). Interviews were obtained from

89% (692) of eligible incident cases and 83% (1683) of eligible controls. Mantel-Haenszel odds ratios were calculated with adjustment for sex, age, race, and study area.

The results are presented for three groups of a priori interest: agricultural workers, painters, and woodworkers. Table 1 presents the results of analyses by duration of employment (less than 10 years or greater than or equal to 10 years). An excess risk of multiple myeloma was observed among construction and maintenance painters and those employed in manufacturing for 10 or more years. An excess risk was associated with employment for over 10 years as a farm worker while a smaller excess was observed for farmers. While an excess risk was observed among persons employed in forestry and logging occupations, no excess was apparent among carpenters and persons employed in lumber and wood products manufacturing. Further adjustment for socioeconomic status (using education as a surrogate) or restricting the analyses to self-respondents did not substantially alter the results.

In an earlier analysis of data from this study, Morris et al. (1986) found increased risks associated with self-reported "high" exposure (either at home or at work) to paints and/or solvents (OR=1.6, 95% CI=1.1-2.4) and pesticides (OR=2.6, 95% CI=1.5-4.6). In order to determine if the excess risks observed among painters and persons employed in agricultural production were due to these exposures, data from the work history and self-reported exposure portions of the interview were combined. Painters who reported exposure to solvents appeared to have a higher risk of multiple myeloma than those who did not (Table 2). The relative risk for multiple myeloma was much higher among agricultural workers who reported that they had been highly exposed to pesticides than for those who did not (Table 3). The analyses in these two tables were restricted to self-respondents because of concern that surrogate respondents may not recall exposures.

The results of these analyses provide support for some of the associations observed by previous investigators. However, there are limitations which should be considered when reviewing these results. Occupation may be a poor surrogate for exposures that could influence the risk of multiple myeloma and, to the extent that occupational and industrial categories combined jobs with

heterogeneous exposures, misclassification was introduced. It seems likely that such misclassification would be non-differential with regard to case/control status, and thus would serve to minimize apparent case-control differences and bias the observed relative risks towards the null value. The potential for recall bias to have influenced the results should also be considered. Although it seems unlikely that cases would selectively recall employment in any one job or group of occupations, cases may be more likely to remember jobs held for shorter periods of time or farther in the past. The number and length of jobs reported by self-respondent cases was quite similar to that of control subjects, while surrogate respondents for the deceased cases provided a less detailed work history.

The full results of this study have been published in the American Journal of Industrial Medicine (Demers et al., 1993).

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Table 1. The relative risk of multiple myeloma by duration of employment

Occupation/Industry Group	Cases	Controls	OR (95% CI)
Farmers			
Employed <10 Years	7	17	1.1 (0.5-3.9)
Employed 10+ Years	19	38	1.3 (0.8-2.8)
Farm Laborers			
Employed <10 Years	21	46	1.2 (0.7-2.5)
Employed 10+ Years	18	25	1.8 (1.0-4.0)
Forestry & Logging Occupations			
Employed <10 Years	10	6	3.4 (1.3-17.0)
Employed 10+ Years	0	1	0.0 (0.0-29.3)
Carpenters			
Employed <10 Years	7	18	0.8 (0.3-2.4)
Employed 10+ Years	10	18	1.1 (0.5-3.5)
Lumber & Wood Product Manufacturing			
Employed <10 Years	21	32	1.3 (0.7-2.7)
Employed 10+ Years	4	11	0.6 (0.1-1.9)
Construction & Maintenance Painters			
Employed <10 Years	11	16	1.9 (0.8-4.5)
Employed 10+ Years	11	8	3.7 (1.3-11.0)
Painters of Manufactured Articles			
Employed <10 Years	5	14	0.8 (0.2-2.8)
Employed 10+ Years	5	3	4.8 (1.1-28.8)

Table 2. The relative risk of multiple myeloma associated with employment as a painter and self-reported exposures to paint or solvents

Ever Employed as a Painter	Reported Exposure to Paints or Solvents	Cases	Controls	OR	(95% CI)
No	No	427	592	1.0	(Reference)
No	Yes	23	60	1.6	(1.0-3.2)
Yes	No	8	19	1.9	(0.6-5.5)
Yes	Yes	14	21	3.1	(1.5-7.5)

Table 3. The relative risk of multiple myeloma associated with employment in agricultural production and self-reported exposures to pesticides

Ever Employed in Agriculture	Reported High Exposure to Pesticides	Cases	Controls	OR	(95% CI)
No	No	402	1494	1.0	(Reference)
No	Yes	13	19	2.1	(0.9-5.6)
Yes	No	49	163	1.4	(1.0-2.3)
Yes	Yes	8	7	7.9	(2.4-46.1)

OCCUPATIONAL PHYSICAL ACTIVITY, SOCIO-ECONOMIC STATUS AND RISKS OF FIFTEEN CANCER SITES IN TURKEY

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A multiple-site case-control study of fifteen cancers (stomach, colon, rectum, larynx, lung, melanoma, skin, female breast, male breast, cervix, ovary, uterus, prostate, testis, and bladder) was conducted to evaluate their association with occupational physical activity and socioeconomic status (SES). A hospital-based study population (3,486 male cases and 379 female cases and 2,127 male and 244 female controls) was established in an oncological treatment center in Istanbul, Turkey, from 1979-1984. Assessment of physical activity and socio-economic status (SES) was based on job titles held by the study subjects. Two measures of physical activity were developed, based on energy expenditure (EE) and standing time (ST) during working hours. Sedentary activity was defined as work with an EE of less than 8kJ/min, such as sitting with only hand work or light two arm work (e.g., office work). Moderate activity was defined as work with an EE of 8-12 kJ/min, such as heavy one arm or moderate two arm work (e.g., sweeping). High activity was defined as work with an EE of more than 12 kJ/min such as heavy two arm work or heavy body work (e.g., wall painting). Three ST scales were defined as sedentary (work requiring sitting more than 6 hours a day), moderate activity (sitting 2-6 hours), high activity (sitting less than 2 hours a day). A SES level (low, medium or high) was assigned for each occupation considering its income and training level. Observed risks were adjusted for age and smoking. Lower SES was significantly associated with excess risks of cancers of the larynx and cervix, while cancers of the prostate and female breast showed significant decreasing risk with decreasing SES. For the EE index, elevated risks were observed among workers who had sedentary jobs for cancers of the colon (OR = 1.6), rectum (OR = 1.3), melanoma (OR = 1.9), male breast (OR = 1.4), prostate (OR

= 5.0) and ovary (OR = 2.0). Cancers of the colon and prostate showed significant increasing trend with decreased activity. Cervical cancer showed significantly decreasing risk with decreased activity (OR = 0.7 and OR = 0.3 for less active and sedentary jobs with p for trend = 0.004). Similar findings were observed for the ST index. Risks of cancers of the colon, rectum, larynx, ovary, and melanoma were enhanced after risks for physical activity indices were adjusted for SES, while the associations between physical activity and cancers of the prostate, cervix, and uterus was weakened after SES adjustment. The results of this study support previously reported associations between physical activity and cancers of the colon and rectum observed in developed countries, and provide new and additional evidence for cancers of the larynx, prostate, cervix, uterus, and melanoma and point out the importance of SES in evaluation of physical activity and cancers of the colon, rectum, larynx, prostate, breast, cervix, and melanoma in developing countries.

MORTALITY AND CANCER INCIDENCE IN A COHORT OF CHIMNEY SWEEPS: AN EXTENDED FOLLOW-UP STUDY

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Despite 200 years of efforts to regulate safety in this occupation, chimney sweeps have increased mortality from cancer, ischemic heart disease, and respiratory disease. We examined mortality and cancer incidence in a cohort of 5542 Swedish chimney sweeps employed through their national trade union at any time between 1918 and 1980. Previous studies of this cohort found increased risks of ischemic heart disease, respiratory disease, accidental deaths, and a variety of neoplasms. By lengthening follow-up, we sought to strengthen previous associations and examine disease time trends. Mortality analysis was extended 7.5 years to cover the period 1952-1990; cancer incidence analysis was extended 6 years to cover the period 1958-1987.

New findings include increased prostate cancer incidence and mortality (SMR 169, 95% C.I. 106-256, 22 observed) and increased incidence of total hematopoietic cancers (SIR 151, 106-209 36 observed).

When we analyzed only the most recent follow-up period, previously observed risks persisted for total lung cancer (SIR 178, 99-293), oat cell lung cancer (SIR 240, 103-472), bladder cancer (SIR 247, 131-422), and esophageal cancer (O/E=2/1.1) Mortality from ischemic heart disease (SMR 98, 76-123) and respiratory disease (SMR 111, 56-199) declined during recent follow-up, though significant excess mortality remained during analysis of the entire study period (ischemic heart disease SMR 128,112-145; respiratory disease SMR 159, 115-213).

In analyses of the entire study period, risks of ischemic heart disease and lung, bladder, and esophageal cancer were adjusted for smoking;

esophageal cancer was also adjusted for alcohol use. All risks remained significantly elevated. Exposure-response analyses revealed significant positive associations between employment duration and risks for lung, esophageal, and total cancer mortality.

Chimney sweeps remain at increased risk for cancers of the lung, esophagus, and bladder. Our study supports a causal role for exposure to chimney soot, which contains carcinogens including PAHs. Extended follow-up of this cohort now demonstrates increased risks of prostate and hematopoietic cancers. The association of these cancers with combustion product exposure deserves further investigation.

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CANCER MORTALITY AMONG URBAN POLICEMEN IN ROME

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Introduction

The potential carcinogenicity of engine exhaust has not been definitely established; exhaust from diesel and gasoline engines has been evaluated as probably and possibly carcinogenic to humans, respectively (IARC, 1989). Lung cancer has been found in excess in several studies of workers occupationally exposed to diesel (Steenland et al., 1992), but the evidence available for exposure to gasoline exhaust is scanty. Also excesses of bladder cancer, kidney cancer and lympho-hematopoietic cancer (multiple myeloma, chronic lymphatic leukaemia and non-Hodgkin's lymphoma) have been suggested to be related to engine exhaust exposure (IARC, 1989).

Urban policemen are exposed to engine exhausts during traffic control, but the health effects related to their occupation have not fully evaluated. To our knowledge, only one study has specifically considered police officers (Vena et al., 1986). In two other investigations (Feuer and Rosenman, 1986; Demers et al., 1992), policemen were considered as a control group when evaluating mortality among firefighters.

We investigated the mortality pattern of urban policemen in Rome through a historical cohort study to elucidate further the increased risk, if any, of cancer in this group. Nested case-control studies were performed to examine mortality differences by job categories.

Methods

Male subjects who were employed at 31 December 1972 by the Local Council of Rome as urban policemen, or who were subsequently hired through 1975, with at least one year of

employment, were enrolled in a cohort. For each subject vital status as of 18 July 1991 was ascertained either through the employment records or through the Registry Office of the last municipality of residence. The I.C.D. code of the underlying cause of death was retrieved through record-linkage with national or regional mortality files (Lagorio et al., 1987). The regional population data were used to obtain the number of expected deaths and to calculate Standardized Mortality Ratios (SMRs).

Nested case-control studies were conducted to evaluate mortality risk by job-categories; subjects employed in jobs with a higher exposure to engine exhaust (traffic guards, car drivers and motorcyclists) were examined in comparison to those employed in jobs with less likely engine exhaust exposure (clerical work). Cases were defined as those cohort members who died from lung, bladder, kidney and lympho-hematopoietic cancer according to the underlying cause of death stated on their death certificate. In the choice of the controls, the case-controls ratio was 1:5 for lung cancer and 1:20 for bladder, kidney and lympho-hematopoietic cancer. The controls were selected from among the cohort members who survived to the age at which the case died. Controls were matched to each case on year of birth ($\pm$ 2), year of hire ($\pm$ 2) and year of termination of employment ($\pm$2). The entire work history of cases and controls were blindly retrieved from the employment records. For lung cancer cases and their matched controls, information on lifetime smoking habit was ascertained through either telephone interview or a mailed questionnaire. Responses were provided by next-of-kin of the cases and of deceased controls or directly by living controls.

Results

A total of 3,868 male subjects were enrolled and 557 were found deceased. A lower than expected overall mortality was observed (SMR=0.87). There were a lower occurrence of circulatory (SMR=0.81), respiratory (SMR=0.49), digestive (SMR=0.67) and genito-urinary diseases (SMR=0.37). Accidents were also extremely low (SMR=0.37). The number of observed deaths for all neoplasms was about as expected (SMR=1.02). No excess was found for lung cancer (82 deaths, SMR=1.05, 95%CI=0.84-1.31). Increased mortality was found for colon cancer (16 deaths, SMR=1.47), melanoma (4 deaths, SMR=2.34), bladder cancer (13 deaths, SMR=1.27), kidney cancer (7 deaths, SMR=1.39) and non-

Hodgkin's lymphoma (6 deaths, SMR=1.51), although none of the excesses was statistically significant. Noteworthy, two male breast cancer cases (SMR=14.36, 95%CI=1.73-52) and three deaths from cancer of endocrine glands (two cases of thyroid cancer and one death from cancer of adrenal glands) (SMR=3.44, 95%CI=0.71-10.1) were found.

No clear trend in the SMRs was evident for all cancers combined and for lung cancer when duration of employment and latency since first employment were analyzed. Among subjects with 20-29 years of employment duration, significant increased risks of colon cancer (SMR=2.32, 95%CI=1.32-3.76), breast cancer (SMR=21.8, 95%CI=2.64-78.8) and cancer of endocrine glands (SMR=5.88, 95%CI=1.21-17.2) were found; non-significantly high SMRs were observed also for melanoma, kidney cancer and non-Hodgkin's lymphoma. Bladder cancer was higher than expected in the category of longest period of employment (SMR=1.88) and with 30+ years of latency since first exposure (SMR=1.58).

The nested case-control study on lung cancer encompassed 81 cases and 405 controls; no association was found between lung cancer and various jobs, nor were the odds ratios increased with duration of employment in a particular job. Bladder cancer (12 cases and 256 controls) was significantly increased among car drivers (OR=4.17, 95%CI=2.93-51.3), especially among those with 10 or more years of exposure (OR=12.2). In the case of kidney cancer (7 cases and 126 controls), a non-significantly increased odds ratio (OR= 2.27) was found among motorcyclists; the risk was higher when considering those with 10 or more years of employment as motorcyclist (OR=7.15, 95%CI=0.67-75.7). Non-Hodgkin's lymphoma (6 cases, 88 controls) clearly clustered among motorcyclists (4 cases, OR=5.14, 95%CI= 0.84-31.2).

Discussion

The working population studied here is extremely select at first employment with regard to health status--and this is reflected in the low SMRs for several causes of deaths. We did not observe an excess for lung cancer in the total cohort and no variation in lung cancer risk was found among different jobs. The results are in contrast with findings from other occupational groups exposed to engine exhaust, mainly from diesel vehicles such as truck drivers

(Boffetta, 1988; Hayes et al. 1989; Steenland et al., 1990; Rafnsson and Gunnarsdottir, 1991; Guberan et al., 1992; Steenland et al., 1992). However, several studies on other working categories, mainly exposed to exhaust from gasoline fuelled vehicles, such as taxi drivers (Balarajan and McDowall, 1988; Koh et al., 1988; Rafnsson and Gunnarsdottir, 1991) and bus drivers (Paradis et al., 1989; Netterstrom, 1988; Michaels and Zoloth, 1991), did not reveal an increased risk for lung cancer. As a limitation of this study, past exposure measurements were not available and job category might have been a poor approximation of true exposure; it might be suggested that if gasoline engine exhaust has a role on lung cancer, it is difficult to detect and requires a more accurate exposure characterization to be demonstrated.

While the SMR for bladder cancer was only slightly elevated in the overall cohort, the excess was present among those with a longer latency and duration of employment; furthermore, the case-control analysis showed an increased risk for bladder cancer among policemen who were car drivers. These results are in line with other observations on professional drivers in the U.S. (Schoenberg et al., 1984; Silverman et al., 1986) and suggest an etiologic role of the occupational exposure.

The excess risks for renal cancer and non-Hodgkin's lymphoma observed in the entire cohort and the increased odds ratios found among motorcyclist deserve consideration. Exposure to polycyclic aromatic hydrocarbons has been suspected to play a role for kidney cancer (Kadamani et al., 1989); gasoline exposure has been directly linked to kidney cancer in a recent case-control study in Finland (Partanen et al., 1991). Non-Hodgkin's lymphoma has been found in excess among professional drivers in England (Balarajan, 1983; Balarajan and McDowall, 1988) and in Sweden (Linet et al., 1993); there is also some evidence that benzene exposure is associated to this form of cancer (Blair et al., 1993). Occupational exposure to engine exhaust among policemen may be of etiological importance for both renal cancer and non-Hodgkin's lymphoma; those subjects riding motorbikes may be at a higher exposure to vehicle exhaust and, at the same time, they inhale gasoline vapors from the tank of the motorbike itself.

Colon cancer was in excess in this cohort especially among subjects with a longer duration of employment. This result is surprising since lack of physical activity is a known risk factor for colon cancer (Fredriksson et al., 1989) whereas most policemen, especially traffic wardens, cannot be considered sedentary workers. Excess of colon cancer among police officers has been already reported in the U.S.A. (Milham, 1983; Vena et al., 1986). An increased risk of colon cancer among subjects exposed to petroleum products has been described (Brownson et al., 1989) and an elevated SMR has been found among petrol station worker (Gerhardsson de Verdier et al., 1992). A potential role of occupational factors in this cohort could be hypothesized.

The excess risks found for male breast cancer and cancer of endocrine glands are puzzling and chance could be the first explanation; on the other hand, breast and thyroid malignancies are somehow linked since also breast cancer has an hormonal dependency (McTiernan et al., 1987). It may be recalled that workers in the production of chlorophenols and chlorophenoxy herbicides, and thus potentially exposed to dibenzodioxins and furans, did show an excess of both male breast cancer and cancer of endocrine glands (Saracci et al., 1991); dioxin formation in exhausts from car fuelled with leaded gasoline has been detected (Marklund et al., 1987). Since an excess risk for thyroid cancer has been also noted among Buffalo police officers (Vena et al., 1986) and among professional drivers in Sweden (Carstensen et al., 1990), it may be speculated that dioxins in car exhaust may be of some interest.

In conclusion, overall cancer mortality and lung cancer were not increased among urban policemen in Rome; excess risks, however, were found for some cancer sites, particularly colon, breast and endocrine glands. Drivers seem to be at risk of bladder cancer, kidney cancer and non-Hodgkin's lymphoma.

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COLORECTAL CANCER AND PHYSICAL ACTIVITY

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Many studies performed in the 1980s on colon cancer and occupational exposures have shown a negative association between physically active work (PAW) and colon cancer with a decreasing risk from right to left. The situation regarding rectal cancer and PAW is, however, less clear since no effect or an increased effect has been found with regard to rectal cancer.

This study included 99 cases of colon cancer and 78 cases of rectal cancer, diagnosed 1984-86. The referents were residents in the same area as the cases and consisted of two different sets. One set of referents was sampled from the population register, 430 persons, and the other set consisted of patients from the surgery departments in the area, that is, patients with hernia, hemorrhoids, fissures or fistulas, in total 371 persons. All cases and referents were alive.

Exposure information was collected by a questionnaire mailed to the subjects (after treatment of cases and hospital referents). The occupations were assigned to different classes depending on the level of physical activity. The years spent in PAW were then used as the exposure variable (0 years = level 1, 1-20 years = level 2 and > 20 years = level 3).

The results, for level 3 compared with level 1, obtained by stratification on age and sex was no clear preventive effect from PAW for colon cancer at all sites from PAW ($OR=1.0, CI_{90}=0.6$-1.6) but with a strong preventive effect for cancer in the left side of colon ($OR=0.4$, $CI_{90}=0.1$-0.9). For rectal cancer there was an increased risk ($OR=1.7$, $CI_{90}=1.0$-3.0).

When the material was divided according to sex and stratified on age, there was a preventive effect from PAW (OR=0.8, CI_{90}=0.4-1.6) for colon cancer and for rectal cancer there was a risk from PAW (OR=1.6, CI_{90}=0.8-3.2). The results for females were contradictory since there was an increased risk both for colon cancer (OR=1.4, CI_{90}=0.4-4.1) and rectal cancer (OR=1.9, CI_{90}=0.6-5.5). It may be noted that the majority of women in these ages have worked most of their lives as housewives coded as an intermediate between PAW and sedentary work so most women were therefore allocated to level 1 of PAW.

The results of this study are consistent with previous findings for PAW and colon cancer, perhaps with the exception of women alone. They are also consistent with findings in some studies of rectal cancer. This experience suggests that there may be a need for separate analyses for colon and rectal cancer when a study concerns physical activity.

CANCER INCIDENCE IN A COHORT OF SEWAGE WORKERS

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Sewage workers are exposed to a multitude of potentially harmful agents. Several reports have described various pathogenic microorganisms and toxic chemicals. Among the identified chemicals are also known carcinogens. Sewage workers are found to have an increased risk for urinary mutagens. One Swedish case-control study found an increased risk for astrocytoma among people living near waste water processing plants. In a U.S. cohort study presented recently, a slight elevation in total cancer mortality was seen among sewage workers. There was also an elevated mortality in some specific cancers, e.g., larynx, lungs, stomach and kidneys.

We have conducted a retrospective analysis of cancer incidence in a cohort of 656 male sewage workers recruited from 17 municipal sewage plants in Sweden. The inclusion criterion was employment for at least 1 year at one of these plants during the years 1965-1987. Four exposure levels were defined by job classification, where the assumed degree of exposure to waste water and aerosols was the main determinant. The mortality and cancer incidence data for the cohort were collected from national registers. The study period was 1965-1987. In the cohort analysis we used a computer program calculating the person-year of observation matrix, expected values, SMRs and 95% CIs. Exposure-response relations were studied by logistic regression.

In the analysis we found lower than expected total mortality (SMR=0.75, 95% CI 0.58-0.97) and cardiovascular mortality (SMR=0.61, 95% CI 0.39-0.91). This is interpreted as a healthy worker effect. No increase in total cancer incidence was found. The incidences for brain tumors, gastric cancers and renal cancer were

higher than expected. The number of person-years at observation were 9443.

	SMR	95% CI	observed number of cases
All cancer	1.02	0.72-1.38	37
Brain tumor	2.19	0.45-6.39	3
Gastric cancer	2.73	1.00-5.94	6
Renal caner	1.68	0.35-4.90	3

When a 10 year latency period was introduced in the calculations, there were no dramatic changes in the results. The person-years at observation were reduced to 4331. The most notable change was an increase of the SMR for renal cancer (SMR=2.39, 95% CI 0.49-6.99).

In the logistic modelling we found a positive relation for renal cancer to a weighted sum of employment times (p=0.051). The weights were chosen arbitrarily to describe the assumed exposure relations. Age was forced in as a regression variable in the model. The other cancers showed no such relations to either total time of employment or the weighted sum of employment times.

Because the results are based on small numbers of cases, they should be interpreted with caution. However, for renal cancer there is more than just one indication on an overrisk. The elevated SMR increased with the introduction of the latency period in the person-years calculation. In the logistic regression we found an almost significant relation to the weighted sum of employment times, while the fitting of total employment time was less successful. These findings point toward a possible effect of the exposure. The power of this study is still low, which is why a future follow-up with increased person-years at observation is needed. The exposures in waste water work need further study to allow for better exposure-response analysis.

EXCESS CANCER INCIDENCE IN WORKERS EXPOSED TO FLUORIDE

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A recent bioassay has shown an increased frequency of bone cancer in rats with a high oral intake of fluoride, and the data were considered to represent equivocal evidence of carcinogenicity (1). However, few data are available on the possible carcinogenicity of heavy occupational exposures to fluoride.

We have therefore extended our previous follow-up (2) of a cohort of 425 men and an additional group of 97 women employed for at least six months during 1924-1961 at the cryolite processing plant in Copenhagen. Cryolite contains about 50% fluoride. A full report of this study has now been published elsewhere (3).

Fluoride exposures at the cryolite plant were considerable, and many workers developed serious skeletal fluorosis. The average daily fluoride absorption could be estimated to be about 35 mg, i.e., more than ten-fold higher than the daily uptake in communities with water fluoridation.

Mortality was recorded during 1941-1989 and cancer morbidity during 1943-1987. For comparison, we used national mortality rates and cancer incidence rates for the Copenhagen area.

A total of 300 deaths occurred among the men, while only 223 were expected. Cancer and violent death were responsible for most of this excess. However, the cardiovascular mortality was in accordance with the expectation from the rates in Danish men in general.

A total of 119 incident cancer cases occurred in the male workers, as compared to 103.6 cases expected from Copenhagen rates. Excesses were seen in cancer of the lungs (N = 35; standard

incidence ratio [SIR] = 1.35), larynx (N = 5, SIR = 2.29) and urinary bladder (N = 17, SIR = 1.84). A maximum cancer morbidity occurred after 10-19 years of exposure, but the cancer incidence did not show any stable relationship to the length of employment. The incidence of respiratory and urinary cancers was particularly high in men who were less than 35 years old at first employment. Although bladder cancer occurred in two female workers (SIR = 2.18), the number of cases seen in the women were too small to allow any detailed evaluation. Cancer of the bone (E = 0.2) was not observed in any cryolite worker. However, due to the small size of the cohort, a relative risk of up to 18 for this rare cancer form could not be excluded.

The increased rates of respiratory cancer could probably be attributed to cigarette smoking, although a partial adjustment for smoking was achieved by using Copenhagen rates for comparison. However, the cardiovascular mortality was not increased in the cohort and would even be slightly below expected numbers for Copenhagen males. More importantly, the disproportionate increase in the incidence rate for bladder cancer is difficult to explain by smoking habits alone. Thus, tobacco smoking would be likely to cause a three-fold higher relative excess in lung cancer than in bladder cancer (4). The pattern in the cryolite workers is almost the opposite, i.e., the excess in bladder being almost three-fold higher than the excess in lung cancer.

The evidence for genotoxicity of fluoride is limited (1), and whether or not bladder cancer is a plausible effect of fluoride exposure is difficult to determine at present. About half of the fluoride absorbed is rapidly excreted into the urine and will therefore reach the epithelium of the urinary bladder shortly after the exposure. Fluoride is mostly stored in bone and will be released only slowly and excreted. With regard to bone cancer, the absence of this rare cancer in a small cohort is not surprising. Further, in rats that showed increased risk of bone cancer in the bioassay (1), continued ossification would occur beyond the first year of life, i.e., for about half of the exposure period (5). In contrast, ossification would have been completed in the cryolite workers at the beginning of their employment.

As the cryolite workers were exposed to high concentrations of fluoride dust and no other suspected carcinogen during their employment, heavy respiratory exposure to fluoride could have contributed to the increased cancer risk observed. The potential role of fluoride in the causation of bladder cancer therefore needs to be explored.

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MORTALITY OF URBAN FIREFIGHTERS IN ALBERTA, 1927 - 1987

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The mortality experience of firefighters has been an active topic of investigation. Collateral toxicological evidence suggests that certain causes of death are likely to be associated with firefighting: lung cancer, heart disease, and obstructive pulmonary disease. To date there has not been a clear and consistent demonstration of excess risk due to occupational exposure for these outcomes, but certain uncommon cancers, including genitourinary, colon and rectum, and leukemias, lymphomas and myeloma, appear to be consistently elevated. A major unproven hypothesis is that risk increased following the introduction in the 1950's of combustible plastic furnishing and building materials known to generate toxic combustion products.

Mortality by cause of death was examined for two cohorts totalling 3,328 firefighters active from 1927 to 1987 in Edmonton and Calgary, the two major urban centers in the province of Alberta, Canada, examining associations with cohort (before and after the 1950's) and years of service weighted by exposure opportunity. The study attained 96% follow-up of vital status and over 64,983 person-years of observation yielding 370 deaths.

A fundamental problem in studies of chronic disease among firefighters is assessing presumed exposure to fire smoke and combustion products. In order to assess the fit of mortality trends to a presumed exposure profile more refined than simply years of service, we repeated the analysis using a weighted employment history. Each year of a firefighter's service was weighted by an exposure opportunity index term reflecting estimates of relative time spent in close proximity to fires by each job classification. These estimates were derived from interviews with active firefighters in Edmonton and reflect their collective judgement. There was

substantial agreement on scaling the relative weights. We could not empirically validate this scaling, but because the number of positions associated with intermediate exposure (weighted 0.2 or 0.1) is much smaller than those in the extremes (1.0 or 0.0), and because chiefs and volunteers are known to go to only a small subset of fires, the scaling is likely to be very robust and insensitive to inaccuracies in middle-weightings.

Table 1 presents the mortality experience of the firefighters, both as combined populations and by city. There are few major differences between the mortality experiences observed in the two cities; most of these involve malignant neoplasms. Mortality by cause of death is discussed below. Overall, mortality was close to that expected for the general male population (SMR = 96.2).

Examined by cause of death, without reference to prior hypotheses, significant or suggestive excesses in mortality were observed for malignant neoplasms (SMR = 127, $p<0.05$), including colon and rectum (SMR = 161, N.S.), pancreas (SMR = 155, N.S.), lung (SMR = 142, N.S.), bladder (SMR = 316, N.S.), kidney and ureter (SMR = 414, $p<0.01$), and leukemias, lymphomas, and myeloma (SMR = 127, N.S.). The risk of death from malignant neoplasms overall was not consistently elevated after the 1950's compared to the 1940's and before.

Of these sites, only lung (ICD 162) was specified in an a priori hypothesis and detailed evaluation of lung cancer was an objective of the study. The peak latency for all exposure groups was <20 years, as it was for those with exposure indices of 0. For groups with increasing exposure opportunity, however, the peak latency appeared to shift progressively to later latency intervals, although none achieved statistical significance given the small numbers involved. The excess mortality in recent years began among workers who began their employment in the decade 1940-49 (7 observed, SMR = 155, N.S.) and persisted above 100 in subsequent decades with great instability because of small numbers of observed and expected cases. In no individual decade did the elevation achieve statistical significance at the 95% level, nor did the excess achieve statistical significance over the period as a whole. Following the 1940's, the risk did appear to increase in magnitude but the largest SMRs were observed in years with single cases. Although the decade-specific

SMRs increased after the 1980's, they were not significantly different statistically from the experience in the 1940's. Many more cases were observed in Edmonton (17) than in Calgary (7); the power for identifying an excess in Calgary alone is <40%, however. The rate in Edmonton alone did achieve statistical significance (SMR 187.3; 95% confidence limits 109.1, 299.9). As expected, lung cancer cases did not appear until the age group 30-34 and did not peak until after age 75, but in no age group did an excess, where present, achieve statistical significance. The youngest lung cancer case was 34 years old at the time of his death and had experienced 6.5 years of exposure beginning in 1980. There were no other cases under the age of 40. Analysis by latency period showed a peak risk at or over 50 years after entry into the workforce (3 cases, SMR 174.6; 36.0, 510.4). Analysis by duration of employment showed a peak risk (SMR 283; 2 cases, N.S.) among firefighters employed for less than 1 year (entirely due to cases from Edmonton) and a generally declining risk thereafter until 40+ (SMR 202; 2 cases, N.S.). Application of the exposure opportunity index demonstrated that the risk was greatest in less heavily exposed firefighters and in workers with no firefighting experience (again due to the cases in Edmonton) until 35+ weighted years; the large excess in that category is almost entirely due to a marked excess in that group in Edmonton, consisting of three cases (SMR 1711; 353, 5000, $p<0.0001$).

Colon and rectal cancers (ICD 152-154) peaked at age 40-44 with 3 individual cases (0.43 expected, SMR 697.6, $p<0.05$) but showed no clear correlation with entry cohort although deaths from this cause remained elevated, without achieving statistical significance, in each decade except the 1920's and 1970's. The latency analysis suggested a peak after 20-29 years among the exposed groups, significantly for those with an exposure index of 1 to 9 (SMR 1146.3, $p<0.01$).

Pancreatic cancer (ICD 157) was not observed before age 60 and peaked after age 80 with two individual cases (0.13 expected, SMR 1444, N.S.). None appeared in members of cohorts entering after 1949. The peak risk (3 cases, SMR 716, $p<0.01$) came more than 50 years after entry into the workforce.

Bladder cancer (ICD 188), on the other hand, did not appear among firefighters prior to age 60, showing a peak latency of 40 years, but was significantly elevated ($p<0.05$) in age groups 60-64 (2 cases;

0.20 expected), 70-74 (1; 0.14), and 75-79 (1; 0.18); the cases did not concentrate in any particular decade and appeared in men entering before 1950. The peak risk (3 cases, SMR 1392.8; 287.4, 4070.3, $p<0.01$) was observed 40-49 years after entry. Bladder cancer was not observed in firefighters with less than 20 years of service or 25 weighted years of service but increased in frequency and magnitude of risk thereafter, although never achieving statistical significance.

Kidney and ureter cancers (ICD 189) did not appear in firefighters below the age of 40 but occurred in age groups 40-44 (1 observed; 0.10 expected), 50-54 (1; 0.26), 55-59 (1; 0.38), 65-69 (3; 0.17, $p<0.01$), and above 70 (1; 0.26). All cases were seen in men entering the fire service before 1915 or after 1950: 2 in 1950-59 (0.60 expected) and 1 in 1960-69 (0.19 expected). There was a similar excess observed in both cities. Although the earliest case appeared 18 years after entry, the peak risk was observed 40-49 years after entry, as for bladder (4 cases, SMR 2129.4; 580.3, 5452.4; $p<0.01$). The frequency appeared to increase with increasing duration of employment and exposure opportunity although one case was observed in a worker without firefighting experience. The highest risk of all was observed in firefighters with more than 35 weighted years (SMR 3542, $p<0.01$) and in the highest exposure opportunity category in the latency analysis (≥ 10 weighted years) at 40-49 years of latency (SMR 2654.2, $p<0.01$).

Leukemias, lymphomas, and myeloma (ICD 200-208) did not concentrate in any age group, latency period, or entry cohort. Stomach cancer (ICD 151) was significantly elevated in the age group 70-74 in Edmonton (3 cases, SMR 718.0; 148.2, 2098.3, $p<0.01$).

There were few statistically significant elevations among nonmalignant causes of death but several were elevated without achieving significance. Two nonmalignant causes of death were considered of interest a priori, heart disease and chronic lung diseases. In both cases, application of the exposure opportunity index did not appreciably change the interpretation because the risk showed no relationship with duration or duration and intensity of exposure.

The three cardinal causes of death suspected of an association with exposures encountered during firefighting activity are lung cancer, ischemic heart disease, and chronic obstructive pulmonary disease. We find no strong evidence for an association with any of these outcomes in our population; the findings for lung cancer are not inconsistent with a weak effect, however. On the other hand, there is a strong suggestion of an excess from genitourinary cancers in this population of firefighters.

Of greatest interest among the positive findings in this study is the excess of cancer for bladder, kidney and ureter. This combination suggests the possible influence of an excreted, urine-borne carcinogenic activity compatible with inhaled constituents of smoke, particularly polycyclic aromatic hydrocarbons. The timing of the excess of kidney and ureter cancer, especially, are suggestive of a cohort effect and a concentration of the risk among those sustaining the heaviest exposure and surviving to the longest latency periods observed. This observation is consistent with findings in other recent studies and suggests a risk additional to that of cigarette smoking.

Table 1. Summary of mortality experience of Alberta municipal firefighters (ICD-9 codes) (cont. next page)

Cause of Death	Observed		Both Cities		Confidence Intervals, 95%	
	Calgary	Edmonton	Expected[a]	SMR	Lower	Upper
All causes (001-999)	188	182	384.7	96.2	86.6	106.5
Infectious, parasitic disorders (001-139)	1	1	6.0	33.3	4.0	120.2
Malignant neoplasms (140-208)	40	52	72.7	126.6*	102.0	155.2
oral (140-149)	0	2	1.8	113.6	13.7	410.4
stomach (151)	3	3	7.4	80.9	29.7	176.0
colon and rectum (152-154)	9	5	8.7	161.4	88.3	270.9
pancreas (157)	3	2	3.22	155.1	50.4	362.0
lung (162)	7	17	16.9	142.0	91.0	211.4
skin (172)	0	0	1.1	0.0	0.0	331.2
prostate (185)	2	6	5.5	146.1	63.1	287.9
bladder (188)	1	3	1.3	315.7	86.0	808.3
kidney and ureter (189)	3	4	1.7	414.0*	166.4	853.1
brain (191)	3	0	2.1	146.6	30.3	428.5
leukemia, lymphoma, myeloma (200-208)	6	4	7.9	126.5	60.6	232.5
Endocrine disorders (240-279)	2	1	6.4	46.9	9.7	137.0
Blood disorders (280-289)	1	1	1.7	102.3	12.4	369.5
Mental disorders(290-319)	13	6	4.2	455.4*	274.2	711.1
Nervous system disorders (320-389)	2	2	5.4	73.5	20.0	188.3
Circulatory disorders (390-459)	79	78	152.3	103.1	87.6	120.6
heart (b)	66	64	117.8	110.4	92.2	131.1
ischemia heart (410-414)	53	56	102.9	105.9	86.9	127.7
cerebrovascular (430-438)	6	3	23.3	38.6*	17.7	73.3

Table 1. (cont.) Summary of mortality experience of Alberta Municipal Firefighters (ICD-9 codes)

Cause of Death	Observed		Both Cities		Confidence Intervals, 95%	
	Calgary	Edmonton	Expected	SMR	Lower	Upper
arteriosclerosis (440-448)	4	8	8.0	149.7	77.3	261.5
Respiratory disorders (460-519)	11	10	22.1	94.9	58.8	145.1
COPD(c) (490-496)	5	6	7.0	157.3	78.5	281.4
Digestive system disorders (520-579)	6	3	19.2	46.9*	21.4	89.0
Genitourinary system disorders (580-629)	4	4	6.1	132.0	57.0	260.1
External causes (800-999)	28	21	74.7	65.6*	48.5	86.7
motor vehicle (810-825)	10	6	23.7	67.5	38.6	109.6
accidental falls (880-888)	2	1	5.25	57.1	11.8	166.9
fire-related (890-899)	7	3	2.1	486.4**	233.2	894.5
suicide (950-959)	3	4	18.2	38.5*	15.5	79.2
homicide (960-969)	0	0	2.3	0.0	0.0	162.0
Other and unknown (d)	1	3	12.8	31.2*	8.5	80.0

* $p < 0.05$ **$p < 0.01$

a To estimate the expected mortality for either city, take half of the expected figure for both.

b (390-398, 402, 404, 410-416, 420-429)

c Chronic obstructive pulmonary diseases includes emphysema, asthma, and chronic bronchitis.

d (209-239, 630-739, 780-799)

CANCER INCIDENCE IN THE POLYURETHANE FOAMING INDUSTRY

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Introduction

The annual world production of aromatic isocyanates as toluene diisocyanate (TDI) and methylene diphenyldiisocyanate (MDI) has rapidly increased during the last decades and had reached the figure of 1 million tonnes each (1). The main use of these compounds is in the polyurethane foam manufacturing industry.

Both TDI and MDI are mutagenic in bacterial test systems (2,3). Oral administration of TDI caused increased incidence of tumors among male and female rats and female mice (4). TDI has been classified as carcinogenic in animals and a potential occupational carcinogen (3,5). No data have been published on the testing of MDI for carcinogenicity.

TDI and MDI are converted to aromatic amines on contact with water and 2,4-TDA and 2,6-TDA has been detected in urine and plasma from subjects experimentally exposed to TDI (6) as well as from employees in the polyurethane foam industry. 4,4-MDA has been detected in blood and urine from welders exposed to pyrolysed MDI-based polyurethane (unpublished results). The carcinogenic effect of aromatic isocyanates may be due to endogenous formation of these aromatic amines. Both 2,4-toluenediamine (2,4-TDA) and 4,4-methylenedianilin (4,4-MDA) are established animal carcinogens (5).

No epidemiological study on cancer risks for humans occupationally exposed to isocyanates has previously been published. The aim of the present study was to investigate the cancer risk among employees in the Swedish polyurethane foam manufacturing industry exposed to TDI and MDI.

Subjects and Methods

Altogether 4,154 workers employed for at least 1 year were identified from the company records of nine Swedish polyurethane foam manufacturing plants in which TDI or MDI had been used. Information on work place or job task was available for all of these subjects except for 139. None was lost to follow-up.

Three of the plants have produced flexible foam blocks (block-foaming) mainly for the furniture industry, while the remaining six plants have manufactured dead cast moulding materials mainly for the car industry. The start of the polyurethane foam manufacturing has varied from 1958 to 1974 for the different plants.

Airborne exposure to isocyanates has been measured on 6 to 18 occasions at each plant. Sampling has been performed on totally 7-24 days (Table 1). The first measurement was performed in 1965. The time weighted average levels of TDI have normally been below 100 $\mu g/m^3$ and are presently below 20 $\mu g/m^3$. The corresponding values for MDI have been < 10 $\mu g/m^3$. However, much higher values (TDI: up to 3 mg/m^3; MDI: up to 0.35 mg/m^3) have repeatedly been measured. In addition, there are reports of numerous occasions of accidental exposures to isocyanates due to spills and leakages.

The chemical exposure has, however, not been restricted to isocyantes but also includes expanding agents, mould lubricants, amine accelerators, organic solvents. These other chemicals have, however, been monitored very sparsely.

Each work-place in each of the nine plants was categorically assessed for each calendar-year, by an experienced occupational hygienist, with respect to "no exposure," "low or intermittent exposure," or "apparent exposure" to TDI or MDI. The classification "apparent exposure" denotes direct exposure at the foaming or moulding processes or work in the same premises. The classification "low or intermittent expósure" denotes, for instance, handling of cured materials in premises situated close by those used for foaming or moulding, or only intermittent exposures. The average length of employment in the cohort was 6.5 years, the average first year of exposure was 1976, and the average length of follow up was 10.6 years.

Information on tumors (coded according to the ICD, 7th revision) diagnosed from 1959 to 1987, and the yearly incidence rates for cancer during the same period was obtained from the National Swedish Tumour Register. Cause-specific standardized incidence ratios (SIRs) and 95% confidence intervals (CI) were calculated according to the Poisson distribution, or to the X^2 distribution if the expected values were greater than 10. Significance was indicated when the 95% CI for SIR did not include a value of 1. All tests used were two-tailed.

Results

Site-specific cancer incidence is shown in Table 1. There was an almost statistically significant deficit for all malignant neoplasms. Slight, and not significant, excesses were found for rectal cancer and non Hodgkin's lymphoma (NHL).

Table 1. Cancer incidence 1958-1987 in 4,154 subjects employed for at least 1 year

Tumor site	ICD-7	O	E	SIR	95% CI
Colon	153	4	5.6	0.71	0.19-1.83
Rectum	154	6	3.6	1.66	0.61-3.61
Lung	162-164	4	7.9	0.51	0.14-1.30
Prostate	177	7	8.8	0.80	0.32-1.65
Urinary bladder, ureter	181	4	4.5	0.89	0.24-2.28
Lymphomas, myelomas	200-203	6	4.7	1.27	0.47-2.76
NHL	200,202	4	2.6	1.53	0.42-3.91
Leukemia	204,207	3	2.4	1.27	0.26-3.70

All	140-209	72	89.4	0.81	0.63-1.02

(O = observed number of cases, E = expected number of cases, SIR = standardized incidence ratio, 95% CI = 95% confidence interval).

Applying at least a 10-year induction-latency period, SIR for rectal cancer as 1.92 as compared with 1.30 during the first 10 years since start of exposure (Table 2). This discrepancy was even more obvious for lymphomas and myelomas. All six incident cases were diagnosed 11-21 years since start of exposure. The SIR for NHL when the first 10 years since first exposure were excluded from the observation period, was 2.80. In contrast, years since first exposure did not affect the incidence of all malignant neoplasms or, e.g., lung cancer incidence.

Table 2. Cancer incidence by time since first exposure

		Years since first exposure					
		1-10			> 10		
Tumor site	ICD-7	O	SIR	95% CI	O	SIR	95% CI
Rectum	154	2	1.30	0.16-4.70	4	1.92	0.52-4.92
Lung	162-164	2	0.60	0.07-2.17	2	0.44	0.05-1.58
Lymphomas	200-203	0	0.00	0.00-1.59	6	2.49	0.91-5.42
NHL	200,202	0	0.00	0.00-3.10	4	2.80	0.76-7.16

All	140-209	32	0.78	0.54-1.12	40	0.82	0.59-1.13

When the observation periods were separated with regard to exposure level to TDI or MDI, this hardly affected the SIRs for all malignant neoplasms (Table 3). In contrast, the SIR for rectal cancer, associated with "no exposure" exposure level was 0.70, but 2.73 (95% CI 0.89-6.38) associated with "apparent exposure." A much weaker tendency in the same direction was seen for non Hodgkin's lymphoma. When a minimum latency period of 10 years for job tasks with "apparent exposure" to TDI/MDI was applied, the SIRs increased further for both rectal cancer (3.19, 95% CI 0.66-9.33), and non Hodgkin's lymphoma (3.03, 95% CI 0.37-10.9). These estimates were however based on very few incident cases.

Table 3. Cancer incidence by exposure to TDI or MDI in the work-places

		Exposure to TDI or MDI in the work-place					
		No exposure			Apparent exposure		
Tumor site	ICD-7	O	SIR	95% CI	O	SIR	95% CI
Rectum	154	1	0.70	0.02-3.90	5	2.73	0.89-6.38
Lung	162-164	3	0.98	0.20-2.86	0	0.00	0.00-0.92
NHL	200,202	1	1.01	0.03-5.63	2	1.45	0.18-5.24

All	140-209	29	0.79	0.54-1.14	39	0.85	0.61-1.17

Discussion

The main result of the study was the non-significant risk excess for rectal cancer and non Hodgkin's lymphoma, which increased with a 10-year induction-latency period as "apparent exposure" for TDI and MDI.

As TDI had been used in all plants and MDI in all but one, it was impossible to separately evaluate their possible effects. The exposure levels for TDI and MDI have varied considerably both between

different work-places in the plants and within them. The information derived from the company records on the work place and job tasks for the subject in the cohort, has not always been very specific. This has probably caused misclassification of exposure. The quality of these exposure data have not been affected by the health outcome for the subjects in the cohort. Thus, the misclassification of exposure has been non-differential, which will decrease the precision but not affect the validity of the study. As a meansA of minimizing the exposure misclassification, a case-referent study within the cohort is now performed, allowing a more detailed and precise exposure assessment.

The manufacturing of polyurethane foam has caused exposure not only to isocyanates but also to other chemicals. Regrettably, these other chemicals have been monitored very sparsely. The chemicals used have varied between the plants. This can be illustrated by the amine accelerator MOCA, which is carcinogenic to animals (7), but has only been used in one of the plants. The exposure to isocyanates is thus the only common chemical characteristic of the plants.

The overall cancer incidence was low in the cohort, probably reflecting a "healthy worker effect." Occupational exposure to aromatic amines may cause bladder cancer (8), but no excess risk was seen. The observed non-significant excess of rectal cancer and NHL may be due to chance, but a true association cannot be ruled out. NHL has previously been associated with occupational exposure to organic solvents (9,10), phenoxy acids and chlorophenols (10-12), and various insecticides (13). Rectal cancer in young men has been associated with jobs in which dusts or fumes were inhaled (14). Further, excess rectal cancer has been found in metal workers (15-17), including workers grinding stainless steel (18).

It must be considered that the cohort is still young and relatively little time has elapsed since the start of exposure. The possibility for a full evaluation of the long-term health effects of exposure was thus limited. Future follow-ups will of course be more fruitful.

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A NESTED CASE-CONTROL STUDY OF LUNG CANCER MORTALITY IN WELDERS AND OTHER METAL WORKERS

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Welding occupies a large fraction (1-2%) of the work force world wide. Several reports have indicated an association between welding fume exposure and lung cancer. Much focus has been on the exposure to stainless steel welding fumes, which contain known carcinogens such as hexavalent chromium. However, there is still some uncertainty about the significance of the association. We have conducted a nested case-control study on lung cancer mortality within a cohort of 10,059 welders and other metal workers who had worked for at least one year in a welding company between 1964 and 1984. In a follow-up until 1985, 94 had died from lung cancer (cases), and 376 cohort members with a "non-respiratory" cause of death (used as controls) were matched on year of death and age at death. The comparison of exposures was carried out according to work histories and smoking habits, obtained by interviews of long time colleagues and spouses.

Exposure to the potential confounding factors (tobacco smoking and asbestos) revealed significant elevated risk estimates. An increasing trend in the risk estimate with increasing tobacco consumption was demonstrated, but no important differences in smoking habits in welders and non-welders were found. Welding exposure of any kind showed a significant elevated odds ratio (OR) corresponding to a 70% excess of lung cancer (OR 1.67, 95% CI 1.04-2.67). The overall OR for mild steel welding ever was 1.65 (1.03-2.65). The risk estimate showed an increasing trend up to a duration of 11-15 years of welding exposure (4.21, 1.50-11.86, 8 obs.) The picture of stainless steel welding looked like that of mild steel welding with an overall OR for stainless steel welding ever of 1.54 (0.83-2.84) and 2.36 (1.02-5.49) after 11 or more years of stainless steel welding. Welding in stainless steel with fume producing welding processes,

such as MMA, for two decades or more, exhibited a doubling of the risk estimate.

In conclusion our data showed an increase in lung cancer risk associated with stainless steel welding as well as mild steel welding, and the data indicate a dose-response relationship.

CANCER MORTALITY AMONG JEWELRY WORKERS

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Mortality was investigated for the years 1950-80, in 1,009 male members of a New York jewelry workers union, and for the years 1984-88 among 812 men and 528 women identified as jewelry workers on death certificates from 23 states. Malignant neoplasms were excessive for union members (PMR=1.17) as well as for female jeweler deaths from the 23 states (PMR=1.16). Deaths due to other causes were not unusual, except for excesses of circulatory system (PMR=1.10) and arteriosclerotic heart disease (PMR=1.25) in union males, and rheumatic heart disease in union males (PMR=3.02) and in male jewelers from 23 states (PMR=3.11). Significant excesses were identified for cancer of the colon among union males (PCMR=1.53), esophageal cancer among males from 23 states (PCMR=2.52), and stomach cancer among females from 23 states (PCMR=2.36). Females from 23 states also had a slight excess of cancer of the esophagus (PCMR=1.68); the men and women from 23 states had small excesses of colon cancer. Union men also had a slight excess of pancreatic cancer. Combining the results from all study groups showed a statistically significant excess only for cancer of the colon (PCMR=1.30; 95% C.I.: 1.02-1.63). Of the other cancers, excesses were shown for malignancies of the hematolymphopoietic system, with a combined PCMR=1.24 (95% C.I.: 0.96-1.59). Both non-Hodgkin's lymphoma and leukemia showed marginal excesses in all three study groups. The combined results for the three study groups were PCMR=1.32 (95% C.I.: 0.92-1.84) for non-Hodgkin's lymphoma, and PCMR=1.17 (95% C.I.: 0.75-1.74) for leukemia. The lack of site specificity for malignancies found to be in excess raises questions about the etiologic significance of these findings, although the wide variety of exposures in this industry, particularly to metals and solvents, could possibly involve excess risk for malignancy at multiple sites.

20-YEAR FOLLOW-UP OF MORTALITY OF COKE WORKERS IN BRITAIN

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A 12 or 13-year follow-up of men employed by two companies in 1967 as coke workers at 27 plants throughout Britain had shown less lung cancer than in American studies. A 20-year follow-up aimed to examine further if lung cancer, and other causes of death, were work-related. Vital status was established for all but 153 (2%) of the 6673 men studied. Detailed job-names from work histories up to 1976 were allocated to 10 groups, according to broad area of work and results from 1630 measurements of benzene soluble materials (BSMs) from routine monitoring at 19 plants 1971-88, showing geometric mean levels of 1.5-2.0 mg/m^3 BSM in ovens tops jobs. Cumulative exposures to BSMs up to 1967 assumed that earlier concentrations were similar to those in the 1970s. Data on smoking habits were available from surveys 1968-73 for 1767 men. The all-cause SMR, based on 2208 deaths, was 92 relative to the local (regional) population. The 319 lung cancer deaths (SMR 126) were a statistically significant excess. Cox regression analyses showed a positive association between lung cancer mortality and estimated exposure to BSMs in data from one company, with an indication of a positive interaction between exposure and cigarette smoking. BSM data from the other company were sparse. Excess laryngeal cancer (SMR 260, 9 deaths) was not associated with estimated BSM exposures. Stomach cancer mortality in the second company (SMR 130, 95% CI 89-183) was related to time worked in the by-product plants. These results are broadly consistent with those from other studies. A negative trend with age in IHD SMRs remains unexplained.

ACUTE MYELOID LEUKEMIA AMONG PETROL STATION ATTENDANTS

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Acute myeloid leukemia (AML) may be caused by environmental exposure to benzene and ionizing radiation. We have studied the risk of AML within different occupations to identify occupations with a previously unknown increased risk and to generate hypotheses on unknown environmental etiologies of AML. The study population was the gainfully employed Swedish population, 20-64 years in 1970. The census information was linked to the information on incident cancer cases in the National Swedish Cancer Register during the period 1971-1984. The observed number of AML cases within an occupation was compared to the expected number. The only occupational group showing a substantially elevated risk of AML based on at least five cases was male "petrol station attendants and demonstrators." Ten cases of AML occurred versus 2.8 expected, yielding an observed/expected ratio of 3.6 (95% CI 1.7-6.6). For several decades Swedish petrol has contained 2-5% of benzene. Thus a hypothesis was that benzene had contributed to the excess risk. The work histories of the 10 cases were reconstructed through interviews with surviving relatives and were compatible with the hypothesis. However, since the air benzene exposures at petrol stations always have been lower than benzene exposures previously associated with an increased risk of AML, the leukemogenic effect of benzene may have been potentiated by other petrol or vehicle exhaust components.

OCCUPATIONAL EXPOSURE TO CHEMICAL AGENTS AND RISK OF LYMPHOMAS AND LEUKEMIAS IN THE WOOD INDUSTRY

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Previous epidemiologic studies have suggested an excess of lymphomas and leukemias in woodworkers. The risk of these diseases was studied in the Finnish wood industry with a specific objective to identify possible causative agents. The cases were traced during the follow-up of a cohort of 7307 male workers from sawmills, particleboard mills, plywood mills, construction joinery mills, furniture factories and a plant manufacturing glues for the wood industry. There were altogether 24 cases including 8 non-Hodgkin's lymphomas, 4 cases of Hodgkin's disease, and 12 leukemias. Each case was matched by age and survival status with one to eight referents (152 in all) selected from the cohort. Exposures to wood dust, formaldehyde, chlorophenols, terpenes, solvents, engine exhaust, pesticides and phenol were assessed on the basis of the occupational histories and a plant- and period-specific job-exposure matrix.

Increased odds ratios (OR) were found for lymphomas and leukemias (combined) and exposure to solvents (OR=5.6; 95% CI 1.0-32; 4 exposed cases) and formaldehyde (2.5; 0.8-7.6; 7 exposed cases) in conditional logistic regression analysis. Confounding was controlled by mutual adjustment but the ORs remained close to the unadjusted ORs both for solvents (OR=5.1) and formaldehyde (OR=2.3). Exclusion of the subjects exposed to both of these agents gave rather similar results (OR=3.4 and 2.0 respectively). The solvents involved in this study were generally mixtures containing several types of chemical agents, such as aromatic hydrocarbons, aliphatic hydrocarbons, esters, alcohols, ketones and glycol ethers. Small numbers of exposed cases did not allow an accurate analysis by the specific type of cancer, but both solvent exposure and formaldehyde exposure were more common among the cases of non-Hodgkin's lymphoma than among other cases. In conclusion, our study

suggests that solvents related to woodwork may cause non-Hodgkin's lymphoma. The role of formaldehyde exposure should also be scrutinized more closely, even though there are only a few previous studies supporting this association. No clear associations were found between lymphomas or leukemias and other exposures including wood dust (mainly from pine, spruce and birch) and chlorophenols (mainly tetrachlorophenol).

COHORT MORTALITY STUDY OF FILLING STATION ATTENDANTS

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Introduction

Gasoline has been classified by the International Agency for Research on Cancer as a possible human carcinogen, mainly on the basis of the established carcinogenicity of some component chemicals, such as benzene, light straight-run naphtha and 1,3-butadiene (1). In a cohort mortality study on workers at petroleum distribution centers from U.K., only a threefold excess of mortality due to myelofibrosis was detected (2). However, increased risks for neoplasms at different sites among filling station workers were reported in occupational mortality or cancer incidence analyses and in case-control studies (3-18). Furthermore, a number of specific studies on this occupational group has recently been published. In a census cohort of Swedish petrol station attendants, a standardized incidence ratio of 3.6 (95% CI 1.7-6.6) for acute myeloid leukemia was detected (19). An increased risk of respiratory cancers was found among Danish filling station attendants (20). An elevated risk of renal cell cancer and an exposure-response relationship were reported for exposure to gasoline vapors in a Finnish case-control study (21). An excess risk of acute leukemia was found in a Swedish case-control study for professional drivers exposed to gasoline and diesel (22).

Attendant-served stations predominate in Italy, and self-service stations operate mainly at night. We present in this paper preliminary results of a cohort study of filling station attendants from a region of Central Italy.

Methods

Cohort design: A nationwide survey of service stations was carried out in Italy in 1980. Information on several characteristics of the stations and their managers was collected during the survey, such as the name, date of birth and length of employment of the manager, the number of attendants, the quantity of fuel sold in the previous four years, and the number of fuel supplies to the station per year.

Detailed data for the Latium Region (Central Italy) were obtained and managers who were clearly identifiable as individuals (not commercial houses) were considered eligible for the study. Findings concerning the subcohort of filling station attendants from Rome are reported herein.

Vital status of the cohort members was ascertained from January 1981 through July 1991. For the SMR analysis, expected number of deaths were calculated based upon age- and period-specific rates of the Regional population.

Exposure assessment: Information on duration of employment at entry along with a series of indicators of workload were available for all cohort members from the 1980 survey. No vapor recovery system has been enforced in Italy, and the relative quantity of fuel sold stayed relatively stable. Unleaded gasoline, in fact, still accounts for less than 5% of total marketed fuel. Due to the characteristics of Italian service stations, the yearly average quantity of gasoline sold per full-time employee may be considered as an indicator of the average intensity of exposure experienced by the manager at refuelling. Mean values for this index, by size of the station, are shown in Table 1.

A more detailed exposure assessment is underway, based on the correspondence between quantity of super premium gasoline sold and concentrations of some aromatic hydrocarbons measured during an environmental monitoring survey on 111 current filling station attendants. The stations investigated were a random sample of all those located in the center and the north-east districts of Rome. Eight repeated personal samples per employee have been collected along one year, in order to account for seasonal variations in fuel composition and in meteorological conditions. Sampling was scheduled to cover three different weekdays, in order to account for

day-to-day variations in workload. During each sampling day, the attendant recorded the quantity of fuel dispensed by type and the number of vehicles filled. Vapor samples were collected at the breathing zone of the worker, during the eight hours of the workshift, by charcoal tubes and personal pumps. Determinations of a number of spy-chemicals were carried out by HR gas-chromatography. Mean values of benzene, toluene and xylenes measured during the survey and their variability are reported in Table 2.

Results

The cohort consists of 1,446 service station managers from Rome (1,312 men and 134 women). At entry in the study, the subjects had worked for 15 years on average, and their mean age was 45 years (Table 3). At the end of the study, 1214 subjects were still alive, 141 had died, and 91 had not been traced (Table 4). No information on the cause of death was available for 7 deceased individuals (5%).
The cause-specific mortality among men is described in Table 5. All cause mortality was significantly decreased, mainly due to a deficit in cardiovascular diseases. All cancer mortality did not differ from expectation. However, increased risks were found for non-Hodgkin's lymphoma and for cancer of the esophagus. One case of soft-tissue sarcoma was observed versus 0.1 expected. Risks for colon cancer and bladder cancer were slightly elevated, while mortality due to lung cancer and leukemia was not raised. No kidney cancer death was recorded while one case was expected. Mortality from tobacco- and alcohol-related causes (lung cancer, respiratory diseases and cirrhosis of the liver) was not raised.

Some relevant characteristics of the non-Hodgkin's lymphoma and of the esophageal cancer cases (age and duration of employment at entry in the study, age at death) along with some workload indicators of the stations where they worked (size of the station and yearly sales of super premium gasoline per full-time employee) are reported in Table 6. Further analyses by intensity of exposure and latency were postponed until the completion of the follow-up of the whole regional cohort.

Conclusions

This study shows that filling station workers are exposed to gasoline vapors, and the current levels of exposure to benzene, toluene and xylenes have been evaluated. An increased risk of non-Hodgkin's lymphoma and of esophageal cancer was observed, but the low power of the study precludes any firm conclusion. The findings, however, support the hypothesis that occupational exposure to gasoline fuel and exhausts might entail an increased risk of cancer. The feasibility of a retrospective exposure assessment based on findings from the environmental monitoring survey among current employees is under study. We are now about to complete the follow-up of further 1,300 gas station workers from the remainder of the Latium region, and we are trying to replicate the study in other Italian regions.

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Table 1. Average quantity of super premium gasoline sold in 1980 by full-time employee (thousands liters) in the 1,446 Rome service stations included in the cohort study, by size of the station

	Yearly gasoline sales per employee			
Size of the station	No	(%)	Mean	(SD)
Large	154	(11.0%)	220.04	(119.94)
Medium	260	(18.6%)	257.44	(121.81)
Small	986	(70.4%)	300.74	(136.32)
Total	1400	(100.0%)	283.82	(132.02)

Table 2. Levels of aromatic hydrocarbons measured among 111 current filling station attendants from Rome (703 personal samples, 8 hours TWAs, mg/m^3)

CHEMICAL	No	Mean	(SD)	Median	Min	Max	G-Mean	(GSD)
BENZENE	703	0.55	(2.46)	0.11	0.001	28.02	0.12	(3.82)
TOLUENE	703	0.70	(3.14)	0.17	0.040	33.77	0.18	(3.41)
XYLENES	703	0.32	(1.21)	0.09	0.003	15.37	0.10	(3.31)

Note: Mean = arithmetic mean; SD = standard deviation; Min = minimum; Max = maximum; G-Mean = geometric mean; GSD = geometric standard deviation.

Table 3. Filling station attendants by age and length of employment at entry (1/1/1981). Rome, Italy

	Length of employment				
Age	<10	10-19	20+	Total	(%)
<30	86	16	0	102	(7.3%)
30-39	102	121	38	261	(18.8%)
40-49	103	238	126	467	(33.7%)
50-59	66	147	167	380	(27.4%)
60+	22	54	101	177	(12.8%)
Total (%)	379 (27.3%)	576 (41.5%)	432 (31.2%)	1387* (100.0%)	(100.0%)

* Missing data on length of employment for 59/1446 cohort members.

Table 4. Vital status of the 1446 Rome cohort members at the end of follow-up (July 31, 1991)

Vital status	Men		Women		Total	
Alive	1098	(84%)	116	(87%)	1214	(84%)
Deceased	132	(10%)	9	(7%)	141	(10%)
Lost	82	(6%)	9	(7%)	91	(6%)
Total	1312	(100%)	134	(100%)	1446	(100%)

Table 5. Mortality of Rome filling station attendants (1981-1991) Males

Cause of death (IX ICD)	OBS	EXP	SMR	95% C.I.
All causes (001-999)	132	158.66	0.83	0.70- 0.99
Malignant neoplasms (140-208)	52	53.45	0.97	0.73- 1.28
Pharynx (140-149)	1	1.45	0.69	0.02- 3.83
Esophagus (150)	3	0.90	3.33	0.69- 9.72
Stomach (151)	3	4.96	0.61	0.13- 1.77
Intestine & colon (152-153)	5	2.87	1.74	0.57- 4.07
Rectum (154)	1	1.59	0.63	0.02- 3.51
Liver (155)	2	3.08	0.65	0.08- 2.35
Pancreas (157)	1	1.96	0.51	0.01- 2.85
Larynx (161)	1	1.56	0.64	0.02- 3.58
Lung (162)	19	18.02	1.06	0.64- 1.65
Connective tissue (171)	1	0.09	10.55	0.26-58.79
Prostate (185)	2	2.70	0.74	0.09- 2.67
Bladder (188)	4	2.56	1.56	0.43- 4.00
Kidney (189)	0	1.23	–	
Brain,eye,nervous system (190-192)	2	1.41	1.42	0.17- 5.12
Lympho-hematopoietic(200-208)	5	3.58	1.40	0.45- 3.26
Non-Hodgkin's lymphoma(200,202)	3	0.94	3.19	0.66- 9.33
Hodgkin's lymphoma (201)	0	0.33	–	
Leukemia (204-208)	2	1.75	1.15	0.14- 4.14
Blood diseases (280-289)	1	0.41	2.43	0.06-13.54
Diabetes mellitus (250)	5	4.99	1.00	0.33- 2.34
Nervous system (320-359)	1	2.28	0.44	0.01- 2.44
Circulatory system (390-459)	44	60.78	0.72	0.53- 0.97
Respiratory system (460-519)	8	10.13	0.79	0.34- 1.56
Digestive system (520-579)	8	11.91	0.67	0.29- 1.32
Cirrhosis of the liver (571)	5	7.86	0.64	0.21- 1.49
Genitourinary system (580-629)	1	2.18	0.46	0.01- 2.56
Accidents & violence (800-999)	6	8.01	0.75	0.28- 1.63
Unknown cause of death	6	–		

Table 6. Relevant characteristics of the non-Hodgkin's lymphoma and of the esophageal cancer cases

Cancer	Case #	Age at entry*	Age at death	Length of employment at entry*	Gasoline sales per employee	Station size
Non-Hodgkin's Lymphoma	1	60	69	20	293.5	Small
Non-Hodgkin's Lymphoma	2	62	64	2	308.0	Medium
Non-Hodgkin's Lymphoma	3	69	76	25	143.2	Small
Esophageal Cancer	1	53	55	26	278.5	Small
Esophageal Cancer	2	63	73	32	375.0	Small
Esophageal Cancer	3	60	64	42	395.7	Small

* Age and length of employment as recorded in 1980, at entry in the study.

THE 1891-1920 BIRTH COHORT OF QUEBEC CHRYSOTILE MINERS AND MILLERS: A PRELIMINARY REPORT ON MORTALITY TO 1988

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Introduction

A research program established at McGill University in 1966 included a mortality survey with the primary aim of "defining as accurately as possible the quantitative relationship between exposure to chrysotile asbestos and the incidence of lung cancer." A birth cohort was set up consisting of all persons born in the years 1891 through 1920, and ever employed for one month or more in the Quebec chrysotile mines and mills. The cohort comprised nearly 11,000 men (and almost 450 women), who have been followed from first employment; the first of the cohort to start work did so in March 1904, at the age of 12 years, 8 months. Results to four points in time, the latest to the end of 1975, have been reported;[1-4] a few figures in earlier publications have had to be very slightly revised. By the end of 1975, of the 10,925 men registered in the cohort, 1090 (10%) had been lost to follow-up, mostly never traced after leaving very short employment before 1930, and 4485 had died (41%); this left a cohort of 5350 men (49%) alive. Overall excess mortality was 2% at Asbestos and 10% at Thetford Mines; the lung cancer excess was around 25%.

Methods and materials

In October 1990, we initiated a further follow-up of the 5350 male members of the cohort who had survived into 1976, extending the original aim to the fuller determination of exposure-response relationships for respiratory, abdominal, and other cancers, for mesothelioma, and for pneumoconiosis. We terminated this follow-up in May 1992, when details of vital status at the end of 1988 had been obtained for all but 15 men (0.3%).

An annual record of exposure from 1904 to November 1966 had previously been obtained for each of the 10,925 men in the cohort.[3] Over 2400 of these men (22%) were still employed in 1967, and their work histories up to retirement, the last in 1985, have been collected (A Dufresne, personal communication), but details of exposure had not been completed at the time this preliminary report was prepared. However, dust exposure accumulated to age 45 could be calculated for each man, in terms of (million particles per cubic foot) × years, or mpcf·y.

Preliminary analyses have been carried out by the subject-years method,[5] using the PYRS program,[6] with Quebec rates as reference;[7] rates for the years 1980-85 were replicated to give estimates for 1986 through 1988.

Results

From 1976 through 1988, there were 2827 deaths, bringing the accumulated total to 7312 (almost three-quarters of the 9820 men of known vital status). Of the 2752 men born 1891-1900 and living in 1930, only 88 (or 3%) were still alive in 1989; there were 644 survivors (19%) of the 3417 in the corresponding 1901-10 cohort, and 1776 survivors (48%) of the 3675 in the 1911-20 cohort.

Subject-years analyses have been carried out on the 2827 deaths 1976-88. The Standardized Mortality Ratio (SMR), all causes, was 1.07. At Asbestos and Thetford Mines, SMRs (all causes) were 1358/1330.9 = 1.02 and 1469/1304.0 = 1.13, both closely similar to those for the years to 1975. The SMRs for various cancers were as follows. **Respiratory**: lung (code 162 in ICD-9) 321/229.7 = 1.40; larynx (161) 18/13.8 = 1.30. **Abdominal**: esophagus (150) 10/13.7 = 0.73; stomach (151) 56/47.9 = 1.17; colon/rectum (152-154) 73/88.9 = 0.82; other abdominal (155-159) 63/60.3 = 1.04; whence all abdominal (150-159) 202/210.8 = 0.96.

Preliminary examination of cancer risks in relation to dust exposure (mpcf·y) accumulated to age 45 has also been carried out by subject-years analysis. There were no indications of exposure-response relationships for cancer of larynx, esophagus, stomach, or colon/rectum, or other abdominal cancers. In each of six classes of exposure up to 300 mpcf·y, the lung cancer SMR was close to 1.3 (a total of 250 cases of lung cancer, among 4383 men, against 190.6

expected), similar for Asbestos and Thetford Mines; there was no evidence of trend. For the 789 men exposed to between 300 and 1000 mpcf·y, the lung cancer SMR was 51/32.8 = 1.55, and for the 163 men exposed to at least 1000 mpcf·y it was 20/6.3 = 3.16. These findings are illustrated in Figure 1.

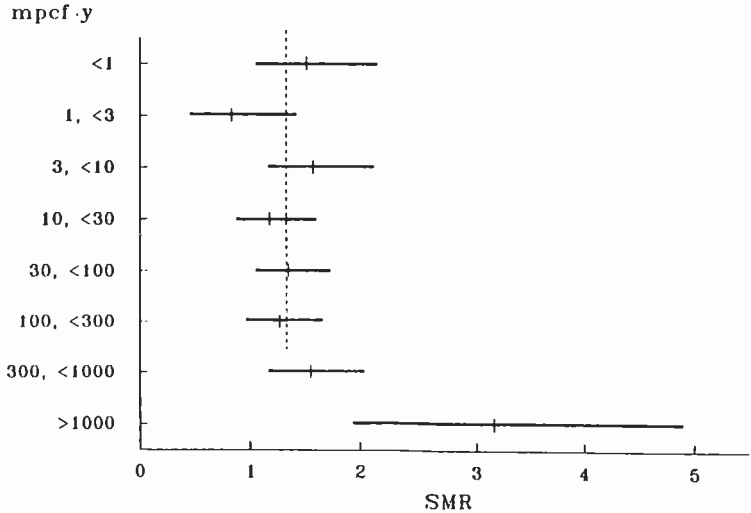

Figure 1. Lung cancer SMRs according to exposure (mpcf·y) accumulated to age 45: point estimates, | , with 95% confidence interval estimates shown as horizontal bars. The broken vertical line indicates the SMR for all 4383 men exposed to less than 300 mpcf·y.

Of the total of 7312 deaths to the end of 1988, ninety-four were ascribed on death certificates to pneumoconiosis, all but one since 1946. In all, there have probably been 33 deaths due to mesothelioma, 28 in miners and millers; these form the subject of another preliminary report in these proceedings.[8]

Discussion

Except in the last paragraph, the results given in the preceding paragraph relate to mortality 1976 through 1988, but no great differences up to 1975 have been detected. In particular, overall excess mortality at Asbestos was 2% in both periods, while at Thetford Mines it was very similar: 10% to 1975; 13% during 1976-88.

The preliminary nature of the analyses must be emphasized: those reported here are of cancer mortality (excluding mesothelioma) in relation to asbestos exposure accumulated to age 45. However, it is worthy of note that no excesses have been found for exposures up to 300 mpcf·y, and then only of lung cancer, and that there was no excess of abdominal cancers overall.

Definitive assessment of exposure-response is being carried out by case-referent analysis[3] of the entire mortality experience of the cohort. As there have been a total of 565 deaths from lung cancer, there is opportunity to exploit recent developments in analysis, both in selection of referents and in evaluation of exposure.[9,10]

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MALIGNANT MESOTHELIOMA IN QUEBEC CHRYSOTILE MINERS AND MILLERS: A PRELIMINARY REPORT

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In 1966, a cohort comprising nearly 11,000 men born 1891 through 1920 and ever employed for one month or more in the Quebec chrysotile production industry, half at Asbestos and half at Thetford Mines, was registered for study. Reports on mortality to the end of October 1966, and to the end of 1969, 1973 and 1975 have been published.[1] At these four points, the accumulated numbers of deaths thought due to malignant mesothelioma, as a proportion of all deaths, were 3 out of 2413, 6/3216, 8/4037 and 10/4547.[2] Two of these cases had later to be deleted, leaving eight, all pleural in type.

A further follow-up was initiated in 1990 to determine the vital status on January 1st 1989 of 5335 survivors into 1976. All but 15 have been traced, bringing the total deaths to 7312, 7116 since 1925. Scrutiny of clinical and pathological information on the 2827 additional deaths indicates that there have probably been a further 25 cases of mesothelioma.

Of the 33 cases in the cohort to date, 15 were coded to ICD 163 and 18 to a variety of other codes. Final diagnosis was based on an autopsy in 23 and on a biopsy in 10. A detailed review of all available evidence suggests that the probability of a correct diagnosis was high in 17, moderate in 11 and low in 5. All 33 cases were primarily of the pleura but in one of the five with low diagnostic probability the peritoneum was also affected.

The average age at death of the 33 suspected cases was 67 years; one was at age 40, the others at ages between 57 and 79 years. In the decades 1951-60, 1961-70, 1971-80 and 1981-88, the numbers of deaths from mesothelioma, as a proportion of all deaths in the period, were 1 out of 872 (0.1%), 4/1684 (0.2%), 11/2118 (0.5%) and 17/1725 (1.0%) respectively.

There were more than twice as many cases in miners and millers from Thetford Mines (20) as from Asbestos (8); the remaining five cases were among men employed in a small asbestos products factory in Asbestos. The median duration of employment was 36 years (range 2½ to 49 years). All eight men employed five years or less had left work by 1945, three from the mines and mills in Asbestos and three from the factory there; these six comprised almost half the cases at Asbestos. Time from first employment to death ranged from 21 to 60 years (median 48 years); see Table 1.

Table 1. Characteristics of mesothelioma deaths by place of work

	Thetford Mines	Asbestos	Factory
Number of men	5,628	4,505	792
Cases	20	8	5
Employed less than 6 years	2	3	3
Median latency (years)	48	46	39

There was no case of mesothelioma among the 4371 members of the cohort (40% of 10,925) employed for less than 2 years, 8 cases among those 2396 (22%) employed for 2-10 years, and 25 mesotheliomas among the 38% of the cohort (4158 men) with at least 10 years' employment; see Table 2.

Table 2. Mesothelioma risk by duration of employment

Duration (years)	Number of men	Cases	Rate/1000
less than 2	4,371	0	0
2, less than 10	2,396	8	3.3
10 or longer	4,158	25	6.0
all durations	10,925	33	3.0

The value of the parameter b in the exponential mortality model:[3] $incidence = b \times (years\ since\ first\ exposure)^{3.2}$ was estimated as 0.24

$\times 10^{-8}$ for Thetford Mines; in Asbestos, ***b*** for miners and millers was about half as large (ca. 0.1×10^{-8}), but that for factory workers was appreciably greater (ca. 0.5×10^{-8}), probably related to the known use of crocidolite in that plant.[4] The parameter ***b*** makes no allowance for duration or intensity of exposure, but it seems possible that the higher fibrous tremolite exposures thought to have occurred at Thetford Mines were sufficient to affect the risk of mesothelioma in the two mining areas.

As there have been no direct measurements of the concentrations of fibrous tremolite to which chrysotile miners and millers were exposed over the past half century, resolution of this etiological question is likely to depend on the analysis of an adequate number of carefully selected lung tissue samples from ex-employees for mineral fiber content, a very difficult task. Data from a small number of samples collected some 10 years ago showed that tremolite was present in both mining areas but that the level of exposure at Thetford Mines may have been about two or three times higher than at Asbestos.[5]

Conclusion

The proportional mortality from mesothelioma in Quebec chrysotile miners and millers has steadily increased with each succeeding follow-up, in parallel with time since first employment. It seems likely that eventually the overall proportion may reach 5 or 6 per thousand deaths, nevertheless very much lower than has already been observed in cohorts exposed to the commercial amphiboles. The extent to which deaths from mesothelioma in the Quebec chrysotile industry are attributable to contaminating fibrous tremolite cannot yet be resolved. The absence of cases in men employed for less than 2 years is noteworthy.

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CANCER RISK AMONG 3,890 WORKERS EMPLOYED AT THE INDUSTRIAL BRANCH OF THE SHIPYARD OF GENOVA, ITALY: A RETROSPECTIVE COHORT

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We have conducted a retrospective cohort study of workers who were employed between 1960 and 1988 at the Industrial Branch of the shipyard of Genova, Italy. These workers were assigned to ship repair, refitting, and construction. Occupational exposure to asbestos, silica dusts, welding fumes and gases, solvents, and paint removers are likely to have occurred right after World War II until the mid 1970s (1). We identified 3,890 males who met the inclusion criteria and their vital status was ascertained from January 1, 1960, through December 31, 1990. We ascertained vital status of each worker from the Demographic Registry of his place of residence. Causes of deaths were coded by the trained nosologist according to the International Classification of Diseases (ICD), 9th Revision (2). A conversion table was used to allow a correct pooling of the data over the three revisions of the ICD (i.e., 7th, 8th, and 9th) that were used to code the causes of death in the referent population across the follow-up period. The expected number of deaths were calculated by applying quinquennial age-, cause-, and calendar-time specific mortality rates for the male population of Genova to the person-years of observation. Standardized mortality ratios (SMRs) and their exact 95% confidence intervals (95% CI) were computed by using the software EPILOG PLUS (3). The vital status of the cohort at the close of the follow-up is reported in Table 1.

We observed 1,833 deaths, 611 from malignant neoplasms (219 deaths from lung cancer and 46 from pleural mesothelioma). The completeness of the follow-up was satisfactory: only 16 subjects (0.4%) were lost to follow-up.

Overall mortality for the whole cohort was slightly, but significantly higher than the expected (total deaths = 1833, SMR = 108.8, 95% CI = 104-114). Higher than the expected mortality from specific

causes was observed for all cancers (611 deaths, SMR = 122.6, 95% CI = 113-133), and respiratory tract diseases (601 deaths, SMR = 122.8, 95% CI = 106-141).

Table 1. Vital status of the cohort at the end of the follow-up

Vital Status	No.	%	ICD-9th revisions
Alive	2041	52.5	
All deaths	1833	47.1	
All cancers	611	33.3	140.0 - 208.9
Lung cancer	219	35.8	162.0 - 162.9
Pleural mesotheliomas	46	7.5	163.0 - 163.9
Lymphatic-Hematopoietic	20	3.3	200.0 - 208.9
Lost to Follow-up	16	0.4	
Total	3890		

Mortality from site specific cancers (Table 2) was higher than the expected for lung cancer (219 deaths, SMR = 148.2, 95% CI = 129-169), pleural mesothelioma (46 deaths, SMR = 442.0, 95% CI = 324-590), and cancer of the larynx (25 deaths, SMR = 138.6, 95% CI = 90-205).

Table 2. Mortality from selected neoplasms among shipyard workers

Cause of Death	Obs	Exp	SMR	95% CI
Malignant Neoplasms	611	498.2	122.6	113-133
Stomach	54	54.3	99.5	75-130
Rectum	22	20.0	110.0	69-165
Larynx	25	18.0	138.6	90-205
Lung	219	148.2	147.7	129-169
Pleural mesothelioma	46	10.4	442.0	324-590
Kidney & bladder	37	36.2	102.3	72-141
Lymphatic-hematopoietic	20	27.6	61.9	8-224

Analyses by time since the onset and duration of employment at the shipyard showed clear increasing dose-response relationships with

mortality form lung cancer (Figures 1 and 2) as well as pleural mesothelioma (data not shown). The positively graded relationships that we observed in this study suggest that the general level of exposure to lung and pleural carcinogens at the workplace has decreased over time (4).

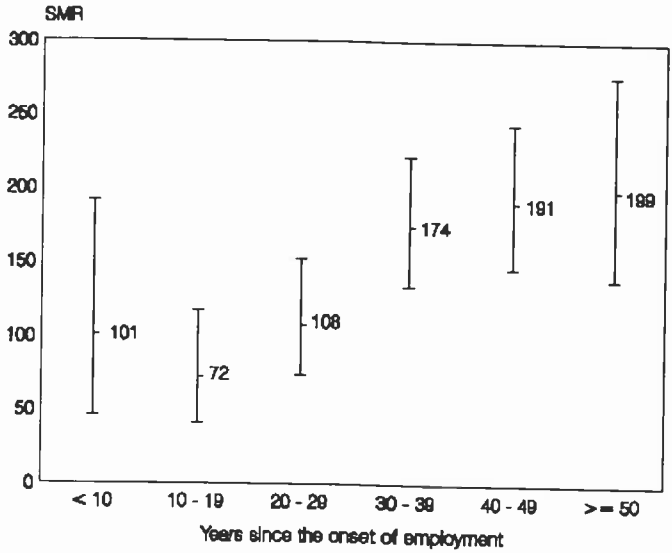

Figure 1. Mortality from lung cancer by years since the onset of employment

Figure 2. Mortality from lung cancer by length of employment.

Indirect correction for smoking habits (5) ruled out smoking as a serious confounding factor in the excess mortality from lung cancer detected by the study. The excess mortality that could be attributed solely to smoking due to the higher proportion of smokers observed in the study cohort than in the local referent population was less than 29%.

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A COHORT MORTALITY STUDY OF WORKERS EMPLOYED IN A FRENCH STAINLESS STEEL FACTORY

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A prospective historical mortality study was carried out among the workers of a factory producing stainless steel in order to assess (i) the relationship between lung cancer and exposure to chromium compounds, to nickel compounds, to polycyclic aromatic hydrocarbons (PAH) and to silica; (ii) the risk of morality from cardiovascular diseases due to heat exposure. Men (4,227) having at least 3 years of employment between 01.01.1968 and 31.12.1984 were followed up for mortality. Complete job histories since data of first employment were abstracted from the company files. In addition, a job-exposure matrix was set up in order to determine sub-groups of workers according to occupational exposure. The smoking habits of 24% of the cohort members were known from the interview of workers still active when data were collected.

The observed number of deaths (obs) were compared with the expected ones based on national and regional rates with adjustment for age, sex and calendar time (Standardized Mortality Ratio, SMR). The overall mortality did not differ from that expected (obs=484, SMR=1.02, 95% CI = 0.93-1.12), whereas a significant excess was observed for mortality from cirrhosis of the liver (obs = 57, SMR = 1.66, 95% CI = 1.26 - 2.15).

With regard to lung cancer mortality, non-significant excesses appeared in the whole study population (obs = 42, SMR = 1.30, 95% CI = 0.94 - 1.75) and among workers ever employed in stainless steel production (obs = 7, SMR = 1.04, 95% CI = 0.42 - 2.15), rolling mills (obs = 17, SMR = 1.51, 95% CI = 0.88 - 2.42) and maintenance (obs = 9, SMR = 1.45, 95% CI = 0.66 - 2.75) workshops. A significantly high SMR, however, was observed for mortality from lung cancer among foundry workers (obs = 11,

SMR = 2.29, 95% CI = 1.14 - 4.09). This excess was higher for duration of employment ≥ 30 years (obs = 2, SMR = 3.33, 95% CI = 0.40 - 12.04) and for time since first employment ≥ 30 years (obs = 6, SMR = 3.24, 95% CI = 1.19 - 7.05). This excess was unlikely to be explained by smoking habits. When using the job exposure matrix in order to take into account exposure of interest, no significant lung cancer excess was observed among workers exposed to welding fumes, chromium VI, silica, PAH and acid mists. Neither did any excess appear when taking into account duration of exposure to these compounds and time since first exposure.

Concerning health adverse effects of heat exposure, no excess was observed for all cardiovascular diseases and for ischemic heart diseases, whereas for cirrhosis of the liver, significantly high SMRs were observed with an increasing trend with duration of exposure.

LUNG CANCER MORTALITY AMONGST FORMER WORKERS AT THE RADIUM HILL URANIUM MINE IN SOUTH AUSTRALIA

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This retrospective study examines the risk of radon-induced lung cancer mortality (LCM) amongst former workers at the Radium Hill (RH) uranium mine. The study cohort, identified from archived payroll information, comprised 2,574 workers (2,521 males and 53 females) employed at the mine from 1948-1962. The 66% trace rate previously reported (Woodward et al., 1991) was improved to 74% through subsequent trace activities which included matching the RH and Wittenoom-Gorge asbestos miner cohorts and a reunion of ex-RH residents. The 1,894 individuals traced included 616 deaths (54 lung cancer deaths). Questionnaire information on smoking and relevant occupational histories was obtained for 61% of the cohort, including 49% of the deaths.

The mean age at commencing work in RH was 31 years and mean employment duration was 17 months. The mean underground employment duration amongst 1,459 underground workers was 12 months (range 10 days-9 years); levels of cumulative radon daughter exposures ranged from .07-112 WLM, with mean 7 WLM and median 3 WLM per person. The average intensity of exposure was 8.5 WLM/year (range 1.5-22 WLM/year).

We observed a significantly higher rate of LCM amongst underground workers at RH (SMR = 191, 95% CI 125-257) with reference to the Australian population, after age and calendar-year standardization; the elevated rate observed amongst surface workers (SMR = 155) was not statistically significant. The percentage of ever-smokers was 86% and 83%, respectively, for underground and surface workers. Comparative analysis between exposure categories was based on time related allocation of person-years-at-risk to categories of exposure and attained-age and age and calendar-year standardized mortality rates. Results from Poisson regression

modelling showed that workers exposed to over 40 WLM had a significantly higher LCM risk than surface workers (RR = 4.7, 95% CI 1.6-13.7), after age and calendar-year adjustment. We conclude that the elevated LCM risk observed is unlikely to be due entirely to the effect of smoking and other confounders. These findings indicate increased risk of radon-induced LCM amongst workers exposed to relatively low levels of ionizing radiation. The average cumulative radon daughter exposure of below-ground workers at RH is considerably lower than that of any other mining cohort followed for a comparable period, but the excess risk per WLM is slightly larger than that from other low dose populations. These findings are relevant to risk assessments in modern mining and domestic radon epidemiology.

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EVALUATING THE EFFICACY OF COLORECTAL CANCER SCREENING IN PATTERN AND MODEL MAKERS

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Introduction

Colorectal cancer is the second most common malignant neoplasm, next to lung cancer, in the United States. It affected an estimated 157,500 Americans and proved fatal for approximately 60,500 individuals during 1991. With an incidence nearly equal for males and females, 112,000 new cases were of the colon and 45,500 of the rectum. On the basis of mathematical modeling, a 50-year old man of average risk for colorectal cancer without any means of early detection, has a 5.4 percent chance of developing invasive colorectal cancer sometime in his life and a 2.8 percent chance of dying from it. With mortality rates remaining stable over the past few decades and the etiology of colorectal cancer still under investigation, their is a need for detection of pre-malignant and early malignant lesions.

The National Cancer Institute (NCI) and The American Cancer Society (ACS) have published similar guidelines for early detection of colorectal cancer that include digital rectal examination annually after age 40, stool occult blood testing annually after age 50, and sigmoidoscopy every 3-5 years following two consecutive negative procedures after age 50.

Several occupations have been shown to be at high risk for colorectal cancer. A number of epidemiologic studies have identified pattern and model makers (PMMs) as being at increased risk for colonic polyps and colorectal neoplasia, with twofold and greater risk in both incidence and associated mortality. Members of this occupation, who construct prototypes and patterns used for mass production, are exposed to various woods, metals, plastics, solvents, cutting oils, fiberglass, epoxy resins, and dusty work environments.

This investigation focuses on the impact of an ongoing, union sponsored, colorectal cancer screening program initiated in 1981 for

PMMs. Intra-cohort comparisons of invasive colorectal cancer rates are made between PMMs voluntarily participating and those who did not wish to participate during any of the program's first four screening examinations. Comparisons of invasive cancer rates also are made with Detroit area population-based incidence rates derived from the Surveillance, Epidemiology and End Results (SEER) program to estimate the risk of the specific cancers experienced by this cohort. Analyses are directed to the question of whether systematic screening of this high risk population decreases the incidence rates of colorectal cancer among screening participants.

Methods

The study sample consisted of 1,641 white male PMMs eligible to participate in a voluntary colorectal cancer screening program initiated in 1981. These men were employed in small to medium shops, numbering 10 to 200 employees, located in the Detroit metropolitan area. Our population does not overlap with other large cancer studies involving Detroit area PMMs. The eligible participants were identified from employee roster lists of two large local unions in the Detroit area. Eligibility for entrance into the study was based on two criteria: (1) medical insurance coverage current as of 1981, and (2) union membership current as of 1981. Retirees were also included if eligibility criteria were met. Men participating in the screening program but not identified as eligible according to study criteria were excluded.

Over the course of the program's first 10 years, a total of five screening examinations have been offered free of direct, out-of-pocket charge to union members. Initial examinations began on November 1, 1981, and continued for 6 months. The second screening was offered in late 1982; the third in 1985; and the fourth in 1988. A fifth examination was held in 1991, but was not included in these analyses since follow-up was only complete through 1990. The timing of the examinations conformed to NCI and ACS guidelines for screening high risk individuals. Union members of all ages were eligible although those 40 years of age and older were actively encouraged to participate.

For a typical program examination year, participants completed an occupational and medical history, physical examination, digital rectal examination, three serial stool occult blood tests, 60-cm flexible

sigmoidoscopy, and other tests unrelated to colorectal cancer screening. A comprehensive questionnaire assessing work related exposures, smoking status, and other demographic information was also administered. The 60-cm flexible sigmoidoscopy procedures were administered by a team of experienced physician endoscopists. Participants with positive findings were actively referred to specialists for biopsy and appropriate management. Reasons for referral included positive stool occult blood test on one or more slides, suspicious mucosal lesions (usually on adenomatous appearing polyps), and any lesion appearing consistent with neoplasia.

To identify cancer case subjects, the study cohort was linked with the Metropolitan Detroit Cancer Surveillance System (MDCSS), a participant in the National Cancer Institute's SEER program. The MDCSS collects cancer data on individuals who are residents of the Detroit area (Wayne, Oakland, and Macomb counties) at the time of diagnosis. Over 92% of those eligible resided in this three county area in 1981. At the time of linkage, the registry was complete through 1990, thus defining the termination date of our active study period. In addition to cases identified by the MDCSS, follow-up also was accomplished through linkage with the Michigan Death Tape from 1980 through the first quarter of 1991. This linkage was performed for the purpose of obtaining vital status of eligible subjects allowing for a more accurate follow-up of those having moved away from the Detroit area subsequent to cohort identification in 1981. Any underlying cause of death, as stated on the death certificate, related to malignant neoplasm (International Classification of Diseases, 9th edition (ICD-9) 140-199) was considered as a cancer case. For the purpose of standard incidence ratio (SIR) analysis, case subject's date of death was considered as the date of diagnosis of the cancer.

Eligible subjects began accumulating person-years of observation from the start of the screening program on November 1, 1981, until the study termination date on January 1, 1991. Allocation of person-years of observation was based on the following criteria: First, eligible subjects diagnosed during the program were removed from accumulating person-years of observation on the date of diagnosis of their first invasive primary cancer or on date of death, if not diagnosed with cancer before the start of the screening program. Second, eligible subjects diagnosed with any primary site

neoplasm other than colorectal cancer before the start of the screening program (n = 13) or during the active study period were considered at risk for developing a primary colorectal carcinoma. Third, subjects with in situ cancers were considered to be at risk for developing any primary invasive cancer, thus were not removed from accumulating person-years of observation (n = 6).

For the standardized incidence ratio (SIR) analysis, expected cancer cases were calculated using age-specific invasive cancer incidence rates per 100,000 white males residing in the Detroit SEER area. Incidence rates were derived from data collected by the MDCSS. Incidence rates were collapsed over 5-year intervals for the years, 1980-1984, 1985-1989. Expected cancers were stratified by age and screening participation for the two 5-year intervals and for 1990 then summed across strata to obtain the final expected value.

Results

Screening Participation: There were 1,641 pattern makers eligible to participate in the voluntarily screening program. Over the course of 10 years and four available screening examinations, 59.4% subjects participated on at least one occasion (herein identified as the "screened sub-cohort"). Of those participating at least once, 84.2% had their first examination during the 1981 program year, 2.6% in 1982, 10.2% in 1985, and 3.0 % in 1988. Sixty percent of this screened cohort participated in two or more program years and 14.5% participated in all four program years. Forty percent (40.6%) of the cohort did not participate during any program year and are herein identified as the "unscreened sub-cohort."

The mean age for the entire cohort at the start of the program (1981) was 41.6 years (SD 13.4). The screened sub-cohort had a significantly lower mean age of 40.6 years (SD 12.5) compared with the mean age of unscreened subjects at 42.9 years of age (SD 14.6, $t=3.40$ two-tailed $P<0.01$). The very young (<20) and those over 60 years of age, many of whom were retired at the program start-up, reflected the lowest rates of participation. Subjects aged 40+ years at the start of the program constituted 51.4% of the entire cohort.

Standard Incidence Ration (SIR) Analysis: Expected cancers were computer generated using the Mortality Analysis System (MAS). MAS is written in SAS and developed as a vehicle in epidemiological

research for the analysis of cohort data. Over the course of approximately 10 years, a total of 14,1513 person-years of observation has accrued, with the screened cohort contributing 8,748 person-years and the unscreened cohort 5,765 person-years of observation. There was no significant excess or decreased incidence of any invasive cancer experienced by this cohort as a whole compared to the general population. A total of 68 invasive cancers (excluding the two prevalent colorectal cases) were diagnosed during the active study period vs. 77.60 expected cases (SIR=0.88, 95%CI 0.68, 1.11). The screened cohort contributed 32 (prevalent colorectal cases excluded) of the incident invasive cancers vs. 41.37 expected cases (SIR=0.99 95%CI 0.70, 1.38). The SIR for colorectal cancer among the unscreened was 1.62, and for the screened was 0.21, both showing trends toward, but not reaching statistical significance at the $p<0.05$ level.

Intra-Cohort Colorectal Cancer Cases: A total of 10 invasive cancers of the lower gastrointestinal tract were observed during the active study period in the total cohort. There were nine invasive cases of the colon and one of rectal cancer. Subjects participating in the screening program contributed three of the nine invasive cancers of the colon. Two of these cancers were prevalent at the time of their initial screening examination in the 1981 program year and therefore were excluded from the analysis of incident cases. Six invasive incident cancers of the colon and one rectal were diagnosed in the unscreened cohort.

Statistical comparisons using a Mantel-Haenszel Rate Ratio test controlling for men < 40, and men 40 + years of age, revealed the unscreened cohort exhibited a statistically significant ten-fold greater risk for developing invasive colorectal cancer (RRMH=10.39, 95%CI 1.94, 55.78; $p<0.01$) than their fellow workers who chose to participate in screening. The relative risk increases to 13.35 if in situ cases are included in the analysis. Addition of the two prevalent cases discovered among screenees in 1981 results in an age adjusted odds ratio of 3.46 ($p = 0.055$). When prevalent cases and in situ cases are included, the age-adjusted odds ratio is 4.45 ($p = 0.02$).

Discussion

Pattern and model makers choosing not to participate in the first 10 years of this union sponsored screening program experienced over a

ten-fold greater incidence of colorectal cancer than did the participants. The difference is considered a possible benefit of this colorectal cancer screening program. The authors appreciate the limitation of this non-randomized study, but also note that limitations can serve to render the results either less or more positive than are shown. For example, the exclusion of prevalent cases from the screened members of the cohort may appear to accentuate the differences in cancer incidence rates between the two groups. Obviously, prevalent cases can not be excluded from non-screened participants, since they were not examined during the onset of the program. Exclusion of prevalent cancer cases from the screened group decreased the relative risk to 3.5 for unscreened cases, still approaching a statistically significant difference of $p = .055$. A p value of 0.02 is achieved when in situ plus prevalent cases are entered into the analysis, since both in situ cases were identified in the unscreened cohort. Overall conclusions based on whether in situ or prevalent cases are entered into the analysis are left to the reader. In the opinion of the authors, the evidence clearly suggests a benefit of colorectal cancer screening in reducing incidence of this cancer.

The standardized incidence ratio (SIR) analyses provide readers with different information. As noted above colorectal cancer incidence has been observed to be significantly excessive among members of this trade. The fact that this total study cohort, including both screened and unscreened individuals, showed colorectal cancer incidence rates not significantly different from the general population, with further analysis showing lower incidence in screenees vs. non-screenees, suggests that this program has reduced the overall rates in this high risk group to those approximating the general population.

Further tracking of this cohort is needed. It is anticipated that 10 additional years of screening program availability will result in overall participation rates of over 80%, enhancing the possibility of evaluating program benefits in reducing both colorectal cancer incidence and mortality. Additional years of tracking will also make possible needed mortality analysis of this cohort.

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PANCREATIC CANCER AND OCCUPATIONAL EXPOSURES

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Very little is known about workplace chemicals that affect the risk of pancreatic cancer (PC). Results of epidemiologic studies on occupational branches and jobs associated with an excess PC risk are heterogeneous and inconsistent (3).

Occupational determinants of PC were studied in a case-referent setting, the cases comprising the primary exocrinic PCs (N=1419), and the referents comprising the stomach, rectum, and large intestine cancers (N=3510) diagnosed in Finland between 1984 and 1987 inclusive at 40-74 years of age, known to be dead April 1990. The number of responders to a mail questionnaire on work histories, living habits, and diseases, addressed to the next-of-kin, was 662 for the cases and 1,770 for the referents. The response rate was 47% for the cases and 50 % for the referents. The main industry where employed, main occupation held, and 17 occupational exposures were reconstructed from the elicited job histories from first job until 1974. The associations of PC risk with industries and occupations were scrutinized with logistic regression models, adjusted for gender, age, alcohol consumption, cigarette smoking, diabetes, and pancreatitis. Exposures were analyzed the same way, excluding administrators and managers from the analysis to control for social class.

Significantly elevated PC risks were observed for the following three industries: market gardening, fruit, flower and seed growing; production of cement and building materials; and distribution of non-food goods (Table 1). Farming and stock-rearing were associated with significant deficit. The following occupations were associated with a significantly enhanced risk: gardeners and groundsmen; textile

fabrics production process workers (excluding weavers); transport and communications inspectors and supervisors; and warehousemen, storekeepers, and assistants in warehouses and assistants in warehouses and stores.

Table 1. Significantly elevated or depressed odds ratios (OR) and 95% confidence limits (95% CL) for industrial branches and occupational titles. Adjusted for age, gender, smoking, alcohol consumption, and diabetes.

	OR	95% CL
Branch		
Farming and stock-rearing	0.77	0.61-0.96
Gardening	4.01	1.37-11.8
Cement and building materials	11.1	1.20-102
Distribution of pharmaceutical products	12.9	1.42-116
Occupation		
Gardeners, groundsmen	3.60	1.08-12.0
Textile fabrics, etc., production process workers	5.75	1.04-31.9
Inspectors, supervisors (transport)	9.23	1.02-83.3
Warehousemen, storekeepers, assistants	2.48	1.19-5.15

When low-level and substantial exposures were pooled for each of the 17 exposures (Table 2), no significant elevations were observed in any of the adjusted ORs. The highest elevations were observed for organic solvents (1.4) pesticides (1.6), and wood dust (1.3). The OR for substantial exposure to organic solvents was 2.0 (1.0-4.1, 14 exposed cases).

In conclusion, and in agreement with the overall results of similar studies (1,2), direct occupational determinants probably do not account for a substantial share in the etiology of PC, at least in conditions resembling Scandinavian or U.S. working environments 15-40 years ago. This study pointed toward the possible role of unidentified organic solvents and pesticides, but the excess risks were not high, and the evidence remained somewhat imprecise.

Table 2. Odds ratios (OR) and 95% confidence limits (95% CL) for occupational exposures. Adjusted for age, gender, smoking, alcohol consumption, and diabetes. Subjects in highest social class excluded.

Exposure	OR	95% CL
Organic solvents	1.14	0.66-1.95
Gasoline	0.72	0.34-1.55
Welding fumes	0.82	0.53-1.27
Chromium (VI)	0.86	0.38-1.96
Lead	1.10	0.68-1.78
Cadmium	0.77	0.20-2.88
Asbestos	0.58	0.35-0.97
Mineral wool	0.81	0.50-1.30
Pesticides	1.60	0.80-3.19
Chlorophenols	1.35	0.25-7.22
Polycyclic aromatic hydrocarbons	1.33	0.69-2.57
Formaldehyde	0.63	0.28-1.38
Aromatic amines	1.87	0.41-8.48
Textile dust	0.95	0.48-1.88
Engine exhaust	0.89	0.51-1.53
Silica dust	0.89	0.62-1.28
Wood dust	1.30	0.79-2.14

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LUNG CANCER MORTALITY IN THE SWEDISH MINERAL WOOL PRODUCTION INDUSTRY - A FOLLOW UP STUDY

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Since 1938 man-made vitrous fibers (MMVF) have been produced in Sweden. Two rock wool plants and one fiber glass plant were investigated regarding cancer incidence and mortality as a part of a collaboration in a multi-national European cohort study of 24609 subjects, organized by IARC (International Agency for Research on Cancer), Lyon. The Swedish cohort, earlier followed up to 1982 has now been followed up to 1990.

Lung cancer incidence was followed 1958-1987 and mortality 1952-1990. Subjects not exposed to MMVF were eliminated from the cohort now comprising 3539 subjects identified by company records, and contributing 58229 person-years of observation. The eligibility criteria was at least one year of employment fiber with exposure since the start of MMVF production.

Historical MMVF exposure profiles were estimated for each individual from plant data using a model for historical exposure estimation based on a plant model of past MMVF exposure. Retrospective exposures to combustion gases and curing fumes were estimated on a job title level.

Lung cancer mortality subdivided by fiber type (expected number were based on national death rates) (see Table 1).

The number of observed cases of lung cancer was close to the expected number, based on national statistics. However, there was a tendency to an increased SMR for lung cancer after a latency of 30 years.

The mean cumulative MMVF exposure in the Swedish rock wool cohort was estimated to be 0.9 f/ml*year. There was no dose-response relationship for estimated MMVF exposure and lung cancer mortality. For the other exposures there were too few cases to draw any conclusions.

The number of lung cancer cases in the Swedish sub-cohort is relatively small. The large IARC study will probably allow more precise conclusions. So far this study supports the results from the last Swedish follow-up study with a slight excess risk for lung cancer after a latency of > 30 years since first exposure (ysfe).

Table 1. Lung cancer mortality subdivided by fiber type (expected number were based on national death rates)

	1983-1990			1952-1990			30 ysfe* (1952-1990)		
Plant	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95%CI
FG**	6	140.0	(52-306)	14	119.7	(65-201)	8	204.1	(88-402)
RW***	5	99.2	(32-232)	12	98.2	(51-172)	5	131.9	(43-308)
Total	11	118.2	(59-211)	26	109.0	(71-159)	13	169.0	(90-288)

* years since first exposure
** RW = Rock wool
*** FG = Fiber glass

MODIFYING EFFECTS OF FAMILIAL PREDISPOSITION AND OCCUPATIONAL EXPOSURES ON THE RISK OF LEUKEMIA AND NON-HODGKIN'S LYMPHOMA

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Leukemia and non-Hodgkin's lymphoma (NHL) have been linked with agricultural and other occupational exposures, but the possible modifying influence of genetic susceptibility has not been extensively investigated. To investigate this relationship, we used data from a population-based interview study of 578 white men with leukemia, 622 with NHL, and 1245 controls residing in Iowa and Minnesota. There was about twice the risk of leukemia and NHL for subjects reporting a parent or sibling with lymphatic or hematopoietic cancer compared to subjects without a family history. We recently examined possible interactions of occupational exposures and familial predisposition to lymphatic or hematopoietic cancer in this population. Using non-farmers without a family history as the comparison group, we found that farmers who had a positive family history and exposure to herbicides had a leukemia risk of 3.4 and a NHL risk of 1.8, non-exposed farmers with a family history had a leukemia and NHL risk of about 2.0, and exposed farmers without a family history had no leukemia risk and a NHL risk of 1.2. To evaluate the interaction of various non-agricultural occupational exposures with family history, we used subjects who did not have a family history or exposure to a specific substance as the referent group. Leukemia risks of 2.0 or greater were observed for subjects with a family history and exposure to gasoline/diesel exhausts and machine oils while exposed subjects without a family history had no risk. Significantly elevated risks of NHL were seen for subjects with a family history and exposure to gasoline/diesel exhausts, machine oils, and solvents. These findings suggest that a familial predisposition to lymphatic and hematopoietic cancer may be a modifier of leukemia and NHL risk among workers exposed to certain occupational exposures.

CAUSE OF DEATH AND CANCER INCIDENCE AMONG NURSES

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Nurses endure emotional and physical effects of stress at the job. They are exposed to potential carcinogens such as ionizing radiation, cytostatic drugs, anesthetic waste gases, infectious agents and variety of chemicals. Former studies have found an increased risk of suicides and have demonstrated increased cancer risk at all sites, breast, corpus uteri, colon, rectum, nervous system, kidney and stomach among nurses.

The objective of this study was to describe the mortality pattern and the cancer morbidity among a cohort of Icelandic nurses with a special focus on suicides and breast cancer. They are compared with the female general population. Information on the nurses was obtained from the Nurses Associations membership rolls, which included all registered nurses in Iceland, who worked and lived in Iceland. The cohort comprised 2168 female nurses. Altogether 1265 (58%) graduated 1970 or later, 389 (18%) 1960-69, 246 (11%) 1950-59, 268 (12%) before 1949. No valid information was available on job categories or work tasks of the individual women. Through the membership rolls it was possible to identify each individual and register their ten-digit personal identification number. These numbers were used to link the cohort with the files of the National Register, the Register of Deceased and the Cancer Register. Standardized mortality ratio (SMR) and standardized incidence ratio (SIR) were calculated on basis of person-years and mortality and cancer incidence rates for the general female population in Iceland.

A healthy worker effect was observed in the total cohort (SMR 0.75, CI 95% 0.64-0.88) mainly explained by significant deficit of mortality from ischemic heart disease (SMR 0.56, 0.35-0.85). An excess was seen from cancer of intestine, uterus, kidney, bladder, nervous system and leukemia, all based on few cases. Suicide was

in excess. When analyzing the mortality data with requirement of 20, 30, 40 and 50 years latency, a significant increase in SMRs was seen for all causes, all cancers and bladder cancer.

The SIR for all cancers was 1.07 (0.89-1.29). SIR was elevated for cancer of liver, lung, breast, kidney, bladder, brain, thyroid, and lymphosarcoma and leukemia. When analyzed with latency, there was a gradient in SIR for most cancer sites;, a significant trend was found for all sites, cancer of lung, breast and bladder.

In conclusion: The data show an excess of incidence of cancers particularly breast cancer, but also lung cancer and kidney cancer. The mortality from lung and breast cancer was not as high, although elevated, which could indicate that nurses benefit from their profession, getting diagnosis and treatment early in the course of their disease. Excess of suicides was only seen in the total cohort. The cohort is small and relatively young, thus leaving us with small numbers.

COLON AND STOMACH CANCER MORTALITY AMONG AUTOMOTIVE WOOD MODEL MAKERS

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Introduction

Since 1979, epidemiologic studies on cancer risks among pattern and model makers have focused on colon cancer. Three studies, commissioned by a major automobile manufacturer on overlapping groups of its own model makers, have all indicated excess risks for cancer of the colon and other sites among automotive wood and other pattern and model makers.[1-3] In 1979, the U.S. National Institute for Occupational Safety and Health (NIOSH) was asked by the United Auto Workers and by the General Motors Corporation to investigate indications of excess colon cancer and other cancers among automotive wood workers. In 1980, NIOSH researchers published a proportionate mortality ratio study on members of the Pattern Makers' League of North America in which excess colon cancer mortality was confirmed for wood pattern makers.[4] In 1985, NIOSH researchers published a detailed industrial hygiene investigation of exposures in automotive wood working shops. This survey did not identify known agents or exposure levels which would explain the apparent excess risk for colon or other cancers.[5-6] We now report the findings of a retrospective cohort mortality study of automotive wood model makers and the findings of case-control studies for colon and stomach cancer mortality within the cohort.

Methods

Cohort: 1. Selection. The cohort included all automotive wood model makers who had worked for at least 1 month at one plant of each of the three major U.S. automobile companies in metropolitan Detroit, Michigan, at any time between 1940 and 1980.

2. Exposure. We used total duration of employment at the three study plants as a proxy measure for exposure. **3. Follow-up.** Vital status was followed through December 31, 1984, using the records of the Social Security Administration and the National Death Index. Death certificates were coded by a nosologist according to the appropriate revision of the International Classification of Diseases (ICD). **4. Analysis.** The cohort was analyzed using a modified life table system.[7] Person-years at risk of dying were accumulated from the date 1 month after the start of wood model making at a study plant until either death or the end of the study. Expected deaths were calculated by multiplying person-years by the U.S. mortality rates for white males.

<u>Case-Control:</u> **1. Case definition.** We defined cases as cohort members who died from colon (ICD 9th Revision, 153) or stomach cancer (ICD 9th Revision, 151) according to the underlying cause of death stated on their death certificates. **2. Control Selection.** We selected 15 controls per case matched on year of birth. Controls were selected at random from the pool of potential controls consisting of all members of the cohort who survived to the age at which the case died.[8] **3. Exposure.** We used both duration of employment in wood model making and cumulative weighted exposure to wood dust as exposure variables. To calculate duration of employment, we coded work histories for all jobs at the study plants. This allowed us to remove time spent laid off, on leave, or working in jobs with exposures other than wood. To calculate the cumulative weighted exposure to wood dust, each job was given an exposure assignment--high, medium, and low wood dust; plastics; metals; and solvents. A total of 106 personal wood dust samples were used to calculate geometric means in mg/m^3 for our three wood dust categories. The geometric means were then multiplied by the duration worked in each job and summed for all jobs. **4. Prior Exposure.** We collected available information on employment prior to the three study plants. Each case or control was assigned a "yes," "no" or "missing" depending on whether he had exposure to wood working from prior employment. **5. Analysis.** We used conditional logistic regression models[9] to test six measures of plant exposure to wood model making: 1) duration employed, 2) duration employed lagged by 10 years, 3) duration employed after 1955, 4) cumulative weighted wood exposure, 5) cumulative exposure weighted wood

exposure lagged by 10 years, and 6) cumulative weighted wood exposure after 1955.

Results

1. Cohort: Cohort Status. Vital status follow-up for the cohort is indicated in Table 1. **2. Cohort Exposure.** The mean duration of employment was 15 years; other descriptive statistics for the cohort are also given in Table 1. **3. Cohort Mortality.** The SMR for all causes of death was 0.8 (95% C.I., 0.73-0.85), a statistically significant deficit. Diseases with significant deficits in mortality risk included: heart disease, cerebrovascular disease, respiratory disease and nonmalignant digestive disease. No cause of death was estimated to be statistically significantly elevated. Statistically nonsignificant excess mortality risks were estimated for cancers of the stomach, colon, and for other digestive cancers as well as for cancers of the kidney and brain and for unspecified neoplasms.
4. Colon and Stomach Cancer Mortality. The SMRs for colon and stomach cancer mortality compared to U.S. mortality rates are shown by decade in Table 2. Except for the period 1940-49, for which the colon cancer SMR was 5.0, the SMRs by decade were relatively unchanging in general agreement with U.S. colon cancer mortality rates from 1940 to 1984.[10] The SMRs for stomach cancer by decade increased over time when measured against the U.S. stomach cancer mortality rates which decreased steadily from 1940 to 1984.[10]

Case-control: 1. Case Definition. Twenty of the deaths due to colon cancer and 17 of the deaths due to stomach cancer observed in our cohort study were defined as cases in our case-control studies. **2. Control Selection.** A total of 543 controls were included in the study--293 in the colon cancer and 250 in the stomach cancer analyses. Table 3 gives statistics on some of the relevant variables for cases and controls. **3. Analysis** Table 4 gives the means for cases and controls for our six wood-exposure variables for both colon and stomach cancer. None of our six wood-exposure variables indicated a significant positive dose-response for either colon or stomach cancer mortality. All of the logistic regression coefficients for wood-exposure variables were negative. Table 4 also shows the odds ratios indicating the change in risk for 20 years of exposure calculated from these coefficients. The 12 odds ratios in Table 4 are for models which included only the single wood-exposure variable specified. We included the following variables in the logistic

regression models to test for confounding or interaction with the exposure variables: year first employed, years since first employment, prior employment in wood model making, exposure to metals, exposure to plastics, and plant. All these variables were dropped from the final models shown in Table 4 because we found no model in which the coefficients for the wood-exposure variables changed appreciably as a result of their inclusion.

Discussion

This is the first analysis of automotive wood model makers in which associations between specific exposures associated with wood model making and both colon and stomach cancer mortality have been tested. In performing these tests our analyses had the following strengths, we: (1) lagged our exposure variables by 10 years to account for latency, (2) tested exposures only after the introduction of impregnated wood products in 1955, (3) adjusted for prior exposure to wood model making and other occupational exposures, and (4) ascertained deaths over a period of 44 years, over four times longer than other studies.[1-4]

The elevated risk for colon cancer mortality in our cohort analysis (SMR=1.2, 95% C.I., 0.8-1.9, based on 21 observed deaths) was lower than observed in other mortality and incidence analyses of pattern and model makers.[1-4] Misclassification of colon and rectal cancer as the cause of death on death certificates has been noted.[11] Had we used a combined category for colon and rectal cancer, our SMR would have fallen to 1.0, 95% C.I. 0.6-1.5. The elevated risk for stomach cancer mortality in our cohort analysis (SMR=1.6, 95% C.I., 0.9-2.6, based on 17 observed deaths) was higher than observed in other mortality and incidence analyses of pattern and model makers.[1-4]

Epidemiologic results must be interpreted in terms of the endpoints chosen for analysis. Cancer incidence is more appropriate than mortality as a measure of risk (endpoint) for diseases such as colorectal cancer where there is relatively good survival. The U.S. 5-year survival rate for the period 1979-1984 was 53 percent.[10] This was less important for stomach cancer with a 5-year survival rate of 16 percent over the same period.[10] Two of the previous studies[1,2] used incidence rather than mortality as their endpoints.

Differences between our results and the results of other studies[1-4] may have been attributable to differences in length of follow-up, the fact that incidence rather than mortality was observed in some other studies and in the populations chosen for analysis. However, limitations and potential biasing factors in both our studies must also be considered.

A major limitation of our cohort analysis was the lack of information about work in wood model making before employment in the three study plants. This provided the main rationale for using our nested case-control studies, not our cohort study, to test the relationships between wood model making exposures and colon and stomach cancer mortality. The mean age first employed at a study plant for men in the cohort was 34 years (Table 1). A review of work records from the three study plants showed that a high percentage of these men had had previous experience in wood model making (Table 3). Therefore we reported only overall SMRs from our cohort analysis because we decided that SMRs by duration of employment and time since first employment, based only on employment at the study plants, were not meaningful for testing exposure-disease relationships.

We attempted to account for prior exposure in our case-control studies by collecting the available data on prior employment for cases and controls and including a variable for prior employment in our logistic regression models as a possible confounder. After controlling for prior employment in wood model making and for other possible confounding or interaction variables in our logistic regression models, we found no positive association between plant exposure to wood model making and risk of mortality for either colon or stomach cancer (Table 4).

In summary, in our cohort analysis we found elevated SMRs for colon and stomach cancer for automotive wood model makers compared to U.S. rates, although neither SMR was statistically significant. The SMR for stomach cancer approached statistical significance and, unlike the SMR for colon cancer, remained elevated even when compared to local mortality rates to control for ethnicity. In our nested case-control analyses, we found odds ratios for colon and stomach cancer mortality within this cohort which did not indicate an association with cumulative occupational exposure to

wood model making within our ability to measure it. Any future analyses of colon and stomach cancer should include: (1) more direct quantification of occupational exposures, (2) quantification of other risk factors, such as diet, ethnicity, and family history, and (3) specific pathology information on disease incidence.

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Table 1. Automotive wood model makers cohort 1940-1984

A. Vital status	Number	(%)
Alive	1,560	(68%)
Deceased	706	(31%)
Certificate Obtained	691	(98%)
Certificate Not Obtained	15	(02%)
Unknown	28	(01%)
Total	2,294	(100%)
Person-years	57,378	

B. Cohort characteristic	Mean
Year of birth	1919
Year first employed	1953
Age first employed	34 years
Duration employed	15 years
Age at end of study	60 years
Time since first employment	26 years

Table 2. Colon and stomach cancer SMRs for white male model makers by decade: U.S. rates comparison

Site	Decade 1940-49	1950-59	1960-69	1970-79	1980-84	Total
Colon						
SMR	5.0	0.9	1.0	1.0	1.3	1.2
95%CI	1.4-12.8	0.1-3.3	0.3-2.6	0.4-2.1	0.4-3.1	0.8-1.9
obs/exp	4/0.8	2/2.2	4/4.0	6/6.2	5/3.8	21/17.0
U.S. rate per 100,000 males[10]	27	25	25	25	24	25[a]
Stomach						
SMR	0.8	0.4	1.8	2.1	3.1	1.6
95%CI	0.02-4.2	0.01-2.3	0.6-4.2	0.8-4.7	0.8-7.9	0.9-2.6
obs/exp	1/1.3	1/2.3	5/2.8	6/2.8	4/1.3	17/10.5
U.S. rate per 100,000 males[10]	29	20	17	10	7	10[a]

[a] 1982-1983 mortality rate per 100,000 males

Table 3. Case-control data: colon and stomach cancer

	Year of death /plant	Age at death	Years since employed	Year first employed	Prior wood employment	Plant metal employment	Plant plastic employment
Colon Cancer							
Case means N=20	1969	66	25	1944	60% yes	10% yes	10% yes
Control means N=293	---	--	24	1945	48% yes	7% yes	4% yes
Stomach Cancer							
Case Means N=17	1970	66	22	1948	59% yes	0% yes	6% yes
Control Means N=250	---	--	22	1947	55% yes	10% yes	6% yes

Table 4. Case-control analysis: wood exposure means and odds ratios

Wood Exposure Variable	[—Colon Cancer—] Case Means[a]	Control Means[a]	Odds Ratio[b]	[—Stomach Cancer—] Case Means[a]	Control Means[a]	Odds Ratio[b]
			Weighted wood exposure (mg/m^3-years)			
Cumulative exposure	4.2	6.8	0.2 0.02-1.6	5.5	6.2	0.7 0.2-3.4
Cumulative exposure lagged by 10 years	2.9	4.8	0.2 0.01-2.2	4.3	4.4	0.9 0.2-5.0
Cumulative exposure after 1955	1.7	3.2	0.1 0.002-3.1	2.9	3.5	0.6 0.1-6.2
			Duration employed in wood (years)			
Cumulative duration	10.8	15.2	0.4 0.1-1.0	12.0	13.8	0.6 0.2-2.0
Cumulative duration lagged by 10 years	7.9	11.3	0.3 0.1-1.1	8.2	10.2	0.5 0.1-2.0
Cumulative duration after 1955	3.6	5.9	0.2 0.03-1.2	5.3	6.2	0.5 0.1-3.6

a. Unmatched
b. Odds ratios and 95% confidence intervals for 20 versus 0 years exposure.

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A CASE-CONTROL STUDY OF MESOTHELIOMA AND EXPOSURE TO BIOGENIC SILICA FIBERS

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The authors conducted the first study to test the hypothesized association between biogenic silica fiber (BSF) exposure and malignant mesothelioma. BSFs are respirable, non-crystalline silica fibers originating from the mechanical breakdown of plants (e.g., sugarcane and rice). We measured exposures to BSF among workers in the Hawaii sugarcane industry. Harvest tractor drivers have the greatest average exposure (0.089 fibers/cc), other field workers have lower average exposures (0.016 fibers/cc), while the remaining sugarcane workers have almost no exposure to these fibers (<0.001 fibers/cc). Cases and category-matched cancer controls were identified through the Hawaii Tumor Registry for the years 1960-1987. Employment in the Hawaiian sugarcane industry was determined from union records, death certificates, and a population census conducted in 1942-43. The authors controlled for occupational asbestos exposure and sampled for both BSF and asbestos to document exposure in the sugarcane industry. A total of 93 cases and 281 controls were included in the analysis. Seven cases and nineteen controls had been sugarcane workers (Odds Ratio [OR]=1.1, 95% Confidence Interval [CI] 0.4, 3.8). Mesothelioma was associated with exposure to asbestos (OR=2.2, 95% CI 1.2, 4.2). The findings suggest that BSF exposure in the Hawaiian sugarcane industry is not likely to pose as a risk for malignant mesothelioma.

AN EXPOSURE-RESPONSE ANALYSIS OF CANCER MORTALITY AMONG A COHORT OF WORKERS EXPOSED TO ETHYLENE OXIDE

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Ethylene Oxide (EtO) is widely used in the production of chemicals, and in the sterilization of medical devices and pharmaceuticals. An excess in leukemia, lymphoma and other cancers has been observed in experimental studies of animals exposed to EtO. Excess leukemia mortality has also been reported in some studies of workers exposed to EtO. We previously reported the results from the largest cohort mortality study of EtO-exposed workers conducted to date. Here we extend our previous work by quantitatively examining the relationship between cancer mortality and EtO exposure estimated by an industrial hygiene based model. Historical exposures to EtO were estimated for all cohort members based on a regression model. Standard life-table analysis was used to examine the cancer mortality in three categories of cumulative exposure to EtO. The Cox proportional hazards model was also used to examine cumulative and other measures of EtO exposure as continuous predictors of cancer mortality. A weak positive trend in all lymphatic and hematopoietic cancer mortality with cumulative EtO exposure was observed in the life-table analysis. This trend was only evident for males with SMRs of 95 (95%CI=26-243) in the lowest exposure category (<1200 ppm-days), 143 (95% CI=62-283) in the middle exposure category (1200-8500 ppm-days) and 196 (95% CI=101-343) in the highest exposure category (>8500 ppm-days). A significant exposure - response relationship with cumulative EtO exposure ($\beta=1.1X10^{-5}$, $x^2=4.96$, $p=0.03$) was observed for all lymphatic and hematopoietic neoplasms when exposures were lagged 10 years in the Cox model. The most pronounced relationship was observed for cumulative EtO exposure lagged 5 years with a model combining lymphocytic leukemia and non-Hodgkin's lymphoma ($\beta=1.2X10^{-5}$, $x^2=8.44$, $p=0.004$). Duration, average, and maximum exposure were not found to significantly predict mortality from all lymphatic and

hematopoietic neoplasms in the Cox model. Mortality from all leukemias, stomach, pancreatic, kidney and brain cancers were not found to have a significant positive association with any of the exposure measures. We believe our findings provide some support for the hypothesis that exposure to EtO increases the risk of mortality from lymphatic and hematopoietic neoplasms.

IS CANCER AFFECTED BY THE HEALTHY WORKER EFFECT?

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Introduction

This investigation attempts to determine whether the healthy worker effect (HWE) biases estimates of cancer risk. Three approaches are used: (1) Review of SMRs calculated for workers exposed to carcinogens found in published literature; (2) Calculation of site-specific SMRs for a large cohort of (mostly white) employed males; and (3) Calculation of SMRs for a representative sample of persons in the U.S. population whose longest held occupation was managerial, professional or clerical using workers in blue collar jobs as referents.

The results of these analyses indicate that estimates of relative cancer risk may be biased by the HWE.

Analysis and discussion

One question that has remained unanswered is whether the HWE biases cancer risk estimates. Ideally the existence of an HWE for cancer risk estimates would be established by calculating site specific cancer SMRs for a cohort of employed persons whose work does not expose them to carcinogens. Unfortunately such studies are not available nor are they likely to be undertaken. However, there are mortality data available for a wide range of groups that make it possible to draw some conclusions.

Reports of industrial and occupational health studies of populations exposed to possible carcinogens very often calculate and report a wide range of SMRs for specific cancer sites. In many instances, SMRs of less than 1.0 are reported. Table 1 lists the studies and SMRs reported for all Causes, all Cancers, and cancers of the oral cavity, stomach, pancreas, lung, brain and nervous System, lymphatic and hematopoietic system, and leukemia in occupational

health studies published in the *American Journal of Industrial Medicine*, the *Scandinavian Journal of Work Environment and Health*, the *Journal of Occupational Health* and the *British Journal of Industrial Medicine*, between September 1991 and September 1992. All studies that used the entire population as the referent for SMRs and had reported SMRs for all causes and all cancers were included. Nineteen SMRs out of 24 for all causes are less than 1.0, supporting the conclusion that the HWE influenced estimate of all cause SMRs. More than half of the SMRs for all cancer and for cancers of specific sites also are less than 1.0, again indicating the likely influence of the HWE. To this number must be added the SMRs that are greater than 1.0 in response to exposure to carcinogens that was sufficiently strong enough to overcome the HWE.

Available mortality data for a large cohort of employed, mostly white male U.S. veterans who hold U.S. government life insurance policies show SMRs of significantly less than 1.0 for cancers, for all cancer and for cancer of various sites. These data come from a cohort study of approximately 250,000 U.S. veterans who held active government life insurance policies in December 1963, and who had served between 1917 and 1940.[1] Persons who served in the Armed Forces were certified healthy at the time of their induction so that these veterans are analogous to an employed population of mostly white males (seriously disabled veterans are not included because they are supported under a special public law).

Table 2 shows cause-specific SMRs, using all U.S. white males as the referent. (The veterans are almost exclusively white males.) SMRs for all causes, all cancers, and cancers of the respiratory system, lung, oral cavity, upper digestive tract, colon, rectum, prostate, and bladder for ages 35-84 are significantly less than 1.0. Also SMRs for cancer mortality do not differ from those of other causes of death such as heart disease, stroke and accidents.

Similar findings were also obtained by Seltzer and Jablon for another group of veterans (1974).[2]

SMRs for decedents in the National Mortality Followback Survey (NMFS) whose employment would not tend to expose them to carcinogens show an SMR of less than 1.0 when compared with

decedents whose longest held occupation might exposed them to such antecedents of cancer. The data for this analysis come from the 1986 NMFS[3] and the 1987 Cancer Epidemiology Supplement of the National Health Interview Survey (NHIS).[4] The 1986 NMFS selected a representative sample of 18,733 death certificates of persons 25 years of age and older who had died in the United States during 1986. The NHIS collects information on a nation-wide sample of households as part of the ongoing activity of the National Center for Health Statistics. Both the NHIS and the NMFS collected information about the longest held occupation both among decedents and the U.S. population.

Table 3 shows that SMRs for All Cancer and for Lung Cancer are less than 1.0 with the effect larger for males than for females. (Calculation of SMRs and Confidence Intervals using the NMFS and NHIS are described in Weinkam 1992[5])

There are then three groups of observations that support the conclusion that cancer SMRs are biased by the HWE:

First, SMRs smaller than 1.0 occur with a considerable frequency in occupational health studies of workers exposed to suspected carcinogens in the workplace. This frequency of SMRs less than 1.0 is very likely less than it would be if these studies had been of cohorts not exposed to carcinogens.

Second, a cross-section of employed males shows a clear-cut decrease in cancer SMRs equal to that seen for other diseases. This observations is perhaps the strongest evidence that the HWE biases cancer risk estimates.

Third, our analysis of SMRs for person whose longest held jobs were unlikely to expose them to carcinogens shows a consistent and mostly significant decrease in cancer SMRs.

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Table 1. Distribution of SMRs reported in four occupational health journals during September 1991 - September 1992

Author	Type of Employment	All Causes	All Cancers	Oral	Stomach	Pancreatic	Lung	Brain & Nerv.	Lymphatic & Hematopoetic	Leukemia
Burchfiel et al.	Chemical Production	0.80	0.87		0.66	0.75	0.91		1.13	1.87
Dagg et al.	Petroleum Refinery	0.73	0.81	0.57	0.81	0.64	0.75	1.24	1.07	0.98
Demers et al.	Firefighters	0.81	0.95	0.81	1.07	0.89	0.96	2.07	1.31	1.27
Grandjean et al.	Gas Station Attendant	1.12	1.24							
Gustavsson et al.	Prefab. House Const.	0.89	1.02		1.59	1.34	0.68	0.24	1.05	0.91
Hall et al.	Pathologists	0.44	0.45		0.17	0.39	0.19	2.18	1.44	1.52
Hansen	Foundary Molders	1.17	1.52							
Macaluso et al.	Oil Refinery	0.81	0.90		0.56	0.85	0.88	0.56	0.88	2.14
Macaluso et al.	Oil Refinery	0.79	0.88		0.70	0.78	0.87	0.74	0.99	1.51
Rafnsson et al.	Truck Drivers	0.95	1.18		0.92	1.50	2.14	1.40	2.30	0.79
Rafnsson et al.	Taxi Drivers	1.02	0.97		0.53	1.76	1.39	0.63	0.85	
Rapiti et al.	Seamen - sailors	0.83	1.09		0.79	1.66	1.71		0.73	1.01
Rapiti et al.	Seamen - shore workers	0.81	0.83				0.57		2.62	2.73
Roscoe et al.	Auto Wood Model Making	0.8	1.0	0.2	1.6	1.1	1.0	1.6	1.0	
Sathiakumar et al.	Chemical Production	0.97	1.20	3.88			1.50		1.44	
Sorahan et al.	Semiconductor Manfg.	0.72	0.79	1.59						
Spinelli et al.	Aluminum Reduction Plant	0.77	0.92				0.93	2.17		1.75
Swaen et al.(a)	Herbicide Applicators	0.76	1.14		0.48	2.18		3.18		
Swaen et al.(b)	Chemical Production	0.78	0.83	1.59	0.46	0.84	0.82	1.75		0.53
Swaen et al.(b)	Chemical Production	0.77	0.76	0.57	0.80	0.76	0.72	1.16		1.00
Teta et al.	Chemical Production	1.00	1.10							
Walker et al.	Chemical Prod. - Plant 1	0.90	0.96	0.60	0.69	0.91	1.00		0.60	0.69
Walker et al.	Chemical Prod. - Plant 2	0.97	1.02	0.29	1.64	0.96	1.01		1.04	1.09
Walker et al.	Chemical Prod. - Plant 3	1.06	1.13	1.57	0.65	0.82	1.47		0.98	0.45

Table 2. Standardized mortality ratios for all causes and for specific causes observed in a population of 250,000 U.S. veterans, holders of government life insurance. (Extracted from Sterling and Weinkam, 1986.)

Cause	35-84
All Causes	0.73
All Cancer	0.76
Respiratory Cancer	0.64
Lung Cancer	0.65
Oral Cancer	0.60
Upper Digestive Tract	0.57
Colon and Rectum	0.85
Prostate Cancer	0.85
Kidney Cancer	0.97
Bladder Cancer	0.80
Heart Disease	0.74
Stroke	0.63
Accident	0.66

Table 3. SMRs and 95% confidence intervals computed for a large representative sample of the U.S. population with managerial, professional or clerical jobs as their longest held employment

FEMALES			MALES		
TYPE	NON-WHITE	WHITE	TYPE	NON-WHITE	WHITE
All Causes			All Causes		
SMR	.650	.814	SMR	.712	.824
Confidence Intervals	(.464,.913)	(.746,.888)	Confidence Intervals	(.525,.965)	(.742,.914)
All Cancers			All Cancers		
SMR	.554	.909	SMR	.694	.801
Confidence Intervals	(.367,.837)	(.797,1.036)	Confidence Intervals	(.463,1.040)	(.683,.940)
Lung Cancer			Lung Cancer		
SMR	.428	.912	SMR	.561	.576
Confidence Intervals	(.208,.881)	(.692,1.202)	Confidence Intervals	(.314,1.002)	(.438,.759)

NESTED CASE-CONTROL STUDY OF RECTAL CANCER IN AUTOMOTIVE WORKERS EXPOSED TO MACHINING FLUIDS

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Several studies have previously reported excesses of rectal cancer among workers exposed to machining fluids, agents used to cool and lubricate metals during machining and grinding operations. We have recently completed a large cohort mortality study of automotive workers in which we noted an association of exposure to one of the major types of machining fluids--straight oils--with rectal cancer risk. To investigate this finding further, a case-control study nested within the cohort was undertaken. In the case-control analysis, it was possible to make full use of the extensive exposure data that have been assembled, allowing control for other exposures and development of evidence implicating specific etiologic agents within the fluids. For each of the 57 deaths attributed to rectal cancer in the cohort, 20 controls were selected from subjects at risk of dying at the age of the death of the case, matched on year of birth (in 5-year categories), plant, gender, and race. Exposure data available for analysis included duration and intensity of exposure to each of the three major types of machining fluids (straight oils, soluble oils, and synthetic fluids) and duration of exposure to a number of additives and contaminants of machining fluids. In a conditional logistic regression model containing terms for all three of the major fluid types, a dose-response trend was evident for straight oils, with an odds ratio for the highest cumulative exposure category (exposure to more than 2.5 mg/m^3 - years) of 3.3 (95% confidence interval: 1.6-6.9). Models are currently being fitted that incorporate terms for specific components of straight oils, including PAHs, sulfur additives, chlorine additives, and certain metal contaminants. The case-control analysis provides strong evidence that exposure to straight oil is associated with risk of rectal cancer.

CANCER RISKS AMONG FEMALE AGRICULTURAL WORKERS IN SWEDEN

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Introduction

Farmers have lower cancer and overall mortality but also lower cancer incidence than the general population. In a public health perspective it would be worthwhile to study the lifestyle of farmers and use that knowledge for primary prevention, but it is also important to identify risk factors that are associated with increased morbidity and mortality.

There are few studies on cancer risks among female farmers, in particular breast cancer and cancer in female genital organs. In Sweden female farmers have not been working with the physically demanding or technically advanced tasks on the farm. Traditionally they have worked more with livestock, mainly milking. Few women have license for pesticide application and have not handled pesticides to the same extent as men. Of the Swedish licensed pesticide applicators, only 1% are females. However, they are likely to have experienced passive exposure to pesticides and other agricultural chemicals to a larger extent than the general population. Hazards of such chemicals would therefore presumably first be seen in those exposed occupationally, either active or passive, and before they appear in the general population.

The aim of the present cohort study of female farmers was to analyze cancer risks in comparison with the general female population. More attention was paid to breast cancer and cancer in genital organs, but also to malignant lymphomas and soft tissue sarcomas due to the occupational exposure, active and/or passive, to pesticides.

Material and methods

The study cohort consisted of 50,682 women who claimed that they

work at least 20 hours per week in agriculture in the 1970 Population and Housing Census in Sweden.

The cohort was followed-up in the nationwide population-based Swedish Cancer Register from January 1, 1971, until death or until December 31, 1984, in the so-called Cancer-Environment Register.

Expected number of cases was calculated on the basis of annual cancer incidence among women in five-year age groups for the whole country.

The standardized incidence ratio (SIR) was computed as the ratio between observed and expected number of cases. The observed number of cases was assumed to be Poisson-distributed and 95 percent confidence interval for SIR was derived by means of Poisson distribution tables.

Since there is a lack of individual exposure data as regards pesticides, we attempted to get crude and hypothetical surrogates for pesticide exposure by dividing the material into time periods, birth cohorts and geographical area.

The follow-up period was divided into three: 1971-75, 1976-80, and 1981-84. The use of pesticides has increased very steeply from the introduction in the late 1940's until the middle of the 1970's whereafter it has levelled out. Birth cohorts were analyzed in five year-of-birth groups; -1904, 1905-14, 1915-24, 1925-34 and 1935-, since younger persons tend to use more pesticides. Residence according to the census was split into six geographical production regions according to main type of agriculture as regards crops and use of pesticides. Region 1 is the southernmost part of the country. About one third of all pesticides in Sweden is used in this region. Region 6 consists of the four northernmost counties, where there is and has been little use of herbicides and almost no use of fungicides and insecticides.

Results

Totally 3,458 cases of cancer were observed in the cohort of women, who were occupied in agriculture in the 1970 census, during the follow-up period from 1971 until 1984 versus 4,060 expected, resulting in a significantly decreased SIR of 0.85.

Individual sites with significantly decreased cancer risks were colon (SIR=0.87, Observed=251), lung (SIR=0.41, Observed=60), breast (SIR=0.83, Observed=903), cervix uteri (SIR=0.43, Observed=71), urinary organs (SIR=0.61, Observed=55), and non-Hodgkin lymphomas (NHL) (SIR=0.77, Observed=67). Other sites with decreased risks, however not significantly, were found for rectum (SIR=0.84, Observed=127), kidney (SIR=0.83, Observed=98) and connective tissue or muscle (SIR=0.67, Observed=17).

No individual cancer site showed a statistically significant increased risk, however non-significant increased risks were noted for vulva and vagina (SIR=1.34, Observed=44), Hodgkin's disease (HD) (SIR=1.31, Observed=24) and multiple myeloma (SIR=1.21, Observed=61).

For cancer in corpus uteri and tumors in ovary, tube, and broad ligament, SIR was close to unity.

For those tumors earlier found to be associated with phenoxy acid herbicide exposure, i.e. malignant lymphomas and soft tissue tumors, SIR was 0.83 (Observed=108) for these tumors together.

There was no statistically significant trend over time in SIR for all sites together or for any individual cancer site. Notable is that SIR for HD was 1.03 (Observed=7) in the first period, 1.36 (Observed=9) in the second, and 1.61 (Observed=8) in the last. For NHL the corresponding SIRs were 0.64 (Observed=13), 0.80 (Observed=24) and 0.90 (Observed=30).

There was no significant difference in cancer risk between birth cohorts. The relative risk of breast cancer was lower than unity in all age groups. Ovary cancer and cancer in vagina or vulva were increased in the youngest birth cohort, born 1935 or later. The risk for HD was elevated in all birth cohorts. The phenoxy acid herbicides associated cancer sites were all elevated in the youngest birth cohort.

SIR for overall cancer differed significantly in the six studied geographical areas: between 0.79 in region 4 (Observed=408) and 6 (Observed=465) to 0.91 in region 1 (Observed=605) and 5 (400).

There were significant differences for malignant melanoma of skin: 0.39 (Observed=6) in region 6 (northernmost) and 1.31 (Observed=24) in region 1 (southernmost); for rectum cancer: 0.42 (Observed=8) in region 4 and 1.32 (Observed=32) in region 1; for breast cancer: 0.69 (Observed=126) in region 1 and 0.96 (Observed=111) in region 5 (which early had mammography screening); and for cancer in cervix uteri: 0.24 (Observed=4) in region 5 and 0.79 (Observed=17) in region 4. SIRs for ovary cancer and NHL were elevated, though not significantly, in the southernmost region, which has the highest use of pesticides and other agricultural chemicals.

EVALUATION OF METHODS TO CONTROL THE HEALTHY WORKER SURVIVOR EFFECT: AN EXAMPLE USING ARSENIC EXPOSURE AND RESPIRATORY CANCER

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The healthy worker survivor effect (HWSE) is a component of the healthy worker effect whereby those individuals who remain employed are healthier than those individuals who leave employment. The HWSE attenuates any true effect of an occupational exposure. In a reanalysis of an occupational cohort from Tacoma, Washington (N=2802), Poisson regression, using the lowest dose category as an internal referent, was used to derive rate ratios (RR) in a reanalysis of arsenic exposure and respiratory cancer. This paper compares results from an unadjusted analysis with results obtained using each of four methods, and from a combination of these methods, to control the HWSE.

From the lowest to the highest dose category, the "unadjusted" RR's were 1.3, 1.4, 1.5, 1.7, and 2.2. Lagging cumulative exposure demonstrated greater RR's at each dose category than an unlagged analysis. For example, at a 5 year lag the RR's by increasing dose categories were 1.5, 1.9, 1.7, 2.1, 2.8 and at a 15 year lag the RR's were 1.7, 1.8, 2.0, 2.6, 3.2. Restriction to those employees who survived at least 5 years demonstrated results similar to an unrestricted analysis; the RR's were 1.3, 1.2, 1.5, 1.5, and 2.1. However, a 15 year restriction period demonstrated greater RR's at each dose category; the RR's were 1.9, 2.0, 2.6, 2.3, and 2.8. A third method incorporates a covariate representing work status: (Currently employed versus retired or otherwise not employed). Inclusion of work status yielded a higher RR than its exclusion. Without work status, the RR's were identical to the unadjusted analysis; with work status, the RR's were 1.3, 1.5, 1.7, 2.0, and 2.6. The combination of lagging exposure and including work status resulted in RR's of even greater magnitude. For example, including work status with a 15 year lag resulted in RR's of 1.7, 1.8, 2.0, 2.7,

and 3.2. A fourth method, Robins' G-Null estimation procedure is operationally different. The G-Null method uses a matched, nested case-control strategy to run multiple "clinical trials." With the lowest dose as an internal referent, odds ratios (OR) are calculated for the other exposure levels. However, these exposure levels are not comparable to those of the previous methods as exposure is not considered in a cumulative or average manner. From lowest to highest exposure category, the G-Null algorithm produced OR's of 1.2, 1.5, 2.3, 1.5, and 3.3. The results were similar when exposure was lagged at 5 and 10 years.

To some extent, each method was successful in controlling the HWSE. However, restricting the cohort reduces the generalizability of the results in addition to the loss of information. Lagging exposure imposes a latency period on the exposure-response relationship. The inclusion of a work status covariate considers an employee's off-work and on-work time to be independent of each other. The G-Null method has two important advantages: one, exposure is not a function of follow-up time; two, the off-work experiences of an employee are not independent of past exposures.

The general shape of the dose-response curve was similar for all methods with a relatively greater increase in risk at the lower levels of exposures. The inclusion of a covariate for work status resulted in larger risk estimates than the lagged or restricted analyses; the shape was also modified with an indication of a greater increase in risk at higher exposure levels than when the covariate was excluded. As the G-Null method handles exposure in a different manner, its results are not directly comparable. From the G-Null analyses, the overall shape of the dose-response curve was similar to the other methods; however, these results implied an even greater risk at lower levels of exposure. Lagging the G-Null analysis did not alter these findings; this agrees with a current hypothesis that arsenic is a late-stage carcinogen. The assumptions underlying each method need to be considered in their application.

NONDIFFERENTIAL MISCLASSIFICATION AND THE POTENTIAL OF BIOLOGICAL MARKERS TO IMPROVE VALIDITY OF STUDIES IN OCCUPATIONAL EPIDEMIOLOGY

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Job category is frequently used as a measure of exposure in occupational epidemiology or surveillance studies. Any nondifferential misclassification which arises from use of job category as a surrogate exposure measure causes a disease-producing effect of the exposure to appear weaker. When the true Relative Risk (RR) is greater than 1 and the surrogate exposure measure is dichotomous, the observed RR will be smaller than the true RR. Although the negative direction of this bias is well accepted, the potential magnitude of the attenuation has not been widely discussed. The simple numerical example which follows illustrates the potential magnitude of the bias and, by implication, the potential contribution of biological markers to correct this bias and improve the validity of studies.

In the 1970s, it might have been considered plausible that health care workers would have an elevated risk of Primary Hepatocellular Carcinoma (PHC), since some evidence existed linking Hepatitis B Virus (HBV) with PHC, and health care workers were known to be at elevated risk for Hepatitis B infection. If no serologic marker had been available, a study of PHC might logically have included the job category "Health Care Worker" as a surrogate exposure variable. Studying health care workers for PHC because they are exposed to Hepatitis B is analogous to studying firefighters for lung cancer because they are exposed to Benzo(a)Pyrene and other lung carcinogens in firesmoke. The following example was chosen because a biological marker (HB_sAg carrier state) with known relative risk for PHC is available for comparison with job category as a measure of exposure.

Consider a hypothetical population-based case control study. The measure of disease outcome is PHC vs. NO PHC. The measure of exposure is the job category "Health Care Worker" (HCW vs. NON-HCW). When hepatitis B Virus carrier state (HB_sAg vs. NO HB_sAg) is used as the measure of exposure, the relative risk for PHC has been reported to be approximately 200. Assuming this as the "true" RR, and assuming realistic population incidences of PHC and prevalences of HB_sAg carrier state in the general population and among HCWs, we will see that the observed Relative Risk (RR) for the association between the surrogate exposure HCW and the disease outcome PHC is 2. The use of job category as a surrogate measure of exposure has resulted in a hundredfold attenuation of RR, compared with the RR of a biological marker of a much more precise and relevant measure of exposure, HB_sAg carrier state. An alternative and more encouraging interpretation is that the use of the biological marker has corrected a hundredfold attenuation in RR due to nondifferential misclassification bias.

Numerical assumptions

1) 4% of the general population are health care workers.
2) Prevalence of HB_sAg carriers among HCWs is 1%.
3) Prevalence of HB_sAg carriers among Non-HCWs is 0.25%.
4) Risk of PHC for HB_sAg carriers is 400 per 100,000 = .004 over the 2 year risk interval.
5) Risk of PHC for non-HB_sAg carriers is 2 per 100,000 = .00002 over the 2 year risk interval.
6) Accordingly, RR of PHC due to HB_sAg is 200.
7) RR of PHC due to being a HCW is to be calculated using the above assumptions. For a rare disease like PHC, this is equivalent to the Odds Ratio (OR).

Epidemiological assumptions

1) Misclassification of "gold standard" HB_sAg state due to using HCW as a surrogate measure of exposure is **nondifferential** which implies, by definition, that:
   A) Sensitivity of surrogate exposure, $P(HCW|HB_sAg)$ is the same for PHC and NO-PHC groups.
   B) Specificity of surrogate exposure, $P(NO\ HCW \mid NO\ HB_sAg)$ is the same for PHC and NO-PHC groups.

2) For simplicity, we ignore possible misclassification of disease outcome, as well as possible misclassification of current acute and subclinical hepatitis cases as carriers.
3) The NO-PHC group is a random sample of the general population.
4) For cases, HB_sAg is measured in blood immediately after diagnosis of PHC, while they are still alive.

Assume a hypothetical population of 10,000,000 adults in a state with a tumor registry. The case group includes all cases of PHC occurring over a 2 year risk interval. The control group is sampled randomly, 2 controls per case from the general population (NO PHC). Both cases and controls are asked their usual occupation and have a blood test for HB_sAg, a marker of chronic carrier state. In the general population, given numerical assumptions 1,2 and 3, we expect to find the following numbers of HCWs and non-HCWs, by HB_sAg carrier state. First, 10,000,000(.04)= 400,000. Then, 400,000(.01) = 4,000 and 9,600,000(.0025) = 24,000. The values of the other cells follow by subtraction.

	HB_sAg	NO HB_sAg	Total
HCW	4,000	396,000	400,000
NON HCW	24,000	9,576,000	9,600,000
Total	28,000	9,972,000	10,000,000

In the 2 year risk interval we expect 4,000(.004) = 16 cases of PHC among HCW carriers of HB_sAg. In the same 2 year interval, we expect 396,000(.00002) = 7.92 cases among HCW noncarriers of HB_sAg. The approximate total is 16 + 7.92 = 24 cases in HCW group.

Among non-HCWs, we expect 24,000(.004) = 96 cases among non-HCW carriers of HB_sAg and 9,576,000(.00002) = 191.52 cases among non-HCW noncarriers of HB_sAg. The approximate total is 96 + 191.52 = 288 cases in the non-HCW group. We randomly sample 2 controls for each case from the general population, for a total of 312 X 2 = 624 controls. Of these controls, 4% = 25 are HCWs and 96% = 599 are not.

	HCW	NON-HCW	Total
PHC	24	288	312
NO PHC	25	599	624
Total	49	887	936

The Odds Ratio (OR) = 24(599)/25(288) = 2 for the association between the surrogate measure of exposure and the disease outcome, and is approximately equal to the RR for this rare disease. By assumption, the RR for the association between the "gold standard" measure of exposure, HB_sAg carrier state, and the disease outcome, PHC, is 200. This strong attenuation is due to nondifferential misclassification, and not to confounding, selection bias, dichotomization of continuous measures, statistical power considerations or rarity of disease. We can demonstrate that the misclassification is, in fact, nondifferential by showing that the sensitivity and specificity of the surrogate for the marker do not vary by disease status.

Sensitivity

For the case group, $P(HCW|HB_sAg) = 16/(16 + 96) = .1429$
For the general population, $P(HCW|HBsAg) = 4000/28000 = .1429$

Specificity

For cases, $P(NON\text{-}HCW \mid NO\ HB_sAg) = 191.52/(191.52 + 7.92) = .9603$
For the general population, $P(NON\text{-}HCW \mid NO\ HB_sAg) = 9{,}576{,}000/9{,}972{,}000 = .9603$

Discussion and conclusions

This example shows that negative bias due to nondifferential misclassification can potentially be of greater magnitude than would be predicted by intuitive considerations of the study design. Corollary to this, a potentially large increase in relative risk may be observed when a biological marker that is part of the causal chain is used as the measure of exposure in place of job category. If biological markers of exposure are successfully developed for exposures of scientific and public health interest, it is likely that they will contribute to the ability of epidemiology to accurately identify

not only occupations at risk, but also the particular exposure subgroups that are at highest risk. Another implication of this example is that occupational epidemiologic studies with purportedly null results which have used job category as the measure of exposure should be carefully scrutinized for possible negative bias due to nondifferential misclassification of exposure. This example lends support to the movement to develop more and better biological markers for use in occupational epidemiology.

The present example demonstrates the **potential** for real life biases to be extremely large, but does not necessarily imply that they are large. Several caveats must be noted that may limit the contribution biological markers can make to eliminating these biases. First, HB_sAg carrier state is a biological marker of long (maybe lifelong) duration, without the time variability and resultant hit-or-miss sampling error that has caused problems in research using DNA adducts and other short-lived markers of exposure. With shorter-lived markers, the bias due to nondifferential misclassification could be only partially eliminated, leaving some residual bias toward the null. In this case, the potential contribution of the biological marker beyond the surrogate exposure measure would be more limited. Second, it remains to be seen empirically how frequently the misclassification is truly nondifferential.

It is noted that HB_sAg carrier state is really a marker of both exposure and susceptibility, located along the causal chain several stages downstream from HBV exposure toward PHC. In general we would expect that, other factors being equal, the farther along a linear causal chain the marker is located (i.e., closer to disease outcome), the larger will be the true RR of that marker for the outcome. In this way, it is hoped that molecular epidemiology utilizing biological markers may be able to contribute to molecular biology research on the mechanisms of disease.

ARSENIC, CIRCULATORY DISEASE, AND THE HEALTHY WORKER SURVIVOR EFFECT

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This report concerns the healthy worker survivor effect. Methods to control the healthy worker survivor effect are applied to an analysis of occupational arsenic exposure and circulatory disease mortality to determine whether bias from differential survivorship is masking an effect. The paper begins by defining the healthy worker survivor effect, presents the evidence from the literature that motivates an examination of arsenic in relation to circulatory disease, describes the data to be used in the present investigation and the methods proposed in the literature to control the healthy worker survivor effect, outlines results of applying these methods, and discusses the results and implications for further occupational studies.

Definition of the healthy worker survivor effect

The healthy worker effect describes the difference in health status between those who are employed and those who are not employed. It is comprised of two selective processes. One is the healthy hire effect, which involves selection into the workforce of those who are relatively more healthy than those not hired. The second is the healthy worker survivor effect: among those hired, there is an attrition of the less healthy, so that those who remain on the job are healthier than those who leave. Note that the cohort itself is not limited to survivors. Once a worker is in an occupational cohort, he/she continues to be followed, but only those who survive at the plant of interest continue to accrue exposure. Hence survivorship is associated with both disease and exposure.

The healthy worker effect operates strongly for cardiovascular disease. Standardized mortality ratios (SMRs) are usually below 1.0, and often below 0.6 or 0.5. Thus, control for both the healthy hire and healthy survivor effect may be necessary to detect any impact of occupational exposures on cardiovascular mortality.

Evidence regarding arsenic exposure and circulatory disease

A possible effect of arsenic on the circulatory system is suggested by three sources of data: toxicology experiments in animals, ingestion studies in humans, and occupational mortality investigations.

First, experimental animal studies suggest electrocardiographic changes and altered vascular responsiveness after exposure to arsenic. Second, peripheral vascular lesions have been documented in human populations whose drinking water supply has a high arsenic content (Wu et al., 1989), including sites in Silesia, Poland, and parts of Chile where Raynaud's Syndrome has been observed. In an area of Taiwan with elevated arsenic levels in well water, a high prevalence of Blackfoot Disease, a gangrenous vascular disorder in which the feet literally turn black (Tseng, 1977), has been observed, along with increased mortality from peripheral vascular and cardiovascular disease (Wu et al., 1989).

Third, in two large cohorts of arsenic-exposed smelter workers, the relation with circulatory disease mortality has been examined. Among the Ronnskar smelter workers, the SMRs for ischemic heart disease are above 100 for six of seven exposure categories, but show little, if any, suggestion of a dose-response trend (Jarup et al., 1989). Among the Anaconda smelter workers, all SMRs are elevated for atherosclerotic heart disease with a very slight dose-response, rising from 128 at the lowest cumulative exposure to 142 at the highest (Higgins et al., 1985). In both cohorts, cerebrovascular disease shows no suggestion of a monotonic relation to dose, though all SMRs are elevated in the Anaconda cohort.

Materials and methods

The third major cohort of smelter workers with arsenic exposure has been investigated extensively for associations with respiratory cancer but not circulatory disease (Enterline and Marsh, 1982, Enterline et al., 1987). These data were used in the current analysis of cardiovascular, peripheral vascular, and cerebrovascular disease mortality.

The subjects comprise a cohort of 2802 white male employees of a single copper smelter in Tacoma, Washington. Follow-up covered the period 1940-1976, and included 73,000 person-years.

Cardiovascular disease deaths numbered 525, about half of all deaths during that period. Arsenic exposures for individual workers were assigned based on industrial hygiene air monitoring data and on work histories of each employee. Further details on construction of the cohort and on exposure assessment are found in previous publications (Enterline and Marsh, 1982, Enterline et al., 1987). Cumulative exposure for each person-year of follow-up was based on summing exposures from the start of employment or from 1940 (for those employed earlier) to the year of follow-up under analysis.

Four methods have been proposed to control for the healthy worker survivor effect

1. Restriction method (Fox and Collier, 1976): The analysis is limited to a subset of the cohort which has already survived a certain number of years on the job. The justification is that such restriction eliminates the variability in survivorship, and hence the differences in opportunity for exposure.

2. Lagging of exposure (Gilbert, 1982): Since survivorship implies further accumulation of exposure, the most recent exposures should perhaps be discounted, to equalize exposure opportunities between survivors and job-leavers. Lagging exposure accomplishes the discounting of recent exposure, regardless of survivorship.

3. Work status (Gilbert and Marks, 1979, Steenland and Stayner, 1991): Survivorship is related to both exposure (enabling accrual of more exposure) and outcome (job leavers are less healthy than those who remain). Hence, survivorship is a confounder, and one might control for it using standard multivariate methods, in which "currently working" is treated as a binary time-dependent covariate.

4. G-methods (Robins, 1986, 1987, Robins et al., 1992): If survivorship is also an intermediate variable, then standard approaches are not appropriate. Since job-leaving may be associated with prior exposures, survivorship is both an intermediate and a confounding variable. Under this paradigm, cumulative exposures are "polluted" by differential survivorship. Comparing those on vs. those off work is invalid because underlying health status already differs: the two groups are not comparable, irrespective of exposure. Thus, with the G-methods, cumulative exposure, since it is determined by job-leaving, is replaced by exposure rate of the current year or time

interval. For the G-null method, cases are matched with surviving members of the cohort who have a similar exposure history; the analysis proceeds by examining exposure differences at points where cases and their matched controls diverge. A modified form of this analysis loosens the matching criteria so that matches need only be for a five-year consecutive exposure pattern rather than from the start of follow-up.

These four methods were applied to the cohort described above in analyses of cardiovascular disease mortality. Causes of death codes #390-458 from the 8th revision of the International Classification of Diseases (ICD) were included. In addition, a cause of death expected a priori to have no association with arsenic, namely accidents, was selected to serve as a "negative control," as a form of validation of the different analytic strategies to control the healthy worker effect. Only the first three methods were applied to accidents.

For the first three methods, all analyses are compared with a baseline regression model, in which age, birth cohort and year of hire are covariates, but the healthy worker survivor effect is not controlled. Because there were no unexposed workers in this cohort, all employees are compared with the lowest exposure category for the calculation of rate ratios. For the G-null method, p-values are reported but comparable measures of association are not directly available.

Results

The baseline model shows a dip in cardiovascular mortality at relatively low exposure levels, with rate ratios rising to 1.0 and then slightly higher as cumulative exposure increases. We note that this pattern appears to resemble the checkmark dose-response discussed by Flanders et al. (1992) who demonstrate that such a pattern can result if disease influences exposure, an observation that is consistent with job survivorship acting as an intermediate variable.

As compared with the baseline model, the use of the restriction method reduces the rate ratios for cardiovascular mortality at all levels of arsenic exposure, with a greater reduction for a more stringent (20 year) minimum follow-up than for a 10 year minimum. For death due to accidental causes, application of restriction analyses

has little effect using 10 years minimum follow-up, but reduces all rate ratios using a 20-year minimum.

The use of lagged exposures increases cardiovascular mortality rate ratios at all levels of exposure, as compared with the baseline model. For most exposure categories, the increase was greater with longer lag periods (e.g., 20 years) than with shorter ones (10 years). Rate ratios are all above 1.0 and the dose-response curve is steepest at low cumulative exposures with a flattening or even a slight decline at the highest exposure category. In contrast, lagging exposures have little influence on the rate ratios for accidental deaths. Because there is some shifting of person-years between exposure categories, some rate ratios rise a little and some fall, but the overall lack of pattern is unchanged.

Adjustment for employment status with two dummy variables (one for those actively employed under 60 years of age and the other for those actively employed and 60 years or older) also results in an increase in rate ratios at all exposure categories. All rate ratios are now 1.0 or greater and there is a suggestion of a dose-response. In the analysis of accidents, inclusion of covariates for employment status had no impact on the rate ratios.

G-null analyses on the circulatory disease mortality suggested no adverse effect of exposure, with all chi-square statistics (1 degree of freedom) less than 2.0. Lagging exposure 20 years increased the chi-squares in cells that had sufficient numbers of workers, but not by a large amount. It was also found that most of the divergences occurred after the first year of follow-up. Analyses which required an exposure history to match only for five years (modified G-null analyses) rather than for the full period of employment produced similar results.

Finally, the circulatory deaths were divided into subcategories of ICD codes: cardiovascular, peripheral vascular, and cerebrovascular deaths. Adjustment using the employment status covariate indicated that most of the excess mortality was for cardiovascular disease, as the rate ratios for cerebrovascular mortality were reduced. Peripheral vascular disease deaths did not show a consistent pattern, partially because of small numbers.

Discussion

Reduction of rate ratios using the restriction method was also observed for the well-established association with respiratory cancer (Arrighi and Hertz-Picciotto, 1992), suggesting a drawback of this method. It is also clear that the number of years of survival to which the analysis is restricted is an arbitrary number. The method assumes cessation of biased survivorship after a certain number of years of employment when, in fact, nonrandom job-leaving probably continues and the differentials between leavers and survivors could increase rather than decrease.

Both lagged analyses and control for employment status resulted in increased rate ratios for cardiovascular mortality but not accidental deaths. To the extent that the healthy worker survivor effect acts solely as a confounder, control for employment status appears in these analyses to control the bias produced by nonrandom job-leaving. For lagging to be effective, the lag between exposure and disease (in this case mortality) must be longer than the period over which the healthy survivor effect operates.

The paradigm of the healthy worker survivor effect acting as both a confounder and an intermediate variable would seem to be the most theoretically sound, though the implementation of this method engenders difficulties in finding sufficient matches for each case. In addition, among those for which matches are identified, the points of divergence of exposure may tend to be very early in the exposure history and may not reflect the time period of exposure most relevant to the disease process. A more flexible approach is provided by G-estimation (Robins et al., 1992) which is a modeling-based extension of the G-null method.

Further work is needed using this approach in occupational cohorts

Based on prior evidence in animal studies and in ingestion studies, an association between occupational arsenic exposure and increases in circulatory disease mortality is plausible. This investigation appears to provide further evidence for such an association. Given how common these causes of death are in the population, detection of small rate ratios is difficult; differential survivorship in workplaces with hazardous exposures exacerbates the problem. Yet rate ratios of

1.2 and 1.3 for such events translate into far more deaths than rate ratios of 3 and 4 for respiratory cancer. Thus, the public health significance of these findings could be large.

Both the healthy hire effect and the healthy worker survivor effect have a strong influence on the risk of cardiovascular events. Investigations of circulatory disease effects from occupational chemical exposures cannot ignore these biases. Use of internal comparisons and of methods to control for the healthy worker survivor effect are needed in studies that investigate occupational exposures in relation to cardiovascular disease.

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INTERVENTION IN OCCUPATIONAL MEDICINE AS BASED ON INDIVIDUAL A PRIORI DISEASE RISK

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There is ample evidence that work-related exposure results in numerous disease cases and that it contributes to a great number of other cases. Exposure at work is rarely the only cause of an illness, though, with some exceptions, e.g., mesotheliomas among asbestos-exposed subjects for whom asbestos exposure generally contributes 50-90% of all new mesotheliomas. Epidemiologists who commit themselves to causalities between work-related exposure and disease are generally less preoccupied with using this knowledge in actual prevention of such illnesses.

The purpose of this presentation is to address the question of whether it is possible to use the currently available knowledge on causal relations between work-exposure and disease to prevent the diseases that otherwise would occur in the population at risk.

Individual disease risk is determined by those host and environmental factors which characterize the subject. The term "risk" may be used for the experienced (a posteriori) risk, as well as for projected (a priori) risk. Disease risk is frequently affected by interaction between the determinants of concern. In such situations, the total absolute risk of a given illness is greater than the sum of the absolute risk resulting directly from each separate environmental disease determinant. Hence, interaction should be accounted for when using individual a priori risk as basis for prevention.

A model for risk determined intervention (RDI) permitting individual risk estimation will be presented, as well as a proposal for the practical use of this model in populations of limited size. Estimation of a priori lung cancer risk will be used as practical example. It will be shown how the etiologic fraction can be used for practical intervention against asbestos-related cancers among subjects with asbestos exposure and tobacco smoking.

To gain measurable results when choosing these two lung cancer determinants as targets for intervention, it is considered preferable to carry out intervention in a population with an a priori lung cancer risk which is much higher than that of the general population. This can be achieved by choosing subjects who are heavily exposed to both determinants. As disease risks resulting from host factors are frequently unknown, it is chosen not to attempt to identify these determinants.

In the chosen example, subjects with an a priori risk of lung cancer, as projected to any time in future, exceeding the national absolute age-adjusted lung cancer risk significantly, e.g., by a factor of five, are enrolled for individual RDI counseling. If the available resources for RDI permit only small numbers of participants, projected absolute disease risk exceeding national averages by seven, eight, or 10 times, can alternatively be chosen as criterion for participation. Actually, once the individual a priori risk is determined, any risk level or risk interval can be chosen as criterion for participation and exclusion, respectively, in both RDI and screening. Further details of the method (RDI) will be presented and discussed at the presentation.

How RDI can be combined with other methods of prevention, e.g., lung cancer screening among high risk groups, will also be discussed. Lung cancer screening could be performed as four-monthly or six-monthly two-angle chest x-rays, alone or along with yearly three-day exfoliative cytology examination.

G-ESTIMATION OF THE EFFECT OF FORMALDEHYDE EXPOSURE ON THE MORTALITY OF CHEMICAL WORKERS

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We use the method of G-estimation to estimate the effect of formaldehyde exposure on all cause mortality in a cohort of 25,000 chemical workers studied by Blair et al., (JNCI, 1986). We show that, in this cohort, employment history is simultaneously a confounder and an intermediate variable on the casual pathway from formaldehyde exposure to death. Further, we show that all standard methods such as Cox and Poisson regression that use a summary of exposure history up to time t (e.g., cumulative exposure, average exposure, duration of exposure) to predict the mortality rate at t will be biased for the casual effect of exposure when there is a covariate that is simultaneously a confounder and an intermediate variable (whether or not one adjusts for the covariate in the analysis). In contrast, a G-analysis is specifically designed to control for confounding by intermediate variables by never lumping exposures at different times. Specifically, we find a statistically significant negative association between cumulative formaldehyde exposure and age-specific mortality (controlling for age, calendar year, race, sex, plant, salary status, and time since hire) using a time-dependent Cox model with cumulative exposure as the exposure variable ($p=.02$). We show this artifactual negative association is due to the fact that unhealthy workers at increased risk of death terminate employment early. Further we find no association between cumulative formaldehyde exposure and age-specific mortality when controlling for employment history, ($p=.947$).

In contrast, a G-analysis estimates a 6% loss in life expectancy for a subject exposed to one part per million of formaldehyde beginning at age 20 [95% confidence interval (1%, 11%)]. We also estimate a casual rate ratio of 124 [95% confidence interval (1.04, 1.44)] had the entire cohort been exposed at one part per million throughout versus had the entire cohort been unexposed throughout. The method

of G-estimation generalizes and improves upon the G-computation algorithm and the G-null test previously proposed by Robins (Journal of Chronic Diseases, 1987).

MISCLASSIFICATION OF A POLYCHOTOMOUS EXPOSURE VARIABLE ADJUSTING FOR MULTIPLE CONFOUNDERS

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Many epidemiological analyses are carried out under the assumption that the amount of exposure to an agent of interest is known without error. However, information on effective dose is rarely available and misclassification is especially prevalent when a surrogate is used to estimate the true exposure level. We examine the problem of estimating the true relative risk in the context of an imprecisely measured polychotomous exposure variable, adjusting for an arbitrary number of discrete confounding variables. Unlike the dichotomous case, misclassification of a polychotomous exposure variable may introduce bias of the estimated risk away from the null value. The true risks may be obtained as the solution to a set of simultaneous linear equations involving the observed risks and the matrix of (possibly unknown) misclassification probabilities.

Estimation of the risk associated with exposure to some agent is often complicated by difficulties in accurately assessing the degree to which study subjects are exposed to the agent, with the result that a large number of subjects' exposures may be incorrect. Misclassifications occur even if exposure is measured only on a categorical scale. It is often easier to classify study subjects on the basis of some surrogate exposure variable (such as job classification) believed to be highly correlated with actual exposure. Again, misclassifications of exposure are inherent in exposure approximations through surrogate variables. Whether direct assignment of some exposure level or surrogates are used, resulting misclassifications affect the value of the risk estimate. Without adjustment for misclassification, these apparent risks are incorrect estimates of true risks.

Assume members of a population are classified by an apparent exposure variable with levels $h_1,\ldots, h_l$ which serves as an index of

true effective exposure levels $x_1,\ldots, x_I$. The h_i may measure some environmental state or be some surrogate (such as job classification) of true exposure. h_1 and x_I are taken to index the groups with no apparent or true exposure respectively. We adjust over a (possibly multivariate) confounder with levels $a_1,\ldots, a_J$. Data on confounder level and disease outcome are assumed not subject to misclassification.

Let $\pi_{x_i h_l a_j}$ denote the proportion of the population with true exposure level x_i, apparent exposure level h_l and confounder level a_j, and $\pi_{Dx_i h_l a_j}$ denote the proportion of the population who have like characteristics and are also cases. Summation over a variable is indicated by omission of that subscript, so for example $\pi_{x_i a_j}$ is the proportion of the population with true exposure level x_i and confounder level a_j. The corresponding rates are given by for example, $\pi_{D|x_i h_l a_j} = \pi_{Dx_i h_l a_j} / \pi_{x_i h_l a_j}$.

$\mathbf{P}_H$ and $\mathbf{P}_X$ are the I x J matrices with entries $\pi_{h_l a_j}$ and $\pi_{x_i a_j}$ respectively. Similarly $\mathbf{R}_H$ and $\mathbf{R}_X$ are I x J matrices with entries $\pi_{D|h_l a_j}$ and $\pi_{D|x_i a_j}$.

The apparent and true exposure distributions in the population are related through the I x I misclassification matrix **M** whose r,cth entry is given by $\pi_{x_r|h_c}$, i.e., the probability that a person with apparent exposure h_c has true exposure x_r. Thus the entries in each column of **M** sum to 1.0. Exposure misclassification is assumed to be independent of confounder level.

The nondifferential misclassification hypothesis says that $\pi_{h_l|Dx_i a_j} = \pi_{h_l|x_i a_j}$ (or equivalently $\pi_{D|x_i h_l a_j} = \pi_{D|x_i a_j}$ for all $1 \le i$, $1 \le \mathbf{I}$, $1 \le j \le \mathbf{J}$.

For any $1 \le i \le \mathbf{I}$, $1 \le j \le \mathbf{J}$

$$\pi_{x_i a_j} = \sum_{l=1}^{\mathbf{I}} \pi_{x_i h_l a_j} = \sum_{l=1}^{\mathbf{I}} \pi_{x_i|h_l a_j} \pi_{h_l a_j} = \sum_{l=1}^{\mathbf{I}} \pi_{x_i|h_l} \pi_{h_l a_j}$$

or in matrix terms $\mathbf{P}_X = \mathbf{M}\mathbf{P}_H$.

Under the nondifferential misclassification hypothesis

$$\pi_{D|h_l a_j} = \sum_{i=1}^{I} \frac{\pi_{Dx_i h_l a_j}}{\pi_{h_l a_j}}$$

$$= \sum_{i=1}^{I} \frac{\pi_{Dx_i h_l a_j}}{\pi_{x_i h_l a_j}} \frac{\pi_{x_i h_l a_j}}{\pi_{h_l a_j}}$$

$$= \sum_{i=1}^{I} \pi_{D|x_i h_l a_j} \pi_{x_i|h_l a_j}$$

$$= \sum_{i=1}^{I} \pi_{D|x_i a_j} \pi_{x_i|h_l}$$

In matrix terms, $\mathbf{R}_H = \mathbf{M}^T\mathbf{R}_X$, so that $\mathbf{R}_X = \mathbf{M}^{T\,-1}\mathbf{R}_H$.

These equations recover the true exposure distribution and true conditional probabilities of disease from the observed data and a given misclassification matrix **M**. These estimates of the true distributions may then be used to compute estimates of other measures of risk such as odds ratios, relative risks or population attributable risks. When more than two levels of exposure are used, the apparent risk estimates need not be biased toward the null. Furthermore, misclassification of a polychotomous exposure variable may mask or even reverse a true monotone dose response relationship.

This technique may be used to compute corrected risk estimates when $\mathbf{P}_H$ and $\mathbf{R}_H$ are known. In some cases, however, only the estimated apparent risks and an assumed misclassification matrix are sufficient to recover estimates of the true risks.

The standardized morbidity (or mortality) ratio (SMR) associated with true exposure level x_i is given by

$$S_{x_i} = \frac{\sum_{j=1}^{J} w_j \pi_{D|x_i a_j}}{\sum_{j=1}^{J} w_j \pi_{D|x_1 a_j}}$$

where w_j is a standardizing weight attached to confounder level a_j.

The apparent SMR associated with apparent exposure level h_l is given by

$$S_{h_l} = \frac{\sum_{j=1}^{J} w_j \pi_{D|h_l a_j}}{\sum_{j=1}^{J} w_j \pi_{D|h_1 a_j}}$$

Suppose that SMRs are computed using a set of referent weights w_j obtained independently of the exposure classification.

Since

$$\pi_{D|h_l a_j} = \sum_{i=1}^{I} \pi_{D|x_i a_j} \pi_{x_i|h_l}$$

we have the system of equations

$$S_{h_l} = \frac{\sum_{ij} w_j \pi_{D|x_i a_j} \pi_{x_i|h_l}}{\sum_{ij} w_j \pi_{D|x_i a_j} \pi_{x_i|h_1}} \qquad l = 2, \ldots, I$$

so that

$$\sum_{ij} w_j \pi_{D|x_i a_j} (\pi_{x_i|h_1} S_{h_l} - \pi_{x_i|h_l}) = 0 \qquad l = 2, \ldots, I$$

or

$$\sum_i (\pi_{x_i|h_1} S_{h_l} - \pi_{x_i|h_l}) \sum_j w_j \pi_{D|x_i a_j} = 0 \quad l = 2, \ldots, I \qquad (1)$$

Let

$$L_i \equiv \sum_{j=1}^{J} w_j \pi_{D|x_i a_j}$$

be the standardized rate corresponding to true exposure level x_i and let

$$A_{il} \equiv \pi_{x_i|h_1} S_{h_l} - \pi_{x_i|h_l}$$

, so that (1) is the system

$$\sum_{i=1}^{I} A_{ij} L_i = 0 \quad l = 2, \ldots, I \tag{2}$$

Since we are interested only in the true SMRs, we divide each equation in (2) by L_l to obtain the I - 1 equations in I - 1 unknowns (S_{x_i} $2 \leq i \leq I$)

$$\sum_{i=2}^{I} A_{il} S_{x_i} = -A_{1l} \quad l = 2, \ldots, I$$

This system of equations may be solved to obtain the S_{x_i} . Such a technique would be useful in estimating the degree to which published SMRs might be affected by exposure misclassification.

SELECTING AN EXPOSURE LAG: IS THE MODEL WITH THE LARGEST EXPOSURE EFFECT THE BEST MODEL?

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In epidemiology, we are generally inclined to consider more credible those associations showing a stronger exposure-response relation, such as higher relative risks or rate ratios. Higher parameter estimates look particularly credible, because one usually exercises care to avoid sources of upward bias, such as bias from selection or misclassification or confounding. Higher relative risks or rate ratios are often emphasized as a criterion to choose among various hypothesized exposure-lag values. The purpose of exposure lagging, or in general of exposure weighting, is to discount exposures which are thought not to be relevant for the outcome under study. Whereas this "highest estimate" approach may often work in practice, the validity of such a criterion is not demonstrated. The purpose of this presentation is to compare exposure-lag choices based on the highest estimate approach vs. those based on a statistical goodness-of-fit criterion (likelihood ratio test). It seems likely that many epidemiologists believe that the two criteria are equivalent i.e., they would lead to the same choice of exposure-lag parameter estimates or they may at the most show trivial differences. The examples shown are based on both previously published studies and hypothetical data, in which an exposure-lag parameter is estimated by trial-and-error fitting: the behavior of the goodness of fit statistic obtained over the assigned values of the parameter is compared with that of the relative risk. The examples show that the magnitude of the point estimate and goodness-of-fit criteria based on the likelihood may disagree. In particular, it is possible to generate examples in which for different hypothesized lags one obtains: 1) an unchanging goodness-of-fit statistic accompanied by a wide variation in relative risk, or 2) an unchanging relative risk accompanied by a wide variation in goodness-of-fit statistic, or 3) a strong disagreement between the exposure lag at which the highest relative risk is obtained and the lag at which the goodness-of-fit statistic is maximized. In summary, the examples built on hypothetical data

indicate the possibility of major discrepancies between these two criteria; these discrepancies can be substantial even with real data. Additionally, situations may exist in which the highest estimate is a biased estimate: the lag may be correlated with the exposure (e.g., duration or cumulative exposure) and it may be a determinant of the outcome (more cases may be counted in the unexposed category as the lag increases). Small-sample bias may also play a role in determining an upwardly biased estimate, since the more extreme lags are often associated with very few observations in the exposed categories. In conclusion, it is suggested that the highest-estimate criterion should not be used for the estimation of exposure-lag or exposure-weighting parameters. A priori biological knowledge and/or goodness-of-fit criteria should be relied upon.

ASSESSING JOINT EFFECTS OF MULTIPLE TIME-DEPENDENT EXPOSURES

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Statistical tools useful for the exploratory analysis of complex time-dependent exposure data in a multi-plant occupational setting are illustrated using preliminary data from three of the fiberglass plants included in the ongoing update of a cohort of U.S. man-made vitreous fiber (MMVF) production workers. As part of the current update of this cohort sponsored by the Thermal Insulation Manufacturer's Association, exposure data for several agents (asbestos, asphalt, formaldehyde, phenolics, polycyclic aromatic hydrocarbon compounds, and silica) are being obtained in addition to quantitative fiber measurements. The focus of this descriptive analysis is to characterize associations between exposure to fiber and exposure to the other agents in the context of a relative risk regression model for respiratory system cancer risk, and to identify collinearities which could affect model stability and interpretation. Near-dependencies in the data can degrade parameter estimation by causing unstable parameter estimates with inflated standard errors. Pairwise correlations among either the exposure variables or the estimated parameters are inadequate measures of collinearity because they may not identify the contributions of more than two variables to a collinearity (Davis et al. (1)).

A collinearity diagnostic proposed by Belsley, Kuh and Welsch (2) for multiple linear regression has been extended by Weissfeld (3) to relative risk regression models. The basis for this diagnostic is that convergence to a well-determined set of parameter estimates depends on the non-singularity of the variance-covariance matrix of the estimated parameters, Σ. The singular value decomposition of Σ provides a measure of the numerical stability of the estimates through the condition indices and the corresponding variance proportions.

The condition indices, $_k = \mu_{max} / \mu_k$, quantify discrepancies in the relative sizes of the singular values of Σ, and the variance proportions measure the contribution of each independent variable to the variance of each parameter estimate. The interpretation of the diagnostic is that two or more "large" variance proportions corresponding to a "large" condition index indicates a potentially problematic collinearity. In the setting of multiple time-dependent covariates, the diagnostic can be applied to identify problematic near-dependencies among the exposure variables.

The relative risk model we considered is an extension of the proportional hazards model (Cox (4)) which accommodates time-dependent covariates. A risk set is formed at each event time (age at which a death from respiratory system cancer occurs) and for each member of a risk set, the duration of each exposure is computed at the age of death of the corresponding case as a vector of time-dependent covariates z(t). The hazard of respiratory system cancer death at age t for someone with covariates z(t) is given by $\lambda_{z(t)}(t) = \lambda_0(t) \exp(z(t))$, where $\lambda_0(t)$ is the corresponding hazard for an unexposed worker. By matching within each risk set on year of birth within one year, we controlled for birth cohort and calendar time. Some analyses were further matched on plant. The risk sets were formed explicitly, and maximum partial likelihood estimates obtained using the conditional logistic regression program in EGRET (5).

These methods are illustrated using preliminary exposure data for 91% of the 3723 male production and maintenance workers in fibrous glass wool plants 1, 4, and 6 of the 1985 follow-up of this cohort, including 70 of the 81 identified respiratory system cancer deaths (Marsh et al. (6)). The work histories were updated for the time period of the 1985 update, and more recent work history and more recent mortality are not yet included. Location-specific industrial hygiene measurements were linked to the individual job histories (Smith et al. (7)). Exposure to respirable fiber is quantified as duration of exposure in years for this preliminary analysis. Exposures to the possible confounders asbestos, asphalt, formaldehyde, phenolics, and silica are also measured as duration of exposure in years.

Preliminary findings for this subset of workers indicate that duration of exposure to formaldehyde and to phenolics are indistinguishable statistically. There is consistent evidence of collinearity between duration of exposure to fiber and to formaldehyde/phenolics within each plant and across the three plants. There is some evidence of a three-way collinearity involving asphalt in plants 1 and 6. These variables were so collinear that the model would not converge for plant 4. However, looking across the three plants it appears feasible to estimate the separate effects of asphalt.

The collinearity diagnostic provides a useful numerical summary of linear associations between multiple time-dependent exposure variables that allows identification of problematic near-dependencies. Strategies for model assessment can then be focused on particularly sensitive aspects of the analysis.

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COMPARISON OF SEVERAL TESTS FOR HETEROGENEITY

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Introduction

One approach to control for extraneous variables like age or smoking is stratification. The whole sample either in a cohort- or case-control study is divided into several strata by these variables. In order to give an estimate of the overall effect, odds-ratio or relative risk, it has to be considered, whether it is appropriate to accumulate the information of all strata. This is done by test on heterogeneity. The same problem is given by more than one study to the same question. Before pooling the effect of all studies to an overall result, the effects in each study have to be tested on heterogeneity. For case-control studies there have been recently some publications dealing with the performance of several tests on this topic (e.g., Jones et al., 1989; Paul and Donner, 1992).

We want to focus our intention to cohort-studies in the field of occupational medicine, where the risk is measured in terms of the standard mortality ratio (SMR). The performance of the common test is compared to three alternative tests. The motivation for this comparison is the analysis of an association between ethylene-oxide and stomach cancer. Six studies have been published with different results. The SMRs are ranging from 0.81 to 10.0 (Steenland et al., 1991).

The overall SMR of 1.2 is not statistically significant. But before pooling all results it is necessary to test the SMR of each study on heterogeneity.

Methods

If we denote in strata i (i=1, ..., k) the observed number of events with O_i, the expected number of events with E_i and $SMR_i = \frac{O_i}{E_i}$ for the estimated standard mortality ratio in each strata i, then $SMR = \frac{\Sigma O_i}{\Sigma E_i}$ is the common standard mortality ratio. The hypotheses for a test of the heterogeneity of the standard mortality ratios are written as:

H_0: $SMR_1 = .. = SMR_k = SMR$
H_1: $SMR_i \neq SMR_j$ for at last one pair (i,j)

It is assumed, that O_i is the realization of a Poisson distributed variable with mean λ_i. The common test is obtained using the approximation of the Poisson distribution by the normal distribution with mean λ_i and variance λ_i.

Under the null hypothesis and because the O_i are independent the following approximative distribution assumptions are valid (Breslow and Day, 1987):

$$O_i \approx N(E_i * SMR, E_i * SMR) \qquad Z_i = \frac{O_i - E_i * SMR}{\sqrt{E_i * SMR}} \approx N(O,1)$$

$$T_1 = \sum_{i=1}^{k} Z_i^2 = \sum \frac{(O_i - E_i * SMR)^2}{E_i * SMR} \approx \chi^2_{k-1}$$

This standard test was compared concerning its properties with the following three alternative test procedures:

A) Square root transformation of a normal distributed variable with similar mean and variance stabilizes the variance (Rao, 1973):

$$\sqrt{O_i + \frac{3}{8}} \approx N\left(\sqrt{E_1 * SMR + \frac{3}{8}}, \frac{1}{4}\right) \qquad Z_i = 2 * \left(\sqrt{O_i + \frac{3}{8}} - \sqrt{E_i * SMR + \frac{3}{8}}\right) \approx N(0, 1)$$

$$T_2 = \Sigma Z_i^2 = 4 * \Sigma \left(\sqrt{O_i + \frac{3}{8}} - \sqrt{E_i * SMR + \frac{3}{8}}\right)^2 \approx \chi^2_{k-1}$$

B) Use of the maximum likelihood theory leads to the following test statistic (Breslow, 1978):

$$\ln(SMR_i) \approx N(\ln SMR, \frac{1}{Oi}) \qquad Z_i = \sqrt{O_i} * (\ln SMR_i - \ln SMR) \approx N(0,1)$$

$$T_3 = \Sigma Z_i^2 = \Sigma O_i * (\ln SMR_i - \ln SMR)^2 = \Sigma O_i (\ln O_i - \ln(E_i * SMR))^2 \approx \chi^2_{k-1}$$

C) Likelihood ratio test for the approximative Poisson distributed variable O_i with maximum likelihood estimate $\lambda_i^0 = E_i * SMR$ under H_0 and $\lambda_i^1 = E_i * SMR$ under H_1 in each strata i. The ln of the corresponding likelihood functions (ln $L(H_0)$ and ln $L(H_1)$) are as follows:

$$\ln L(H_j) = \Sigma(-\lambda_i^j + O_i * \ln\lambda_i^j - \ln(O_i!))$$

The likelihood ratio test R may be written as:

$$R = 2 * (\ln L(H_1) - \ln L(H_0)) = 2 * \Sigma(O_i * \ln(\frac{SMR_i}{SMR}))$$

$$T_4 = \Sigma 2 * O_i * (\ln O_i - \ln(E_i * SMR)) \approx \chi^2_{k-1}$$

The four presented test statistics are all under H_0 χ^2_{k-1} -distributed. Each of them measures the weighted differences between observed and expected number of events under H_0 with some transformations. T_1 has weights containing the expected number of events; T_3 and T_4 have weights containing the observed number of events.

Results

Applying these tests to the ethylene-oxide study leads to the following different results:

$T_1 = 24{,}45$ $\quad T_2 = 7{,}95$ $\quad T_3 = 19{,}08$ $\quad T_4 = 12{,}46$

At the significance level $\alpha = 5\%$ ($\chi^2_5(95\ \%) = 11{,}07$), T_1, T_3 and T_4 are significant; T_2 is not. The question now is, which decision will be the right one, that is, which test procedure will be preferred?

For this the distributions of the four test statistics and the χ^2-distribution were compared concerning their upper 10 %-percentile.

This was done by a permutation test; for every regarded situation--that means for a given combination (E_1, ... E_k) - all possible combinations (O_1, ..., O_k) and the respective T_1, T_2, T_3 and T_4 were calculated. The frequencies of the obtained values were multiplied by the probability of their appearance and then a distribution for every test statistic calculated. These distributions were compared with the χ^2-distribution.

Only situations with small expected numbers of events were considered. With similarly sized strata, there were no appreciable differences between statistics. Approximation to the χ^2-distribution was reasonable (Figure 1).

If the strata were of different size, the four test statistics yielded different distributions (Figure 2). All tests often did not exhaust α; T_1 sometimes doubled α. Only T_2 kept α in almost all situations considered. T_2 is the most conservative test of the four suggested test procedures and is therefore recommended.

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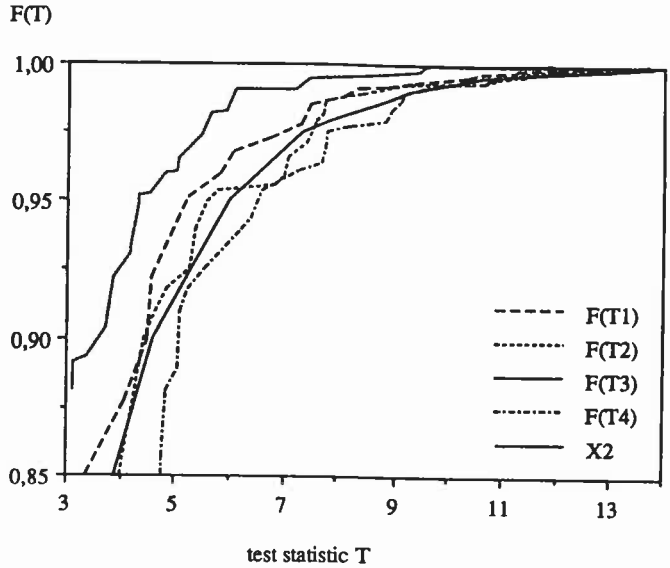

Figure 1. Distributions of the test statistics T1 - T4 and the χ^2-distribution for comparing 3 groups with expected values of 2, 3 and 4 under the assumption of SMR=1.

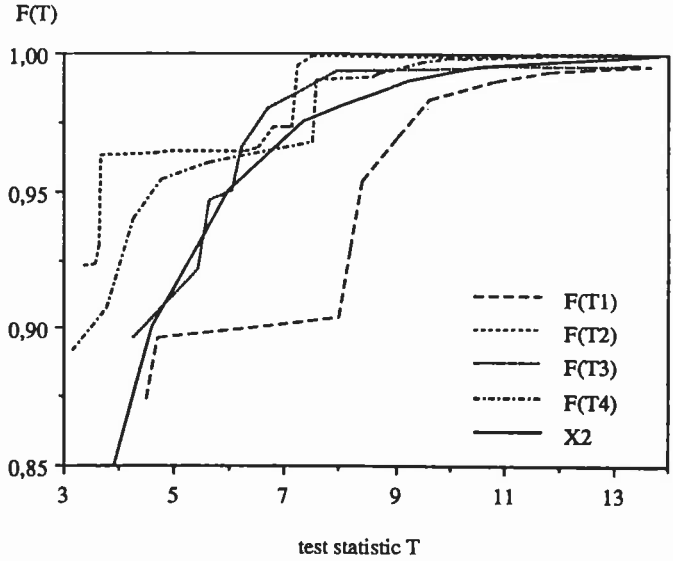

Figure 2. Distributions of the test statistics T1 - T4 and the χ^2-distribution for comparing 3 groups with expected values of 0.1, 3 and 5.9 under the assumption of SMR=1.

DOES THE HEALTHY WORKER EFFECT DECLINE WITH TIME?

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Introduction

It is well recognized by now that a Standardized Mortality Ratio (SMR) obtained by comparing the mortality experience of an occupational cohort with that of the entire regional or national population is biased downward by the healthy worker effect. Occupational studies that base their conclusions on such SMRs often find that the values of crucial SMRs are less than 1.0 or at least not significantly greater than 1.0. In such circumstances an occupational risk may have been masked by the healthy worker effect. Therefore, a question of importance is whether the healthy worker effect is more-or-less constant in magnitude throughout the working years or whether it diminishes as the initial selection advantage of the employed population "wears off" with the passage of time.

Analysis

A paper by McMichael[1] is frequently cited to support the assumption that the healthy worker effects wears off with time. However, McMichael actually discusses a number of different examples, and the pattern of apparent decline of the healthy worker effect with increasing age varies depending on the nature of the population followed. For example, in a population of rubber workers described as mostly active with numbers of disabled workers and early retirees increasing with age, the SMR increases from 0.75 at age 40 to 1.0 at about age 75. On the other hand, in a population of active Bell System employees, the SMR increases from 0.54 at age 40 to a maximum of about 0.74 at age 57 then declines to 0.68 at age 64. More recently, Steenland and Stayner[2] have shown the importance of active versus inactive employment status. They found that an inverse relationship of SMR with age in the combined data from 10 large cohort studies disappeared when the data were stratified by employment status.

We have examined a number of published studies which included SMRs for all and specific causes of death. Some of these studies stratified their results by duration of followup and some also stratified by duration of active employment or otherwise took employment status into account.

There are a number of studies which present SMRs by duration of followup but which do not take account of change of employment status during the followup period. For example, Seltzer and Jablon[3] followed 85,491 World War II Veterans for 23 years. Veterans are similar to an industrial cohort in that they had, at one time, been fit enough to be employed by (inducted into) the armed services. Reporting of deaths was estimated to be 95 to 98 percent complete. Table 1 shows SMRs for various diseases for successive 5 year intervals extracted from Seltzer and Jablon's study. The category "trauma" and those causes with a small number of decedents are now shown. In general, mortality ratios are greater in the later years than they are in the earlier years, although the increase is not monotone for all diseases. Nevertheless, except for vascular lesions, the mortality ratios remain less than 1.0. Table 2 shows SMRs from Milham's[4] study of aluminum reduction plant workers stratified by duration of followup. SMRs increase monotonically for 20 to 25 years then decrease for the interval corresponding to longest followup. Since proportionately more of the most recent deaths would be expected among those followed the longest, the SMRs for the interval corresponding to longest followup may be biased downward (relative to the other categories) because of less complete reporting of deaths. SMRs in the Ott et al.[5] study of styrene product workers (not shown) follow a similar pattern.

In summary, when employment status is not considered, SMRs appear to increase with increasing duration of followup for many years, perhaps indefinitely.

There are also studies in the literature which present SMRs for which employment status has been taken into account to some extent. Fox and Collier[6,7] present SMRs for a cohort of polyvinyl chloride workers who were alive 15 years after entering the industry (see Table 3). SMRs for those still employed after 15 years are much lower than for those who had left the industry. Milham[4] also presents the SMRs of aluminum reduction plant workers stratified by

duration of employment as shown in Table 4. Stratification by duration of employment can serve as an approximate index of active employment. In general, SMRs increase with increasing duration of employment, reaching a maximum after 10-15 years and then decrease for longer durations. For the most part, the peak SMRs in Milham's data occur 5-10 years earlier when the data are stratified by duration of employment than when the same data are stratified by length of followup (see Tables 2 and 4). The decrease of SMRs with longer duration of employment is inconsistent with the assumption that the healthy worker effect declines with time. Henderson and Enterline[8] (not shown) analyzed two cohorts ascertained 10 years apart. Some 1700 men who belonged to both cohorts had lower SMRs for most causes of death than did either cohort I or cohort II. Gilbert and Marks[9] (not shown) studied 20,482 white male Hanford employees hired before 1965 and followed until 1974. The SMRs for those employed 2 years or more are substantially lower than for those employed less than 2 years. The 2 years or more category includes many long term employees and again these lower SMRs are inconsistent with a wearing off of the healthy worker effect.

In summary, each of these studies suggests that the healthy worker effect is larger for active employees than for those who have left employment.

In two previous papers[10,11] we analyzed populations which consisted almost entirely of actively employed persons or separated the actively employed from the unemployed. In (10) we studied the healthy worker effect on morbidity rates from chronic conditions using data from the 19679-1974 National Health Interview Surveys. Table 5 shows age specific morbidity ratios for males by employment status using the entire U.S. male population as the referent. The morbidity ratios for employed individuals are consistently lower than for unemployed individuals regardless of whether or not they are seeking employment. In addition, the ratios for employed males are less than 1.0 and decline with increasing age. The results for females (not shown) are similar.

In (11) we compared the mortality experience of some 290,000 primarily white male U.S. veterans followed from 1954 to 1962 to that of the U.S. white male population. All of these veterans saw some service between 1917 and 1940 and were premium-paying

holders of U.S. veterans life insurance policies in 1953 and presumably employed since they were able to keep up premium payments. Because there are separate benefit programs for those with disabilities, disabled veterans were likely to be included in the cohort. Table 6 shows SMRs for All Causes, Respiratory Cancer, and Lung Cancer. SMRs are lowest for subjects in their 40's, and the SMRs for ages 35-39 are little different for those for 70-74. The veterans population is unique in that it consists mostly of employed individuals who represent a cross section of all occupations.

Discussion

In studies which truly compare the mortality of employed individuals with that of the general population, the age specific mortality ratios exhibit little or no systematic variation with age or duration of followup. Studies which appear to demonstrate a decline in the healthy worker effect compare the mortality of a group of persons who had been employed at one time but who may or may not continue to be employed with that of the general population. The assertion that the healthy worker effect declines with time appears unfounded. Therefore the procedure of discarding the first several years of followup in the belief that the healthy worker effect wears off with time[12] does nothing to control for the healthy worker effect.

The only satisfactory control for the healthy worker effect is to avoid using the general population as a referent altogether. Instead, risk estimates should be calculated by comparing more exposed to less exposed workers. For this reason, the work of Stewart, Blair et al.[13] in developing career exposure estimates may be of particular importance. However, another bias can arise because of differential termination of employment related to dose, especially of irritants such as formaldehyde.

When comparison of more exposed with less exposed workers is not possible, it may be useful to adjust a cause specific SMR by dividing it by the SMR for all causes provided employment status is taken into account. Properties of such an adjustment need further study.

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Table 1. SMRs of U.S. veterans by cause of death and time period

	Time Period				
Cause of Death	**1947-51**	**1952-56**	**1957-61**	**1962-66**	**1967-69**
All Causes	0.74	0.69	0.86	0.87	0.86
All Disease	0.43	0.68	0.82	0.85	0.86
Tuberculosis	0.21	0.60	0.45	0.49	-
All Cancer	0.55	0.85	0.98	0.90	0.89
Diabetes	0.37	0.17	0.28	0.55	0.98
Vascular Lesions	0.68	0.63	1.02	0.85	0.86
Arteriosclerotic Heart Disease	0.76	0.85	0.82	0.93	0.89
Other Cerebro-vascular Disease	0.22	0.31	0.50	0.58	0.61
Influenza, Pneumonia	0.30	0.44	0.71	0.66	0.98
Other Disease	0.47	0.67	0.84	0.75	0.89

Extracted from Seltzer and Jablon, Table 1, (3).

Table 2. SMRs of aluminum reduction workers by cause of death and years between hire and death

	Latency					
Cause of Death	**3-4 yrs**	**5-9 yrs**	**10-14 yrs**	**15-19 yrs**	**20-24 yrs**	**25+ yrs**
All Causes	0.28	0.58	0.62	1.03	0.87	1.54
All malignant neoplasms	0.51	1.14	0.69	1.45	0.84	1.58
All circulatory disease	0.27	0.46	0.49	0.88	0.78	1.56
Emphysema	–	–	1.56	1.54	2.05	4.19

Extracted from Milham, Table 5, (4)

Table 3. SMRs of polyvinyl chloride workers by cause of death and long term employment status

Cause of Death	Workers Still Employed After 15 Years	Workers Who Had Left Employment
All Causes	0.74	1.08
All Cancer	0.89	1.30
Lung Cancer	0.50	1.56
Circulatory Disease	0.75	1.01
Respiratory Disease	0.63	1.11

Extracted from Fox and Collier, Table IV, (7).

Table 4. SMRs of aluminum plant reduction workers by cause of death and duration of employment

	Duration of Employment					
Cause of Death	3-4 yrs	5-9 yrs	10-14 yrs	15-19 yrs	20-24 yrs	25+ yrs
All Causes	0.52	0.87	0.89	1.10	0.82	0.73
All malignant neoplasms	0.89	1.01	1.08	1.52	0.88	0.87
All circulatory disease	0.41	0.86	0.70	0.96	0.67	1.13
Emphysema	–	1.65	2.12	3.40	1.73	–

Extracted from Milham, Table 4, (4)

Table 5. SMRs of U.S. white males for all chronic conditions by employment status and age

	Age						
Employment Status	25-29	30-34	35-39	40-44	45-49	50-54	55-59
All Employed	0.94	0.95	0.94	0.91	0.89	0.85	0.81
All Unemployed	1.56	1.76	2.16	2.31	2.28	2.32	2.21
Seeking Employment	1.34	1.24	1.26	1.14	1.26	1.26	1.25
Not Seeking Employment	1.65	2.01	2.56	2.71	2.54	2.49	2.24

Extracted from Sterling and Weinkam, Figure 1, (10)

Table 6. SMRs of U.S. veterans by cause of death and age

	Age							
Cause of Death	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74
All Causes	0.79	0.63	0.66	0.72	0.75	0.71	0.70	0.73
Respiratory Cancer	0.67	0.36	0.34	0.63	0.61	0.54	0.58	0.71
Lung Cancer	0.71	0.33	0.37	0.68	0.60	0.55	0.60	0.72

Extracted from Sterling and Weinkam, Table 5, (11)

THE SEMICONDUCTOR HEALTH STUDY: AN OVERVIEW OF THE EXPOSURE ASSESSMENT STRATEGY

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The Semiconductor Health Study included three component epidemiologic investigations of adverse health effects that may be associated with working in silicon based wafer fabricating clean rooms. The study was conducted at 14 companies across the U.S. The exposure assessment for these studies was complicated by several factors: chemical exposures are quite low by normal occupational standards; exposure assessment also needed to consider many physical and ergonomic exposures in semiconductor manufacturing, the industry is rapidly changing and over 50 highly variable fabrication rooms had to be evaluated, and there was no specific a priori agent identified for adverse reproductive effects. Three levels of exposure assessment, of increasing specificity, were developed. The simplest categorization was based on whether or not a subject worked in the fabrication rooms for a minimum period of time. A better separation of qualitatively different exposures was based on an analysis of the work structure, which led to assigning subjects to work groups, which were formulated as a part of this research. Finally, potential exposure to several chemical and physical agents and ergonomic stressors were estimated based on the tasks each subject performed. Questionnaires to evaluate exposures were developed and administered to each subject. These included questions about job description as well as the tasks performed. Site visits were made to each of the 50 fabrication rooms by study industrial hygienists, who used a standardized notebook to collect data on work structure and stability, process equipment, chemicals

used, and work practices or engineering controls which might increase or decrease exposure. A limited number of measurements, for magnetic fields, fluoride, and solvents, were made for each fab as well. Based on an analysis of the work structure at each of the 50 fabs, a study wide definition of 8 work groups was developed. Subjects were assigned to work groups based on a four tiered evaluation of their questionnaire responses. Potential exposure scores were developed from which subjects were classified into 3 or 4 exposure categories. The scores were generated from algorithms which combined each individual's questionnaire responses with fabrication room specific information gathered by study industrial hygienists. The fab status of each subject was determined, a work group assigned, and a category of exposure to each of approximately a dozen chemical agents calculated. These three levels of exposure assessment thus provided classification with large numbers in each category (with fab/non-fab having the maximum power) and as well as two levels of specificity: work groups, which included sets of exposures common to most members, and agent analyses, which were most specific.

RETROSPECTIVE EXPOSURE ASSESSMENT USING AN INDEPENDENT PANEL OF EXPERTS

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Epidemiologic research involves measuring the effect of exposures to specific agents on selected aspects of health in populations. Information on the time, amount and duration of exposure to agents enables investigators to develop estimates of "dose" and to study the magnitude of the effect of exposures on the development of disease. Certainty is impossible in the absence of adequate data and assessments of historical or retrospective exposures in the workplace are plagued with speculations. The more prolonged the history of exposures, the greater the speculation. A systematic, documented approach to developing an assessment of exposures retrospectively is described. Information concerning previous exposures to acrylonitrile (AN) was compiled for a cohort study of 467 exposed workers. The information included a comprehensive chronological history of the facility, detailed information on selected jobs and all available industrial hygiene data. Seventeen job titles were selected for assessment from a total of 265 job titles previously determined to have been associated with AN exposure. The selected job titles had to have been used consistently for at least five years for at least five employees and they represent the most common jobs in production, maintenance and the laboratory. Standardized interviews concerning these jobs were conducted with senior employees to determine major tasks, changes and perceived exposures. A panel of four highly qualified industrial hygienists was convened for three days to review the information and to classify job titles on the amount of exposure to AN throughout 1960-1985. Prior to arrival at the facility, each panelist received a protocol along with background information on the facility and the manufacturing process. Upon arrival, each panelist was given a concise summary of information about each job title. A tour of the facility and interviews with senior personnel were provided during the first day. Panelists individually classified each job title. Each panelist's

decisions were then entered on a spreadsheet and given to other panelists on the third day to permit a review by the group. The panel established four exposure categories: <0.2 ppm, 0.2-2.0 ppm (low); 2.1-20.0 ppm(medium); and >20.0 ppm (high). The primary determinants for exposure classification were major process changes, time intervals and initiation of OSHA regulations. Disagreements among panelists regarding allocation of exposure classifications were few and resolved readily in group discussions. Other exposed jobs were classified using clearly specified assumptions. This approach to estimating exposures retrospectively can easily be reviewed by others to determine if and where misclassifications may have occurred.

A HIERARCHICAL CODING SYSTEM FOR CHEMICALS AND OTHER OCCUPATIONAL EXPOSURES

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As part of a research program aimed at identifying occupational cancer risk factors and workplace carcinogens,[1] we are developing a job exposure matrix (JEM) for the main industries of British Columbia. An important consideration in the establishment of a JEM is the coding of occupational exposure. Specifically, the coding method should be systematic and permit analysis of highly specific compounds, similar classes or broad groups of compounds. Since such a system is not available, we have developed a comprehensive, hierarchical approach to the coding of chemicals found in the occupational environment.[2] Each substance is categorized by its chemical nature, subclassified and coded according to chemical composition, chemical and physical properties. Coding of chemicals in such a manner offers two major advantages: 1) information concerning a substance's structure, properties and chemical family affiliations can be readily retrieved; 2) classes of similar compounds may be grouped for analysis. For example, a list of nitrogen-containing compounds could be initially classified into broad categories (e.g., inorganic versus organic) and then further subdivided into classes of agents (e.g., inorganic nitrates, organic aliphatic amines versus aromatic amines).

Ten digits are used to classify substances according to their structures, chemical and physical natures. The first digit denotes chemical nature, differentiating between: simple inorganic substances; complex inorganic salts; organic compounds; inorganic/organic substances (e.g., organometallics); complex mixtures (a comprehensive categorization of trade name products and industrial chemical formulations); physical hazards; and biological agents (includes biomolecules, organisms and pharmaceuticals). The

significance of digits 2 through 10 differs depending on chemical nature. For inorganic, organic and inorganic/organic combinations, digits 2-10 are determined using the nomenclature rules of the International Union of Pure and Applied Chemists (IUPAC).[3-5] Digits 2-10 for complex mixtures and physical hazards are assigned based on physical properties and methods of industrial use. Codes for biological substances are dependent on biological classification and biological origin and are determined using the nomenclature rules of the International Union of Biochemistry (IUB).[6] Each category is described in further detail below.

Inorganic Substances: In keeping with IUPAC nomenclature convention, inorganic substances are coded as binary compounds, composed of a principal element (the cationic species) and a substituent secondary group (the anionic species). The principal element is identified by its atomic number, while the secondary chemical group is coded according to the general class of compound to which the group belongs (e.g., sulfur compounds: sulfate, sulfide, sulfite). The principal element is further described by its oxidation state, its relative amount in a compound, and the family of elements to which it belongs.

Complex inorganic salts (e.g., aluminum sodium oxide, lead chromate silicate) are coded as follows: *Inorganic Acid Salts: Inorganics with 2 Principal Elements*. Both principal elements are identified by their respective atomic numbers. The secondary group is coded in the same way as simple inorganic compounds. Properties of the principal element are not coded. *Inorganic Basic Salts: Inorganics with 2 Secondary Groups.* The principal element is again indicated by its atomic number, with both secondary groups being identified as above. The order in which the secondary groups are coded is determined by IUPAC convention.

Organic Substances: Because of the structural complexity of organic molecules, IUPAC nomenclature rules for organic substances are much more complicated than those for inorganic compounds. As a result, organic coding procedures are correspondingly more complex than those developed for inorganic substances. However, to maintain internal consistency between coding categories and to keep coding procedures relatively simple, organic compounds are coded as consisting of a principal alkyl or aryl parent group and a substituent

chemical functional group, having a particular chemical function. Other properties coded include: saturation state and general hydrocarbon class, the presence of halogens, and the degree of "cyclization" (i.e., straight chain versus cyclic or heterocyclic).

Inorganic/Organic Substances: Substances comprised of both organic and inorganic molecules are coded using combined coding procedures for both inorganic and organic substances. These compounds are coded as consisting of an inorganic principal element, an organic parent group and an organic functional group.

Complex Mixtures: Exposure to specific components of trade name products and industrial chemical formulations is often difficult to characterize because the composition of these compounds is typically unknown or can be varied by changing the components' concentrations. Consequently, codes for these materials are by definition less specific than previously described categories. Complex mixtures are coded initially on the basis of product origin and are subsequently differentiated into "product categories" (e.g., abrasives, pesticides, waxes). To distinguish between materials having slightly different formulations, the chemical nature of the product (i.e., inorganic, organic, biological) and the general chemical class into which it falls are also coded.

Physical Hazards: Physical agents are first classified and coded according to the hazard category to which they belong: ionizing and non-ionizing radiation; magnetic and electric fields; noise and vibration; temperature; and pressure. Exceptions to this approach are the radionuclides and radioisotopes. Rather than being assigned to specific hazard categories, they are identified by their atomic numbers. Other information included in the code: the type of wave field (i.e., continuous vs. pulsed or impact); frequency; and modes of entry. Again, the exceptions are the radionuclides and radioisotopes. They are further defined by atomic mass, and decay or disintegration modes.

Biological Substances: Biological substances have been divided into two broad categories: organisms, their tissues, extracts and products; and molecular compounds. They are then coded on the basis of taxonomic relationships, properties and biochemical class. Although some pharmacologically-active compounds are extracted

from biological sources, many have been either modified extensively or are completely synthesized in the laboratory. Thus, rather than coding pharmaceutical compounds as biomolecules, separate procedures were developed to classify pharmaceuticals into categories based on pharmacological activity, with consideration of chemical relationships where possible. Any substituents on the parent drug and any metals or halides present in the substance are also coded.

Coding Examples: Table 1 illustrates our hierarchical coding procedures for nine representative inorganic and organic compounds. As shown, it is possible to distinguish between compounds having different carcinogenic potential (e.g., arsenic pentoxide vs. arsenic trioxide) and to group those having similar structures or properties (e.g., carbonate compounds: digits 7-10 = 0320; substances containing lead: digits 2,3 = 82; and organic aromatic amines: digits 4-8 = 45005). The first five substances in Table 2 exemplify codes assigned to organisms, their tissues, extracts or products and can be grouped together on the basis of taxonomy (digits 4-7) or biological origin (digit 2). The final three are biomolecules -- carbohydrates, in particular -- that can be grouped together for analysis by biological complexity (digit 3) or biochemical family (digits 4,5).

Summary: This coding system is unique compared to existing systems because it codes substances on the basis of their chemical structures and properties using conventional IUPAC and IUB nomenclature rules and enables them to be grouped for analysis by common features and chemical class. Since our system can be used easily to distinguish specific substances, classes of compounds or broad groups of compounds, we feel that it will become a valuable epidemiological tool. Although our coding system was primarily developed to assist in the identification of potential carcinogens in occupational studies using JEMs, it has wider applications; specifically, it could be used by industry to comprehensively catalogue chemicals and to facilitate monitoring of health hazards in the occupational environment.

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Table 1. Examples of Codes for Representative Inorganic and Organic Substances

Substance	Code
arsenic trioxide*	1333150513
arsenic pentoxide	1335150515
magnesium carbonate	1122020320
sodium carbonate	1111110320
calcium carbonate	1202020320
lead carbonate	1822040320
lead chromate	1822041400
aminobiphenyl*	4414500502
toluidine* (aka aminotoluene)	4514500501

* suspected carcinogens

Table 2. Examples of Codes for Representative Biological Substances

SUBSTANCE	CODE
cow	8618371247
goat	8618374247
cow's hide	8628371232
skim milk (cow's)	8648371285
goat's milk	8648374280
glucose	8854313000
fructose-6-phosphate	8854322400
sucrose	8454522100

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PATTERNS OF ELECTRIC AND MAGNETIC FIELD EXPOSURE IN THE UTILITY INDUSTRY

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Introduction

Epidemiologic research on exposure to electric and magnetic fields (EMF) has been limited by the lack of quantitative exposure data. The situation is even more problematic than in studies on chemical exposures; not even sparse, biased exposure data exist to permit semi-quantitative estimates of historical EMF exposure. Nevertheless, estimates of past EMF exposures will have to be made for retrospective studies. The only available approach is to study the variability of present exposure to EMF. If the present nature of exposure to EMF can be understood and the underlying exposure determining factors can be recognized, it might be possible to extrapolate present exposure into the past. Therefore, the within-worker and between-worker variability in EMF exposures was analyzed and compared to the variability seen in occupational exposure to chemical agents. Also, the most efficient grouping strategy based on general descriptors (utility, job, work environment) was studied. Efficiency was based on resolution in exposure between groups and precision of mean exposure in a group.

Materials and methods

To assess the variability of EMF exposure, we used data from the EPRI EMDEX-100 project, in which the exposure of utility employees at 59 sites in the US and three other countries was measured between October 1988 and September 1989 (EPRI, 1990). Approximately 50,000 hours of magnetic field and 23,000 hours of electric field exposure records taken at 10-second intervals were obtained, of which 70% were from work environments.

Using 4086 magnetic field and 1870 electric field measurements with an averaging time of more than 4 hours, within- and between-worker exposure variability was estimated by applying the random-effects ANOVA model for 16 job groups and 9 primary work environments. The between- and within-group variability was estimated similarly in a two-way random effects ANOVA model, for groups based on job, primary work environment, utility, and combinations of those general descriptors. As a measure for resolution in exposure between groups the so-called elasticity ratio (between-group/between-group + within-group) was estimated. As a measure of precision the median value of the standard errors of mean exposure of each group was chosen.

A second analysis focused on the influence on the exposure of variables like year and month of measurement, job, and during the measurements occupied environment (yes/no and time spent).

Results

For both electric and magnetic field exposures the between-worker component was largest for the majority of jobs. Linemen had the largest day-to-day variability in magnetic and electric field exposure, and this component outweighed the between-worker component. For the majority of job groups the between-worker component for electric field exposure was smaller than the between-worker component for magnetic field exposure (Figure 1). However, the job groups "electricians" and "substation workers" showed considerably more between-worker electric field exposure variability.

The within-group (pooled between-worker, within groups) component was in both cases larger than the between-group component for grouping by job. The elasticity ratio (ϵ) for magnetic fields was only 0.28 (28% of the between-worker variance could be transformed in between-group variance by grouping the workers by job). Classifying the workers by primary work environment was somewhat more elusive ($\epsilon=0.35$). The elasticity ratio for grouping by job was similar for the exposure to electric fields ($\epsilon=0.28$), but lower for grouping by primary work environment ($\epsilon=0.31$). Both for exposure to magnetic and electric fields grouping by primary work environment and utility was most efficient ($\epsilon=0.49$ and $\epsilon=0.43$, respectively) (Table 1). The estimated elasticity ratios for exposure to electric and magnetic fields in the utility industry were relatively

low when compared to ratios for exposure to chemical agents in five industries (rubber manufacturing, reinforced plastics, refineries, animal feed, and brickworks).

Table 1. Effectiveness of different grouping schemes for the exposure to electric and magnetic fields in the utility industry

Exposure	N	k	Grouping scheme (n)	Elasticity	Precision
magnetic fields	4086	1574	job (16)	0.28	0.11
			pwe (9)	0.35	0.08
			utility (55)	0.11	0.20
			job & pwe (78)	0.35	0.23
			job & util (446)	0.39	0.27
			pwe & util (367)	0.49	0.26
electric fields	1882	798	job (16)	0.28	0.13
			pwe (9)	0.31	0.12
			utility (53)	0.10	0.30
			job & pwe (64)	0.34	0.22
			job & util (298)	0.23	0.24
			pwe & util (301)	0.43	0.22

N: number of measurements
k: number of workers
n: number of groups
pwe: primary work environment
util: utility

For both electric and magnetic field exposure, occupied environment and season (month of the year) had a significant effect on exposure level, but together explained respectively only 23% and 24% of the total exposure variability. Differences in job content, size, production, etc., between utilities undoubtedly contributed to the large amount of unexplained exposure variability. Occupied environment explained almost 6% more of the variance than job group (R^2 respectively 0.22 and 0.16 for electric field and respectively 0.23 and 0.17 for magnetic field). Using occupied environment either as a dummy variable or as a time variable in the model did not make a difference (R^2 respectively 0.20 and 0.22 for electric field and respectively 0.22 and 0.23 for magnetic field). Exposure levels were significantly elevated in September and March for exposure to electric fields and in December for exposure to magnetic fields.

Conclusions

These analyses have convinced us of assessing historical EMF exposure by company and the necessity of unravelling the exposure determining factors, since the 16 job groups and 9 work

environments are not specific enough to prevent serious exposure misclassification. Information on EMF exposure determining factors which are available in the past will have to be assessed for each of the five involved companies and applied to randomly collected repeated measurements of utility workers' present exposure to EMF.

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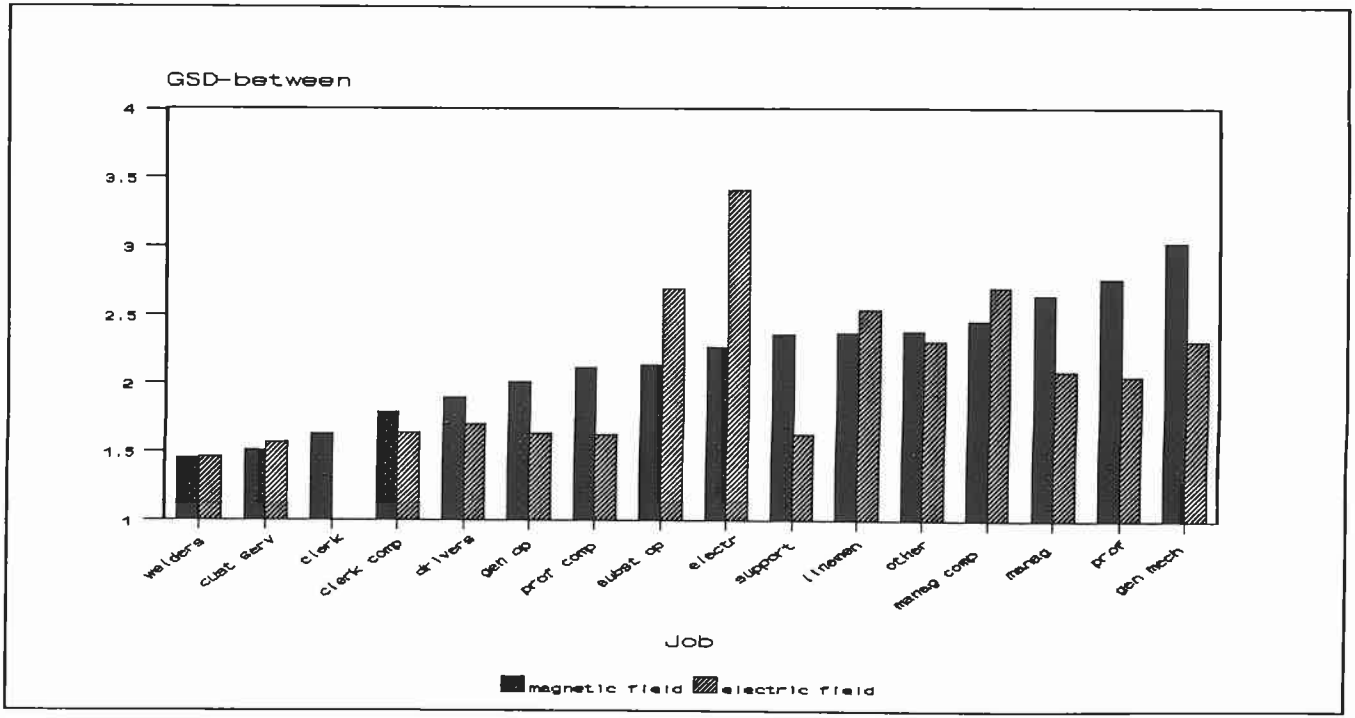

Figure 1. Between-worker variability of exposure to magnetic and electric fields for each job

AN EVALUATION OF NEW FIBER AND CO-EXPOSURE DATA FOR THE U.S. COHORT OF FIBROUS GLASS PRODUCTION WORKERS

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The ongoing U.S. historical cohort study of fibrous glass production workers has, to date, provided equivocal evidence on the relationship between fiber exposure and respiratory system cancer. A total evaluation of exposure-response has not been possible because of the lack of complete and accurate individual worker data on employment history, cigarette smoking, lifestyle factors, racial composition, and historical workplace exposures to fibers and other non-fiber agents. To provide a framework for a more comprehensive and rigorous evaluation of exposure-response, mortality surveillance and exposure assessment programs for the U.S. cohort were initiated in 1987 and 1988, respectively, by the University of Pittsburgh, Department of Biostatistics and the University of Massachusetts, Department of Family and Community Medicine, at the request of the Thermal Insulation Manufacturers Association. The programs include enlargement and enhancement of the original cohort database and an expanded nested case-referent study of respiratory cancer that parallels the proposed IARC case-referent study of lung cancer among European workers.

Historical exposure profiles for individual members of the current study were estimated using an approach developed by Smith and co-workers that effectively integrates epidemiological and industrial hygiene methods. Included in the profiles are time period, plant and job-specific data on workplace exposures to respirable glass fibers and on co-exposures to six groups of agents: asbestos, arsenic, formaldehyde, phenolics, polycyclic aromatic hydrocarbon compounds, and silica.

An extensive descriptive analysis of the expanded exposure profile data for fibrous glass production workers from four of 11 study plants included a comparison of the original and new assessments of fiber exposure. Measures of fiber exposure included duration, cumulative, and average exposure. Important differences in estimated fiber exposures were found relative to time period and plant. The six co-exposures were characterized individually, jointly, and in conjunction with fiber exposure. The exposures to fiber and the other agents occurred at various levels and in various combinations in the different plants. The extent to which independent exposure effects can be identified statistically is addressed in a separate paper by Stone and Marsh.

RETROSPECTIVE PESTICIDES EXPOSURE ASSESSMENT IN CASE-CONTROL STUDIES. INTER-RATER AGREEMENT

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Some epidemiological studies suggest that exposure to pesticides may increase the risk of cancer. The most consistent findings refer to non-Hodgkin's lymphomas and soft-tissue sarcomas and exposure to phenoxy acid herbicides and chlorophenols; leukemia, multiple myeloma and brain cancer have been associated with insecticides (1). Among the studies the relative risks vary, often are not large and in some cases deficits are shown. One of the possible explanations in the variability of the relative risks could be the difficulty in providing detailed pesticides exposure assessment.

The method used for retrospective pesticides exposure assessment in two Italian multicentric case-control studies is presented. One study is investigating the association between hematolymphoietic malignancies and occupational exposures, including agricultural chemicals (2); the other is a multi-site, multi-factor case-control study aimed at detecting carcinogenic risk associated with pesticides (3).

To infer exposure in agriculture, local experienced agronomists review information collected by the questionnaire and translate it into a history of pesticide exposures. The questionnaire contains a specific section with 24 forms explicitly designed for the crops prevalent in the study areas. In each crop-form, information on specific crop diseases and whether pesticides have been applied are collected. Information on period and frequency of treatment, mode of application, and reentry in the field after the treatment are also

collected in detail. Furthermore, each study subject is interviewed about protective equipment adopted, personal habits during and after the treatments and where the pesticides are stored. In Figure 1 an example of crop-form, referring to the vineyard, is presented. The agronomists, on the basis of data contained in the questionnaire, attribute to each subject the probability and the intensity of exposure. Probability of usage is expressed in terms of chemical families and active ingredients and is assessed in ordinal scale (low, medium, high) considering period and crop and type of crop-disease or treatment applied. For assessment of intensity of exposure, the agronomists consider the information on operation carried out by the subject, the storage, the mode of application, the protective equipment adopted, the personal habits during and after the treatments and also information on frequency and duration of treatments and the number of acres treated. They also express a judgment on quality of information reported by the subject.

In addition, an "a priori" crop exposure matrix (CEM) was developed in the contest of the two studies. The CEM is specific to 14 areas and to 10 major crops (barley, maize, rice, wheat, flowers, olive tree, orchard, sugar beet, vegetables, vineyard). A time axis, starting from 1950 until now, has been incorporated in the matrix, and the exposure axis is made up of a list of 440 active ingredients or mixtures used in the last 40 years in the areas of interest(4). Therefore, we have two independent procedures for exposure assessment, one "a priori" based on the crop exposure matrix and one "a posteriori" based on interpretation by agronomists of job histories. The reliability of the described exposure assessment approach by experts is evaluated using the procedure described by Goldberg(5). A trial was carried out in one of the study areas in order to determine the degree of agreement between two raters in identifying exposure to chemical families. The two raters examined independently the crop descriptions and utilized the local CEM as a checklist.

The agreement was assessed on binary scale (present, absent) considering each crop separately. The Cohen's kappa was used as the index of agreement(6). In the trial, 18 crop descriptions were examined by two raters and a checklist of 48 chemical families was utilized. The agreement was excellent in vineyard (k=84%) and cereals (k=75%) and good in olive tree (k=65%) and vegetables

(k=0.65%) (Table 1). The results of the trial, which evaluated the reproducibility of this type of retrospective pesticide exposure assessment, are encouraging.

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Table 1. Inter-rater agreement in the province of Florence (two raters, 18 crop description): k values by crop.

CROP	n° of crop descriptions	k
VINEYARD	7	0.84
OLIVE TREE	3	0.65
VEGETABLES	3	0.65
CEREALS	5	0.76

VINEYARD N.ID.____

ACRES ____ FROM ____ TO ____

____ ____ ____

IN THE CULTIVATION WHERE YOU WORKED

DID YOU APPLY TREATMENTS AGAINST PHYTOPHAGOUS OR ANY OF THE FOLLOWING PLANT DISEASES?:	PLASMOPORA VITICOLA YES NO — —	UNCINULA NECATOR YES NO — —	BOTRYTIS YES NO — —	CLYSIA AMBIGUELLA YES NO — —
IN WHAT YEAR WERE THE TREATMENTS FIRST APPLIED?	_____	_____	_____	_____
IN WHAT YEAR WERE THE TREATMENTS LAST APPLIED?	_____	_____	_____	_____
HOW MANY YEARS IN TOTAL WERE THE TREATMENTS APPLIED?	_____	_____	_____	_____
HOW MANY DAYS PER YEAR?	d/y _____	d/y _____	d/y _____	d/y _____
WHO USUALLY APPLIED THE TREATMENTS, DID YOU?	yes__ no__ from to	yes__ no__ from to	yes__ no__ from to	yes__ no__ from to
HOW MUCH TIME DID YOU SPEND SPRAYING?	__ __ h/day _____	__ __ h/day _____	__ __ h/day _____	__ __ h/day _____
WHO USUALLY PREPARED THE MIXTURE, DID YOU?	yes no — —	yes no — —	yes no — —	yes no — —
HOW MUCH TIME DID YOU SPEND MIXING?	__ __ h/day _____	__ __ h/day _____	__ __ h/day _____	__ __ h/day _____
DID YOU ASSIST IN THE APPLICATION OF THE TREATMENTS?	yes no — —	yes no — —	yes no — —	yes no — —
HOW WERE THE TREATMENTS APPLIED?	yes no	yes no	yes no	yes no
BACKPACK	— —	— —	— —	— —
MECHANICAL PUMP AND MANUAL NOZZLE	— —	— —	— —	— —
SPRAYING BAR	— —	— —	— —	— —
BACKPACK ATOMIZER	— —	— —	— —	— —
TRAILER ATOMIZER	— —	— —	— —	— —
TRACTOR	— —	— —	— —	— —
OTHER(specify)_____	— —	— —	— —	— —

DID YOU GO INTO THE FIELD AFTER THE TREATMENTS? yes__ no__ IF YES, WHY? _____

AND HOW SOON AFTER THE TREATMENTS? ____ AND HOW LONG DID YOU REMAIN IN THE FIELD? ____

Figure 1. Example of crop-form referring to vineyard

USING THE VIDEO IMAGING TECHNIQUE FOR ASSESSING EXPOSURE IN LIVESTOCK INSECTICIDE APPLICATIONS

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The Assessment Methods for Pesticide Exposure (AMPE) study was conducted collaboratively by the National Cancer Institute and the University of Iowa - Institute of Agricultural Medicine and Occupational Health. The study was a methodological investigation to gather information on the reliability and comparability of differing approaches in obtaining historical information on agricultural pesticide exposure and to relate work practices with current monitoring techniques. An integral part of the Assessment of Methods for Pesticide Exposure (AMPE) has been the inclusion of the VITAE© (Video Imaging Technique for Assessing Exposure©) system developed by Dr. Richard Fenske of the University of Washington. Before the pesticide application by each farmer, a series of still frame video images were acquired using the VITAE© system. These image series include the front, left and right side, and back views of the head, arms, legs and torsoes of the applicators. This same video image series was acquired after the entire application process, to be used for calculation purposes at a later date. Immediately before the mixing step in the application process, fluorescein dye, Uvitex OB {2,5- Bis (5-tert-butyl-2-benzoxazolyl) thiophene}, was added at the rate of .3 gram per gallon of end product. The application process was then monitored, with times, rates and application methods noted on an industrial hygiene monitoring form. Video tapes of the applications were also made to document the operational setting. Eleven of the twenty farmers monitored exhibited dosages to livestock insecticide in time weighted average dosages ranging from 20 μg/hour to 66,797 μg/hour. The VITAE© system proved to be quite capable as a monitoring tool for pesticide exposure. Although there are limitations with the VITAE© as opposed to the dermal dosimeter technique, VITAE© has many advantages. First and foremost, is the ability for the applicator and

researcher to visually see where and how dosage occurs. A second advantage of the VITAE© system is the lower cost per analysis as opposed to the cost per analysis for the dermal dosimeter technique. Another advantage is not encumbering the applicator with the sets of dosimeters that sometimes alter application technique. The VITAE©25 system is by far the least invasive of the two techniques. Images stored by the VITAE© system can be reviewed, restudied, recalculated, printed or turned into photographs for educational purposes.

MENTAL RETARDATION AND PARENTAL OCCUPATIONAL EXPOSURE: A COMPARISON BETWEEN PERSONAL INTERVIEWS AND JOB-EXPOSURE MATRICES

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In occupational epidemiologic studies, several methods can be used to gather information about exposure retrospectively.[1] Personal occupational histories obtained by postal questionnaires or interviews may supply very detailed information, but are liable to recall bias.[2] Job-exposure matrices on the other hand, provide for every person a general list of (potential) exposures in which severe misclassification is not to be excluded.[3,4] In a case-referent study on mental retardation in offspring and occupational exposure of the parents, these two methods for the identification of risk factors were evaluated.[5] Mental retardation is a developmental defect of the central nervous system with a prevalence of approximately 3% in school-age children. Among others, occupational and non-occupational exogenic exposures are considered risk factors for this disorder. In the study, detailed occupational histories obtained by means of personal interviews with the parents were compared with the exposures generated by a British[3] and an American[4] job-exposure matrix. The applicability of job-exposure matrices for reproductive epidemiologic studies in general was inferred from the results of the present study.

Population and methods

The case group consisted of 340 mentally retarded children with unknown origin, using an IQ < 80 as diagnostic criterion. The 362 referents were children with physical congenital handicaps for which the cause was known and not related to the occupation of the parents. Both groups were selected from medical files in the University Hospital in Nijmegen, The Netherlands, and were diagnosed between

1979 and 1987. The referent group was chosen for its comparability to the case group on relevant characteristics in order to avoid information bias.[6] Both parents of these children were invited to participate in a personal interview which comprised the period from 3 months preconception to 6 months postnatally, subdivided into 5 time intervals. The overall response rate was 89.5%; the parents of 306 cases and 322 referents were interviewed by 2 trained interviewers using a structured questionnaire. The interviews consisted of a detailed occupational history and questions about living environment and life-style habits (e.g., smoking, alcohol and medical drug use). A calendar was used to focus the attention of the participants on the period under study. In the occupational history, questions about job title, industry and physical working environment were supplemented with a description of an ordinary working day and with industry-specific exposure check lists.

The information on job title and industry was used as input for the two job-exposure matrices. Exposures were generated for each parent who had been employed in the period under study (308 mothers and 611 fathers); unemployed parents were not considered to have been occupationally exposed. In the analyses for the British matrix, 30 out of 49 exposure items could be compared with self-reported exposures in the interview. For the American matrix, 42 out of the 367 exposure items were included. As measures of agreement, the average number of concordant and discordant exposures in the preconceptional period were calculated, as well as sensitivities and percentages of false-positive exposures when the interview was set as a gold standard. Furthermore, the odds ratios with 90% confidence intervals obtained through interviews and matrices were compared for each exposure item per time interval. Where necessary the odds ratios were adjusted for confounding. To avoid unstable estimates, substances to which less than 1% of the population had been exposed were excluded from the analyses.

Results

The measures of agreement are presented in the table below, from which it becomes clear that the majority of exposures were neither reported in the interview, nor generated by the matrices (interview - / matrix -). Also, the number of concordant positive exposures was small compared to the discordant exposures. As a result, the agreement between interview and matrices was low: the sensitivity

ranged from 17.9% (American matrix, mothers) to 32.4% (British matrix, fathers) and the percentages of false-positive exposures from 66.7% to 96.0%, due to the high frequency of matrix-generated exposures that were not reported by the parents in the interviews.

	AVERAGE NUMBER OF EXPOSURES			
	British matrix		American matrix	
measures of agreement between personal interview and two job-exposure matrices	mother [n=308]	father [n=611]	mother [n=308]	father [n=611]
concordant exposures:				
interview + / matrix +	0.3	1.0	0.2	1.1
interview - / matrix -	27.2	24.7	35.8	32.9
discordant exposures:				
interview + / matrix -	0.9	2.2	1.0	2.8
interview - / matrix +	1.6	2.1	5.0	5.2
sensitivity of matrix	26.8%	32.4%	17.9%	29.3%
false-positive exposures	83.1%	66.7%	96.0%	82.0%

In the analyses for the mothers, the odds ratios have been adjusted for primi-gravidity, prematurity, alcohol consumption and some leisure time activities. The most pronounced associations between mental retardation and maternal occupational exposure were observed in late pregnancy (months 6-9). By the interview method, statistical significantly increased odds ratios were found for exposure to heat (OR=1.7), vibration (OR=2.9), mercury (OR=8.7), organic solvents (OR=1.7), alcohol (OR=1.9), paint, pigments and dyes (OR=2.7) and dust (OR=2.2). In contrast, the British matrix showed a reduced odds ratio for heat (OR=0.3), odds ratios of approximately unity for mercury and dust, and almost no exposure to solvents. Only for paint, the odds ratios were comparable (OR matrix=3.9). The American job-exposure matrix also yielded odds ratios of unity for mercury and dust, and for heat and alcohol as well. Odds ratios for paint and vibration could not be calculated in this matrix. For ionizing radiation, metals, welding fumes, diesel fuel, several organic solvents, ethylene oxide, printing inks and adhesives, one or both of the matrices produced a large number of exposed persons, whereas according to the interview almost no

mothers were exposed. Of these exposures, only the odds ratio for diesel fuel (OR=2.0) was statistically significant.

On the other hand, a number of exposures were reported in the interviews that were not included in the job-exposure matrices, but were relevant to the study on mental retardation. A series of markedly increased risks were observed among those exposures: working with copying machines (OR=3.0) and occupational exposure to non-ionizing radiation (OR=9.3), hair cosmetics and dyes (OR=3.7), hexachlorophene/phenylphenol (OR=3.1) and antibiotics (OR=2.9). The British matrix produced an interesting finding for the exposure variable 'contact with public' (OR=1.7, 90%CI: 1.2-2.5).

The number of fathers exposed to a particular agent was high compared to the mothers, but the majority of odds ratios varied around unity. Statistical significance was reached for working in a hot environment (OR=1.3), and for exposure to microwaves/radiofrequencies (OR=2.5), ultrasound (OR=4.9) and exhaust fumes (OR=1.3) according to the interview, as well as for exposure to beryllium (OR=2.3) in the British matrix and ultraviolet light (OR=1.3) and pesticides (OR=1.4) in the American matrix. Decreased odds ratios were observed for iron/zinc (OR=0.7) and welding fumes (OR=0.7) in the matrices.

Discussion

The agreement between the personal interviews and the job-exposure matrices was low, mainly due to the large number of false-positive exposures generated by the matrices. In the interview data, a series of increased odds ratios were observed for occupational exposures of the mother; a few paternal exposures were also associated with mental retardation. Analyses of the matrix data confirmed only a minority of these associations and added hardly any new findings. These results seem not to be influenced by selection bias, confounding or information bias in the interviews. Cases and referents were comparable with respect to almost all background variables and the majority of life-style factors; the confounding variables were adjusted for in the analyses. In a validity study, no information bias on exposure could be detected.[6] Therefore, the personal interviews were considered the gold standard in this study. The applicability of job-exposure matrices, however, is determined

by the coding schemes for occupations and industries and the input of exposures, which usually are very country-specific and depend on the purpose for which the matrix is designed.[7] Moreover, variations in the kind and level of exposure across time and place cannot be taken into account. These limitations may lead to serious misclassification of exposure generated by job-exposure matrices, as reflected in the results of the present study. It is concluded that the job-exposure matrices did not offer a good alternative for the personal interviews, which provided detailed information on parental occupational exposure resulting in a number of associations with mental retardation. The job-exposure matrices showed low sensitivity for the identification of occupational risk factors is this study. In general, they seem to have limited applicability for reproductive epidemiologic studies.

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A FLEXIBLE DOSE METRIC FOR THE EPIDEMIOLOGIC ANALYSIS OF CHRONIC OCCUPATIONAL HAZARDS

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Epidemiologic analyses of chronic occupational hazards have generally used simple cumulative exposure as dose metric. The use of simple cumulative exposure implies three assumptions about the relationship of exposure to disease. First, there is a linear relationship between contaminant concentration and outcome. Second, it implies that there is a linear relationship between the length of time an exposure occurs and the outcome. And third, that outcome is independent of the time between when exposure occurs and outcome is observed. An alternative expression was developed in order to address these assumptions. This expression is:

$$EI_i = (T_{ij}^{b} D_{ij}^{c} F_{ij})$$

where D is the contaminant concentration, T is the time prior to the outcome measurement (or T^* is the time after initial exposure) and F is the length of time spent by the individual i in job j. The exponents b (or b^* where T^* is used) and c are parameters of the exposure response relationship that may be estimated in the epidemiologic analysis.

If b is greater than one, there is proportionately more weight given to distant past exposures, whereas if it is less than one, past exposure receive less emphasis in the exposure-response relationship. If b^* is large, then proportionately more weight is given to recent exposures. Similarly, if c is large, high concentrations receive proportionately more importance in predicting the outcome. Further note that with $c=0$ and $b=0$ years worked is obtained and with $c=1$ and $b=0$ simple cumulative exposure results. The exponents may be interpreted in reference to the pathophysiologic processes involved in the disease and their interpretation may be used to further our understanding of the disease process.

To help understand the potential importance of these exponents under different exposure histories, consider five individuals, all with a cumulative exposure of 20 mg/m3-years represented in Figure 1. Individual A has a 1 mg/m3 exposure for 20 consecutive years. B had a high exposure of 5 mg/m3 for the first four years and no exposure after that, whereas C had the opposite, high exposure in the last four years. D and E each has intermittent exposures: D had 2 mg/m3 every other year, while E had 5 mg/m3 every fourth year with no exposure in between.

Using different values of the exponents b and c for each of these exposure scenarios demonstrates the potential importance of selection of the appropriate weighting factors. Using b=0 and c=0 or c=1, all five individuals would have an exposure of 20 cumulative exposure units. However, if b=1 and c=1 are used, differences emerge: individual A would have 210 exposure units while B would have 370, and C would have only 50. With higher weights such as b=2 and c=2, A, B, C, D and E would have 2870, 34370, 750, 6160 and 18750 exposure units, respectively. Thus, the choice of the appropriate weights for exposure concentration and time of exposure greatly affects the relative exposures placed on the individuals. If an inappropriate metric were chosen, a great deal of misclassification would occur and one would be less likely to observe a true exposure-response relationship.

This formulation of cumulative exposure was implemented for a study of obstructive lung disease in 1185 underground coal miners who began work after 1969 when quantitative exposure data began to be collected on a systematic basis in the U.S. The results for FEV_1 are presented in Figure 2. Each bar represents a specific regression model with specified values of b, b^* and c varying from 0 to 2. Each model includes the same covariates for age, height, race/ethnicity, smoking status and pack-years. The height of each bar represents the coefficient/standard error for the exposure index, which is an expression of the model fit. The results for FEV_1 suggest an optimal model fit for cumulative exposure using the square root of concentration, and time prior to outcome raised to the first power. The results may be interpreted to suggest some potentiation of repair mechanisms at higher concentrations and a cumulating effect of lung burden over time.

Similar models were run for other outcomes with results indicating a variety of optimal values for the exponents in the cumulative exposure metric. A comparison of these results with the usual measures of years worked and simple cumulative exposure is given in Table 1. It can be seen that the alternative expressions for cumulative exposure can significantly improve the model fit compared with the usual a priori expressions.

The expression for cumulative exposure described has several advantages over the usual expression. First, it avoids a priori assumptions about the appropriate representation of exposure for a particular disease under study and may therefore help to avoid serious misclassification bias which might result in false negative studies. Second, it allows the epidemiologic data to be used to help explore the pathophysiologic mechanisms at work in a particular disease process. Specifically, the exponents for time since exposure and exposure concentration may be interpreted in terms of underlying tissue injury and repair processes.

The expression also has limitations. The results indicate very little overall improvement in the model r^2s and a very flat likelihood surface across different values of the exponents. In part this is a result of the large number of parameters being estimated in the model. It is important to avoid over-interpretation of the results of these models, especially in terms of their pathophysiologic mechanisms, since slight and perhaps statistically insignificant changes in the surface may result in large differences in interpretation. Nevertheless, as we begin to sharpen our analyses to observe low level effects, and use epidemiologic methods to address disease mechanisms, exposure metrics such as this one will need to be explored further.

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Seixas NS, Robins TG, Becker M. A novel approach to the characterization of cumulative exposure for the study of chronic occupational disease. Am J Epidemiol 1993;137:4:463-471.

Adapted from article owned by American Journal of Epidemiology (Seixas et al., 1993).

Table 1. Comparison of Exposure Indices in Regression Models: Years Worked, Cumulative Exposure, Estimated Optimal Model

Outcome	Years Worked	Cumulative Exposure	Optimal Model
FVC	b0,c0	b0,c1	b2,c0
coefficient	0.0060	-0.0012	-0.00009
standard error	0.0056	0.0030	0.00005
p	0.280	0.677	0.069
FEV_1	b0,c0	b0,c1	b1,c0.5
coefficient	-0.0090	-0.0056	-0.0020
standard error	0.0047	0.0025	0.0008
p	0.055	0.025	0.017
Bronch.	b0,c0	b0,c1	b2,c0.5
coefficient	0.0135	0.0196	0.0002
standard error	0.0219	0.1154	0.0001
p	0.538	0.089	0.065
Obs.Bronch.	b0,c0	b0,c1	b2,c1
coefficient	0.0328	0.0348	0.0004
standard error	0.0368	0.0207	0.0001
p	0.374	0.092	0.013
Breathless	b0,c0	b0,c1	b0,c2
coefficient	0.0086	0.0252	0.0105
standard error	0.0210	0.0112	0.0042
p	0.684	0.025	0.012
Wheeze	b0,c0	b0,c1	b2,c2
coefficient	0.0081	0.0184	0.00007
standard error	0.0201	0.0108	0.00003
p	0.685	0.090	0.016

FVC = Forced Vital Capacity
FEV_1 = Forced Expiratory Volume in 1 second
Obs.Bronch. = Obstructive Bronchitis

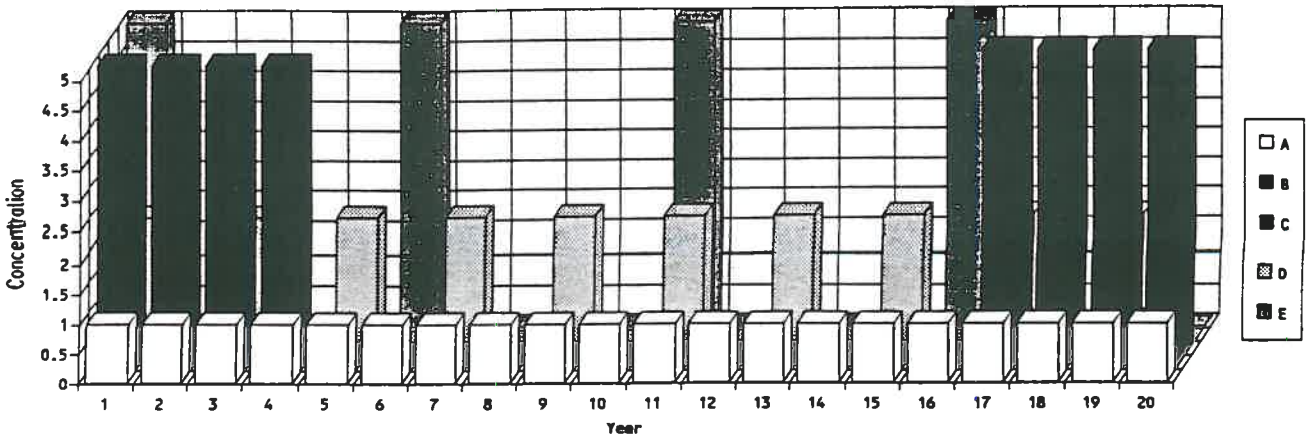

Figure 1. Five Exposure Scenarios

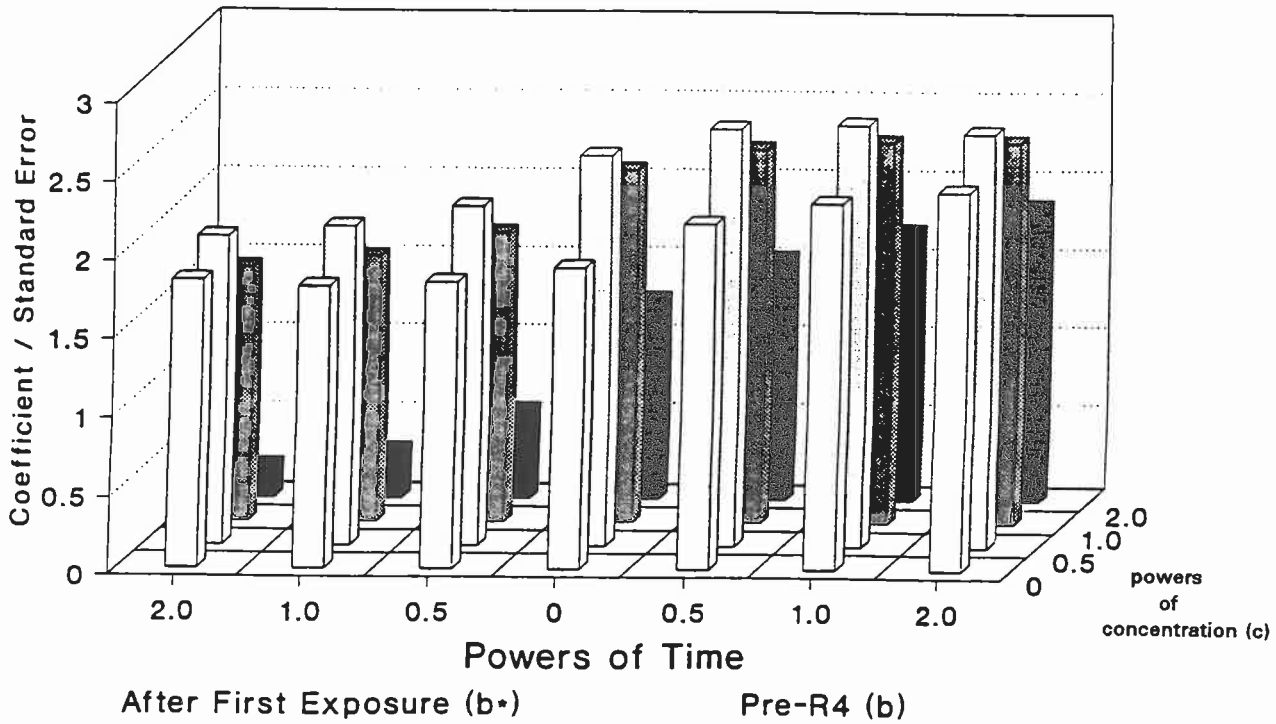

Figure 2. Model fit statistics for regressions of FEV_1 for varying values of b, b^* and c.

HOW MANY EXPOSURE ASSESSMENTS: A GUIDE TO OPTIMUM DESIGN STRATEGY

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Many occupational health studies relating workers' health to industrial exposure are often started with pilot studies so that the investigators could decide on sufficient number of measurements at a minimum cost to the study. This paper describes and utilizes one such technique for deciding optimum experimental design, based on the variability of the IH samples in a pilot study. Nested random effects model is suggested in which the exposure measurements are collected once a day, n_d days per week, n_w weeks per period in n_p periods of study. The variance of mean exposure is the sum of three components: the variance among the periods o^2_p, the variance among the weeks within period o^2_w, and the variance among the days within week o^2_d. Estimation of variance components in a pilot study can be used to gauge the change in precision and costs of various possible designs. It is necessary to balance precision and costs. Among all possible choices, the designs that keep precision of the mean exposure and the associated costs at acceptable levels could serve as potential designs for further studies.

Application is made on a pilot data set in an ongoing study of the effect of certain chemical exposure to an Air Force base worker population. The measurements were collected for 2 periods, 3 weeks within each period, and 5 days per week, thus giving as a (2-3-5) design in the pilot study. Based on the estimation of variance components, 30 designs were compared. Four designs appeared to perform as alternatives for the full scale study. The design, (2-4-3) and (3-2-4), cost 20% less than that of the pilot study and lose about 8% of accuracy in the mean exposure estimate. The design (3-3-3) cost 10% less than that of the pilot study and provided approximately the same accuracy. The design (3-4-2) appears to be more preferable choice because it costs 20% less than that of the pilot study and gives approximately the same accuracy of the mean exposure estimate.

A JOB EXPOSURE MATRIX FOR IDENTIFICATION OF POTENTIAL EXPOSURES IN OCCUPATIONAL SETTINGS

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Introduction

In studying occupational health, a knowledge of occupation-specific exposures is useful since exposures to many potentially hazardous substances may occur in the workplace at high concentrations. Because exposures vary for occupations and industries, several approaches have been used to identify occupation-specific exposure information. Direct quantitative exposure measurements, if available, have been used to determine exposure categories. However, many studies of mortality or morbidity are conducted by using vital statistics or other record systems where the only exposure data recorded are the decedent's or respondent's occupation or industry. For analysis of such studies, a classification system or matrix linking industry, occupation, and exposure would be useful. A Job Exposure Matrix (JEM) is such a classification system linking occupational titles with occupational exposures.

The JEM developed by researchers at the National Institute for Occupational Safety and Health (NIOSH) uses data collected during the 1981-1983 National Occupational Exposure Survey (NOES) (1). Previous occupational exposure classification systems have been based on reports from the literature (2) or on exposures assigned by panels of chemists of industrial hygienists (3). Such efforts have been hampered by the lack of a national profile of occupational exposures and by a lack of standardization in job titles. The classification system used at NIOSH was developed using field data collected during walk-through surveys of a probability sample of American industries, and was coded using Bureau of the Census occupation codes and Standard Industrial Classification codes.

Development of the JEM

Data: The 1981-1983 National Occupational Exposure Survey (NOES) was a two year field study conducted by NIOSH. Like its predecessor, the 1971-1973 National Occupational Hazard Survey (NOHS) (4), the NOES was intended to describe health and safety conditions in the American workplace and to determine the extent of potential worker exposure to chemical, physical, and biological agents. The NOES was a cross-sectional survey representative of all non-agricultural businesses covered under the Occupational Safety and Health Act of 1970 and employing 8 or more employees. The survey sample consisted of 4,490 establishments throughout the United States.

Data were collected by 21 industrial hygienists and occupational health specialists specifically trained for the NOES. Potential exposure information was collected during walk-through inspections of each establishment. Potential exposure to continuous noise was recorded if its measured level was equal to or greater than 85 dBA (slow response), and to impact noise if noises occurred one second or more apart and the intensity was greater than 130 dBC (fast response). Potential exposure to other agents was recorded if certain guidelines were met: 1) a chemical, physical, or biological agent or a trade-named product must have been observed in sufficient proximity to an employee such that one or more physical phases of the agent or product was likely to enter or contact the body of the employee, and 2) the agent or product must have presented a potential exposure for at least 30 minutes per week on an annual average, or be used at least once per week for 90% of the work weeks of the work year. The number and gender of employees in each occupational group potentially exposed to the agent was recorded, as well as data on the duration of potential exposure and presence of control measures over exposure. In cases where the exposure agent was a trade-named product, ingredient information was obtained from the manufacturer. Roughly 80% of the data collected in the NOES was associated with trade-named products, and considerable effort was expended in the trade-named product component determination process.

Industry, occupation, and agent were coded using standard coding systems. Establishment activity was coded by 4-digit 1972 Standard Industrial Classification (SIC) code, occupation by 1980 Bureau of

the Census occupation codes, and agent by a 5-digit code ('Hazard code') assigned at NIOSH. Unique agent codes were assigned because many agents were observed during the NOES which had not been assigned codes by other conventions (such as Chemical Abstracts (CAS) number or by the Registry of Toxic Effects of Chemical Substances (RTECS) number). Cross referencing of agent codes by CAS and RTECS numbers is possible, however. Potential exposures to 14,000 chemical, physical, or biological agents observed across 377 occupations and 521 industries are included in the JEM.

Construction of the JEM

The JEM is a three-level classification system in which potential occupational exposure information collected during the NOES walk-through inspection is classified by industry and occupation. Each level of classification is nested within the previous one. The three levels of classification in the JEM are thus industry, occupation within industry, and potential exposure within occupation within industry. The nested structure is important for flexibility in the use of the JEM since the maximum data may be included at each level of classification, and data may be easily obtained at each level of classification. For example, information about agent exposure may be obtained for a given occupation in a given industry, across all industries, or across all occupations.

Different information is included at each level of classification in the JEM. The first two levels, industry and occupation within industry, include employment data for the industry or industry-occupation group. Information about potential worker exposure in the industry-occupation group is included at the third level. The percent of employees exposed to the agent, percent exposed full time to the agent, percent exposed to the agent through the agent's presence in a trade-named product, and percent of employees working in facilities with no form of control over exposure may be found using data at the third level. All information in the JEM is broken down by gender and size of establishment. Size is defined by the number of employees: small, 8-99 employees; medium, 100-499 employees; large, 500 or more employees.

The JEM consists of a computer file of 590,000 records stored on magnetic tape. The matrix is so large because many of the same

agents may be found in different occupations and industries. The JEM system consists of the JEM file, appropriate documentation, and sample computer programs to access data from the JEM. Parts of the JEM file specific to individual industries or agents have also been abstracted from it for use on a microcomputer. JEMs containing exposure information for the construction industry and for physical agents have been developed.

Uses of the JEM

The Job Exposure Matrix may be used to profile potential exposures to specific agents in occupational settings. For example, occupational settings where potential exposure to inorganic lead or its ores occurs may be determined. Using the matrix, more than 50 employees in each of 53 occupations across 73 industries had potential exposure to inorganic lead or its ores. Those occupational groups where more than 500 employees were observed, and the percentage of employees in those groups with potential exposure are shown in Table 1. All assemblers engaged in manufacturing wire telephone and telegraph equipment (193 observed) were found to be potentially exposed, while 38.9% of assemblers engaged in manufacturing radio and TV apparatus (718 observed) were potentially exposed. Seventy-seven percent of the telephone equipment assemblers (1459 observed) were females and all were potentially exposed, while 81.2% of the radio and TV assemblers were females, of which 31.7% (583 observed) were potentially exposed. Lists of all potential exposure agents observed in the specific occupational groups may also be obtained from the JEM.

Potential exposure data from the JEM may be used to determine occupational groups for studies of exposure (5). Such data may also be used for an objective measure of exposure in occupational health research studies. Data from the JEM may also be linked to other data sets because of the use of standard coding conventions. Linkage of the JEM to Health Interview Survey (HIS), Occupational Safety and Health Administration (OSHA), or census data would provide exposure data in these data bases for a more thorough analysis of data already collected for these surveys.

Summary and conclusions

The Job Exposure Matrix is a compact representation of data

collected during the 1981-1983 National Occupational Exposure Survey. The JEM contains an inventory of occupational exposure agents cross-classified by industry and occupation. Potential exposure data by gender and size of establishment is included. The occupational information is coded using standard systems for ease in retrieving occupation-specific data. Use of a standard system also allows for the conversion of occupational codes into other coding systems and the possibility of linkage of data from the JEM with other data sets. Potential occupational exposures in the JEM were catalogued during field surveys, rather than constructed from secondary sources.

Since it is based on survey data, the JEM has some limitations. Data from the JEM are limited to those facilities and employees originally surveyed in the NOES. No indication of individual workers exposed to agents is included and the potential for misclassification within occupational groups exists. Except for noise exposure and certain other physical agents, exposures in the JEM are potential rather than measured ones. Nevertheless, the large inventory of agents included in the JEM and the use of data from a large national survey coded in a standard manner make the JEM a useful tool for the study of occupational disease.

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Table 1. Occupational groups with potential exposure to elemental lead and its ores

Manufacturing		All Employees Potentially Exposed		Females Potentially Exposed	
Industry	Occupation	N	Percent	N	Percent
Telegraph Apparatus	Assembler	1,903	100.0	1,459	100.0
Industrial Controls	Technician	200	92.6	150	91.5
Measuring Instruments	Assembler	938	70.2	606	75.6
Ship Building/ Repair	Carpenter	381	49.5	0	0.0
Radio and TV Apparatus	Assembler	718	38.9	583	31.7

EXTRAPOLATION OF PAST FIBER EXPOSURES IN THE PRODUCTION OF MAN-MADE VITREOUS FIBERS

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The current update of the U.S. historical cohort of man-made vitreous fiber (MMVF) production workers includes employees at one or more of twenty glass plants that produced mineral wool, fiber glass filament, and/or fiber glass wool. As part of the current update of this cohort sponsored by the Thermal Insulation Manufacturers' Association, exposure data for several agents (asbestos, asphalt, formaldehyde, phenolics, aromatic hydrocarbons, and silica) are being obtained in addition to quantitative fiber measurements. This paper presents the methodology for estimating past fiber exposures. The plants started production as early as the 1930s. Exposure monitoring for fiber was not started until the 1960s, and the majority of measurements were made after the mid-1970s. Consequently, exposure intensity must be extrapolated for the earlier operations and jobs. These exposures were extrapolated using a three step procedure: (1) a process-exposure model was developed to identify sources of emissions and factors that might affect personal exposures in a work area; (2) an analysis was conducted of fiber exposure data (approximately 4,000 air monitoring measurements and associated production factors) to estimate average exposures and factors associated with significant differences across jobs, work areas, and time periods at each plant; and (3) multipliers associated with differences in exposure factors were used to extrapolate exposures for job/work area combinations that had not been measured. The factors affecting job exposure were associated with six types of exposure setting characteristics: work area (proximity to emission sources), product type (blanket, textile, etc.), product characteristics (fiber diameter, binder, etc.), process equipment, local exposure controls, and general plant characteristics. At a given plant, each job, work area, and time period had a subset of these factors which

were associated with significant differences in exposure intensity. Differences across plants for the same types of jobs making the same products with similar equipment were attributed to differences in the general plant settings, e.g., makeup air. For retrospective extrapolation, it was assumed that if the job, product, equipment, and other factors remained constant then exposure also was constant. Past exposures were extrapolated using factors developed from the measured exposures. Potential errors in the extrapolation were evaluated and the possible effects on the epidemiologic analysis were assessed in a statistical analysis by Marsh and coworkers (reported in another Symposium paper).

"BACKGROUND" LEAD LEVELS IN CONSTRUCTION WORKERS

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Introduction

Construction workers who demolish metal structures are at risk for extremely high bursts of lead exposure causing overt, symptomatic lead poisoning. Lead paint coating these structures becomes airborne in the form of lead fume during hot work, and dust during sandblasting operations, rivet removal, etc. Even in outdoor settings, airborne exposures reaching tens of thousands of mcg/M^3 have been documented, and the problem may be exacerbated by containment structures designed to protect the environment from lead contamination. This exposure is typically quite sporadic, however, since construction workers alternate various types of new construction with work on older structures, since the amount and location of lead coatings varies widely, and since the work is seasonal and susceptible to long layoff periods. The type of sustained, prolonged exposure common to the classic lead industries is usually not encountered, and blood lead levels return to "normal" within months of cessation of exposure. Skeletal storage and subsequent remobilization provides endogenous lead exposure both in the general population and in exposed industrial groups. The extent of this problem among construction workers is not known.

The OSHA lead standard covers fixed industry only and contains no provisions for biologic monitoring, medical surveillance or medical removal protection for construction workers. However, the state of Maryland has included construction workers in its lead standard since 1984. Consequently, construction workers in this state are much more likely to have had lead monitoring performed, to be aware of lead as a hazard, and to have elevated lead levels recognized and

treated. It is also likely that their exposure may be somewhat less than in states without similar legislation.

This study was conducted to screen construction workers at risk for episodic lead exposure to determine whether they had long-term increases in blood lead levels, and to identify job and other characteristics that predict elevated lead levels.

Methods

A cross-sectional survey of unionized construction workers not currently known to be performing lead work was performed.

Participants were members of two local Ironworkers' union and two local Laborers' International Union of North America. Union members, including apprentices and retirees, were invited by the local leadership to participate in screening sessions held in the local union hall during a Saturday morning, signing up in advance for scheduled appointments. Informed consent was obtained according to an IRB-approved protocol on the morning of the screening. Written summaries of the hazards of lead exposure were distributed in advance by the unions, and verbal presentations were made at union business meetings to enhance turnout. A total of five screening sessions were held between late September 1989 and March 1990.

Participants completed an interviewer-administered questionnaire obtaining information about demographics, work history, other possible sources of lead exposure and health status (including hypertension, noise-induced hearing loss and renal disease). Blood was then obtained via venipuncture for whole blood lead level, hematocrit and free erythrocyte protoporphyrin determination at an EPA certified university laboratory using atomic absorption spectrophotometry for the lead determination. Blood pressure was measured three times for each individual, at five minute intervals, using an appropriate size cuff, in the right arm while seated. Height and weight were measured. Participants with abnormal blood pressure determinations were informed verbally at the session and subsequently in writing of the need for medical follow-up. Participants with anemia were informed of the result in writing and of the need for further medical evaluation.

Data were entered on a Paradox program and analyzed on a mainframe using SAS.

Skewed data were normalized by log transformation for parametric analysis; however, this did not alter results and these are reported without transformation for clarity.

Results

Two hundred and sixty-four active or retired union members participated, including 198 Ironworkers and 66 Laborers. There were 262 men and 2 women, with a mean age of 43 years, ranging from 18 to 79 years. Whole blood lead levels were skewed towards lower levels, with a median of 7 mcg/dl, a mean of 8.0 mcg/dl, and a range of 0 to 30. Participants who had "ever" worked in demolition (N=130) had higher blood lead levels than those who had not (8.55 mcg/dl vs. 7.33 mcg/dl). Those who had ever burned paint and metal and who had welded outdoors (N=79) had higher levels than those who had done none of these activities (N=49) (8.56 vs. 6.82 mcg/dl, p=.01). Current demolition work was associated with higher lead levels (N=63, lead level = 8.95 mcg/dl), although burning paint or metal on the current job was not (lead level = 7.9 mcg/dl). Fifty-eight workers had had workplace lead monitoring performed; as a whole, they had higher lead levels (9.69 mcg/dl, p=.004), but levels did not correlate with recalled results ("high," "normal," etc.). Ten workers had been told they were lead poisoned, and these had a mean lead level of 9.5 mcg/dl. However, the eight who had been previously treated had lead levels indistinguishable from the group as a whole (8.0 vs. 7.9 mcg/dl, p=.93).

Lead levels correlated weakly with age (r=.15, p=.02). Blacks (N=69) had higher lead levels than whites (N=188) (8.90 mcg/dl vs. 7.54 mcg/dl, p=.02). Log (pack-years of cigarettes smoked) correlated with lead levels (r=.19, p=.002), although cigar and pipe smoking did not. There were only 2 women enrolled, and their lead levels were 7 mcg/dl and 21 mcg/dl. Although this sample size is extremely small, the difference between men and women reached statistical significance because of the magnitude (14 mcg/dl vs. 7.9 mcg/dl, p=.04). Lead levels increased with increased moonshine consumption, to a high of 10.5 mcg/dl among the 24 in the highest exposure category. Multiple comparisons for lead levels based on

years of education did not achieve statistical significance. Lead levels were higher in those who had ever been struck by a bullet (N=32, lead level = 9.25 mcg/dl, p=.09).

No overall relationship between lead and blood pressure was found in this study. Among black men, there was a tendency towards a positive association between lead and diastolic pressure, while white men showed an inverse relationship between lead levels and systolic blood pressure.

Discussion

Population differences among unionized construction workers in Maryland reflect past contributions of demolition work as well as other specific exposures. This is not a heavily leaded population, and these workers have current whole blood lead determinations in the range of the general population. The state of Maryland's leadership in regulation may be a factor, along with the work of the two international unions. These findings, therefore, are likely to represent the best of what is available in the construction industry.

Nevertheless, there is a demonstrable mobilization of endogenous stores occurring in this group, as reflected by the significant blood lead elevations among various subgroups with specific risk factors. Increases in lead levels of this magnitude have been well documented to adversely affect fetal neurologic development, and have been associated with population increases in blood pressure among adults in several studies. Better control is an achievable goal and should focus on prevention, more frequent biologic monitoring and earlier removal than either the Maryland or the fixed-industry OSHA standards currently do.

Age, race and cigarette smoking are all associated with elevated lead levels. Moonshine whiskey use and bullet injuries were also associated with increased blood lead levels. Although the sample size in this study was not large enough to evaluate an interaction between lead and blood pressure, it did suggest that such an interaction might be race-dependant.

EXPOSURE ASSESSMENT FOR A STUDY OF WORKERS EXPOSED TO ACRYLONITRILE. I. JOB EXPOSURE PROFILES: A COMPUTERIZED DATA MANAGEMENT SYSTEM

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Retrospective exposure assessment is crucial in the investigation of causality of disease and exposure, but it is a difficult and complex process. Where sufficient air monitoring data are available, statistical models can be developed. Unfortunately, most studies do not have sufficient data, and other methods must be used to develop historical estimates. In such studies, the investigator may use descriptive or anecdotal information to supplement the air measurements in assessing exposures. No one, however, has described an efficient way to systematically organize and document the large amounts of narrative information often collected in studies.

In an epidemiologic study of 27,000 workers exposed to acrylonitrile (AN) in eight AN producing or using plants from the 1950's through 1983, a systematic approach was developed to assemble, organize and computerize this type of information that made the information readily accessible to the user making the assessments and to reviewers. A computerized data management system, called job (and department) exposure profiles (JEP and DEP), was developed which stored exposure and other job-related information (other than air monitoring results) that might be needed to develop quantitative exposure estimates for each of the approximately 3000 jobs (and departments).

Job titles were abstracted from each company's personnel records. Company-generated air monitoring data and descriptive information on exposures were obtained during walk-through surveys of the AN-

handling operations, interviews with long-term workers and supervisors at each facility and various company records such as plant layouts, job descriptions, etc. Each site visit generally resulted in a collection of over 400 pages of paper per plant. The information was in a variety of formats, and often discussed different departments or jobs on the same page. In addition, information about the same department was often present in many different documents. Review of these documents made it apparent that reorganizing the information into a single document organized by job title was impractical. The information was therefore organized by type of document and compiled into document control notebooks.

A menu driven computer program was designed to provide the organizational framework for the information. Two exposure files were developed: a Department Exposure Profile (DEP) and a Job Exposure Profile (JEP). A DEP was developed for each department and contained information that was common to all jobs within that department, such as a process description and production rates. Similarly, for each job title, a JEP was developed which contained information specific to the job, such as frequency of exposure and frequency of peak exposures. In addition, an interactive data entry and access system linking the DEP and JEP files was developed so that entry of an item into the DEP allowed the user to view the data in the associated JEPs.

Prior to using the system, the investigator reviewed the relevant department information for a plant. The appropriate information was then entered into the DEP. The information collected on the jobs in this department was then entered into the JEPs with the DEP information displayed. The system included six screens per job/department/plant (hereafter referred to as job): years of the department/job, the number of times this combination appeared in the personnel records, a description of the process, the location of the job, a description of tasks and duties of the job, the significant changes that took place in the department, unusual occurrences in the department, production rates, the occurrence of overtime in the department, the frequency of AN exposure in the job, the frequency of AN peaks in the job, reported health effects in the department and job, the frequency of the job's dermal exposure, the use of personal protective equipment in the job, the level of the job's physical

activity, a ranking of the jobs in the department by exposure and other chemical exposures.

For each field on the screen, two additional items were entered: the source of the information and the confidence. The sources of the information included records supplied by the company, interviews of employees and/or management, and judgment. The level of confidence that the investigator had in the accuracy of the information was also identified.

The system was developed with several quality control checks. Every field of each profile identified the page number of the document where the information was found, or if a judgment was made, the basis of that judgment. This notation allowed easy retrieval by a second reviewer. Also, there were several internal logic and range checks in the system, as well as edit reports to identify inconsistencies. A user's manual was developed which described use of the JEP system step-by-step, including completion and examples of the screens, the purpose of the logic checks and generation of the edit reports.

The advantage of having a computerized system is that it organizes and documents in an efficient way the large amounts of data collected in industry-based epidemiologic studies. This characteristic is particularly important because exposure information may come from many different sources and a single document may contain references to several departments or jobs. Developing a paper copy form for each job would allow compilation of the exposure information, but it would result in much information being repeated on an unmanageable amount of paper. It would also prevent easy reference back to the original document.

The methodology developed for this system is adaptable to other studies. It addresses the basic components of exposure and, further, it provides a structure which indicates what information should be collected during site visits to companies under study. It was developed for the information collected in this study; but changes in the data collection (and therefore the system) can be made in future studies.

Although designed as a tool to manage a data base to reconstruct

historical exposures, the JEP system could be used in the workplace to retain exposure information. An annual evaluation of all jobs in such a format would be a valuable resource for investigators performing exposure assessments both currently and in the future. The system could also be used to simply document descriptive information collected on jobs or departments in an epidemiologic study by itself.

This system is the first computerized program developed for the exposure assessment part of this epidemiologic study on AN workers. A second system, the linkage system, allows the industrial hygienist to link the job/department titles in the personnel records to the job and department titles in the air monitoring records. After computerizing the air monitoring data, a third system, the exposure assessment program (EAP) interacts with the first two systems to develop exposure estimates. The EAP system links the monitoring data with the JEP/DEP information and guides the user through a step-by-step process to develop the exposure estimates for every job in the study. The JEP/DEP system and the accompanying user's manual is currently being developed for use by the public.

EMPIRICAL ASSESSMENT OF THE EFFECT OF DIFFERENT SUMMARY WORKLIFE EXPOSURE MEASURES ON THE ESTIMATION OF RISK IN CASE-REFERENT STUDIES OF OCCUPATIONAL CANCER

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One of the major impediments to etiologically oriented occupational health studies is the paucity of data on individual exposures. Researchers must devise effect measures in the form of indices of exposure to putative hazardous agents. These are usually calculated from estimates of (i) duration of tasks or of assignments at defined employment locations and (ii) concentrations of agents at those sites and times. Even when duration and concentration variables have been well assessed, there remain problems in the choice of the most appropriate summary measure by which to classify each worker's lifetime exposure experience.

A summary exposure measure is determined by the respective weight it attributes to either duration or concentration exposure or both. Thus different measures may produce different results (1). Ideally, the summary measure selected should be based on a set of defensible assumptions regarding the postulated biological mechanism for the agent or disease association under study (2). This procedure is not, however, always possible. Very often, the biological effect of the duration of exposure or the concentration of the agent under study is unknown. In this context the use or different exposure measures may be useful to suggest a mechanism by which exposure exerts its effect.

Two matched case-referent studies associating sulfuric acid exposure and cancer from Baton Rouge and Southern Ontario were used. Five summary exposure measures were converted to discrete levels of exposure through the selection of equivalent percentile points on each measure's respective percentage frequency distribution for logistic regression modeling purposes.

Summary worklife exposure measures

Five different summary worklife exposure measures were used in the present study (Table 1).

Cumulative exposure index. The cumulative exposure index (CEI) is equivalent of "dose" in toxicologic studies and represent the sum, over a working lifetime, of the products of exposure grade and exposure duration for each successive job title. It includes time in its units.

Mean grade. The mean grade (MG) cumulates the products of exposure grade and exposure duration for each successive job title and change (i.e., the CEI) and divides by the total time exposed at any grade greater than zero. MG is independent of time in its units; the summary measure for a person exposed for a long period at a high concentration will be similar to that for a person exposed for a short period at a high concentration. Within any matched set, MG is an average grade of exposure per unit of time exposed. It is an average grade for the time actually exposed to the agent under consideration.

Highest grade ever. The highest grade ever (HG) was determined from scanning the work history for the highest grade assignment in the period of observation to which the worker was exposed at least 7 d. The HG could misrepresent a person's worklife exposure because, by its very formulation, it is based on a maximizing rather than on an averaging procedure and is therefore independent of duration of exposure in its units.

Time-weighted average grade. The time-weighted average (TWA) grade is the cumulative exposure index (CEI) divided by the total time employed. Within any matched set, the TWA grade averages over total time employed. It differs from MG, which averages only over total time actually exposed. Thus, TWA grade can be viewed as an average exposure per unit of time in the full term of employment regardless of exposure per se.

Total time exposed. The total time exposed (TTE) accumulates all time periods associated with expose in units of time. TTE has appeal for it simplicity. However, it is well accepted that health effects

must be related not only to duration of chemical exposure, but also to the intensity of that exposure (i.e., the concentration or grade).

The southern Ontario data set exhibited only minor differences across all five exposure measures. The Baton Rouge data set, however, produced different results, and the time-dependent measures appeared to underestimate risk. It is possible, therefore, to obtain different estimates of risk depending on the exposure measure selected.

The purpose of the present analysis was not to demonstrate an association between sulfuric acid exposure and laryngeal cancer, but to examine empirically the effects of using different summary exposure measures in the estimation of risk.

It is recommended that, in the absence of proved models for assessing exposure, a variety of summary measure be used to estimate risk. This approach would facilitate the comparison of findings across studies.

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Table 1. Formulas and dimensions or units of the five selected summary measures of worklife exposure

Exposure measure	Formula	Dimensions/units
Cumulative exposure index (CEI)	Σ (grade x time exposed)	Grade and time
Mean grade (MG)	$\frac{\Sigma \text{ (grade x time exposed)}}{\text{Total time exposed}}$	Grade
Highest grade ever (HG)	Highest grade to which exposed for 7 d	Grade
Time-weighted-average (TWA) grade	$\frac{\Sigma \text{ (grade x time exposed)}}{\text{Total time employed}}$	Grade
Total time-exposed (TTE)	Time exposed	Time

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VISUAL DYSFUNCTION AMONG STYRENE EXPOSED WORKERS

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Disorders of the visual system have long been associated with exposure to toxic substances. Recent studies suggest that exposure to styrene, a well-known neurotoxin, may alter normal visual functions at early stages of intoxication. Gobba et al.[1] observed a higher prevalence of acquired color vision loss among styrene exposed workers compared to a referent population; results remained constant in a subgroup of workers, tested immediately following one-month vacation with no exposure, indicating no recovery over this period. Falls reported a high prevalence of acquired dyschromatopsia among styrene exposed workers,[2] as well as contrast sensitivity loss among the older workers.[3] The objective of the present study was to examine the relationship between internal and external parameters of styrene exposure and visual functions, namely chromatic discrimination and near visual contrast sensitivity. This study is part of a prospective study, whose overall objective is to examine the reversibility of styrene-related nervous system changes following reduction of exposure in the workplace.

Methods

The study was carried out in 3 plants which manufacture reinforced plastic items. Environmental evaluation was done for styrene, toluene, acetone and methyl ethyl ketone. Personal sampling for all workers was achieved with passive dosimeters, which were worn over the 8h workshift; analysis was carried out by flame ionization detection gas chromatography. Post-shift urinary samples were taken on the same day as environmental sampling, to assess mandelic acid

concentrations. These were analyzed by high pressure liquid chromatography and the results were corrected for urinary creatinine.

Testing for neurotoxic effects was carried out on the day following the exposure assessment, at least 12 hours following cessation of exposure. At this time the workers completed a questionnaire including socio-demographic information, work conditions and work history, and health symptoms, including symptoms of visuo-ocular disorders or discomfort, such as eye irritation, tearing and blurred vision.

Color vision was assessed using the Lanthony D-15 desaturated panel, which provides both a quantitative measure - color confusion index - and a qualitative evaluation of acquired dyschromatopsia. This test, which was developed to detect mild and moderate acquired chromatic discrimination loss, is performed monocularly; 15 pale colored caps are placed in random order in front of the subject under standard lighting and the subject is required to place them in order of chromatic similarity; there is no time limit placed on the subject, who indicates when he or she is satisfied with the result.

Near visual contrast sensitivity was assessed with the Vistech 6000, which assesses contrast sensitivity threshold at 5 spatial frequencies (1.5 cycles/degree, 3 cycles/degree, 6 cycles/degree, 12 cycles/degree, 18 cycles/degree). A card with sinusoidal gratings in circles with a diameter of 1.3 cm is placed 36 cm in front of the subject and held in place on a stand supported on the subject's chin. The subject is required to indicate whether the sinusoidal gratings are inclined to the left, the right or straight up and down. Three different cards are used to determine threshold level.

The total population employed in the 3 plants was 151; of these, 128 (85%) participated in all stages of the study. For the present analysis, the following exclusion criteria were used: less than 6 months of exposure in the plant, poor near visual acuity, eye injury, congenital color blindness, cataracts or diabetes, use of potentially ophthalmotoxic medication, solvent exposure other than in these plants and incomplete exposure data. The results presented here included 88 workers. They were young, (mean age: 29y $\pm$ 8) with little seniority (mean: 5y $\pm$ 4); mean educational level was 11y $\pm$

1.7 and mean alcohol consumption was 160 g/week, which is approximately 12 small bottles of beer per week.

Results

Exposure and post-shift mandelic acid levels showed a log normal distribution. For 28 workers (31.8%), environmental styrene levels exceeded the ACGIH recommended level of 213 mg/m^3, while 21 workers (23.9%) had post-shift urinary mandelic acid levels superior to 0.6 mmol/mmol creatinine. Post-shift mandelic acid levels were highly correlated (r=0.92) to environmental styrene measurements for those who were not wearing a mask.

On the symptoms questionnaire, 37.5% of the workers reported eye irritation, 33.0% reported blurred vision and 23.9% reported tearing. The distribution of these reported symptoms with respect to exposure parameters are given in Table 1.

Table 1. Reported symptoms

	styrene		mandelic acid	
	<213mg/m^3	≥213mg/m^3	<0.6mmol/ mmol cr	≥0.6mmol/ mmol cr
symptom	n=60	n=28	n=67	n=21
eye irritation	16(27%)	17(61)**	20(30%)	13(62%)*
blurred vision	16(55%)	13(45%)	18(27%)	11(52%)*
tearing	11(19%)	10(36%)	12(18%)	9(43%)*

Chi square: *P<0.05; **P<0.01.

Acquired dyschromatopsia was present among 34.1% of the workers. Those with high levels of mandelic acid had a significantly higher prevalence of acquired dyschromatopsia as compared to those with lower levels. This was not the case when one considered environmental exposure to styrene, which includes persons with and without masks (Table 2).

These results suggest that, contrary to symptoms of eye irritation and blurred vision, acquired color loss does not result from the direct action of styrene on the eye. Mostly Type III (blue-yellow deficits) were observed. Only one worker presented Type II loss. The former reflects external retinal changes, while the latter is indicative

of more advanced damage, involving the internal retinal layers and/or the optic nerve. No relationship was observed between acquired dyschromatopsia and symptom reporting.

Table 2. Acquired dyschromatopsia

	styrene		mandelic acid	
	<213mg/m^3	≥213mg/m^3	<0.6mmol/ mmol cr	≥0.6mmol/ mmol cr
	n=60	n=28	n=67	n=21
acquired dyschromatopsia	20(33%)	10(36)	18(27%)	12(57%)*

Chi square: *p<0.05

The quantitative variables were analyzed using regression models. First, the relationship was examined with respect to the covariables, which have been reported to influence acquired color vision. Both age and alcohol consumption contributed significantly to color vision loss (Table 3); this is consistent with our findings in other studies of acquired dyschromatopsia.

Table 3. Covariables

	age t	alcohol t	model F
color confusion index	3.09**	2.15*	6.94**
contrast sensitivity			
1.5 cycles/degree	1.89	1.17	2.37
3.0 cycles/degree	1.13	0.55	0.76
6.0 cycles/degree	1.74	0.62	1.66
12.0 cycles/degree	2.94**	0.69	4.49**
18.0 cycles/degree	4.22***	0.57	8.99***

Alcohol consumption did not influence contrast sensitivity, however, there was a significant relationship between age and contrast sensitivity loss at the higher frequencies. For the subsequent analyses, with respect to exposure parameters, the color confusion indices and contrast sensitivity scores at the higher frequencies were adjusted by the method of covariance.

Adjusted color confusion index increased with the log of mandelic acid ($F=5.95$; $p<0.05$) and with the log of environmental styrene for those who did not wear masks ($F=9.39$; $p<0.01$). The scatter of the data points suggests that there may be a threshold effect. No relationship was observed between the adjusted contrast sensitivity scores at all spatial frequencies and internal or external parameters of exposure or years of employment in the plant.

The findings of this indicate that although this group of workers was young with relatively few years of exposure, color vision loss increased with exposure and there appeared to be a threshold effect. No relationship was observed between contrast sensitivity and exposure. The overall portrait of visual dysfunction, including color vision loss in the blue-yellow range, absence of contrast sensitivity loss or of a relationship between visual symptoms and visual outcomes, suggest that these are early stages of impairment. A previous prospective study that we carried out among laboratory workers exposed to multiple solvents led us to expect that at this stage, damage to the neuro-optic pathways is reversible[4]. Changes have been made in the ventilation system and work practices in the 3 plants under study with a view to reducing exposure and we will be reassessing the visual functions of these workers at a future date.

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A NEUROBEHAVIORAL EVALUATION OF PCE EXPOSURE IN PATIENTS AND DRY CLEANERS I: A POSSIBLE RELATIONSHIP BETWEEN CLINICAL AND PRE-CLINICAL EFFECTS

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Introduction

Long-term deficits in visuospatial function, short-term memory, cognitive flexibility, and disturbances in mood have been clinically identified and followed in patients occupationally exposed to perchloroethylene (PCE). A frontal/limbic hypothesis is offered as the site of pathology. A separate cross-sectional study evaluating the relationship between occupational exposures to PCE and neurobehavioral performance (visual reproductions, pattern memory and recognition, digit span, symbol-digit, trailmaking, and vocabulary), mood (POMS), and symptoms was conducted among 65 currently employed dry cleaner personnel to provide similar evidence of impairment, suggesting a continuum between clinical and pre-clinical effects.

Evaluating dry cleaners provides a valuable opportunity to examine central nervous system (CNS) effects of PCE without interference by other solvent mixtures. Clinical evaluations suggest that solvents, including PCE, affect attention and executive function, short-term memory, and mood functions thought to be mediated by the frontal and limbic systems of the brain. Based on this clinical experience, this exploratory study of dry cleaner personnel evaluated the a priori hypothesis that tasks assessing frontal and limbic system functions of the brain are susceptible to PCE exposure. We also predicted that tasks utilizing visuospatial stimuli are potentially more sensitive to PCE than verbal tasks. A battery of tests was designed to assess both these predictions. We also evaluated other skill areas which have been reported to be affected by other solvents and field-tested some computerized tasks.

Acute neurotoxic effects of PCE are in general agreement with the World Health Organization's (WHO) definition of organic solvent syndrome Type I, characterized by poor concentration, poor memory, lightheadedness, headaches, and shifts in mood.[1]

The concept that chronic exposure to chlorinated solvents has adverse effects on the nervous system, in the absence of anoxia, is supported by positive results from epidemiologic studies,[2-4] but the specific evidence for PCE chronic effects is incomplete. Two previous studies compared symptoms and behavior in PCE exposed dry cleaners to that of laundry workers. Tuttle et al.[3] and Lauwreys et al.[4] found a positive association between exposure and symptoms consistent with Type I solvent effects. Tuttle et al. evaluated a broad number of symptoms, neurologic functions, and some behavioral functions. Significant chronic neurologic effects were attributable to prior stoddard solvent exposure. Significant acute neurobehavioral decrements were strongly correlated with fatigue due to the time of day rather than PCE exposure based on pre- and post-exposure results. The Lauwreys study[4] found no chronic effects on an attention task, simple and choice reaction time, and a critical flicker fusion test. Both studies remain inconclusive since their industrial exposures were low (18 ppm over a mean of 8.25 years[3] and 21 ppm over a mean of 6.4 years[4]) and the sample sizes were small.

PCE exposures in the current study were considerably higher. Recent industrial hygiene surveys of dry cleaners in Michigan[5] report 8-hour time weighted average exposures of 44 ppm (SD=38), 24 ppm (SD=12), and 11 ppm (SD=15) for operators, pressers, and counter clerks respectively. At these exposure levels the central nervous system (CNS) may be a sensitive target organ. This study evaluates the relationship between clinical and pre-clinical effects among these PCE exposed employees, using a specific neurobehavioral hypothesis.

Materials and methods

Sixty-five people employed in 24 shops in the Detroit area were stratified into low, moderate, and high, current and cumulative PCE exposure groups. An unexposed group was unavailable. Industrial hygiene measurements identified three PCE exposure zones for the counter clerks, pressers, and operators. For the current exposure analysis within each shop, a lower exposed counter clerk or presser

was matched on age and education for each higher exposed operator. For the chronic lifetime exposure analysis, an index was used, based on the sum of the current exposure category for each job title multiplied by duration on each job.

Subjects were tested for one hour and ten minutes after work on the first or second day of their work week. Subjects were tested in groups of two in a mini-van parked off the premises of the shop. Each subject signed a consent form, provided a breath sample, completed a medical and symptom questionnaire, and was administered six neurobehavioral tests. The behavioral tests were chosen because they had either measured behavior related to known clinical impairments, or covered a wide variety of functions. One of the authors (RW) evaluated 4 patients for neuropsychologic assessment of possible PCE encephalopathy. The battery of clinical assessment tools used has already been described in a companion paper in this series[6] as have the principles on which differential diagnosis is based. Briefly, the patients' data most consistently reported PCE-related complaints of fatigue and confusion on mood scales accompanied by cognitive deficits on tasks assessing memory, motor, visuospatial and executive function with milder attentional deficit. There was some variability among subjects, however all subjects performed below expectation on one or more tasks within each functional domain. Verbal functions were overall unaffected and formal language function (naming, reading comprehension) was unaffected. This pattern of deficits is similar to that which we have described as typical of solvent-induced encephalopathy and is consistent with our hypothesis that solvents affect functioning of the cerebral frontal lobes[7] (mediating complex organizational behavior, attention, executive function and reasoning) and the limbic system (mediating mood and memory).

Thus the underlying neuropsychologic theory to be tested among dry-cleaners was that PCE would show more selective effects on frontal system mediated functions. The POMS six mood scales were used both as potential covariates and health effects and to ascertain the degree of agreement with the WHO definition of Type II mild organic solvent effects. Given the hypothesis that memory for visuospatial material should be more affected by PCE exposure than simple attention and basic verbal skills, tests of visuospatial, perceptual recognition, complex cognitive tracking, psychomotor

speed, mood, and verbal skill were included in the test battery. The tests are: Visual Reproductions Subtest, Wechsler Memory Scale, Pattern Memory, Pattern Recognition, Symbol-digit Substitution Test, Trailmaking Test, NES Digit Span, Profile of Mood States, Vocabulary, Fatigue Checklist, and Symptoms.

This study investigated an exposure-effect relationship between the chronic index of lifetime exposure and behavior consistent with the *a priori* hypothesis. Thus, for example, one would expect the three visuospatial tests to be more affected by PCE than the digit-span test which involves a verbal rehearsal component. Subject performance was analyzed using adjusted mean scores corrected for age, vocabulary level, education, alcohol consumption, and other solvent exposures affecting performance found on multiple linear regression models. The chronic cumulative exposure index was the independent variable simultaneously controlling for acute PCE exposures. The significance level for including a term ranged from $p < .1$ to $p < .001$ given that behavioral data is subjective information. The chronic index of lifetime exposure to PCE was categorized into low moderate, and high exposure groups. The adjusted and unadjusted mean performance scores for each category were used to compute the percent loss in performance or $100 \cdot$ [Low-High/Low].

Symptoms, fatigue, and hours of sleep were based on an administered checklist on the day of testing. Symptoms over the last three months and mood were based on a computer-administered questionnaire. Each outcome was treated as an acute measure. Each item was examined independently for consistency with a linear trend, and differences in means was by Scheffe 95% CI contrasts between low and high categories of PCE exposure. Longer term symptoms and mood scales were also examined as chronic outcome measures in the correlation matrix and multivariate regression analysis using the index of lifetime exposure to PCE.

Results

The average duration of employment for the low, moderate, and high exposure groups were 2.1, 3.9, and 14.6 years. The long duration of employment among the high exposed group of operators permitted discrimination between job titles based on the concentration of PCE in breath. The breath levels for counter personnel, pressors, and

operators were 0.9 ppm, 6.5 ppm, and 11.4 ppm PCE, corresponding to respective air levels of 11.2, 23.2, and 40.8 ppm.

Significant behavioral decrements were found among the same individuals for visual reproductions (14.4%), the number correct (6.7%) and the latency (10%) for pattern memory, and the number correct (3.9%) for pattern recognition. There was no interaction between alcohol use and PCE exposure. Consistent with prior epidemiology studies, a correlation analysis found age, education, vocabulary, and alcohol consumption associated with lifetime PCE exposure and performance. Test scores did not vary between sexes. Verbal skill, measured by a vocabulary test, was more strongly associated with age (R^2=.26) than with years education (R^2=.15), suggesting that verbal skill was acquired from the social environment rather than formal schooling.

None of the mood scales or the fatigue checklist were associated with acute PCE exposure in air or in breath. However, tension and the number correct of the pattern recognition test was associated with cumulative lifetime exposure. Among symptoms, reports of "dizziness from rapidly standing up" and "solvent related dizziness" statistically increased with PCE exposure. Otherwise, symptoms were not associated with current or chronic PCE exposure and were ranked by their prevalence. Greater than 40% of the subjects reported being tired or thirsty. About 20% of the subjects reported eye irritation, headaches, and nervousness; and under 10% reported lightheadedness and nose irritation.

Discussion

Among operators, subclinical impairments in visually mediated functions support the available clinical evidence on a possible continuum of severity. The two tests most sensitive to PCE exposure measure short-term memory for visual designs (pattern memory and visual reproductions). The ability to match designs without relying on memory was affected to a lesser extent but was not seen on the copy condition of visual reproductions, therefore it does not seem reasonable to attribute the visual memory results to a purely perceptual process because the effect was smaller under matching conditions. Attention can not be held responsible either, as PCE was not found to affect tasks such as digit span which could detect a 5% difference in performance (alpha=.05; beta=.80), well

within the range of expected subclinical impairments. One possible explanation which is not well addressed by the current battery is that memory for abstract visuospatial material is particularly difficult to codify and that these tests are simply harder for subjects. Another explanation, which deserves further exploration, is that PCE may affect the hippocampus, a structure known to mediate memory functions, or diencephalic structures, which are known to be affected by ethanol and to be associated with reduced ability to remember visuospatial material.

Given the findings with PCE-exposed patients, it is interesting that mood effects were not detected in this study. It is possible that persons seeking treatment do so because they feel differently due to emotional effects from exposure, and that they are therefore not comparable to an unselected group of PCE workers. It is also possible that emotional effects occur later in the progression of PCE encephalopathy, that is, when signs and symptoms are becoming clinical rather than subclinical. The lack of a control group also may explain the negative findings.

The findings on the Trailmaking Test, which requires sequencing and cognitive tracking, were in the expected direction but somewhat equivocal and not conclusive. This task is known to be impaired in patients with frontal lobe lesions and is clinically sensitive to other types of solvent encephalopathy. However, in PCE exposure it may be necessary to use a more complex test of frontal lobe function to detect changes in workers who are not identified as ill and remain on the job. There are a number of such tests which could be utilized, such as the PASAT, Stroop or Wisconsin Sorting Test.

It is also interesting that PCE exposure was not associated with impairment in the symbol-digit task even though there was adequate statistical power. The [Low-High] difference in performance appeared great but was statistically insignificant. The correct direction could reflect prior exposure to paint solvents and pesticides, making it a sensitive measure but not specific to PCE exposure. The symbol-digit test is also an analogue of the digit-symbol test, which has frequently been reported to show sensitivity to other solvents. The latter task is, however, administered differently than the symbol-digit: the subject, himself, draws symbols and has to visually scan lines independently, producing a test which is much more complex

both perceptually and motorically than simply pressing computer keys as in the symbol-digit test.

In conclusion, this study provides evidence of subclinical behavioral effects consistent with those seen in moderate CNS effects of solvent exposure, suggesting visually mediated functions are especially affected by PCE exposure. The study shows behavioral testing can successfully be used as an early indicator of clinical CNS health problems. The study provides new information on subclinical impairment (less than 17%) on select performance measures among workers exposed to PCE below 40 ppm. Decrements in visual reproduction, pattern memory, and pattern recognition were consistently found in subjects employed as operators for an average of 14.6 (SD=8.9) years, exposed to an estimated TWA air concentration of 41 ppm, above the OSHA Permissible Exposure Limit of 25 ppm[8] and just below the American Congress of Government Industrial Hygienists (ACGIH-TLV) of 50 ppm.[9] A stratification of PCE exposure suggests more than three years' exposure may be necessary to detect significant behavioral effects. Impairments in visual function and their reversibility still need to be investigated in other industrial populations exposed to PCE and other chlorinated solvents.

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MICROMANGANISM: EARLY NERVOUS SYSTEM DYSFUNCTION AMONG MANGANESE EXPOSED WORKERS

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Manganism, first described by Couper[1] in 1837 among workers employed in grinding manganese ore, has been observed in hundreds of cases throughout the world. With a view to prevent the development of this neurodegenerative disease, recent research efforts have attempted to refine both exposure estimates and means of detecting early nervous system alterations.[2,3,4] The present study was undertaken to further document early nervous system dysfunction in a target population with long-term exposure to manganese, using an extensive battery of neuro-functional tests. The target population comprised workers employed in a large ferromanganese and silicomanganese alloy facility, exposed to manganese dust from the crushing and screening of both raw materials and the alloy products, as well as manganese fume from furnace tapping and cooling of the product in open bays.

Environmental exposure

Industrial hygiene sampling strategy included full shift monitoring for total dust and determination of manganese content for representative groups of workers, and parallel stationary environmental sampling using Dorr-Oliver nylon cyclones and regular filters at 13

representative locations across the plant. Dust was determined gravimetrically and manganese content in the dust by atomic absorption spectrometry using NIOSH Method #173 for Metals (1979). Results indicated that dust levels varied widely across the facility but were, at the time of sampling, for the most part below the recommended exposure levels. The geometric mean for airborne manganese for personal sampling of 8-h shift jobs (n=42) was 0.25mg/m^3 (Q1: 0.14; Q3: 0.48) and for 12-h shifts (n=51) was 0.09mg/m^3 (Q1: 0.04; Q3: 0.23). Results of stationary sampling showed wide variability and that the fraction of respirable manganese is dependent on location, but were, at the time of testing, for the most part, below recommended exposure levels. The overall environmental geometric means for total manganese and respirable manganese were respectively, 0.23 mg/m^3 (Q1: 0.04; Q3: 1.05) and 0.03 mg/m^3 (Q1: 0.01; Q3: 0.17). Preliminary examination of past dust measures suggests, however, that at certain job sites they had been considerably higher.

Study design

The plant is located in an industrialized area with potentially high background levels of environmental pollution. The prevalence of Parkinsonism in this region is reported to be 2-5 times higher than the rest of Québec.[5] A matched pair study design was favoured over other types of study since it provides the best means of minimizing bias. Recruitment for the study was conducted throughout the plant and 115 worker (95% of the total population) participated. Approximately 400 potential referents were recruited from the region and screened on the basis of similar socio-demographics and no occupational exposure to potential neurotoxins; a total of 145 men were retained. Prior to pairing, workers and referents with a previous history of neurological illness, psychiatric disorders, extended psychological treatment or alcohol or drug abuse were excluded.

Pairing was carried out on the variables: age (± 3y), educational level (± 2y), smoking status (smoker/non smoker), number of children (0,1,2,3 or more), while ex-aequos were separated on nearest length of residency in the region. A total of 74 pairs were thus created. The workers who made up this group had worked in the plant for an average of 14 years. Pair comparisons for socio-demographic characteristics and lifestyle other than those that were

matched indicated that the pairs were of similar height; weight; tea, soft drink and alcohol intake; and the smokers consumed a similar number of cigarettes/day; however, the manganese alloy production workers drank significantly more water (paired t-value 2.64; $p > 0.01$) and significantly less coffee (paired t-value -2.38; $p = 0.02$). A possible explanation for the latter differences may be the high temperatures generated during the smelting process. Comparison of reported family medical history, obtained through a self-administered questionnaire, likewise showed inter-pair similarity.

Methods

Participants were examined over 2 three hour periods, prior to commencement of a workshift. Testing was scheduled such that one of the test periods occurred on the final day of the work cycle at which time biological samples were collected. Participants filled out a self-administered questionnaire, were interviewed as to their medical history, and underwent an extensive battery of neurophysiological and neuropsychological tests of motor and sensory functions, speech initiation and regulation attention, concentration and memory, cognitive flexibility and affect. Both examiner administered and the computerized Swedish Performance Evaluation System (SPES) neuropsychological tests were included.

Biological indicators of exposure

The concentration of manganese in whole blood was measured by flameless atomic absorption spectroscopy according to the method described by Peblan and Pearson[6] with some modifications. Determination of manganese in urine was carried out using the method described by Buchet et al.;[7] this method is based on flameless atomic absorption spectrophotometry, utilizing the method of standard additions. Results from the analyses of biological indicators revealed highly significant inter-pair differences for blood manganese (paired $t = 6.20$; $p = 0.0001$); geometric mean values for the workers and their matched pairs were 1.03μg/100ml and 0.68μg/100ml, respectively. No difference was observed for urinary manganese levels; the geometric mean level for the workers was 0.73μg/g creatinine and the referents, 0.62μg/g creatinine.

Results

Symptoms, surveyed for the period when not at work, indicated significant inter-pair differences for symptoms of fatigue, adverse emotional state, memory loss, nightmares, sweating in the absence of physical effort, difficulty maintaining an erection (McNemar Chi square $<23.1>11.4$; $p<0.001$). Among the neuromuscular, musculoskeletal and sensory symptoms, joint pain (McNemar Chi square 7.14; $p<0.01$) best differentiated the two groups.

Significant interpair differences (paired t-test 3.6; $p<0.01$) were observed on the overall score of motor scale of the Luria Nebraska Neuropsychological Battery, which consists of 51 tasks assessing different aspects of motor function. Further analysis, performed on the items for which frequency or duration of movement are recorded, showed that the manganese alloy workers performed significantly more poorly on motor tasks involving rapid alternating, coordinated movements of one or both hands or of the mouth. However, the capacity to perform specific movements, such as drawing figures, were not significantly different between the two groups.

The manganese alloy workers performed more poorly on the Nine-hole Hand Steadiness Test and touched the sides of the holes more frequently than their matched referents (paired t-test 2.04; $p = 0.04$). Results from the manual and computerized versions of the two finger tapping tests are interesting; while the manganese alloy workers demonstrated a tendency, albeit above the 5% significance level, to perform more slowly than their pairs on the manual version (paired t-test 1.6; $p = 0.09$), the reverse was true for the computerized test (paired t-test 1.6; $p = 0.10$). The differences in each subject's performance on the computerized and manual tests were calculated and inter-pair differences were analyzed. For both hands, the manganese alloy workers had significantly larger differences in performance as compared to their matched pair (paired t-test: 3.2; $p<0.01$). This may reflect underlying tremor since on the manual test the person is required to tap on a level which is 3.5 cm high, while on the computerized test, tapping is done on a keyboard. No inter-group differences were observed for total mean simple reaction time or its standard deviation on the SPES Simple Reaction Time test, which was administered over 5 minutes; however the manganese alloy workers showed a greater tendency towards

slowing between the 1st an 5th minute of the test (paired t-test: 1.71; p= 0.09).

Among the sensory functions that were measured (vision, vibrotactile perception and olfaction) only olfactory perception threshold discriminated significantly between the two groups, with the manganese alloy workers displaying significantly lower smell thresholds as compared to their matched pars (paired t-test: -2.3; p = 0.02). Enhanced smell perception is an interesting and unexpected finding since one would have expected reduced smell threshold if only due to the mechanical action of the dust. This finding is confirmed among the non-exposed referents, whose smell threshold improves with increasing blood manganese levels.[8]

On the grapho-motor tests, the manganese alloy workers took significantly longer to draw lines on the Parallel Line Test (paired t-test: 2.3; p = 0.02), although there was no difference in the number of lines drawn by both groups. The manganese alloy workers took longer on Cancellation H (paired t-test: 2.1; p = 0.03) and the Trailmaking Tests, although for latter, the inter-pair difference did not attain the 5% significance level.

No differences were observed on any of the tests of speech initiation and regulation. However, significantly more manganese alloy workers made errors on the second trial of the Digit Naming Test (discordant pairs: 14 vs. 1; McNemar Chi square 11.36; $p<0.001$), while on the first trial, no difference was observed. Although there were no differences on the Word and Color Version of the Stroop Test, the workers performed more poorly on the Color/Word task paired t-test: -2.53; p = 0.01), where there is interference between color and word. Interpair differences on cognitive flexibility were also apparent on the Trailmaking B Test, which requires shifting from numbers to letters; more manganese workers made significantly more errors (paired 5-test: 2.44; $p=0.02$).

Inter-pair differences for mood states, were particularly evident on the Profile of Mood States Test, with the manganese allow workers displaying significantly greater tension (paired t-test: 2.7; $p<0.01$), depression (paired t-test: 2.1; p = 0.04), anger (paired t-test: 2.3; p = 0.02), fatigue (paired t-test: 3.6; $p<0.001$) and confusion (paired t-test: 2.5; p = 0.01). The alloy workers reported less vigor

than their counterparts, but the differences did not reach the 5% significance level ($p=0.07$).

Conclusions

The findings of this study indicate that the manganese alloy workers differed from their matched referents on symptom reporting, emotional state, motor functions (particularly those which require alternating and/or rapid movements and hand steadiness), olfactory perception threshold and certain forms of cognitive flexibility. For the most part, intellectual functions were similar on tests of verbal fluency, basic mathematics, reading capability and attentional capacity. The profile of dysfunction is all the more striking since the workers and the paired referents who participated in this study were very similar, not only for the variables on which they were paired, but also for lifestyle, family medical history.

The pattern of symptoms and deficits that emerges among this group of workers is remarkably similar to classical descriptions of early manganism, and is consistent with current knowledge on the site and mechanisms of manganese activity in the brain. These results suggest that manganism probably progresses infra-clinically on a continuum. Thus, long-term exposure to manganese alters specific functions of the nervous system, which can be detected in actively working populations using a well-designed study and sensitive testing methods. We are currently analyzing the data with respect to internal and external exposure parameters, including a cumulative exposure index derived from past company records.

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SELECTION BIAS IN A CASE-CONTROL STUDY OF PSYCHIATRIC DISEASE AND OCCUPATIONAL SOLVENT EXPOSURE

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Introduction

Exposure to organic solvents has been related to many changes in human nervous system function, as measured by report of symptoms, psychometric and neurobehavioral testing, and occurrence of overt neurologic and psychiatric disease. In this investigation, a case-control approach was used to examine relationships between chronic psychiatric disease and solvent exposure in a group of U.S. automobile assembly plants, to quantify risk in this environment and compare it to that found in other studies. This study used detailed exposure assessment methods to better quantify relationships.

Materials and methods

The study group included 1,129 hourly employees working at 8 large automobile assembly plants any time in 1980-88. Cases were 273 individuals granted medical disability retirement in 1980-88 because of psychiatric disease (6 diagnostic categories). Eligibility required 10 years of employment. Two control groups were identified: "disability" controls included those taking medical disability retirements for disorders other than those of interest (n=326). "Population" controls included hourly workers employed some time in 1980-88 with at least 10 years employment duration (n=530). Controls were individually matched to cases on plant where worked, gender, race, birth date, hire date, and employment duration. Matching ratios varied for matched sets.

Exposure assessment

Study members' individual exposures were estimated using job descriptions taken from personnel records. Study hygienists used company-maintained air sampling records, observations of current plant operations, and interviews with plant personnel to characterize solvent exposure for assembly plant departments and operations. Jobs were designated as having no, low, or high solvent exposure (>50% of the Threshold Limit Value for mixtures). Years of halogenated, nonhalogenated, respiratory, and dermal exposure were cumulated. Potential confounding exposure to lead was also estimated. Exposures to neurotoxicants prior to hire by the auto company were estimated using previous jobs listed on employment applications.

Results

Mean employment duration for the entire group was 15.9 years; average exposure to solvents was 2.3 years. Mean exposures to halogenated and nonhalogentated solvents were 1.7 and 1.9 years, respectively. The mean exposure to lead was 0.9 years. Fifty-nine percent of the group had no solvent exposure; half of those exposed had less than one year of exposure.

Univariate odds ratios calculated using conditional logistic regression are shown in the Table. Exposure to solvents was lower for cases than control groups, regardless of how exposure was expressed. Potential confounding occupational exposures to neurotoxicants did not affect results. Alcohol consumption was significantly related to the outcome (although a large number of participants had missing data).

Additional analyses

Additional analyses were conducted in an attempt to explain the counterintuitive results. Analyses were carried out stratifying by race/gender group, plant, and diagnostic category; by excluding selected individuals (schizophrenic cases and their controls, cases with substance abuse disorders and their controls, individuals with unusually long exposures, cases with disease onset prior to hire and their controls, and controls with (mild) psychiatric disorders. Analyses were also carried out truncating exposures at first job, first year of exposure, first five years of exposure, date of case disease

onset, and 10 years preceding onset. Analyses were also carried out rematching on fewer variables (plant race, gender, and birth date, only). In all analyses, the apparent protective effect of exposure was still observed.

Univariate conditional Logistic regression odds ratios for selected exposure variables and potential confounders

	Disability controls		Population controls	
Variable	OR	p-value	OR	p-value
Solvents >0 yrs[1]	0.86	0.55	0.82	0.35
Solvents ±1 yr[1]	0.60	0.089	0.44	0.001
Solvents ±5 yrs[1]	0.39	0.048	0.26	0.001
Lead ± 0.5 yr	0.93	0.85	0.94	0.82
Pre-auto Lead[2]	—		0.0	0.31
Pre-auto pesticides[2]	0.83	0.76	0.60	0.55
Pre-auto solvents[2]	0.80	0.80	1.04	0.91
Total solvents[3]	0.47	0.070	0.29	0.0001
Alcohol[4]	2.20	0.048		

[1] Assembly plant exposure to solvents: ≥0, 1 and 5 years
[2] Exposure (any) to lead, pesticides, or solvents prior to hire by the auto company
[3] Total exposure to solvents, auto and pre auto-plant combined (≥5 years)
[4] Alcoholic or heavy drinker versus not

Discussion

Design or study population characteristics that lead to observation of biased results include misclassification of exposure or disease status, inappropriate expression of exposure, overmatching, and poor statistical power resulting from lack of adequate exposure levels. In most cases these flaws, some of which could have affected this investigation, tend to bias results toward the null rather than cause the results seen in this study. The apparent protective effect of solvent exposure also did not appear to be related to confounding neurotoxic exposures.

The observed results may relate to unknown selective factors that are unique to this study population. The Healthy Worker Effect (HWE) would be expected to operate in a group of workers who develop

chronic disability--as years passed, absenteeism would increase and employees might be transferred to positions with less responsibility and perhaps concomitantly, less potential for exposure to solvents. One would not expect to see the HWE early in employment, when the workforce is young and purportedly healthy. However, differences in solvent exposure were observed in the very first job assignments held by study participants, suggesting that cases were selected into low-exposure jobs at initial employment. In view of automobile company hiring practices, this seems puzzling, as production (non-skilled) workers are hired as needed and new employees are placed in positions based only on need (little evaluation takes place).

It might be hypothesized that the requirement that participants had worked for 10 or more years led to differential selection of cases and controls based on exposure status. Participants were largely unskilled employees working in a diverse environment with regard to exposure: many jobs and exposure conditions were available in theory, but employees may have had limited opportunity to transfer from undesirable positions and vulnerable individuals may have chosen to leave the workforce. Relatively low entry-level requirements may have allowed disproportionate numbers of individuals with psychiatric problems to enter the workforce. If these workers are more sensitive to chemical exposures, this phenomenon may explain observed results.

THE INFLUENCE OF WORKPLACE FACTORS ON COGNITIVE FUNCTION AS MEASURED BY NEUROBEHAVIORAL TESTS IN AUTOMOTIVE WORKERS: PART I. CUMULATIVE FATIGUE EFFECTS OF OVERTIME. PART II. JOB STRAIN EFFECTS OF MACHINE-PACED WORK.

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Part I. Experimental studies have indicated that fatigue resulting from several days of long work shifts affects cognitive function and job performance. However, review of the occupational epidemiology literature did not reveal any studies of the effects of cumulative fatigue, as a result of long work days sustained over longer period of time (i.e., week, month) due to overtime, on cognitive abilities or job performance. In this prospective cohort study involving 248 workers within the automotive industry, we examined in effect of overtime on behavior and cognitive function as measured by neurobehavioral test performance. Overtime, defined as number of hours worked greater than 8 hours per day and/or greater than 5 days per week, was calculated from company payroll records for the week (7 days) and month (28 days) before test day. Cross-sectional analysis of Year 1 data by multiple linear regression demonstrated that overtime worked the week before testing was significantly associated with increased response times on "time to complete" Trails A and B (a task of attention and executive function), impaired performance on "number of successful sorts" and increased "number of errors" on Wisconsin Card Sort Task (complex task of executive function) and with poorer performance on a computerized Vocabulary task (an attention-requiring task of basic verbal abilities). The findings from Year 1 support the hypothesis that overtime per week results in cumulative fatigue which affects cognitive

performance in the specific functional domains of attention and executive function.

Overtime was not observed to be significantly associated with "time to complete" on the Trails Making Test in the cross-sectional analyses of Year 2 data. It was suspected that fewer subjects working increased overtime hours, loss-to follow-up, and that two of the tests associated with overtime in Year 1 (e.g., Wisconsin Card Sort Test and Vocabulary) were not repeated in the Year 2 battery, contributed to the difference in the findings between the two years. Further studies are recommended to evaluate the hypothesis that overtime work affects cognitive function in the areas of attention and executive function.

Part II. Based on the demand/control model developed by Karasek and Theorell (1990), it was predicted that work on high demand jobs where the worker has little control, e.g., assembly line, machine-paced jobs, will produce a psychological strain. This strain is characterized by reduced attention, impaired ability to learn new skills, and increased anxiety and depression. In this prospective study involving 248 workers within the automotive industry, we examined the effect of machine-paced work on cognitive function as measured by neurobehavioral test performance. Cross-sectional analysis of Year 1 data by multiple linear regression demonstrated that machine-paced work was significantly associated with impaired performance in the areas of attention and executive function, however no significant mood changes were observed. An increased number of errors on Trails B (a task of complex attention and executive function), poorer performance on 4 scores of the Delayed Recognition Span test (a visual memory task involving attention and new learning skills), and reduced percent correct on a computerized version of the Symbol-Digit Substitution test (a task of attention and motor skills) and on the computerized Vocabulary task (an attention-requiring task of basic intelligence) were observed.

Recent work (Part I) suggests that overtime results in impaired cognitive function in tasks of attention and executive function, as measured by neurobehavioral tests. In the present investigation, machine-paced work did not significantly affect the effects of overtime described in Part I. However, in Year 1, the results suggest a different response to the strain produced by machine-paced

work than that observed with overtime, perhaps reflective of decreased motivation to learn new skills. Machine-paced work was predictive of a faster response time with increased errors, whereas the fatigue effects of overtime resulted in a slower time to complete a task without a decrease in accuracy.

In Year 2, the results did not support those findings seen in Year 1, as machine-paced work was not associated with performance on any test. Further study is recommended to evaluate the proposed hypothesis regarding the effects of machine-paced work on cognitive function and to investigate the strategic response difference between overtime and machine-paced work.

PREVALENCE OF DEPRESSION AMONG ELECTRICAL WORKERS

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Since the 1960s, concerns have been raised regarding possible adverse psychological consequences of exposures to electric and magnetic fields (EMF). It has been hypothesized that EMF may act to suppress the normal nocturnal rise in pineal melatonin production, which is potentially linked to depression. To our knowledge no previous study has systematically examined indicators of depression using standardized assessment tools.

The Vietnam Experience Study, conducted by the Centers for Disease Control, included an extensive psychological assessment battery. We compared results from 183 current electrical workers (including 59 electricians, 27 electrical technicians, and 26 telephone repairers and installers) to 3861 other workers with respect to diagnosis of depression based on the Diagnostic Interview Schedule (DIS), symptoms reported in the DIS (weight gain or loss, sleep disturbance, slowness or restlessness, loss of interest in sex, feelings of worthlessness or guilt, trouble thinking, or thoughts of death); and Minnesota Multiphasic Personality Inventory (MMPI) scales for depression, hysteria, subjective depression, psychomotor retardation, physical malfunctioning, mental dullness, and brooding. Each item was dichotomized based on standard criteria and prevalence ratios were calculated comparing electrical workers to non-electrical workers. All results were adjusted for years of work in current job (1-10, 11-15, 15+ years).

For all electrical workers, the prevalence ratio (PR) for depression in the last month was 1.5 (95% CI: 0.6-3.6), the PR for lifetime depression was 1.0 (95% CI: 0.5-1.6), and the PR for recurrent unipolar depression was 0.8 (95% CI: 0.4-1.7). Although results for individual occupations were quite imprecise, evidence of an increased risk of depression in the last month was noted for

electricians (PR=2.6, 95% CI: 1.0-6.8). Depressive symptoms tended to be rarer among electrical workers, most notably weight gain or loss (PR=0.5, 95% CI: 0.1-1.3) and loss of interest in sex (PR=0.2, 95% CI: 0.0-1.1). Only for "trouble thinking" was risk even modestly elevated (PR=1.6, 95% CI: 0.8-2.9), with short-term electrical workers at more notably elevated risk compared to other short-term workers (PR=2.0, 95% CI: 0.8-4.8). Electricians tended to have elevated risks for sleep disturbances and fatigue (PRs=1.4), feeling of worthlessness and guilt (PR=2.4), and trouble thinking (PR=2.1), all imprecise estimates. Prevalence ratios for elevated MMPI scores were all close to the null, with individual estimates ranging from 0.6 (MMPI D Scale, subtle) to 1.3 (MMPI Hy Scale, subtle). Analysis by duration of employment suggested that long-term electrical workers were more likely to have high scores on "brooding" (PR=1.9, 95% CI: 0.7-5.2).

Our ability to detect modest increases was limited by the numbers of such workers included in the study, the inherent uncertainty in attributing EMF exposure based on job title alone, and our inability to adjust for such neurotoxic agents as solvents. Overall these results provide evidence against a widespread or sizable increase in depression or related symptoms among electrical workers.

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CYTOGENETIC STUDY IN FEMALE NURSES OCCUPATIONALLY EXPOSED TO CYTOTOXIC DRUGS

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This study aiming to investigate cytogenetic endpoints as measured by sister chromatid exchanges (SCEs) and chromosome aberrations (CA) among female nurses occupationally handling cytotoxic drugs. 45 nurses working in oncology departments with daily exposure to antineoplastic drugs represented the exposed group. The most frequently used drugs were cyclophosphamide, methotrexate, adriamycin 5-fluoruacil and cisplatinum. The exposed group were matched as regards age, sex and socioeconomic status with 40 nurses who were never exposed to such drugs. All subjects had normal children and were not exposed to x-ray, drug therapy or viral infection for at least six months prior to the study. All were non-smokers. History of hormonal contraceptives, also some other behavioral parameters as cooking, watching television (hours/day), insecticide sprays (days/week) was taken into consideration. Two whole blood lymphocytic cultures were set up for each individual. The culture composed of RPMI media 1640 supplemented with 10% fetal calf serum, 1% phytohaemagglutinin (PHA) 0.5% glutamine, 0.1% sodium heparin, 0.1% penicillin and streptomycin for SCEs. Bromodeoxyuridine was added at a concentration of 50 ug/culture. Harvest was done at 48 hr and 72 hr for (CA) and (SCEs), respectively. The mean $\pm$ SD of age was 38.35 $\pm$ 7.9 ys among exposed group versus 39.87 $\pm$ 4.33 among controls, $p > 0.05$. The duration of handling the cytotoxic drugs was 16.02 $\pm$ 6.8 ys. Regarding (CA), it was 4.79 $\pm$ 1.3 among the exposed group versus 2.47 $\pm$ 0.7 among controls, $p < 0.0001$. As for (SCEs), it was 10.53 $\pm$ 2.7 among exposed versus 8.70 $\pm$ 2.4 among controls $p < 0.0001$. Recorded types of CA were chromatid gaps and breaks, dicentrics, exchange figures and accentric fragments. Correlation was proved between duration of handling cytotoxic drugs and SCEs frequency but not (CA) endpoint. Again, a positive correlation was proved between duration of oral contraceptives and SCEs.

In conclusion, our data revealed that handling cytotoxic drugs on an occupational level have harmful mutagenic effects. Hormonal contraceptives should be avoided as a method of birth control among those nurses handling cytotoxic drugs to avoid synergistic or additive clastrogenic action.

SELF-PERCEPTIONS OF WORKING AND LIFE CONDITIONS AMONG BRAZILIAN PETROCHEMICAL WORKERS

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Introduction

In addition to the usual work risks, workers in continuous processing plants face several disturbances caused by shiftwork. A comprehensive self-assessment study of petrochemical workers analyzed perception of their working and living conditions and the apparent consequences upon their health and well-being. The study was conducted in 1988 and 1989 in a polyethylene production plant in Cubatão, Brazil, 50 Km south of São Paulo.

The specific objectives were: (1) to evaluate the relationships between measurable workload and perceived resulting strain; (2) to determine for day and shiftworkers any self-assessed differences in working and living conditions, and any perceived consequences of these upon their health and well-being; (3) to compare perceived workload and strain among workers performing different functions in the same plant; and (4) to analyze the perceived consequences of the living and working conditions in relation to (a) illnesses, (b) accidents, (c) social and family life, and (d) activities during workers' leisure time. These self-assessment measures were based upon models developed by Colquhoun and Rutenfranz (1980), Haider et al. (1989), and Knutsson (1989).

Material and methods

A sample of 50 workers, following the same distribution of the plant, was randomly selected from a total population of 228, according to age, years of service and plant sectors. A cross-sectional study was carried-out. The sample consisted of 34 male shiftworkers on 8-hr

weekly rotating shifts of 42-hr per week, and 16 dayworkers (all but one male) on 8-hr fixed schedules of 40-hr per week. Mean age of the workers were 34,0 and 33,4 years old, for day and shiftworkers, respectively

Stresses and the resulting strains were self-evaluated using an omnibus questionnaire, constructed after interviewing the workers.

Workloads were determined using a variety of several independent variables. These included the working conditions and individual and family characteristics. Working conditions were self-assessed in terms of characteristics of the tasks, work autonomy, time pressure, rhythm of work, work satisfaction, relationships with colleagues and supervisors, training adequacy, career path, physical and mental stress, potential dangerousness of the workplace in terms of physical, chemical and biological substances causing occupational diseases, discomfort, working time (daily and weekly) hours and overtime, pauses, time working on shiftwork, former experience on shiftwork (for day workers) and benefits. Individual and family characteristics included age of the worker, marital status, number and age of the children, spouse working time, housing conditions.

The dependent variables measures strains. They were represented by the self-assessed consequences to health. These included occupational and non occupational diseases (included among others, health complaints, sleep disturbances, nervous and gastrointestinal disorders), accidents (at and off-work), effects on social and family life, uses of tobacco, coffee and related caffeine drinks, and alcohol.

All self-evaluation responses by the workers were converted into scores. Fisher, Levene and Welch statistics were used to compare the scores according to their work functions, schedules, working conditions, health effects, and well-being. Multiple linear regressions, the Stepwide technique, were used to detect any significance of the independent variables perceived effects upon workers' health.

Results

Comparative results show that shiftworkers perceive themselves as facing worse working conditions than dayworkers ($F=4.83$, $p=.03$) and greater restrictions upon their leisure time activities ($F=6.35$,

p=.01). However, alcohol and tobacco usage were indicated as being more widespread and frequent among the dayworkers than shiftworkers (F=5.17, p=.02). (Please see Table 1 for statistical comparisons). Disregarding work schedules, these habits (alcohol and tobacco usage) were found to be more frequent for persons with management responsibilities than for operations workers (F=2.20, p=.05).

Table 2 shows the results of a multiple regression analysis (MRA) among all variables studied. All coefficients of MRA, except medical leaves due to occupational diseases and accidents at work, were above 0.40. These following dependent variables showed statistically significant differences ($p < .05$) between the perceptions of day and shiftworkers.

(1) Readiness to work was perceived to have been worse the longer a worker was on shiftwork.

(2) Medical leaves resulting from occupational diseases and accidents at work were reported to be more frequent in older workers.

(3) Unexpected events (accidents off-work) were reported to be more frequent both for workers reporting worse working conditions and the longer the time spent on shiftwork.

(4) Interferences of work on social and family life and on activities during leisure time were perceived increasing as the working conditions are worsened. Also, workers living with partners had fewer difficulties in family and social lives than single workers. Leisure time activities became more restricted the longer the time on shiftwork.

Conclusions

This self-response questionnaire study clearly shows that continuously rotating shiftworkers perceived themselves to have significantly more negative factors affecting them both on and off the job than do their fixed-schedule dayworker colleagues. Also, it shows the perceived impact of the working conditions and work organization on the whole well-being of the workers.

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Table 1. Workload and strain between day and shiftworkers

VARIABLES		F	P
1.	Working conditions	4.83	0.03*
2.	Benefits	1.20	0.27
3.	Readiness to work	2.64	0.11
4.	Health Disturbances:		
4.1	Psychosomatic symptoms and infectious diseases	0.01	0.90
4.2	Medical leaves due to occupational diseases and accidents	0.28	0.59
4.3	Unexpected events (accidents)	1.28	0.26
4.4	Sleep (disturbances, quality, conditions)	1.83	0.18
4.5	Drinking habits (coffee, alcoholic beverages), and smoking habits	5.17	0.02*
5.	Socio-family relationships:		
5.1	Interferences caused by the work	1.21	0.27
5.2	Activities during leisure time	6.35	0.01*

*$P < 0.05$ Significant differences

Table 2. Multiple linear regression analysis. Variables influencing the workload and strain of day and shiftworkers

Dependent variable CCM* (R)		Independent variable	F **
1.	Readiness to work (0.40)	Time working on shifts	8.37
2.	Medical leaves due to occupational diseases and accidents at work (0.34)	Age	5.58
3.	Unexpected events: Accidents off-work (0.35)	Working conditions	6.20
	(0.45)	Former experience on shiftwork	5.35
4.	Interferences of work on social and family life (0.43)	Working conditions	9.70
	(0.52)	Marital status	7.98
5.	Activities during leisure time (0.45)	Time working on shifts	11.02

*CCM- Coefficient of Multiple Correlation;
**P < .05

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CROSS-SECTIONAL STUDY OF EFFECTS OF ACETONE EXPOSURE ON WORKERS' HEALTH

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Introduction

Acetone is a very common organic solvent used in many industries, and is considered to be one of the less toxic solvents. Although the present regulated or recommended occupational exposure limits for acetone are relatively high, they vary with each country. For example, the Threshold Limit Value (TLV) of American Conference of Governmental Industrial Hygienists (ACGIH) for acetone is 750 ppm. On the other hand, the Japan Association of Industrial Health recommended an acetone occupational exposure limit of 200 ppm in 1972 based on the results of 250 ppm and 500 ppm acetone exposure experiments to volunteers conducted in Japan.[1,2] The purpose of this cross-sectional study is to clarify the relationships between occupational exposure to acetone and its effects on workers' health with special reference to environmental and biological acetone exposure levels and the magnitude of the health effects.

Subjects

All subjects were male shift work employees of one of three Japanese acetate fiber manufacturing factories. The exposed group consisted of 110 acetone-exposed workers (AC workers). The control group consisted of 67 workers who were working in the same factory area but not engaged in acetone manufacturing. The AC workers were exposed only to acetone without using any protective devices. The control workers could have been exposed to background level of acetone, less than 5 ppm, when passing through the acetate fiber manufacturing plants. The characteristics of study population are summarized in Table 1.

Survey schedule

The schedule of health checks and exposure monitoring is shown in Table 2. Exposure levels of acetone were assessed by personal passive monitors and biological monitoring. Details regarding the method of exposure assessment appeared in another paper.[3] Health assessment consisted of a self-administered questionnaire including acetone exposure-related symptoms, Manifest Anxiety Scale (MAS), and Self-rating Depression Scale (SDS), and a computerized neurobehavioral test battery consisting of five items; Finger Tapping, Simple Reaction Time, Choice Reaction Time, Digit Span, and Benton Visual Retention Test. R-R interval on EKG, hematological and biochemical parameters were also determined.

Results and discussion

Exposure assessment: Exposure levels by each index are shown in Table 3. Two hundred eighty-eight samples of acetone in the breathing zone (AC-E), 293 samples of acetone in alveolar air (AC-A), 108 samples of acetone in blood (AC-B), and 275 samples of acetone in urine (AC-U) were measured, and mean values of each were 361 ppm, 91 ppm, 67 mg/l, and 37 mg/l respectively. Although the ranges of measured acetone levels were very wide, the exposure levels of each individual measured on different days were similar (data not shown). In order to assess the exposure-response relationship, the acetone exposed workers were classified into three groups: higher-exposed, middle-exposed, and lower-exposed. The cut-off levels of each exposure index for classification are also shown in Table 3.

Health effects assessment: Subjective symptoms during the last 6 months (Q1), before starting daily job (Q4), and during or after job (Q5) were recorded in AC workers with higher frequency than in control workers as shown in Table 4. Among these positive Q1 symptoms, the significance of the prevalence of "Palpitation" and "Phlegm in winter or night" disappeared when the effects of alcohol drinking or smoking were adjusted by applying the Mantel-Haenszel method.

In the neurobehavioral tests, simple reaction time and digit span were significantly lower among AC workers aged 30-44. Educational

history, alcohol drinking and smoking habit did not affect these results.

Other items; MAS score, SDS score, RR-intervals, hematological, and biochemical parameters did not show any acetone exposure related differences between AC workers and control workers.

Dose-response assessment: The results of statistical analysis for dose-response relationships using three exposure categories mentioned above, showed significant exposure-response relationships in most of the positive questionnaires (data not shown).

In the neurobehavioral tests, exposure-response relationships were not clear.

Recommendation and conclusion

The outcomes of this study indicate that, at the present exposure level of acetate fiber manufacturing workers, acetone causes irritative and narcotic effects expressed as significantly higher prevalence of subjective symptoms with good dose-response relationships, and as significantly lower simple reaction times and numbers of figures recalled in 30-44 year old workers.

The irritating properties and neurological effects of acetone in humans have been noted both in acetone exposed workers[4,5] and in volunteers of laboratory exposure experiments.[1,2,6] These complaints, however, were reported by workers with higher average exposure than by volunteers (over 900 ppm vs. 100-200 ppm).

We conclude that current TLV-TWA is too high to prevent neurological effects of acetone observed in this study.

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Table 1. Characteristics of male study population

	EXPOSED	CONTROL
Age (years)	37.6(18.7-56.8)	41.9(20.07-57-5)
Working period (years)	18.7(0.5-36.9)	22.0(0.7-38.6)
Exposure duration (years)	14.9(0.5-34.3)	-
Alcohol drinking		
drinkers (%)	70.9	78.7
Frequency (10 days)	7.1(0.5-10.0)	6.8(0.7-10.0)
Consumption (gram/day)	30.5(0.1-93.8)	31.9(0.5-85.5)
Cigarette smoking		
Current smokers (%)	74.7	70.5
Consumption (/day)	21.6(1-45)	20.1(5-37.5)
Education		
Junior high school (%)	53.4	65.6
Higher education (%)	66.0	86.9
Marital Status		
Married (%)	66.0	86.9

Table 2. Schedule of health examinations and exposure monitoring

		QU	RR	NB	BL	EX	BM
DAY1	pre-shift	X	X	X	X	X	X
	post-shift	X	X	X		X	X
DAY 2	pre-shift	X				X	X
	post-shift	X	X	X	X	X	X
DAY 3-4*		X				X	X

QU: Questionnaire administered prior to and at the time of pre and post shift examination.
RR: R-R interval (EKG).
NB: Neurobehavioral test.
BL: Blood sampling.
EX: Exposure (air monitoring acetone).
BM: Biological monitoring (urine and blood acetone).
*If possible to carry out.

Table 3. Acetone exposure assessment and cut-off values for risk assessment

	n*	Mean	Range	LOWER	MIDDLE	HIGHER
AC-E(ppm)	288	361.4	5-1212	-250	-500	501-
AC-A(ppm)	293	90.9	1-476	-70	-140	141-
AC-B(mg/l)	108	60.8	1-225	-45	-80	81-
AC-U(mg/l)	275	37.2	0.84-212	-25	-50	51-

*Blood samples were taken only once, air and urine more than once. AC-A, -B,-U, and -E: Acetone in alveolar air, in urine, in blood, and in breathing zone, respectively.

Table 4. Symptoms with significant increase in acetone exposed workers

	%Responder	
Q1 Symptoms without the last 6 months	EXPOSED	CONTROL
Q1-1. Heavy feeling in the head	25.8*	9.8
Q1-2. Nausea	24.7*	8.0
Q1-10. Faint feeling in the head	23.6**	5.9
Q1-19. Palpitation	31.5*	15.7
Q1-30. Loss of Weight	23.6**	5.9
Q1-58 Slow healing of external wound	7.9*	0.0
Q1-62. Phlegm in winter or night	16.9*	5.9
Q2 Symptoms before starting daily job		
Q2-2. Irritation of eyes	40.2*	21.6
Q2-3. Light inflammation of eyes	22.5**	5.9
Q2-4. Working morale reduction	32.4*	13.7
Q3 Symptoms during or after finishing daily job		
Q3-1. Irritation of eyes	45.1**	23.5
Q3-2. Tearing	13.7*	3.9
Q3-4. Acetone odor	36.3**	5.9
Q3-14. Nausea	25.5**	7.8

*, ** $p<0.5, 0.01$ by chi-square test or Fisher's method.

CYTOGENETIC EFFECTS OF FORMALDEHYDE EXPOSURE IN STUDENTS OF MORTUARY SCIENCE

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Formaldehyde exposure has been associated with nasal cancer,[1,2] nasopharyngeal cancer,[3,4,5] buccal and pharyngeal cancer,[6] and with leukemia.[7,8] The International Agency for Research on Cancer (IARC) found limited evidence for the carcinogenicity of formaldehyde in humans.[9] The National Institute for Occupational Safety and Health (NIOSH) considers formaldehyde to be a potential human carcinogen.[10] The U.S. Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for formaldehyde is 0.75 ppm, calculated as an 8 hour time-weighted-average (TWA).[11]

The effect of low-level exposure to formaldehyde on oral, nasal, and lymphocyte biological markers was studied prospectively in a group of 29 mortician students who were about to take a course in embalming. Students of mortuary science with little or no prior embalming experience were encouraged to enroll in the study. Eight of the subjects had never participated in an embalming prior to the study, six had assisted with from one to four embalmings, and 15 had assisted with five or more embalmings in their lifetimes. The average age of the subjects was 23.6 years. Seven of the 29 subjects were women, and five of the 29 (two of whom were women) were current smokers.

Exposures to formaldehyde were assessed by personal sampling using a passive monitoring device (PF-20 STEL monitor, Air Quality Research, Berkeley California). Prior to using the PF-20 passive monitor, it was evaluated in a laboratory exposure chamber and under field conditions in the embalming area of the mortuary college. In addition to the personal monitoring, short-term (peak) exposure measurements were performed using a continuous reading instrument (Interscan Model 4160 SP, Chatsworth, California).

Subjects were enrolled in the study during the first quarter of school, three weeks prior to their first embalming course. Each subject completed a questionnaire concerning past occupational activity, past embalming experience, smoking, diet, medication, and X-ray exposure. Swabs of the nose and mouth and blood samples were taken. The blood, oral, and nasal sampling was repeated after the first nine weeks in the embalming laboratory, and an interim questionnaire was administered.

All blood and tissue specimens were obtained in the morning, prior to any embalming, and were processed by the cytogenetic laboratory on the same day that they were obtained from the subjects. Assays for micronuclei and sister chromatid exchange (SCE) were done using standard methods. All slides were coded and marked by one of the investigators to blind the reader to the exposure status of any individual. To avoid reader variation caused by analyzing pre- and post-exposure slides at different times, staining of epithelial cell and lymphocyte micronuclei specimens was deferred until both pre- and post-exposure samples had been obtained, and then both sets of slides from each subject were stained together on the same day. Slides from any one individual were then read on the same day by the same reader. A 10% sample of all slides was chosen for quality control analysis. These slides were recoded and then rescored for micronuclei or SCE in the same manner and by the same reader.

Each subject was used as his or her own control in the analysis of change in levels of the various cytogenetic markers. Differences in mean pre- and post-exposure marker values were assessed by using a matched Student's "t" test for values that were normally distributed (SCE) or by the Wilcoxon sign-rank test, a non-parametric test, for values that were not normally distributed (micronuclei).[12] Comparison of the change in cytogenetic markers with cumulative

formaldehyde exposure was done using Spearman's rank correlation coefficient and by linear regression if the regression residuals were normally distributed.

During the 85 day study period, the subjects performed an average of 6.9 embalmings and had average cumulative formaldehyde exposures of 14.8 ppm-hours, with an average air concentration of 1.4 ppm during embalming. Since the average time spent embalming was 125 minutes, formaldehyde exposures calculated as an 8 hour TWA were 0.35 ppm on days when embalmings were done, which was less than the OSHA PEL of 0.75 ppm.

Short-term exposure monitoring during 11 embalmings found peak exposures from 3 to 9 times that of the corresponding TWA. Peak exposures were associated with leaks of embalming fluid occurring during injection into vessels and body cavities, application of embalming gels to hands, feet, or facial parts, and leaks of embalming fluid from tubing and other appliances. Instantaneous peak exposures ranged up to 6.6 ppm and some exposures exceeded the OSHA STEL (short term exposure limit) of 3 ppm for a 15 minute period. Male and female subjects performed similar numbers and types of embalmings and had similar average cumulative exposures and TWA exposures. Air sampling measurements indicated little or no exposure to substances in the laboratory other than formaldehyde.

Epithelial cells from the buccal area of the mouth showed a 12-fold increase in micronucleus frequency during the study period, from 0.046 $\pm$0.17 pre-exposure to 0.60 $\pm$1.27/1000 cells at the end of the course ($p < .05$). Nasal epithelial micronuclei increased 22%, from 0.41 $\pm$0.52 to 0.50 $\pm$0.67/1,000 cells ($p = 0.26$). In blood cells, the frequency of micronucleated lymphocytes increased 28%, from 4.95 $\pm$1.72 to 6.36 $\pm$2.03/1000 cells ($p < .05$) while sister chromatid exchanges decreased 7.5% ($p < .05$). A dose-response relationship was observed between cumulative exposure to formaldehyde and increases in buccal micronuclei in the 22 male subjects but not in the seven female subjects.

We conclude that low-level exposure to formaldehyde is associated with cytogenetic changes in epithelial cells of the mouth and in blood lymphocytes. In vivo cytogenetic changes in humans due to

formaldehyde exposure are of great interest because it is a suspect human carcinogen. The findings of changes in oral and nasal epithelial cells and peripheral blood cells do not indicate a direct mechanism for carcinogenesis but do indicate that DNA alteration has occurred. The changes seen in peripheral lymphocytes indicate that cytogenetic effects can be seen in tissues distant from the area of initial contact. The association of these cytogenetic effects with formaldehyde exposure indicate that they may be useful as markers of biologically effective dose.[13]

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THE INFLUENCE OF LOW LEVEL EXPOSURE TO BENZENE ON WHITE BLOOD CELL COUNTS

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It is generally reported in the relevant literature that exposure to benzene levels below 10 ppm has no hematotoxic effect other than cancer. This conclusion does not seem to be based upon an epidemiological study designed to discover any such potential effect. A retrospective study was done on the effect of low level exposure to benzene on the white blood cell count. Data were available from the occupational health services of two industries: a petrochemical plant with different histories of benzene exposure for different job categories, and a chemical plant without benzene exposure.

The benzene exposure levels in the petrochemical plant were suitable for the purpose of the study. General exposure data were derived from stationary air samples (n=3867), collected from 1978 onwards. The P90 value for benzene concentration varied from 2.3 ppm in 1978 to 0.7 ppm in 1988. Although exposure was probably higher before 1978, exposure to levels above 2 ppm on a time-weighted average was unlikely after 1971.

From the 484 persons who were under preventive medical surveillance (according to Belgian health and safety regulations) in a petrochemical plant and who started employment from 1966 onwards and who were still employed at the end of 1989, a total of 17,404 blood samples were taken. Only 13,544 samples were used and only 363 persons included in order to avoid bias:

- only those persons first employed before 1978 were included because by doing so, the white blood cell counts of the first peripheral blood samples of the different job-exposure categories was highly comparable. The first peripheral blood samples of persons first employed after that period showed lower values for

those in categories with a higher level of exposure. Including those could have resulted in selection bias.

- only periodical blood samples, as required by law, were included. So-called control samples for abnormal results were exluded from the study material.

The samples taken in 1981 and 1982 were all excluded because there were often problems with calibration of the laboratory method during that period. The first sample of each person was excluded because it was taken intravenously, while the others were taken peripherally. By not including persons who left the industry before the end of the observation period (1989), the results could show an underestimation of any possible effect of benzene, in the case where lowered WBC counts constituted a major reason for workers leaving the industry. According to the OHP, selecting out individuals with too low WBC counts was probably never done. Changing job because of too low a WBC count was probably very rare, which makes this population quite suitable for this study.

The hematological data of the chemical plant offered 13,796 white blood cell counts from 1984 to 1988 from a group of 2,589 employees. All those samples were taken intravenously. A markedly higher proportion of white blood cell counts below 4,000 per ml and a global shift towards lower values was found in the petrochemical plant as compared to the reference population of the chemical plant. These differences can not be adequately explained by the differences in the method for sample taking.

A possible dose-response relationship was studied through sub-dividing petrochemical employees into different job categories which stands for different exposure categories. This sub-division was done on the basis of the employee's job category at the end of the observation period. Therefore a previous change of job for medical reasons or following promotion could result in misclassification. These changes were however limited to the categories 1 to 4. This was not the case for category 5, which was the laboratory personnel.

Category 5 always had the highest exposure levels, as a time weighted average.

The proportion of WBC counts below 4000 per ml was always higher in category five, whatever time period was considered, as illustrated by the following table.

WHITE BLOOD CELLS PER ML < 4.000

Exposure Category				
1	6.0	3.7	4.4	1.3
2	7.2	4.2	5.5	1.5
3	4.9	2.2	3.9	1.6
4	6.2	2.1	3.5	1.0
5	9.6	5.9	5.7	3.5
Year	'67—'72	'73—'77	'78—'84 (1981/82 excluded)	

Also comparing the mean values and the standard deviations of category five with the other job categories showed a lower mean for the higher exposure category.

In the petrochemical plant, the method of analyzing the blood samples changed twice during the observation period. The same laboratory assistant made the analysis during the whole observation period. Any abnormal result was always controlled immediately. Laboratory bias could not be directly excluded. However, indirect retrospective evaluation of the laboratory methods, together with the consistency of the differences in the mean WBC levels between exposure categories over time, enables laboratory bias to be excluded as a major explanation for the findings.

Since smoking is associated with an increase in peripheral white blood cells, differences in smoking history between the exposure categories were also considered, but seem to have no bearings on the findings: The percentage of smokers and ex-smokers was even higher among the persons belonging to category 5 than among the other categories.

The differences between the WBC mean values and standard deviations of the petrochemical plant and the chemical plant seemed

to disappear progressively over time, with benzene exposure levels at the end of the observation period showing a P50 between 0.1 and 0.4 ppm as an 8 hour time weighted average with a P90 of between 0.3 and 1.5 ppm.

The study offers forceful arguments against the continuing assumption that exposure to levels of benzene well below 10 ppm has no hematotoxic effects other than cancer.

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IS METAL WELDING CAUSING IMPAIRMENT OF MALE FECUNDITY

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Potential reproductive hazards in the occupational environment of welders include welding fume toxicants (chromium, nickel, manganese; in some instances lead, cadmium and phenol), radiant heat strain and ionizing radiation. Prompted by results of Danish studies suggesting impaired fecundity of welders additional studies were designed to verify suggested effects on the male reproductive capacity. It was hypothesized that stainless steel welders are at risk because of high exposures to water soluble hexavalent chromium. This metal is causing reduced sperm count in rodents.

In a first approach semen quality was examined in a cross-sectional study of 81 welders and 54 non-welding workers. Three semen samples from each participant were provided by masturbation at home and were examined within two hours by one experienced laboratory assistant using manual methods. Total sperm count, proportion sperm with normal forms, linear penetration rate and measures of motility were significantly reduced among male steel welders and evidence for exposure-response relation was revealed.

In a second approach data on reproductive and occupational exposure were obtained by mailed questionnaire from 673 male production workers. Infertile metal workers more often were welding during the period of unprotected intercourse than fertile metal workers during the period preceding a childbirth (OR 2.20, 95% CI 1.02-4.00).

Finally, in a third approach fertility in terms of birthrate was examined in a cohort of 3,702 metal workers over a follow-up of 47.674 person-years. Among subjects who had ever worked as welders the probability of having a child was slightly reduced the year following a year with welding even after control for differences in age, birthcohort, paternal parity, birth of a child in the preceding

5 years, smoking and consumption of alcoholic beverages (OR 0.89, 95% CI 0.83-0.97).

Whenever a distinction could be made, effects were attributable to mild steel, not stainless steel, welding.

Findings in three observational studies of reproductive function of male welders applying different designs, methods and endpoints are remarkably consistent suggesting causal links between mild steel welding and reduced male reproductive capability. This unexpected finding needs verification and - if proven - additional efforts are needed to identify the harmful exposures.

PATERNAL EXPOSURES AND CARDIOVASCULAR MALFORMATIONS

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Associations between paternal occupational exposures and untoward pregnancy outcome have been suggested. Reports corroborating these associations, however, are limited. Methodologic issues that must be considered in studies concerning male effects on pregnancy outcome include: possible bias in the selection of study and comparison groups; sample size with sufficient number of exposed men to yield adequate statistical power; completeness of case ascertainment; use of a critical exposure period; and possible confounding by maternal factors and familial susceptibility. We addressed these issues in evaluating the association between paternal exposures and cardiovascular malformations (CVM), by using data from the BWIS, a population based case-control investigation of CVM and environmental factors (2310 cases, ascertained between 1981-87; 2801 controls, a random sample of infants from the live birth cohort that gave rise to the cases). Home interviews of case and control parents, conducted within a year of the study subject's birth, elicited information on parental occupational and home exposures to: painting; paint stripping; auto body repair; welding; batteries; lead soldering; jewelry making; stained glass crafts; solvents; anesthetics; pesticides; dyes; and ionizing radiation among other factors. Analysis focused on exposures incurred during the first trimester of pregnancy and previous three months. Among controls, paternal exposure reports included: pesticides (30%); carpentry (21%); painting (21%); degreasing solvents (17%); varnishing (8%); paint stripping (7%); lead soldering (6%); auto body repair (6%); welding (6%); laboratory chemicals (2%); ionizing radiation (1%); and dry cleaning solvents (0.4%). Considering all CVM a group, analysis showed no significant

associations with paternal exposures. Analysis by specific cardiac diagnosis yielded similar results for twelve diagnostic groups. Three diagnostic groups, however, did show an association with paternal exposure reports: tricuspid and pulmonary atresia with lead soldering (57 cases; odds ratio [OR] = 3.3, 95% confidence interval [CI]: 1.7-6.7); pulmonic stenosis with dry cleaning solvents (100; OR = 6.6, 1.9-23.7); and atrio-ventricular septal defect with ionizing radiation (201; OR = 4.3, 1.8-10.2). Adjustment by cardiac family history and maternal factors did not alter the results. Although tricuspid and pulmonary atresia were not associated with maternal exposure reports of lead soldering, an association with indirect maternal exposure cannot be excluded. The associations with solvents and ionizing radiation are consistent with previous observations of paternal occupational exposures and pregnancy outcome; however, they have not been reported in relation to CVM and remain to be confirmed in other studies.

THE SEMICONDUCTOR HEALTH STUDY: METHODS FOR PROSPECTIVELY ASSESSING REPRODUCTIVE FUNCTION IN WAFER FABRICATION EMPLOYEES

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Over the past 30 years, increasing numbers of women have entered the workforce, so that now upwards of 70% of women in the United States work outside the home. Thus, many women have occupations that place them in environments that are potentially hazardous to their reproductive health in terms of physical, chemical and psychological stressors or exposures. Often standards for workplace exposures are based on levels that cause acute effects. It is possible that the reproductive system may be compromised at lower levels than these standards. Thus, adverse reproductive health effects may be a sensitive indicator of occupational exposures. In addition, the emotional impact of infertility, adverse pregnancy outcomes, and menstrual cycle disruptions and the prevalence of these conditions make them a source of concern for a large segment of the working population. For all these reasons, in recent years, some investigators in occupational epidemiology have increasingly turned their attention to potential adverse effects of occupational exposures on reproductive health.

One issue arises very early in undertaking such studies: what is the optimal design for conducting an investigation of the effects of workplace exposures on adverse reproductive health outcomes? Case-control studies are generally less labor-intensive and less expensive but raise legitimate concerns about recall bias and validation of past exposures. Historical cohort designs generally

address recall bias and exposure assessment somewhat better but have difficulties with identifying former workers, tracing subjects, and validating outcomes. Prospective designs generally attain more accurate exposure assessment and ascertainment of outcomes but are more labor-intensive and costly and have the potential problems of subject recruitment, compliance, and drop-out.

This paper will describe the design and methodologic issues that arose in a prospective study of potential adverse reproductive health effects in women working in the semiconductor industry. This prospective study was conducted as one component of a larger study which also had historical cohort, cross-sectional and industrial hygiene/exposure assessment components. It is hoped that some of the methodologic results will provide insights into the relative merits of recalled versus prospectively collected information on reproductive health indicators.

This study was originally proposed because of a report by Pastides and coworkers (1), showing an increased risk of spontaneous abortions (SABs) in women working in the photolithography and diffusion areas of the fabrication rooms in one semiconductor company. Because of some concerns about the design of the study, the industry funded a Scientific Advisory Panel of well-known, academic and government researchers in the areas of occupational epidemiology, industrial hygiene, endocrinology and statistics to write a request for proposals and to provide peer review of the proposals. The Scientific Advisory Panel also was advisory during the conduct of the study. Following this peer review, the UC Davis proposal, which included investigators from UC Berkeley and the University of Massachusetts Medical Center, was approved and funded.

The study was designed to examine adverse reproductive health risks in workers who fabricate silicon wafers. A number of potential workplace exposures were of concern in this industry. First, particular interest focused on glycol ethers and other solvents, based on the prevalence of their use and animal and human literature showing adverse reproductive effects (2). In addition, a number of dopants (such as arsenic), which alter conductive properties of the wafers, have also been implicated, largely in the animal literature, as being associated with adverse reproductive outcomes. Finally, the

environment and physical and ergonomic aspects of the workplace were also of concern.

The primary objective of the prospective component of this study was to compare rates of pregnancy and pregnancy loss as well as menstrual cycle function in women currently working in silicon wafer fabrication (fab) and non-fabrication (nonfab) using prospectively collected daily diaries and urine samples.

Since most of the study's recruitment and data collection activities were conducted on company time for the convenience of subjects, much coordination of scheduling took place with supervisors or managers, as well as with the women. Contact with supervisors and women was preceded by putting up posters around the company site, including women's rest rooms. The study sample consisted of all women aged 18-44 years working in fabrication and a sample of women working in nonfab jobs who were frequency matched on age and ethnicity. These women were invited to attend a group meeting on company time conducted by Dr. Gold or Dr. Eskenazi. Over 200 group meetings were held and involved a slide presentation about the study and a question-and-answer period, and accommodated women's work schedules, including night and swing shifts. Subsequently, women were administered a screening questionnaire for eligibility in the follow-up study. This was self-completed in a private room at the company on company time. Over 2600 women were screened. The eligibility criteria are described below. Eligible women were then approached and recruited for follow-up, the details of which are also provided below.

The primary goal was to recruit women at increased likelihood of becoming pregnant. Thus, eligibility was not restricted to women attempting pregnancy. The eligibility criteria were: (a) age 18 through 44 years; (b) not currently pregnant; (c) menstruated within previous two months; (d) had sexual intercourse within previous two months; (d) not sterilized and partner not sterilized; (e) not using oral contraceptives, steroid hormones, or an intrauterine device; (f) had a working freezer; (g) not planning to leave the company within the next three months; and (h) ability to speak English, Tagalog, Spanish, or Vietnamese.

At baseline, following informed consent, eligible women who were willing to participate in the follow-up portion of the study were administered a detailed in-person interview in a private room at the company on company time. Less than half of the follow-up population was white. Approximately 30% were Asian, most of whom were Filipino, and 14% were Hispanic. In anticipation of a diverse population, all of our questionnaires, diaries and advertising pamphlets were translated into Spanish and Tagalog and most into Vietnamese as well. A number of bicultural interviewers who were bilingual in English and Spanish or Tagalog were hired. The baseline interview data included demographic, lifestyle and medical factors, and a detailed reproductive history, as well as questions about workplace activities, which were developed by our industrial hygiene study component. The baseline interview was completed by 481 women.

During follow-up women were asked to complete a daily diary that contained questions about urine collection, menstrual flow, premenstrual symptoms, intercourse, birth control, illness, medications, smoking, caffeine and alcohol consumption, and exercise on a daily basis. In addition, they answered work-related questions about hours worked, lifting, standing, use of video display terminals and other equipment, evacuations, and spills on a daily basis. The daily diary was designed as an outer envelope on card stock which contained the questions and an insert that had each day of the month identified at the top of a column in which the women filled in the answers each day.

Women also collected first morning urine every day for six months or six menstrual cycles. The urine was collected in a beaker and then poured into a 5-ml vial that was labelled with a bar code, the woman's human subject number, and the day and date. The vials were kept in a plain cardboard box that had a calendar in the bottom to ensure that the vial was put in the right place, and the box containing filled vials was stored in the freezer. The women were also provided with a soft-sided cooler and blue ice to transport the frozen urine samples. Once a month they were called and given a brief questionnaire about changes in work or pregnancy status. Kit exchange days were held at the company, and women were informed during the monthly interview when and where these would be held. At the kit exchange each woman would turn in her frozen urine

samples and completed diary insert for the month and would receive a clean urine collection kit and diary insert for the next month and would be paid $35.

The urine samples were screened for the 10 days prior to and 5 days following each onset of menses using an immunoenzymometric assay to detect human chorionic gonadotropin (hCG) (3). All cycles found positive for HCG by this screen were confirmed by an immunoradiometric assay for hCG and urinary steroid metabolites, which provided an objective indicator of conception and early fetal loss (EFL). More than half of the women enrolled completed 5 or more cycles of follow-up.

In addition to assessing conceptions and EFLs, it was possible to examine a number of menstrual cycle characteristics, based on the diary data. Cycles in which a conception occurred were excluded from all menstrual cycle analyses. Mean cycle length/woman (MCL) was used as an indicator of central tendency of cycle length, since comparison of means of all cycles in each group (fab and nonfab) might result in over-representation of women with short cycles. Standard deviation in cycle length/woman (SDCL) provided a measure of variability in cycle length and took into account the number of cycles a woman contributed. Mean days of bleeding and probability of long (>35 days) or short (<24 days) cycles were also examined, the latter two to provide measures of extreme cycle lengths. Most of the small amount of available literature indicates that cycles shorter than 24 days or longer than 35 days would be in the extreme 10% of cycles (4, 5, 6).

One observation of methodologic interest was the difference in the usual cycle length women recalled at baseline compared to their MCL observed using the daily diaries. The latter showed more dispersion than the former. A comparison of the cumulative distribution of usual cycle length reported on the baseline interview with the MCL observed on follow-up by diary also showed that, while the differences in the two measures were small and the medians were essentially the same, longer MCLs were observed during follow-up.

Furthermore, a comparison of the MCL observed during follow-up in women reporting at baseline having regular vs. irregular cycles

revealed a marked shift toward longer cycles for the women who reported at baseline having irregular cycles in the past year. The median of the MCL from the diary follow-up was 34 days in those reporting irregular cycles compared to 28 days in those reporting regular cycles. In addition, self-report of irregular cycles distinguished women with greater variability in cycle lengths as measured by the SDCL observed during follow-up. Women reporting at baseline that they usually had irregular cycles had a median SDCL of 7.5 days, compared to about 2.5 days in women who reported usually having regular cycles.

There is some literature to suggest that long cycles are indicative of delay of ovulation (7), perhaps due to an environmental insult early in the cycle, and that short cycles may be indicative of anovulation (8), which might also be affected by environmental stresses. Thus, both of these measures of extremes in cycle lengths are potentially important indicators and relatively easily obtained in occupational epidemiologic studies and may be indicators of reduced fertility. However, at the moment, the only way to be sure that disruption of ovulation has occurred is to analyze daily urine samples for steroid hormone metabolites, which requires expensive follow-up, laboratory assay and statistical analysis procedures. While the prospective approach is a more costly and labor-intensive method than cross-sectional or historical designs to obtain information about MCL, variability in MCL and extreme cycle lengths, it presumably does provide more accurate measures. If resources are limited, however, these findings suggest that self report of irregular cycles does provide some discrimination of disruption of the cycle, although there was not complete agreement with the data obtained during follow-up. Thus, while a balancing of the need for accuracy vs. available resources must be considered, these findings support both the feasibility of the prospective approach as well as the utility of recalled information when a prospective study is not practical.

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SPONTANEOUS ABORTIONS WITH AND WITHOUT CHROMOSOMAL ABERRATIONS IN RELATION TO OCCUPATIONAL FACTORS.

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A case referent study was performed among all women admitted to Telemark Central Hospital for spontaneous abortions during the 4-year period 1985-89. The reference population was recruited from pregnant women attending the antenatal clinic at 17-18 weeks of pregnancy for ultrasound screening, matched for time of conception. The parents answered a detailed questionnaire concerning work-related and life style exposure factors together with medical and previous reproductive history. Chromosome analyses were performed on all aborted material with appropriate tissue samples and cord blood samples were taken at birth for chromosome analysis of the referents.

In all 793 families with spontaneous abortions answered the questionnaire. Chromosome results were obtained for 375 cases; 242 with normal and 133 with abnormal karyotypes. Among the 808 referents, chromosome analysis was done for 679, one of whom showed abnormal karyotype (45, XO).

There was a significant association between mother's smoking during pregnancy and spontaneous abortions (odds ratio (OR)=1.48, 95% confidence interval (CI) 1.11-1.99). When adjusting for mother's age, previous spontaneous abortions, martial status and smoking in a logistic regression analysis, elevated ORs were found for stress at work (OR=1.89, 95% CI 1.16-3.07) and at home (OR=6.54, 95% CI 1.8-23.6). More than half-day exposure to gases and video display terminals showed in an univariate model OR=2.31 and OR=1.15 respectively, but they were not statistically significant in the logistic regression analysis. Exposure factors which did not show any elevated odds ratios between cases and referents were: job schedule (part-time/full-time), number of working years, physical

strain, heavy lifting, heat, cold, noise, solvents, chemicals, metals, and cosmetics.

When the spontaneous abortions were subdivided into cases with and without chromosome aberrations, odds ratio for smoking was significantly elevated for the group with normal chromosomes only, and mother's age for the group with abnormal chromosomes only, while stress at work and at home both were of significant importance for both groups.

The women with abortions had worked in only twenty different occupational groups (Nordic Classification of Occupations, 3-digit level). Elevated odds ratios for spontaneous abortion were observed for medical staff, office workers, sales workers and service personnel, but the elevations were not statistically significant in an univariate model.

MALE REPRODUCTIVE ABNORMALITIES AMONG LEAD-EXPOSED BATTERY PLANT WORKERS

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Lead has been associated with testicular atrophy in animals and hypospermia, asthenospermia, and teratospermia in both animal and occupational studies. The human studies noted relatively high levels of airborne lead and used relatively inaccurate and imprecise methods of semen quality assessment. This study examined the reproductive effects of men exposed to lower air lead levels using both traditional and computer-aided sperm analysis. A cross-sectional study was conducted at a California battery plant. The evaluation of 66 men (57% participation rate) included: standardized questionnaire, physical examination of the genital area, venipuncture (blood lead, ZPP, FSH, LH, testosterone), and semen analysis. Blood lead ranged from 5 to 51 ug/dL (median=30), and ZPP ranged from 3 to 122 ug/dL (median=28). Exposure categories were used to analyze for trend: 0-24 ug/dL low exposure, 25-39 ug/dl medium, and ≥ 40 ug/dL high. A non-statistically significant positive trend with exposure was observed for LH and testosterone (geometric mean, GM: 7.5, 7.6, and 9.5 mIU/ml, and 5.7, 5.8, and 6.3 ng/ml, respectively). Traditional sperm assessment resulted in a negative trend with exposure for total count (GM: 181, 169, and 145 million), a positive trend for motility (GM: 42.9%, 51.5%, and 52.4%), and no trend for morphology. Computer-aided sperm analysis revealed a positive trend with exposure for linearity of trajectory (mean: 0.57, 0.62, and 0.68, p=0.02), an overall decrease with highest exposure for amplitude of lateral head displacement (mean: 3.5, 3.5, and 2.9 um, p=0.06), a negative trend with exposure for mean angular displacement (mean: 14.8, 14.3, and 12.2 deg, p=0.08), and a decrease with highest exposure for curvilinear velocity (mean: 53.5, 58.7, and 50.3 um/sec, p=0.18). Preliminary computerized morphometric evaluation demonstrated that men with higher blood lead levels had lower sperm head width/length ratios (i.e., longer or

more tapered heads) in comparison to men with lower lead levels. Multiple linear regression analysis to adjust for confounding did not alter these relationships. Thus, sperm abnormalities using traditional and computer-aided techniques, and suggestive LH and testosterone changes were observed among workers with blood lead levels $\geq$ 25 ug/dL. The current occupational OSHA lead standard allows workers with prior elevated blood lead levels to return to their regular worksite after two subsequent levels $\leq$ 40 ug/dL. The results of this study suggest that there may be adverse male reproductive effects among workers returned to the workplace, under the present OSHA lead standard.

RELATIONSHIP BETWEEN BIRTHWEIGHT AND OCCUPATIONAL EXPOSURE TO CYTOSTATIC DRUGS DURING PREGNANCY

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Objectives

The study we carried out aimed at comparing the outcomes of pregnancies between one group of nurses who handled cytostatic drugs during and/or before pregnancy and one group who did not. Results presented here concern birthweight of the babies.

Method

The study was performed in four French hospitals. Departments involved in cancer chemotherapy were selected if each nurse prepared at least 10 perfusions a week. Control units involved departments in which no such perfusions were used. All the female daytime staff, up to 45 years, were asked to participate. Data on previous pregnancies and occupational exposure to cytostatic drug at the time of the study and in previous departments were obtained by interview.

Results

The present results concern the 420 single live births on the 534 pregnancies described by the 466 nurses who agreed to participate (response rate = 87%). Mean birthweight for the 413 babies whose data on birthweight were available was 3265 $\pm$ 483 g. Among the 405 pregnancies for whom data enabled us to determine cytostatic exposure, 90 were exposed before and during pregnancy, 17 were before only, and 298 were not. Using a model of multiple regression that included gestational age, Body Mass Index (BMI), age of the mother at birth, parity, sex of the baby and cigarette consumption, we tested the relationship between birthweight and cytostatic exposure. Results did not display any significant relationship between birthweight and cytostatic exposure.

Relationship between birthweight and selected variables adjusted for the different risk factors considered simultaneously*

Risk Factors (N=384)	Estimate βi*	95% CI of βi
Gestational age (weeks)	131.4	97.4 to 165.3
(Gestational age)^2	-22.1	-33.7 to -10.5
(Gestational age)^3	-2.8	-5.5 to -0.1
BMI (kg/cm^2)x 10^{-4}	3.5	-7.4 to 14.4
Age of the mother at the baby's birth (years)	3.6	-7.9 to 15.1
Smoking during pregnancy	-107.7	-240.8 to 25.4
Parity	84.5	23.4 to 145.5
Sex of the baby**	-134.3	-216.8 to -51.9
Cytostatic exposure	-56.0	-155.1 to 43.1

*Slopes are given in g/unit of risk factors; ** 1 = male, 2 = female

Conclusion

This study does not show any statistically significant relationship between the handling of cytostatic drugs during and/or before pregnancy and birthweight, at the observed level of exposure of 18 perfusions/week/nurse on the average. Although this result does not seem to be explained, either by confounding factors or selection bias, we believe that further investigation are needed before finally concluding that handling of cytostatic drugs during and/or before pregnancy does not have any effect on fetal growth. On the other hand, we previously found that this level of exposure resulted in a frequency of spontaneous abortion twice as high for the exposed as for the non exposed pregnancies (Stücker 1990), a result which argues in favor of a reduction of the exposure level.

THE ROLE OF EPIDEMIOLOGY IN THE DEVELOPMENT OF ENVIRONMENTAL INDICATORS: OCCUPATIONAL AND RESIDENTIAL EXPOSURE TO ORGANO-PHOSPHATE AND CARBAMATE PESTICIDES

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Organophosphate (OP) and carbamate (CB) pesticides account for a significant number of human poisonings. For example, in 1990, there were 17,104 total poisonings with symptoms reported to cooperating U.S. Poison Control Centers, and 38% or 6499 were due to OPs and CBs. The increased regulatory emphasis of pollution prevention, farm worker safety, worker protection, better environmental statistics, safer pesticides, and reducing consumer/residential exposure to pesticidal products all challenge the traditional role of epidemiology in regulatory affairs. The objective of this report is to describe recent applications of epidemiology in the regulatory setting for the development of environmental indices of occupational and residential exposure to pesticides, using surveillance data on pesticide poisonings.

The methods include the use of poisoning surveillance data to rank over seventy-five OP and CB compounds; and the use of environmental epidemiology to inform regulatory priority setting, policy development, and current regulatory decision-making. National Poison Control Center data and worker poisoning surveillance data from California provide the primary source of residential and occupational exposure estimates used in the development of environmental indicators. In the record of U.S. occupational poisonings from 1977-1982, 71% of the hospitalized cases involved poisonings with organophosphates and carbamates, where specific chemicals were noted, e.g., 80% of the time.

Results include the outcomes for parathion, aldicarb and several other compounds. For example, in more recent data from

California, for 1982-89, there were 4764 occupational poisonings and 294 poisonings requiring hospitalization. Of this total, 136 occupational poisonings were for parathion and 27 were for aldicarb. Results also include lessons learned in the development of environmental indicators using environmental epidemiology in the regulatory arena, e.g., cancellation of 90 of the 99 uses of parathion based on excessive risk to workers. We conclude that environmental epidemiology concepts and environmental indices based on epidemiology data can serve to improve the scientific basis of environmental protection decisions and to protect the public health.

Disclaimer: The views expressed are those of the authors and do not necessarily represent the official position of the U.S. Environmental Protection Agency.

PATTERNS OF PESTICIDE EXPOSURE AMONG MIDWESTERN FARMERS: ISSUES FOR EPIDEMIOLOGIC RESEARCH

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Epidemiologic studies from a number of countries indicate that farmers tend to experience higher rates for selected cancers than the general population. The specific agents in the agricultural environment that might be involved have not been clearly identified, but pesticides have received the most attention. Despite strong associations between certain cancers and a few pesticides in several case-control studies, concerns have been raised with regard to exposure assessment. Specific concerns are that individual farmers use many different pesticides, that the specific pesticides used change radically from year to year, and that information from farmers or their next-of-kin is unreliable. Data from U.S. Department of Agriculture (USDA) surveys and from case-control studies conducted in the midwest by the National Cancer Institute (NCI) were used to evaluate these concerns. Annual pesticide use on various crops in the midwest from the USDA indicates that the average number of pesticide applications per crop per year seldom exceeds two. The number of pesticide applications for vegetables and fruit, however, is probably larger. The number of pesticides reported by farmers over their entire lifetime in NCI epidemiologic studies is also small. The proportion of farmers ever reporting use of more than five herbicides was 20% and 7% for insecticides. In a corroborative project involving 130 farmers and their pesticide suppliers, we found that agreement was approximately 70% for herbicides and insecticides. As anticipated, surrogates were not able to provide as much information on pesticide use as the farmers themselves. Approximately twice as many surrogates as farmers were unable to provide clear responses regarding use of specific pesticides, i.e., they responded "I don't know." The relative ranking of pesticides by reporting frequency, however, was similar for the farmers and surrogates with correlation coefficients of 0.87 for herbicides and 0.67 for crop or animal insecticides. A study comparing the number

of pesticides volunteered during an interview with the number after probing i.e., after the interviewer specifically asked about the use of each chemical, showed that probing greatly increased the number of pesticides recalled, particularly for pesticides used long ago and for short duration. These data indicate that many farmers do not use large numbers of pesticides, that surrogate respondents may be able to provide useful information, and that to obtain a complete listing of pesticides used it is necessary to ask the subjects about each directly.

A SURVEY OF KERATOSES AMONG PARAQUAT PRODUCTION WORKERS AND A NONEXPOSED FRIEND REFERENCE GROUP

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Two reports in the literature have suggested an excess of keratoses (a usually benign skin lesion that may be a precursor to skin cancer) among paraquat production workers in England (Bowra et al., 1982) and Taiwan (Wang et al., 1987). However, neither of the previous reports incorporated a comparison group by which to determine the presence or magnitude of the suggested excess. The aim of this controlled study was to evaluate the contribution of occupational exposures to the prevalence of keratoses among workers in a paraquat production plant in Texas while taking into account other major risk factors for keratoses.

The design of this study was cross-sectional. All employees and contractors of the Texas plant who were employed as of July 30, 1990 were identified from company employment records and invited to participate. Two non-family friends were selected for each worker frequency matched by age, race, and sex. Three sources of data for this study included:

(1) During the clinic visit, interviewers solicited demographic and medical history data, a complete occupational and residential history, sun-exposure behavior, and tobacco use.

(2) A full-body dermatology examination was administered by a single board-certified dermatologist specializing in occupational dermatology. To help assure the blinding of the dermatologist to exposure status, study participants and the dermatologist were requested not to discuss any work or medical history information until the exam was completed. The dermatologist

collected data on natural hair color at 15 years of age, hair thickness, eye color, Fitzpatrick skin type (Fitzpatrick and Mosher, 1980), and presumptive skin diagnoses.

(3) The third source of data was from plant records to obtain a complete work history at the paraquat production plant.

Available plant industrial hygiene data indicated generally low values and there was no special focus on any one agent as being etiologically related to keratoses. Therefore, exposure was defined as potential exposure to chemicals in the production process. Study investigators, with consultation with the plant occupational health nurse, safety engineer, and maintenance and production supervisors developed the exposure classification system. Each of 183 separate job titles were assigned exposure values on an ordinal scale from 1 through 6 to represent potential exposure to chemicals in the production process. As shown in Table 1, the exposure scale of 1 through 5 represented increasing levels of potential exposure in the 4'4-bipyridyl process and a separate category of packaging workers represented potential exposure to paraquat only (scale value = 6).

The basic exposure variable was represented by worker status (worker=exposed; friend=unexposed). For workers, a cumulative index (cumulative time-intensity exposure index) based on the individual's work history was calculated by summing over all jobs for each worker the product of the duration in months of each job in the plant times the level of exposure (exposure classification values from 1 to 5 as described above) for that job. Workers exposed only to paraquat (n=8) were put in the lowest category of exposure, since from previous studies there was no reason to suspect that paraquat was a possible etiologic agent.

The major study endpoint was a dichotomous variable indicating the presence or absence of one or more actinic keratoses.

From the interview questionnaire, a residential sun exposure score was calculated for each person by summing over all residences the product of the reported number of hours per day spent outside during the summer times the number of years in each residence (geographic location) times the exposure level for that residence coded from a U.S. solar insolation map (U.S. Department of Interior Geological

Survey, 1970). A similar index was developed for occupational sun exposure.

The enumerated plant population on July 30, 1990 consisted of 95 employees and 51 contractor employees of which 80 employees (84%) and 37 contractor employees (73%) participated. A total of 247 friends of workers also participated in the study for a total study population of 364. The study results presented here are based on an analysis of 344 (112 workers, 232 friends) of the 364 study participants. The 20 exclusions resulted from incomplete forms (n=3), Spanish-speaking participants (n=10), and participating friends whose nominator (plant worker) did not subsequently participate (n=7). However, participating workers (n=112) were similar to non-participating workers (n=34) in terms of age, sex, and cumulative plant exposure. All of the non-participating workers were white. Although workers nominated friends approximately the same age as themselves, there was a higher proportion of workers 40 years or older (47.3%) compared to their friends (42.2%). The study population was predominantly male (nearly 80%) and non-black (only 13.4% of workers and 6.9% of friends had a skin type or V or VI).

The overall prevalence proportion of keratoses was similar among workers and friends, 0.30 and 0.28, respectively. Among high cumulative exposed workers, the prevalence of keratoses was 0.40 and among low-exposed workers, 0.20. The prevalence proportions between high and low cumulative exposure groups are not directly comparable, because the cumulative exposure categories were related to age, as was the prevalence of keratoses.

To account for known risk and possible confounding variables, multiple logistic regression models were fitted. Statistically significant high risks of keratoses were demonstrated for age, freckling before age 16, Fitzpatrick skin type, suntanning behaviors, and potential occupational exposures to polycyclic aromatic hydrocarbons. The cumulative adult residential sun exposure variable was of borderline significance. The multiple logistic results for plant exposures confirmed the crude analyses. After controlling for the known risk factors, there was no overall exposure effect based on the Likelihood Ratio Statistic. However, the odds ratio of keratoses among the two levels of exposure among workers went in

opposing directions. The odds ratio of high-exposed workers compared to friends was 1.9 (CI=0.9-4.2) whereas the comparable odds ratio for low-exposed workers versus friends was 0.6 (CI=0.2-1.7). Interactions were explored between plant exposure and residential sunlight exposure, but were insignificant or unreliable due to small numbers.

In conclusion, data obtained from this survey of actinic keratoses among workers in a low temperature process production plant and a friend reference population do not demonstrate an excess of keratoses overall nor any consistent increase in the odds of keratoses with an increase in plant exposure levels. There may be a small excess of keratoses in a high-exposed subgroup of workers, but an occupational etiology cannot be established. As a marker of skin damage from sun exposure, the high prevalence of keratoses in this study population suggests, at the very least, that efforts should be made to increase protection from sun exposure both on and off the job. Despite their high prevalence, these keratoses are among the least adequately studied diseases using a population-based approach (Harvey et al., 1989), making comparisons of workers to the general population difficult.

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Table 1. Exposure classifications

1. Non-exposed (office personnel).

2. Occasionally in the plant--no contact with chemicals of interest (i.e., engineers and designers).

3. No direct contact with chemicals of interest and is daily in the plant (i.e., foremen, supervisors and electricians).

4. Occasional exposure to chemicals of interest (i.e., I/E technicians, mechanics, and pipefitters).

5. Primary exposure/opportunity for exposure (i.e., process technicians and laboratory technicians).

6. Primary exposure/opportunity for exposure to paraquat only (i.e., packaging operations).

7. Unknown (unable to classify job title).

Adapted from article owned by John Wiley and Sons Publishers (Cooper et al., 1994).

RESPIRATORY SYMPTOMS, SPIROMETRY, AND CHRONIC OCCUPATIONAL PARAQUAT EXPOSURE

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Chronic respiratory disease resulting from acute poisoning with paraquat has been reported. In addition, there have been case reports of poisoning and death from pulmonary fibrosis as a result of dermal exposure to paraquat. However, most epidemiologic studies have not shown long term pulmonary effects of heavy occupational paraquat exposure, although these studies have been flawed by insensitive methods and small sample sizes. In order to determine if chronic respiratory effects occur as a result of heavy occupational exposure to paraquat, a cross sectional study was conducted among workers at 15 large Nicaraguan banana plantations which relied on paraquat for the control of weeds. All workers were interviewed upon receiving job assignments for the day of the survey. Those who reported never having applied paraquat and those who reported more than two years of cumulative exposure as applicators of paraquat by knapsack sprayers were released from work for medical evaluation. One hundred thirty-four exposed workers and 152 unexposed workers were administered a questionnaire based on the British Medical Research Council respiratory questionnaire and a questionnaire interview asking about exposure. All participants underwent spirometric testing of forced expiratory volume in one second (FEV^1) and forced vital capacity (FVC). In the exposed group, 71 (53%) reported having experienced a skin rash or burn resulting from paraquat exposure (highly exposed workers); 32 (25%) reported epistaxis; 77 (58%) nail damage; and 55 (42%) paraquat splashed in the eyes. There was a consistent dose-response relationship between exposure and the prevalence of dyspnea (all grades), chronic bronchitis, and episodic wheezing accompanied by shortness of breath (after adjusting for potential confounders). There was no relationship between exposure

and FEV^1 or FVC. The frequent reports of skin rash or burns suggest that the dermal barrier to absorption may be compromised frequently under tropical working conditions. The high prevalence of respiratory symptoms associated with exposure, in the absence of spirometric abnormalities associated with exposure, in part could be a result of unmeasured gas exchange abnormalities among workers with long-term exposure to paraquat. Further study is needed to elucidate the chronic pulmonary effects of paraquat, a non-selective herbicide used in approximately 130 countries, where it is available to as much as 98% of agricultural workers.

RESPIRATORY DISEASE AND LUNG FUNCTION AMONG TOBACCO FIELD WORKERS

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Respiratory effects of occupational exposure to tobacco dust in plants producing cigarettes and cigars are well known. The aim of the present study was to investigate whether tobacco field workers differ from controls in their symptoms and lung function. A cross sectional survey was conducted among 289 tobacco field workers of both sexes, using questionnaires concerning age, sex, smoking habits, symptoms, exposure to tobacco and respiratory function tests. Two groups of workers (clerical staff from a neighboring agricultural office (n=202) and a sample of farmers (n=202) where selected as possible referents. The average length of exposure was 29.5 years. The mean area of tobacco fields was 11,356 square meters. Most tobacco workers (235) were exposed to T.N.L. variety of tobacco (81.3%). Seventy three subjects (25.6%) were exposed to Burley and 12 (4%) to Virginie. The main stages of processing were plucking off, hand picking and drying. Odds Ratio and 95% confidence intervals were estimated with logistic regression controlling for age, sex and pack-years. We found a significantly higher prevalence of cough (OR=3.17, 1.92-5.25 in comparison with farmers; OR=3.88, 2.37-6.34 in comparison with clerical staff), breathlessness (OR=2.49, 1.36-4.56 in comparison with farmers; OR=1.28-3.4 in comparison with clerical staff), dermatitis (OR=1.71, 1.07-2.76 in comparison with farmers; OR=2.15, 1.37-3.37 in comparison with clerical staff). No pronounced excesses were observed for attacks of shortness of breath with wheezing, asthma, rhinitis, eye irritation and fever. The results of the pulmonary function tests were compared with the predicted values for age, sex, and height (Quanjer, ECCS, 1983). Two hundred seventy two tobacco workers (96.5%) had normal FVC, 270 (95.7%)

had normal FEV1 and 262 (92.9%) had normal MMEF. The functional data, in comparison with those of the reference populations, were not significantly decreased. No differences were found when analysis was conducted by duration of exposure, area of tobacco fields, and varieties of tobacco. Our data suggest that tobacco field workers have increased symptoms (cough, breathlessness, dermatitis). Concerning asthma and results of the pulmonary function tests, we can suspect a healthy worker effect.

SURVEILLANCE OF CUMULATIVE TRAUMA DISORDERS IN NORTH CAROLINA: ADVANTAGES AND DISADVANTAGES OF USING WORKERS COMPENSATION DATA

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Existing surveillance data on cumulative trauma disorders (CTDs) are limited to rates by industry. Workers Compensation (WC) claims data could provide additional detail about illnesses and exposures. We used WC data from 1986-1988 to describe CTD claims in North Carolina (NC). The goals of the study were: (1) To describe the computerized WC data base in NC, including how CTDs are coded, (2) To determine which industries had highest CTD claim rates, and (3) To compare NC CTD rates to rates in published studies of WC CTD claims in Ohio and Washington state.

The injury and illness coding manual used by the NC Industrial Commission is based on the Bureau of Labor Statistics (BLS) coding manual from several years ago. It contains brief clinical coding guidelines for specific disorders, but it does not contain the case definition of carpal tunnel syndrome used by NIOSH. NC enters detailed case information into the data base only when the claim is legally closed, and only for cases which are <u>not</u> classified as "medical only" (medical only cases have no lost work time and are relatively minor, clinically). Tendinitis and carpal tunnel syndrome were examined using nature of injury codes 260, 562, and 563, the accident code was 12 (overexertion) and the body part codes were 300, 310, 311, 313, 315, 318, 319, 320, 330, 340, and 398 (upper extremity). Industries were identified in the data base by BLS standard industrial codes. Industry-specific rates were calculated using denominators obtained from BLS.

These industries had the highest CTD rates (claims per 10,000 workers): Food Products, 5.6; Furniture Manufacturing, 4.2; Rubber and Plastics Manufacturing, 3.4; Electrical Manufacturing,

3.3; Textiles, 2.8; Transportation Equipment Manufacturing, 2.5; Fabricated Metal Products Manufacturing, 2.5.

The types of industries with the highest CTD rates were similar in NC, Ohio, and Washington. NC CTD rates were substantially lower than rates reported in Ohio or Washington, but differences in the way WC claims are coded prohibited a direct comparison of the magnitude of CTD rates in the 3 states. In contrast to NC, the Ohio and Washington articles reported on all incident cases, including those which are medical only cases. The three states use different injury/illness coding systems, although coding in NC and Ohio is similar. In Ohio, 5 additional CTD diagnosis codes are available to code claims. Washington uses a different industry coding system than Ohio or NC. NC CTD rates could be low because of lag in claim closure, selection biases from under-reporting of claims, reduced ergonomic exposures in NC industries, differences in diagnosis coding rules, or under-recognition of CTDs by NC physicians. WC claims data may be of value to identify industries where preventive interventions may be of benefit, and for detecting sentinel events. Standardization of data systems across states would improve the usefulness of WC data for surveillance. Use of standard case definitions for coding WC claims would improve the quality of the data for CTD surveillance.

A CROSS-SECTIONAL STUDY OF CARPAL TUNNEL SYNDROME SYMPTOMS AMONG TRADE AND OFFICE WORKERS

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Carpal tunnel syndrome (CTS) has emerged as a significant occupational health problem resulting in numerous occupational health compensation claims, substantial costs, and disability. The objectives of this study were to assess the magnitude of CTS symptoms among occupational groups that have not been well evaluated from an epidemiologic perspective, and to identify specific tasks associated with CTS symptoms. A self-administered questionnaire was mailed to a sample of workers from three local Southern California unions. The unions represent office workers (n=652, data entry operators, court clerks, and office clerks), construction carpenters (n=389), and sprinkler fitters (n=452). The constellation of symptoms used to define CTS included pain, tingling, and numbness in the wrist, hand, and/or fingers.

Office workers reported the highest prevalence rates of CTS symptoms (21.3%) followed by sprinkler fitters (18.4%) and carpenters (15.7%). Job task information was collected for work that involved repetitive motion activities, hours using a computer keyboard, hours using hand and power tools, and hours working with hands and arms above the shoulder level. Reported hours of work involving repetitive motion was the strongest predicator of CTS symptoms. Prevalence odds ratios (OR) and 95% confidence interval (95% CI) for office workers were 2.4 (0.9, 6.1) for 3-4 hours per day and 3.2 (1.4, 7.2) for five or more hours per day, and 1.5 (0.6, 3.5) and 3.1 (1.5, 6.3), respectively, for carpenters and sprinkler fitters. Office workers with 6 or more hours of work above shoulder height had equivalent odds ratios for CTS symptoms (OR, 2.3 [1.4, 3.8]; OR, 2.3 [1.4, 3.9] respectively). Among carpenters and sprinkler fitters, hand tool use was more strongly associated with CTS symptoms than power tool use (OR, 1.8 [1.1, 3.1] and 1.2

[0.8, 1.9] for 6 hours or more of hand and power tool use respectively).

Epidemiologic research among occupations with dynamic tasks requirements that involve repetition and force is limited. This research has focused on occupations that have a variety of tasks and a wide range of repetition and force demands. Our results suggest that CTS prevalence can be reduced if the hours of repetitive motion work, work above shoulder height, and keyboard work are reduced. Further research is necessary to identify the specific aspects, e.g., posture, intensity of repetitive work, workplace and tool design, that can be modified to reduce CTS prevalence.

MEDICAL INSURANCE CLAIMS AND OCCUPATIONAL DISEASE SURVEILLANCE: CUMULATIVE TRAUMA IN THE AUTO INDUSTRY

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Information sources are needed for occupational disease morbidity surveillance. The Occupational Safety and Health Act mandated the Form 200 Injury and Illness reporting system, but it depends on supervisory or medical staff judgment concerning work-relatedness and misses health complaints never presented. Hospital discharge information used for surveillance usually lacks work history detail. Medical insurance claims can be linked to work history files, but only a few published accounts describe this approach in occupational disease surveillance.

Blue Cross - Blue Shield insurance claims contain ICD-9 diagnostic codes for hospital-based claims ("Blue Cross") and Health Care Financing Administration procedure codes for physician-based claims ("Blue Shield"). Claims throughout the country are transmitted through a computer network to the Blue Cross Plan where an employer is located. A list of potentially work-related health conditions was compiled, including 13 musculoskeletal disorders, along with conditions unlikely to be associated with work for use in case-control studies. For each of the 107 defined conditions, corresponding ICD-9 and procedure codes were specified. Work histories for union members employed at a large automobile manufacturer were compiled from computer tapes that identified current employees semi-annually since 1967. The record specified a plant and department each year for 227,000 employees.

Medical insurance claims over a 3.5 year period were linked with work histories within the Blue Cross computing system, based on the subscriber-ID number (generally an individual's Social Security Number). The resulting 889,000 records were provided to the

investigators with identifiers deleted and the Social Security Number encrypted. Large numbers of cases of potentially work-related diseases, including 30,600 episodes of musculoskeletal disorders, were identified. Although acute injuries would be included among the musculoskeletal disorders, work-related acute injuries would tend to be captured by the workers' compensation system. Five plants were chosen to represent diverse automotive manufacturing activities: assembly, trim (manufacture of interior components), foundry, machining, and stamping. Prior to analysis, plant departments were grouped on expected ergonomic stress factors. Non-production departments such as maintenance and other non-repetitive support functions were classified as "unexposed," and production departments having similar processes plausibly associated with ergonomic hazards were grouped within each plant.

Although insurance claims represent both prevalent (pre-existing) and incident (new) cases, 84 percent of the potential cumulative trauma disorder (CTD) cases identified had all of their claims within six months of the first available claim (89 percent for Carpal Tunnel Syndrome cases). Therefore, the first available claim approximated an incident or index claim for a specific condition and was the basis for incidence rate calculations. For all CTD combined, the rate was 105 per 1000 person-years in the five plants combined (95% CI=101,108), and was highest for the stamping plant (117, 95% CI=110,124) followed by the trim (111, 95% CI=100,121), assembly (106.2, 95% CI=100,112) and axle (95.8, 95% CI=85,107) plants. For specific cumulative trauma disorders, incidence rates within the five plants identified high risk areas, however, known differences in medical insurance coverage by exposure group limited interpretation.

Case-control analyses, with controls also identified by insurance claims, addressed coverage and produced age- and sex-adjusted estimates of risks (Table). For cases, exposure group was the last department assignment in the preceding reporting year. For controls, exposure group was based on one year randomly selected from 1984 to 1987 during which the control worked in one of the study plants. All five plants had departments with statistically significant, elevated risks for one or more of Carpal Tunnel Syndrome (CTS), CTD of other upper extremities, Rotator Cuff Syndrome (RCS), CTD of the neck and of the lower back. CTS risk

was highest for assemblers in an axle plant (OR=4.2, 95% CI 1.9-9.4) and assembly plant spray painters (OR=3.6 95% CI .99-13). The departments with elevated CTS also had elevated risk for other upper extremities, as did several others (frame/body at the assembly plant, small press and finishing (welding) at the stamping plant). RCS risk was highest for stamping plant workers on large press lines (OR=3.3, 95% CI 2.1-5.1). CTD of the neck were elevated in several of the previously identified high risk departments but also in the other-paint (sanding and wiping) department of the assembly plant (OR=2.1). Statistically significant risks of lower back problems were observed in numerous departments with odds ratios ranging 1.4 to 1.7.

Adjusted Odds Ratio and Attributable Cases

Plant	Departmental Grouping	Odds Ratio n[1]	OR	95%CI	Attributable Cases n_a	95%CI
		Carpal Tunnel Syndrome				
	Age (>40)		1.1			
	Sex[2]		2.3	1.6,3.3		
Assembly	Trim/Chassis	60	3.1	2.1,4.6	41	31,47
	Spray Paint	3	3.6	.99,13.1	2	0,3
Trim	Sewing	21	2.0	1.1,3.6	10	2,15
Foundry	All	17	9.0	4.7,17.1	15	13,16
Axle	Assembly	9	4.2	1.9,9.4	7	4,8
Stamping	Large Press	29	2.9	1.8,4.7	19	13,22
		Other Upper Extremities				
	Age (>40)		.89			
	Gender		.98			
Assembly	Trim/Chassis	97	2.1	1.5,2.8	51	32,62
	Other Paint	18	2.0	1.1,3.5	9	1,13
	Frame/Body	26	1.9	1.1,3.0	12	2,17
Trim	Sewing	27	2.0	1.2,3.4	13	4,19
Foundry	All	29	5.6	3.3,9.5	24	20,26
Axle	Assembly	10	2.3	1.1,4.8	5	1,8
Stamping	Large Press	55	2.2	1.5,3.3	30	18,38
	Assembly/ Finishing	26	1.6	1.0,2.7	9	0,16
	Small Press	14	1.6	.87,3.0	5	0,9

(continued)

		Rotator Cuff Syndrome				
	Age (>40)		2.1	1.5,2.9		
	Gender		1.1			
Assembly	Frame/Body	13	2.0	1.1,3.8	6	1,9
	Trim/Chassis	36	1.7	1.1,2.6	15	3,22
Trim	Sewing	23	2.5	1.4,4.5	14	6,18
Stamping	Large Press	39	3.3	2.1,5.1	27	20,31
	Assembly/ Finishing	19	2.1	1.2,3.7	10	3,14
		Cumulative Trauma of the Neck				
	Age (>40)		1.4	1.2,1.7		
	Gender		1.1			
Assembly	Spray Paint	10	2.3	1.0,5.1	5	0,8
	Other Paint	41	2.1	1.4,3.2	21	12,28
	Trim/Chassis	136	1.4	1.1,1.8	39	12,60
	Material	18	1.5	.80,2.6	6	0,11
Trim	Sewing	75	2.1	1.5,3.1	39	25,51
Axle	Assembly	19	1.7	.95,3.0	8	0,12
Stamping	Large Press	100	2.0	1.5,2.6	50	33,61
		Cumulative Trauma of Lower Back				
	Age (>40)		1.3	1.1,1.6		
	Gender		1.1			
Assembly	Frame/Body	93	1.5	1.1,2.1	31	8,48
	Other Paint	62	1.5	1.0,2.2	20	0,34
	Trim/Chassis	265	1.3	1.1,1.6	61	24,99
Trim	Sewing	123	1.7	1.2,3.2	50	20,84
Foundry	All	31	1.2	.72,1.9	5	0,14
Axle	Assembly	34	1.5	.89,2.4	11	0,20
Stamping	Large Press	186	1.7	1.4,2.2	76	53,101
	Small Press	59	1.4	1.0,2.0	17	0,29

1 n - number of cases of cumulative trauma in exposure group
2 Indicator of gender: female

Population attributable fractions were estimated to range from 0.2 (lower back) to 0.5 (Carpal Tunnel Syndrome). For CTDs other than those affecting the lower back, more than half of the work-related cases identified from medical insurance claims were not similarly identified on the plant OSHA 200 logs. The results imply that work-related musculoskeletal disease frequently is not recognized or does not come to the attention of employers. A substantial

proportion of work-related CTD medical costs appear to be carried by private insurance rather than the workers compensation system.

A number of factors must be considered in interpreting these results. The advent of Diagnostic Related Group (DRG) coding in 1984 introduced audits for hospitalization claims but not for those from physicians, and they do not address misdiagnosis of occupational diseases. Conditions for which medical services were not covered by insurance would be underrepresented in claims information, and systematic diagnostic bias could arise from financial incentives that favor some diagnostic procedure or treatments over others. Such bias, however, would be expected to be the same across exposure categories. Altogether, diagnostic misclassification in insurance claims would be expected to reduce the magnitude of observed associations with exposure status.

Female workers married to men employed at the same plant may be classified as dependents on the man's insurance and thus would not generate claims coded with their own Social Security Numbers. Health insurance claims do not record date of onset of a condition and thus represent both pre-existing and incident cases. A reasonable approximation for the incident or index claim was identifiable for CTD cases but for chronic diseases that generate a continuing series of claims, this may not be possible.

Medical insurance claim data linked with work history is a basis for practical and comprehensive surveillance for CTD and, potentially, a variety of other occupational diseases.

Reference

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Adapted from article owned by Journal of Occupational Medicine (Park et al., 1992).

SURVEILLANCE FOR WORK-RELATED CARPAL TUNNEL SYNDROME

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Carpal tunnel syndrome (CTS), compression of the median nerve as it passes through the carpal tunnel, is characterized by pain, numbness or tingling in the median nerve distribution of the hand. Frequently reported work-related factors include repetitiveness, high hand forces, segmental vibration, wrist flexion or hyperextension, local contract stress at the wrist creases, and cold temperatures. The reported incidence of work-related CTS has been increasing since the mid 1980's. CTS has been described as a sentinel event for a variety of work-related upper limb disorders. Thus, identifying high risk workplaces for potential intervention and control is high priority. While workers' compensation data has many limitations, can it be used to distinguish between "true" high and low risk industries and workplaces for CTS?

We used Washington State's exclusive workers' compensation data to calculate incidence rates for CTS. This system, covering 2/3 of the state workforce, used ICD-9 codes for billing purposes. All unique claims for ICD-9 354.0 between January 1, 1987-December 31, 1991 were identified (n=8,860). The 1990 incidence rate (IR) was 0.25 per 100 worker years. Washington industrial classes (WIC) with 15 or more cases during the 4 year period were included in the final data set used to identify "high risk" WICs. "High risk" WICs included those who were in 2 of 3 top 10 categories: 1) highest incident count, 2) highest incidence rate per 100 worker years, 3) highest acceleration ratio (1990 rate/1987 rate). Fish processing (IR 1.5) and poultry farms (IR=1.8) WICs met this criteria. Two fish processing plants and one poultry plant where chosen for study. Their 1990 CTS incidence rates were 7.4, 0.0, and 7.4, respectively. A "control plant" was chosen from a WIC (cloth printing) that had no reported ICD-9 coded CTS cases between 1987-1990, and that was comparable to the "high risk" plants demographically.

Jobs with at least 10 workers were chosen for study. Job analyses teams used check lists of recognized risk factors to quantify current exposures and examination teams performed clinical exams and detailed interviews of current workers. The period prevalence of CTS on interview was 27.5% in fish, 37.4% in poultry and 8.6% in cloth printing. Point prevalence based on examination and interview was 6.6%, 9.6% and 3.4%, respectively. There was no difference in prevalence between the two fish processing plants. For all work-related upper limb disorders, point prevalence on exam and interview was 17.6%, 27%, and 10% respectively. Job analysis indicated that 72% of jobs analyzed in fish, 83% in poultry and 42% in the cloth printing plant jobs had cycle times of less than 30 seconds. In all plants, those specific jobs with the highest prevalence of CTS had the highest number of exertions per hour combined with the highest number of pinches or forceful hand exertions. Thus workers' compensation data may be useful for identifying high risk industrial classes for CTS, but not necessarily identifying specific high risk plants.

PREVALENCE AND WORK-RELATEDNESS OF SELF-REPORTED CARPAL TUNNEL SYNDROME (CTS) AMONG U.S. WORKERS - AN ANALYSIS OF 1988 NATIONAL HEALTH INTERVIEW SURVEY, OCCUPATIONAL HEALTH SUPPLEMENT

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Since the mid-1980's the Bureau of Labor Statistics has reported a sharp increase in the incidence of repetitive trauma injuries or cumulative trauma disorders (CTDs) among the U.S. workers. To estimate the magnitude of self-reported carpal tunnel syndrome (CTS) nationally, data from the Occupational Health Supplement of 1988 National Health Interview Survey (NHIS) were analyzed.

Among 127 million "recent workers" (those who worked during the 12 months prior to the survey), the prevalence rate for self-reported CTS was 1.47% (95% CI 1.30; 1.65). The demographics and work-relatedness of self-reported CTS are described for the subset of 1.62 million "recent workers" with CTS who experienced hand discomfort for one or more days.

The prevalence rate of CTS was 1.63% for females (95% CI 1.39%; 1.87%) and 0.97% for males (95% CI 0.77%; 1.18%). The female/male rate ratio for CTS was 1.7. The median age among those reporting CTS was 40 for females and 38 for males.

Occupational categories with the highest prevalence rates of self-reported CTS were: [1] mail and message distributing (3.24%), [2] health assessment and treatment (2.74%), [3] construction and extractive trades (2.49%), [4] fabricators, assemblers, and inspectors (2.44%), and [5] precision production occupations (2.22%).

Industrial categories with the highest prevalence rates were: [1] manufacturing of food and kindred products (2.46%), [2] repair services (2.40%), [3] transportation industry, excluding railroad and trucking (2.34%), [4] construction (2.11%), and [5] manufacturing

of transportation equipment (mostly automobile) (2.08%).

Among individuals who reported repetitive bending or twisting of the hand and wrists at work, 2.01% (95% CI 1.72; 2.30) reported CTS, compared to 0.55% (95% CI 0.42; 0.68) of those without such exposure (rate ratio: 3.7). Among those who used vibrating tools, 2.03% (95% CI 1.50; 2.56) reported CTS, while 1.11% (95% CI 0.95; 1.27) of those who did not use vibrating tools reported CTS (rate ratio: 1.8).

When the separate and combined effects of these two stressors were examined on male workers, 2.55% (95% CI 1.82; 3.28) of those who were exposed to both stressors reported CTS, while 1.23% (95% CI 0.86; 1.61) of those exposed to bending/twisting only, or 0.46% (95% CI 0.00; 0.99) of those exposed to vibrating tools only, and 0.49% (95% CI 0.32; 0.67) of those exposed to neither stressor self-reported CTS. Female workers showed a similar trend but none of the differences was statistically significant, probably due to small number of those exposed to vibrating tools.

When the relationship of the daily length of bending/twisting of the hands/wrists at work and prevalence rate of CTS was examined (both men and women together), those not exposed had a prevalence rate of 0.73% (95% CI 0.57; 0.88), compared to 1.97% (95% CI 1.23; 2.71) among those exposed for up to 3 hours, 2.07% (95% CI 1.42; 2.71) among those exposed from 3 to 6 hours, and 2.40% (95% CI 2.05; 2.75) among those exposed for 6 hours or more, suggesting a "plateau effect" rather than a step-wise increment.

The NHIS identified occupations and industries with high risk of CTS and supports the relationship between ergonomic stressors and development of this condition. Periodic surveys can be used to monitor trends in disease and identify risk factors and high risk industries/occupations, toward which prevention efforts should be directed.

SURVEILLANCE OF ASBESTOSIS DEATHS IN THE UNITED STATES USING MULTIPLE CAUSE OF DEATH DATA, 1968-1988

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Asbestosis is an occupational lung disease targeted by the Public Health Service Year 2000 National Health Promotion and Disease Prevention Objectives. Trends in asbestosis mortality provide one criterion for evaluating progress toward preventing asbestosis. Most occupational mortality studies have been based on underlying cause of death only. Data tapes listing both underlying and contributing causes of death for all deaths in the United States are prepared annually by the National Cancer for Health Statistics (NCHS). These data are especially attractive for the analysis of chronic conditions such as asbestosis, which may often be listed as contributing rather than underlying cause of death.

For years 1968-1988, we analyzed temporal trends, geographic patterns at state and county levels, and years working life lost (i.e., prior to age 65) in decedents with any death certificate mention of asbestosis. Deaths with asbestosis were identified by the International Classification of Diseases (ICD) Version 8 code 515.2 from 1968-1978 and by ICD Version 9 code 501 from 1979-1988. Sex- and race-specific rates were calculated. State-specific rates were developed for the 1968-1978 and 1979-1988 periods. Data on usual industry and occupation of decedents, available from NCHS since 1985 for selected states, were also analyzed.

From 1968 to 1988, the national annual age-standardized rates for deaths with asbestosis increased from 1 per million to 6 per million in white males. The proportion of deaths with asbestosis occurring in white males over 65 years increased from 50% in 1968-1978 to 76% in 1979-1988. Despite the increased proportion of asbestosis deaths over age 65, years working life lost generally increased from 1968-1988. By state, New Jersey and Washington had the highest

rates in both the 1968-1978 and the 1979-1988 periods. County level mapping identified more detailed geographic patterns of deaths with asbestosis within these states. Construction was the most frequently listed industry, and plumbing, pipefitting, and steamfitting were the most frequently listed occupations among decedents with coded industry and occupation.

Although the use of asbestos has declined in the United States, continued exposure to asbestos indicates the need for an occupational mortality surveillance system for asbestosis. The NCHS multiple cause of death tapes provide data for such a system.

PREVALENCE AND INCIDENCE OF COALWORKERS' PNEUMOCONIOSIS IN U.S. UNDERGROUND MINERS

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Introduction

The results presented here are drawn from the latest data from a long-term epidemiological study on coal miners, denoted the National Study of Coalworkers' Pneumoconiosis (NSCWP). This study was begun in 1970,[1] when thirty-one underground mines around the United States were visited by a mobile examination trailer staffed by a medical team (Round 1). Radiological data, information on ventilatory function and respiratory symptoms, and data on work and smoking history were obtained on over 9,000 miners. The medical surveys were repeated about three years later (Round 2). Collection of the most recent data took place between 1985 and 1988, when a follow-up study of selected miners and ex-miners from Rounds 1 and 2 was undertaken. This paper presents results on the prevalence of coalworkers' pneumoconiosis (CWP) observed at the end of the follow-up period, and on the incidence of CWP observed over the approximately 13 year interval of the follow-up period.

Materials and methods

Participants in Round 1 or 2 of the study who were alive according to Internal Revenue Service (IRS) records and aged 58 or less in 1985 were identified for possible study. The age limit was imposed in order to confine the medical investigation to those of normal working age. After exclusion of anthracite miners (too few for analysis), those who had moved away, and those in thinly populated areas, 5,452 miners and ex-miners remained; these were targeted for examination in 26 medical surveys. The surveys consisted of three mine visits, and 23 "community surveys." In the latter, the mobile examination unit was set up in a central location, to which the miners were invited by appointment. In total, 3,280 miners and ex-miners were examined.

The examination consisted of three main parts: a standard posterior-anterior chest radiograph, spirometry, and a questionnaire on respiratory symptoms, smoking habits, and work history. Ex-miners were placed into one of three groups: current miner, ex-miner health-related (left coal mining because of sickness or injury), and ex-miner work-related (left coal mining to take another job, or laid off). Three groups (high, medium, low) were formed for analysis by coal rank, a mineralogic measure of metamorphosis by heat and pressure.

Two sets of x-ray readings were undertaken. The prevalence readings consisted of independent classifications of all single films from Round 4 by three B readers using the ILO 1980 system.[2] Summary prevalence readings of small opacities for each study participant were obtained by taking medians when either two or three readings were available.

Incidence readings were undertaken on those cases with any sign of CWP (all radiographs for which one or more readers reported category 0/1 or greater profusion of small opacities) on the prevalence reading, and on an age matched control group of the same size drawn from the remainder of the group. Each final film was paired with its initial film from Round 1 or 2, and read side-by-side using the 1980 ILO classification[2] by three B readers, after the pairs had been mixed randomly. Summary determinations of profusion of small opacities were derived using medians. Estimates of CWP incidence and progression for the whole cohort of miners were derived by combining the information from the incidence reading with extrapolated figures for the remainder of the films, using tenure-specific rates from the incidence readings.

Results

Based on replies given during examination, 53% of the group were current miners, while 33% were work-related ex-miners (mostly laid-off because of the recession in coal mining). Health-related ex-miners made up the balance (14%). The average age of the whole group was 46 years, and the group had spent an average of 18 years in mining and 14 years underground. The majority lived in Appalachia (West Virginia, Kentucky, Pennsylvania, Virginia, Ohio, and Tennessee)

Results on prevalence are based on 3,200 participants because radiographs for 80 were classified as unreadable for CWP. Similar overall prevalences of combined opacities of category 1 or greater (CWP 1+) were obtained by the three readers (7%, 7%, and 9%, respectively). CWP 1+ prevalence based on the median determinations (Figure 1) showed a very slight rise with tenure underground between 0 - 19 years, and a much steeper increase after that. Except for the 30+ years tenure group, the prevalence of CWP 2+ was close to 1% (Figure 1).

Prevalences of CWP according to employment status at Round 4 -- current miner, ex-miner (job-related), or ex-miner (health-related) -- are shown in Figure 2. Miners who left mining because of their health were more than twice as likely to have CWP 1+ compared to those who stayed in mining (OR = 2.7, $p<0.001$ based on logistic modeling). Abnormality levels for ex-miners who changed jobs or were laid off were very similar to those who remained in mining (OR = 1.1, $p>0.05$). Similar relationships (not shown) was seen for CWP 2+.

Figure 3 shows the prevalences of CWP 1+ by coal rank group. Differences were only apparent for miners with 20 or more years of tenure. As expected, the high rank area tended to have the greatest prevalence of CWP (OR = 2.0, $p<0.001$ based on logistic modeling). Surprisingly, the prevalences for the low rank group appear to be higher than those for the medium rank group (OR = 1.44), although of borderline statistical significance ($p<0.10$).

In the incidence reading, after deletion of pairs with missing data or unreadable films, data for 3,204 pairs remained. Bivariate tabulation of the initial and final x-ray data from these readings (including the extrapolated scores) (Table 1) shows that there were 152 incident cases of CWP 1+ from category 0, or an overall estimate of incidence of CWP 1+ of 4.8%. The incidence of CWP 2+ was 11/3,159 = 0.3%. The eleven affected miners who suffered incidence of CWP 2+ over the 13 or so years of the follow-up had a mean age of 57, and had worked an average of 33 years in coal mining at the time of final follow-up. Four were from areas where high rank coal is mined, as opposed to about one expected on the basis of the geographical distribution of the participants, consistent with the view that coal rank is linked with CWP incidence.

Examination of incidence by employment status revealed similar findings to those on prevalence, in that ex-miners who said they left work because of their health had elevated incidence of CWP (OR = 2.2, $p<0.01$). In addition, miners in high coal regions had elevated incidence over those in medium regions (OR = 1.8, $p<0.01$), but contrary to the prevalence findings, low rank coal miners did not have an elevated risk compared to medium rank miners.

Conclusions

The conclusions from the study were as follows:

1. Prevalence and incidence of CWP were related to both tenure underground and coal rank.

2. Individuals who left mining for health reasons had higher prevalence and incidence of CWP.

3. Most of the CWP evident at the final examination (Round 4) had developed over the study period.

4. Most of the incident cases were older miners, most of whom had worked in coal mining for extensive periods before the start of the follow-up period.

5. Miners with CWP at the initial survey had high rates of progression.

In general, it appears that CWP prevalences in U.S. underground coal miners are decreasing.[1] This suggests that the compliance measures enacted in 1969 have had some success. Nevertheless, the results of this study indicate that existing measures may not be totally sufficient to prevent all CWP incidence, nor prevent CWP progression among those who do develop the disease. However, because many of the miners in this study had received high dust exposures before dust levels were reduced in 1969, it is difficult to be sure that the degree of CWP incidence and progression observed is not a legacy of past conditions. Hence, continued surveillance of underground coal miners is necessary in order to determine whether these observations apply to miners who joined the work force after 1969. Lung diseases other than pneumoconiosis should similarly be evaluated in relation to work in these dust conditions.

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Table 1. Incidence of CWP over study period derived from median profusion category

		Final x-ray				
		0	1	2	3	All
Initial x-ray	0	3007	141	10	1	3159
	1	2	21	14		37
	2		2	6		8
	3					0
	All	3009	164	30	1	3204

Figure 1. Prevalence of CWP by tenure underground
Median readings

Figure 2. Prevalence of CWP category 1 or greater
by employment status and tenure underground

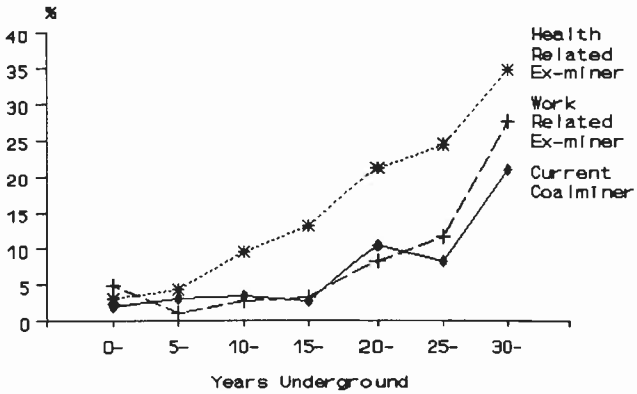
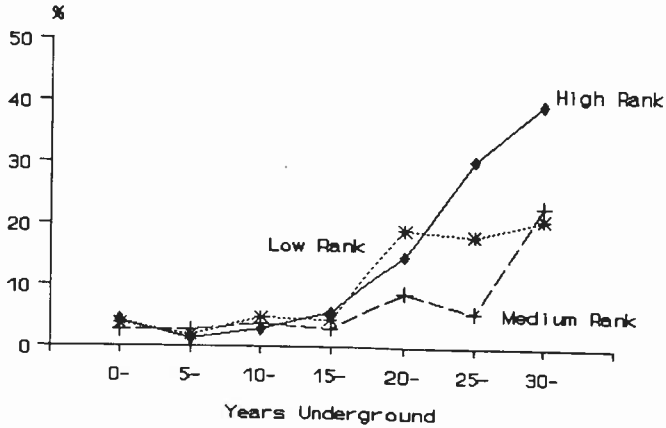


Figure 3. Prevalence of CWP category 1 or greater by coal rank and tenure underground



CORRELATION BETWEEN RESPIRATORY SYMPTOMS AND ACCELERATED LOSS OF VENTILATORY FUNCTION IN ASBESTOS-EXPOSED WORKERS: A LONGITUDINAL ANALYSIS

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Cross-sectional studies assessing respiratory questionnaire validity have demonstrated an association between respiratory symptoms and diminished ventilatory function. Few studies, however, have assessed the association between respiratory symptoms and change in ventilatory function over time. To determine whether respiratory symptoms are associated with accelerated loss in ventilatory capacity, reported symptoms of cough, phlegm, wheeze, and dyspnea on the American Thoracic Society (ATS-DLD-78A) questionnaire were correlated with longitudinal changes in forced vital capacity (FVC) and forced expiratory volume, one second (FEV1) in 446 asbestos exposed workers. Subjects were enrolled in the randomized prospective Seattle Asbestos Chemoprevention Trial (1985-1988), with questionnaire and spirometry data from randomization and after three to five years follow-up. All had worked in specified construction and ship-building trades with high risk for asbestos exposure, with more than 15 years from first exposure to randomization. Symptom prevalence ranged from 23% for wheeze to 45% for phlegm. As a whole, the cohort experienced accelerated loss in ventilatory function of 49ml/yr in FVC, and 50ml/yr in FEV1. Reported respiratory symptoms on initial exam were not predictive of accelerated loss, however the development of any respiratory symptom between initial and follow-up exam was associated with accelerated decline in both FVC and FEV1:

Annual change in FVC and FEV1 (ml/yr)[a] compared to asymptomatic individuals

	FVC			FEV1		
	Group A[b]	Group B	Group C	Group A	Group B	Group C
Cough	+5	-32	-8	+1	-39**	-22*
Phlegm	-2	-50**	-18	-12	-32**	-12
Wheeze	+5	-67**	-29	-4	-38**	-16
Dyspnea	-7	-34*	-26	+3	-28*	-5

[a]1rom MLR model, with covariates: baseline FVC, age, smoking status
[b]Group A=resolution of symptoms between initial and follow-up exam
Group B=development of symptoms between initial and follow-up exam
Group C=persistence of symptoms between initial and follow-up exam
*$p<0.05$, **$p<0.01$

In summary, these results indicate that development of respiratory symptoms was associated with accelerated decline in ventilatory function. The presence of symptoms per se was not predictive of significant decline. We conclude that serial administration of respiratory questionnaires to asbestos exposed workers may effectively identify groups at risk for progressive ventilatory impairment.

OCCUPATIONAL ASTHMA IN HARD CHROME ELECTROPLATERS

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Introduction

Why do the study at all? a) Firstly, chromium compounds, particularly chromium VI, are known skin - and to a lesser extent - respiratory sensitizers, causing asthma. A literature search was undertaken into chrome asthma, numbering seven in total - see references. b) Secondly, at the factory where this study was done, there have already been notified two confirmed cases of occupational asthma. c) Thirdly, in the late 1980s the Institute of Occupational Health here in Birmingham had already started a survey into the prevalence of occupational asthma within the electroplating trade in the midlands.

The aim of the study is: "The prevalence of occupational asthma in hard chrome plating."

Methodology

a) The study population came from an electroplating plant in the West Midlands, United Kingdom, where engineering components are plated with hard chrome plus plating with other heavy metals, namely nickel, cadmium, zinc, and tin.

Fifty-one workers were studied out of a total of 70 employees at this factory, and they were randomly selected and divided into two groups: Group 1 (the study population) hard chrome platers (all male), and Group 2 (control population) 26 other workers (22 males, 4 females).

b) This is a cross-sectional study.

c) Investigations to be undertaken were as follows: i) A Medical Research Council (MRC) modified respiratory questionnaire was used for each employee, which would contain their occupational history plus symptoms and signs of any chest illnesses, with particular relevance to asthmatic symptoms, primarily breathlessness, chest tightness, and wheezing. Other signs of atopy, such as skin irritation, rhinitis, and conjunctivitis were also elicited, together with their smoking histories. ii) Measurements of lung function were done by using a dry wedge spirometer, and these measurements to be followed by serial peak flow measurements. iii) Urine tests, post shift, were done for chrome content and also for nickel, cadmium, zinc and copper. iv) Skin tests for three common allergens - dermatophag, grass pollen, and cat dander - plus three differing strengths for zinc, potassium dichromate, nickel chloride, and copper sulphate, and using histamine as a positive control and cocos solution as a negative control, were done. v) Environmental measurements, together with the aforementioned urinary tests, were taken at the end of the working week, and both static and personal monitoring were done for the following heavy metals - chrome, nickel, cadmium, and zinc.

The results of our study are tabulated as follows, followed by comments:

NUMBERS OF WORKERS WITH SYMPTOMS

	GROUP 1	GROUP 2	95% CONFIDENCE INTERVALS
WHEEZE	6	8	(-0.229 to 0.285)
COUGH	5	6	(-0.247 to 0.220)
++ DYSPNOEA	1	14	(0.546 to 0.136)p<0.5
SKIN IRRITATION (ITCH)	8	9	(-0.0265 to 0.269)
RHINITIS	6	6	(-0.212 to 0.272)
LUNG FUNCTION RESULTS (MEAN % PREDICTED)			
FEV1	99.5	95.8	(-4.5 to 11.9)
FVC	106.9	105.2	(-6.97 to 10.4)
FEF 25/75	71.4	76.8	(-19.5 to 8.7)
PEAK FLOW	94.9	90.8	(-10.7 to 18.9)
URINARY CHROME (nmol/mmol CREATININE-MEAN LEVELS)	17.9	9.9	(-3.05 to 19.1)
AIR HEXAVALENT CHROME/MEAN LEVELS (MEL/HEXAVALENT CHROME VI 0.05 mg/m^3)	0.0066	0.0027	(-0.000113 to - 0.00769)

++ THE NUMBERS OF PLATERS AND CONTROLS WITH DYSPNOEA, NAMELY 1 AND 14, DO NOT REFER TO THE NUMBER OF SUBJECTS WITH DYSPNOEA, BUT TO THE MRC SCORING OF SYMPTOM SEVERITY OF THE DYSPNOEA, GRADING BETWEEN 0-3.

Please note there were twice the number of smokers - namely 22 - under Group 2 (Controls) as compared with the study population of platers, namely 11 smokers.

Further comments are as follows: Looking at the confidence intervals, there was little dissimilarity between the symptoms of the platers or controls, apart from the score of 14 for dyspnoea for controls as compared with 1 for platers, giving a significance of $p < 0.05$.

Again, there is no significant difference between the symptoms that the platers have as compared with controls with reference to skin irritation or rashes plus rhinitis and conjunctivitis.

Then with reference to the spirometry results, there is no significant decrease in lung function in either group, as again shown by the confidence intervals.

With reference to the environmental monitoring, the MEL range for hexavalent chrome showed an arithmetic mean for Group 1 (platers) of 0.0066 and for Group 2 (controls) 0.0027, which in turn gives a p value of $p < 0.5$, 95% significance. This is what would be expected.

Finally, coming to the urinary chrome measurements, there is no real significant difference as noted by the confidence intervals, but the arithmetic mean for the urinary chrome for Group 1 (platers) is 17.9 (nmol/mmol creatinine) as compared with Group 2 (controls) being 9.9, which again is to be expected.

Continuing with the results, I now refer to the interpretation of serial peak expiratory flow (PEF) records from the workers in this same factory:

A. *Methodology:* Out of a total study population of 51 workers, these were workers asked to perform two-hourly serial peak expiratory measurements over a period of three weeks, including a holiday break of three days. Out of this total, 11 workers' records (22%) were inadequate or not returned, thereby leaving interpretation of the records from the remaining 40 workers (65 records, mean

duration: 16 days, mean number of readings per day: 7) to be compared to their respiratory symptoms.

B. *Results: Interpretation of Serial Peak Expiratory Flow (PEF) from Workers' Records.* Of 27 asymptomatic workers, 23 (85%) produced normal records, 3 records were suggestive of asthma, and 1 of occupational asthma (OA).

Of 6 workers with symptoms suggestive of occupational asthma, 2 (33%) produced records suggestive of occupational asthma, 1 of irritant reactions, and 3 had normal records.

Of 5 workers with symptoms suggestive of asthma alone, 4 had normal records, and 1 with a low PEF and low variability were produced.

Of the 2 remaining workers who complained of non-asthmatic non-work related symptoms, 1 produced a record suggestive of occupational asthma and 1 a normal record.

Therefore, there were a total of 7 cases of asthma, including occupational asthma, out of 40 workers studied, giving thereby a total of 17.5%, and there were 4 workers with occupational asthma, again out of a total of 40, which gives a percentage total of 10% in this Study.

These results confirm that workers are, on the whole, able to perform two-hourly serial peak flow measurements.

Referring back to our original two groups, i.e., Group 1 (hard chrome platers) and Group 2 (other workers), when an analysis was done purely from the respiratory questionnaire, in Group 1 there were 3 asthma cases - 2 non-work related and 1 work-related. In Group 2 there were 7 asthma cases, 3 of those being non-work related and 4 being work-related.

This therefore gives a total of 10 asthma cases out of 40 workers studied (25%), of which 5 were work-related, i.e., 12.5% of the total studied.

So, when one combines the results of the respiratory questionnaire with the serial peak flow readings, the total number of asthma cases drops down from 10 to 7, thereby giving a total of 17.5% of total workforce, of which 4 were work or occupationally related asthma, giving 10% of the total studied.

Conclusions

1) The aim of this survey, as stated, was to determine the "prevalence of occupational asthma in hard chrome plating."

2) This was done by the determination of the prevalence of work-related (WR) symptoms and abnormal lung function in electroplating workers exposed to chrome.

3) In order to do this, a comparison was made of work-related symptoms and lung function in electroplaters with that in other workers within the same factory.

4) We have concluded that work-related (WR) respiratory, eye and skin symptoms are prevalent among both groups of workers.

5) No significant difference in symptoms or respiratory function was demonstrated for <u>different occupational groups</u> with <u>different chrome exposures</u>.

So, what has gone wrong? The reasons for this are the following confounding factors: a) The control groups (Group 2) exposed to chrome as well as the platers group (Group 1); b) Good controls of air levels of hexavalent chrome (urinary chrome also reflecting ingestion in addition to inhalation, probably via smoking); c) More smokers/respiratory ill health in the control groups; d) "Healthy Work Effect"; and e) finally the small numbers - namely 49 - studied, divided half into Groups 1 and 2.

Therefore, the only way the study can be improved is by selecting a better control group, which would have to be outside the factory studied.

Referring back to (c) of the Introduction to this paper, the third reason for the study was the existence of a pre-existing survey into the prevalence of occupational asthma within the electroplating trade

in the West Midlands by Dr. A. Boran of the Birmingham Institute of Occupational Health, United Kingdom.

In his paper, there was a study population of 300 electroplaters matched with a control of 100 workers who were employed at one firm only doing zinc galvanizing, with no exposure to plating metals.

Therefore our small survey could be compared with the study population in the aforementioned survey together with using the 100 workers in the same survey as a control group.

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ASBESTOS RELATED DISEASES IN CONSTRUCTION CARPENTERS

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Introduction

During 1987-1988, a clinical survey was conducted in 631 active and retired members of the International Brotherhood of Carpenters and Joiners Union in eastern Massachusetts. Most (97.5%) of the subjects reported having worked with asbestos-containing products (manufacture/use, replacement, or asbestos mining/milling). In this study, we addressed three important questions for these asbestos-exposed workers: Physiological importance of radiographically detected pleural plaques and minimal parenchymal fibrosis (i.e., profusion score of 0/1); contribution of smoking history in the prevalence of interstitial and pleural fibrosis; and differences in disease prevalence for different jobs within the carpenters' union.

Materials and methods

The 631 participants included 506 (80%) construction carpenters, 55 (9%) millwrights, and 69 (11%) other--welders, painters, etc. Ninety-eight percent were active workers at the time of the survey.

All participants completed a modified ATS occupational respiratory questionnaire and underwent spirometry and posteroanterior chest radiographs. The maximum FEV1, FVC, FEV1/FVC were derived and their percent predicted values calculated using reference equations of Crapo et al. (1981). Chest radiographs were interpreted according to the ILO classification system (1980).

Differences in groups based on radiographic findings or pulmonary function tests were detected using two-sided t-tests for continuous variables and chi-square test for discrete variables. Linear regression models were used to evaluate the association between pulmonary function data and findings on the chest radiographs. Multivariate

logistic regression models were used to assess the relation between presence of obstructive or mixed patterns of pulmonary function defects and findings in the chest radiographs. Restrictive pattern was not successfully modeled because the small number of subjects with a purely restrictive pattern.

Results

Demographic characteristics and radiographic findings. This population had a relatively low prevalence of radiographic abnormalities. Of the 631 participants, 457 (72%) had no evidence of x-ray abnormalities. Pleural fibrosis was more prevalent than interstitial fibrosis (IF), which presented predominantly low profusion scores. Pleural fibrosis alone was seen in 67 workers (11%), with only 3 having diffuse pleural fibrosis and the rest having circumscribed pleural fibrosis. Interstitial markings consistent with fibrosis were noted in 43 (6%) workers. Profusion score of 0/1 was present in 23 (4%) workers, and profusion score of 1/0 or higher in 20 (3%) workers: profusion 1/0 in 4 (0.6%) workers, 1/1 in 5 (0.8%), 1/2 in 6(0.9%), and 2/1 in 7 (1%). Those with fibrotic diseases were more likely to be older, have worked more years, and have smoked more pack/years than those with normal radiographs (data not shown).

Demographic characteristics and functional patterns. The obstructive pattern was the functional impairment most frequently seen (15%, n=96), followed by restricted (4%, n=27) and mixed (3.8%, n=24) patterns. Subjects with functional impairment were more likely to be older, have worked more years, and be former or current smokers (data not shown).

Pulmonary function and radiographic findings. The group of workers with pleural plaques alone had significant decreases in the percent predicted values for FEV1 and FVC, and for FEV1/FVC%, when compared to the group with normal radiographs, with evidence of mixed lung function impairment. The group with interstitial fibrosis grades 1 and 2 also had significantly lower mean percent predicted values for FEV1 and FVC, and FEV1/FVC%, with evidence of both obstructive and mixed defects (Table 1).

Table 1. Pulmonary function and radiographic findings.

		Negative X-Ray		Pleural Plaques		IF Grade 1		IF Grade 2	
N (%)		457	(72.4)	64	(10.1)	23	(3.6)	20	(3.2)
FVC mean (s.d.)		4.9	(0.8)	4.4	(0.8)	4.1	(0.9)	3.8	(0.8)
FVC % pred mean (s.d.)		99.1	(12.0)	94.2[a]	(14.7)	88.7[a]	(14.4)	86.7[a]	(13.4)
FEV1 mean (s.d.)		3.8	(0.7)	3.2	(0.7)	2.9	(0.8)	2.7	(0.6)
FEV1 % pred mean (s.d.)		94.4	(13.6)	87.3[a]	(16.4)	78.7[a]	(19.3)	78.0[a]	(17.9)
FEV1/FVC % mean (s.d.)		77.9	(7.2)	74.1[a]	(8.2)	70.3[a]	(10.6)	71.1[b]	(10.9)
FEV1/FVC % pred (s.d.)		95.4	(8.4)	92.4[b]	(10.1)	88.5[b]	(13.1)	89.4	(13.6)
Pattern:	Normal	390	(85.3)	47	(73.4)	10	(43.5)	10	(50.0)
n (%)	Obstructive	42	(9.2)	10	(15.6)	11[a]	(47.8)	8[a]	(40.0)
	Restrictive	18	(3.9)	5	(7.8)	1	(4.3)	2	(10.0)
	Mixed	6	(1.3)	4[b]	(6.5)	4[a]	(17.4)	4[a]	(20.0)

[a] $p<.01$ compared to negative X-Ray group. [b] $p<.05$ compared to negative X-Ray group.

To further study the relationship between radiographic findings and lung function, we constructed multivariate linear models with FEV_1, FVC and FEV_1/FVC as continuous outcome variables, and logistic models with obstructive, restrictive and mixed disease as dichotomous outcome variables (Tables 2 and 3). Due to the small number of workers with "pure" restrictive disease, we were not able to develop a model that could satisfactorily explain the presence of restrictive disease.

After adjusting for confounders, the association of pleural plaques and decreases in FEV1, FVC and FEV1/FVC% was not statistically significant (Table 2). However, when considering the variable pleural fibrosis (i.e., including all subjects with pleural plaques and the three subjects who had diffuse fibrosis), we found significant decreases in both FEV1 (-148 ml, $p=0.046$) and FVC (-161 ml, $p=0.054$), probably indicating a strong effect of the presence of diffuse visceral pleural fibrosis on lung volumes.

Similarly, after adjusting for confounders in our logistic models for obstructive and mixed disease, while the association of pleural plaques alone and airflow impairment was not significant (Table 3), pleural fibrosis was significantly associated with an increase risk of mixed disease, OR= 4.78, 95% CI 1.53-14.89.

Interstitial fibrosis grade 1, i.e., profusion score of 0/1, was also strongly associated with a mixed pattern of impairment when compared with 0/0 profusion category (Table 3).

Smoking habits and pulmonary function. Current smokers had increased risk of obstructive pattern with reductions in FEV1 and FEV1/FVC% related to pack-years smoked. Former smokers did not have a significantly increased risk of ventilatory impairment. However, reduction in their FEV1, FVC, and FEV1/FVC% were significantly related to pack-years (Tables 2 and 3).

Job performed and pulmonary function. After adjusting for smoking, profusion and other confounders, workers that predominantly performed millwright jobs had a significantly increased risk for a mixed pattern. This could be a result of exposures to welding gases, since a considerable larger proportion of millwrights than carpenters (70% versus 13%) had worked as welders.

Table 2. Regression coefficients from multiple linear regression models for pulmonary function

	FEV1		FVC		FEV1/FVC	
	ß	p	ß	p	ß	p
Intercept	−1.47	0.02	−4.70	<0.01	121.2	<0.01
Ages, years	−0.03	<0.01	−0.03	<0.01	−0.21	<0.01
Height, inches	+0.09	<0.01	+0.15	<0.01	−0.48	<0.01
Smoking status: current	−0.11	0.15	−0.02	0.81	−2.05	0.04
former	+0.05	0.40	−0.06	0.38	+0.24	0.78
(vs. non-smoker)						
Pack-years/current smoker	−0.01	<0.01	−0.002	0.44	−0.12	<0.01
Pack-years/former smoker	−0.01	<0.01	−0.005	<0.01	−0.14	<0.01
Job: millwright	−0.01	0.85	−0.08	0.33	+0.80	0.55
other	+0.001	0.99	+0.04	0.63	−0.30	0.75
(vs. carpenter)						
Pleural plaques	−0.12	0.12	−0.12	0.14	−0.83	0.34
Interstitial Fibrosis:						
grade 1	−0.27	0.03	−0.30	0.03	−1.35	0.39
grade 2	−0.31	0.02	−0.39	0.01	−1.23	0.47
Model R^2	0.543		0.517		0.312	
F (df)	66.77 (11)		59.93(11)		25.45(11)	

Table 3. Odds ratios from logistic regression models for pulmonary function

	Obstructive Pattern		Mixed Pattern	
	OR	95% CI	OR	95% CI
Intercept	0.02		0.05	
Years in trade	1.05	(1.02, 1.09)	1.04	(0.99, 1.10)
Smoking status: current	2.81	(1.02, 7.71)	1.97	(0.13, 7.42)
former	0.54	(0.19, 1.50	0.81	(0.17, 3.70)
(vs. non–smoker)				
Pack-years/current smoker	1.02	(1.01, 1.03)	1.00	(0.97, 1.03)
Pack-years/former smoker	1.05	(1.03, 1.07)	1.01	(0.99, 1.04)
Job: millwright	1.49	(0.63, 5.54)	4.32	(1.32, 14.09)
other	0.63	(0.23, 1.70)	0.60	(0.07, 4.98)
(vs. carpenter)				
Pleural plaques	0.82	(0.36, 1.87)	2.33	(0.68, 8.02)
Interstitial Fibrosis: grade 1	2.34	(0.80, 6.87)	5.85	(1.35, 25.23)
grade 2	2.69	(0.89, 8.12)	9.06	(2.21, 37.15)
Chi-square*(df)	131.0	(10) $p<0.01$	32.29	(10) $p<0.01$

*Likelihood ratio test.

Conclusions

This survey shows a significant association between pleural fibrosis (i.e., plaques and diffuse pleural fibrosis) and a mixed pattern of ventilatory impairment. Pleural plaques alone were not significantly associated with any of the defined patterns of ventilatory impairment.

After controlling for confounders, minimally detectable profusions (i.e., 0/1) were associated with ventilatory impairment, particularly a mixed pattern, indicating both airway and parenchymal abnormalities due to asbestos. The higher the profusion score, the stronger the association with a mixed pattern of impairment.

In this population, the risk of obstructive pattern is increased (2.8 times) for current smokers, but not for former smokers. However, the amount of cigarettes smoked reduces the ventilatory function regardless of the smoking status.

After adjusting for smoking, profusion and other confounders, work as a millwright was significantly associated with a mixed pattern, probably as a result of exposures to welding gases.

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RESPIRATORY SYMPTOMS AND PULMONARY FUNCTIONS OF CEMENT FACTORY WORKERS AT A NIGERIAN CEMENT FACTORY

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The cement industry is the most obvious source of industrial air particulate pollution in Nigeria, yet, there have been very few epidemiological studies related to this industry in the country. In this paper, we present the result of a comparative study of pulmonary functions and respiratory symptoms of cement workers in a cement factory in Southwestern Nigeria. We also report on the relationship between the pulmonary functions of the factory workers and the concentration of suspended particulate matter in the different working areas of the factory. A modified medical research council committee questionnaire was administered to 312 workers, randomly selected from different parts of the factory, and 120 non-factory workers from the same area of the country to assess respiratory symptoms of the subjects. Pulmonary function tests were performed with the aid of a spirometer and Wright Peak Flowmeter. Gross and size-segregated suspended particulate concentrations were measured in different parts of the factory using a hi-volume air sampler fitted with a six-staged impactor head. Statistical analysis of data was performed using the student's t-test. The cement factory workers have higher incidence of chronic non-specific lung diseases, and relatively lower lung functions than the control subjects. Among the factory workers, those that were directly exposed to cement dust, especially in the mill and packing plant, have higher incidence of respiratory symptoms than office workers. These results are supported by the finding that a strong correlation exists between each of the Forced Vital Capacity (FVC) and Forced Expiratory Volume per second (FEV) of the factory workers and the Total Suspended Particulate Concentrations (TSP) of the workers' sites, as shown by the following equations.

$FEV_1 = -0.00019\ (TSP) + 3.471$ and

$FVC = -0.00018\ (TSP) + 4.051$.

The factor of cigarette smoking was considered. Non-smoking factory workers had significantly lower lung function parameter than non-factory workers. Cigarette smoking factory workers had marginally lower lung function parameters than their non-smoking counterparts. The latter was however, found to be statistically insignificant.

ACCIDENTAL GASSING INCIDENTS AND THE RESPIRATORY HEALTH OF PULPMILL WORKERS

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Workers in modern sulphate pulpmills are usually exposed to low levels of irritant gasses such as chlorine, chlorine dioxide, hydrogen sulphide, and sulphur dioxide. However, occasional accidental gas leaks can lead to exposure levels well above governmental standards. Studies in Canada have identified decrements in pulmonary function and increases in respiratory symptoms among pulpmill workers who had experienced overexposures to chlorine gas. In the current study, the respiratory health of pulp and paper workers from a company in Berlin, New Hampshire, was investigated. The subjects were selected from participants in a longitudinal study of respiratory health that had been initiated in Berlin, NH, in the 1960's. The participants in the longitudinal study were retested approximately every six years with spirometry and a questionnaire. An earlier analysis based on the 1979 and 1985 surveys revealed decrements in pulmonary function among men who had worked in the pulpmill. The current study utilized data from the 1985 survey and extended the earlier analysis to include both a new predictor variable (history of gassing) and new outcome variables (self-reported cough, phlegm, wheeze, dyspnea). There were 230 male subjects, all <75 years old and with a history of working for the local pulp and paper company. An individual was considered to have been "gassed" if, in response to an item on the survey questionnaire, he reported that he had been affected by gas or fumes at work or elsewhere and had sought medical care as a result of the incident. Those who had been gassed represented 34% of the 114 pulpmill workers and only 9% of the 116 subjects without pulpmill experience. Subjects who had both worked in the pulpmill and been gassed were compared to subjects who had worked elsewhere in the company and never been gassed. The mean percent predicted forced expiratory volume in one second (FEV1) for the exposed subjects (94.6%, SE=3.32) was significantly less than the corresponding value for the unexposed subjects

(104.3%, SE=2.33) ($p=0.03$). Similar differences were observed in the mean percent predicted forced vital capacity (FVC) and FEV1/FVC, although these differences were not quite statistically significant ($0.05<p<0.10$). Also, the prevalences of self-reported respiratory symptoms were not greater among the pulpmill/gassed subjects. With only 12% of the pulpmill subjects still working in that process, the changes in pulmonary function appear to be non-reversible. Since it is not clear if these findings are applicable to current pulpmill workers, a new study was started in January 1992 to address this issue.

OCCUPATIONAL DUST EXPOSURE AND LUNG DISEASE AMONG SHEET METAL WORKERS

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Background and methods

A previous large medical survey of 12,434 active and retired sheet metal workers with 20 or more years in the trade indicated an unexpectedly high prevalence of obstructive pulmonary disease among both smokers and non-smokers.[1] This study utilized interviews with a cross-section of the previously-surveyed group to explore occupational risk factors for chronic bronchitis and chronic obstructive lung disease.

Respiratory hazards identified with sheet metal work include exposure to asbestos, welding fumes, and man-made mineral fibers. Although the craft of sheet metal work does not itself use asbestos, sheet metal workers in construction were, for many years, exposed to asbestos while working in areas that were being sprayed with asbestos for fireproofing, by working on beams fireproofed with asbestos, and by retrofitting asbestos-insulated metal ventilation systems. Man-made mineral fibers, primarily fiberglass, are used in numerous sheet metal applications. In particular, sheet metal workers fabricating ducts for ventilation systems will line metal ducts with fiberglass in the shop, prior to installation on the job site. Some ventilation ducts are made primarily of fiberglass, rather than sheet metal. In addition, fiberglass is removed and replaced in repair and retrofit work on existing duct systems.

Four hundred and seven workers were selected from the previously-surveyed group on the basis of their potential for exposure to fiberglass and asbestos. Selection was independent of health status, and excluded those workers who primarily welded. A detailed occupational exposure history was obtained by telephone interview for 333 of these workers. Data available from the previous medical survey (conducted mostly in 1987) included: a self-administered

occupational and medical questionnaire; results of a physical examination; spirometry, performed according to American Thoracic Society (ATS) guidelines[2] and interpreted according to the predicted equations of Crapo et al.;[3] and PA and lateral chest xrays, interpreted using the ILO classification for pneumoconiosis.[4] Exposure data were analyzed in relationship to previously collected data on chronic bronchitis, obstructive lung disease, and personal characteristics.

The questionnaire for this study was developed to collect detailed information on the fiberglass and asbestos materials with which an individual had worked for at least three months in his career. Fabrication or installation of fiberglass ductboard, and installation or removal of asbestos insulation are examples of tasks/materials which were included. Assessment of the effects of fiberglass exposure as distinct from the effects of asbestos exposure has been problematic in previous studies of construction workers. These experienced workers, however, had performed a diversity of jobs involving exposure to many different types of materials, and each dust exposure could be evaluated separately. Cumulative exposure models were developed to indicate the adjusted number of years of high, medium and low intensity exposure to fiberglass (FG), the adjusted number of years of high and medium intensity asbestos (ASB) exposure, and the adjusted years of welding exposures. "Adjusted years" reflects the number of years that an individual worked with specified materials/tasks, adjusted for the percent of his work time that he reported being exposed.

Results

The methods and results of this study have been previously described in greater detail.[5] Of the 367 individuals contacted, 333, or 90.7%, completed an interview. We were unable to contact 40 (9.8%) of the 407 individuals in the study population; nearly half of this uncontacted group was deceased.

Participants' exposures were characterized up until the time of the medical screening, about 3 years before the interview. Participants had worked an average of 34 years in the sheet metal trade and were, on average, 58 years old at the time of the previous medical survey. Seventeen percent (17%) had ever worked in a shipyard, most for only one or two years. Twenty-three percent (23%) were

current smokers, 52% were former smokers, and 25% had never smoked.

The risk of chronic bronchitis increased sharply by packyears of cigarettes smoked; current smokers also had a doubled risk compared to individuals who had never smoked or had quit smoking. The occurrence of chronic bronchitis also increased with increasing duration of asbestos exposure. Individuals with a history of high intensity fiberglass exposure had a more-than-doubled risk of chronic bronchitis. Table 1 presents the multiple logistic regression results for 309 participants with complete data on all variables considered.

Chronic obstructive lung disease was also found to be related to both smoking and occupational risk factors; results of multiple logistic regression modeling are presented in Table 2. Packyears smoked was the strongest predictor of obstructive lung disease; current smoking status did not have an important effect on obstructive lung disease risk. Duration of direct and indirect exposure to welding fume was also a positive predictor of obstructive lung disease. Duration of asbestos exposure was significantly associated with obstructive lung disease but the dose-response relationship was inconsistent, especially for individuals with higher packyears of smoking exposure. Fiberglass exposure was not a risk factor for obstructive lung disease.

Since results of the multiple logistic regression indicated a higher risk of obstructive disease among individuals with no asbestos exposure compared to those with up to 20 years of exposure, we carried out further analyses, stratified by smoking history, to attempt an explanation. For the group consisting of those individuals who had never smoked (zero packyears) and those individuals with less than 30 packyears of cigarette exposure, the prevalence of obstructive lung disease increased with duration of asbestos exposure. Only 14 (7.4%) of 189 individuals in this group had obstructive disease, so these prevalence estimates are based on quite small numbers.

The prevalence of obstructive disease was nearly three times higher among individuals who had 30 or more packyears of cigarette exposure (23/112 = 20.5%). A steady increase in prevalence of obstructive disease was not, however, observed in relationship to

duration of asbestos exposure for these high packyear individuals. This was because the small subgroup with no asbestos exposure had a remarkably high prevalence of obstructive disease (5/12 = 41.7%); exploratory analysis of the data did not yield clues as to why this subgroup had such a high prevalence of obstructive disease.

Discussion

This investigation found occupational fiberglass and asbestos exposures to be associated with the prevalence of chronic bronchitis. Only a few previous studies have suggested a positive relationship between man-made mineral fiber exposure and chronic bronchitis[6,7] or cough and phlegm.[8] Previous studies have not indicated an association between obstructive lung disease and fiberglass exposure, although two studies[9,10] have found non-specific impairment of pulmonary function. A few studies also link asbestos exposure and chronic bronchitis,[11,12] and in addition, asbestos exposure has been associated with small airways disease.[13,14]

The effects of asbestos exposure on the prevalence of obstructive lung disease in this study appeared to differ by smoking exposure. A stratified analysis indicated that asbestos exposure may have a dose-related effect among never smokers and individuals with fewer than 30 packyears of cigarette exposure. The effects among heavier smokers, however, were inconsistent and not indicative of a causal relationship. Indeed, the effect of heavy smoking may overwhelm any effect of asbestos exposure. The results of this study would suggest that future studies should look separately at non-smokers in assessing whether asbestos increases the risk of obstructive disease. Given the high prevalence of current or former smokers in occupational groups exposed to asbestos, it is essential that the relationship between asbestos exposure and chronic bronchitis or obstructive disease be examined either in a large group of non-smokers, or by accounting for smoking in a logistic regression model. The data presented here suggest that findings that have been attributed to smoking in the past may in part be due to asbestos exposures.

High intensity fiberglass exposure was associated with chronic bronchitis in this study; neither the adjusted years of lower intensity exposures nor the total adjusted years of fiberglass exposure were identified as risk factors for chronic bronchitis. It should be noted

that fiberglass ripout was the only task for which fiberglass exposure was rated as "high." Since lower exposure intensity tasks were not associated with lung disease in this study, the results indicate that control of fiberglass dust exposures to low levels may prevent the development of non-malignant lung disease in working populations. The importance of detailed exposure assessment in future research must be emphasized; assessment of task-specific exposures is especially important for epidemiologic studies of construction workers.

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Table 1. Risk factors for chronic bronchitis: results of multiple logistic regression analysis[a]

Variable	Odds ratio	95% Confidence limits
Intercept[b]	0.014	0.003 - 0.060
Packyears of cigarettes		
None	1.00	
1-59 packyears	5.21	1.17 - 23.20
≥ 60 packyears	10.48	1.85 - 59.52
Smoking status		
Never/former	1.00	
Current	2.12	1.00 - 4.50
Adjusted years of asbestos, all levels		
Increase of 1 year	1.04	1.01 - 1.07
Increase of 10 years[c]	1.51	1.08 - 2.10
Level of fiberglass exposure		
None, low, or medium exposure only	1.00	
Ever had high level exposure	2.28	1.07 - 4.86

[a]N = 309 individuals, 44 with chronic bronchitis; model R=.347.
[b]Odds ratio for intercept equals the adjusted rate of disease for individuals with values equal to zero for all variables in model.
[c]Years of asbestos exposure was modeled as a continuous variable, so the estimate for an increase of 10 years is not independent from the estimate for one year increase. Categorical analyses indicated that years of asbestos exposure was appropriately modeled as a continuous variable.

Table 2. Risk factors for obstructive lung disease: results of multiple logistic regression analysis

Variable	Odds ratio	95% Confidence limits
Intercept[b]	0.03	0.006 - 0.13
Packyears of cigarettes		
None	1.00	
1-29 packyears	3.01	0.76 - 11.93
30-59 packyears	6.28	1.62 - 24.41
≥ 60 packyears	17.21	3.57 - 82.91
Adjusted years of asbestos exposure		
None	1.00	
>0 - < 10 years	0.19	0.06 - 0.62
10 - < 20 years	0.41	0.12 - 1.44
≥ 20 years	1.36	0.43 - 4.28
Adjusted years of welding exposure		
None	1.00	
1-3 years	2.86	0.95 - 8.58
≥ 4 years	4.09	1.27 - 13.22

[a]N = 2301 individuals, 37 with obstructive lung disease; model R = .323.
[b]Odds ratio for intercept equals the adjusted rate of disease for individuals with values equal to zero for all variables in model.

IMMUNOLOGIC SENSITIZATION TO TETRACHLOROPHTHALIC ANHYDRIDE (TCPA) IN RELATION TO EXPOSURE MEASURES

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There have been two reports of occupational asthma (OA) associated with tetrachlorophthalic anhydride (TCPA) (Venables, 1989): in the U.S., Schlueter et al. (1978) were unable to demonstrate specific antibodies to a TCPA-protein antigen; in the United Kingdom, Howe and colleagues (1983) demonstrated prick test reactivity and serum specific IgE to a conjugate of TCPA and human serum albumin.

In April 1990, the Ontario Ministry of Labour received a request to evaluate breathing problems among TCPA-exposed workers at a plant in Ontario that manufactures solenoid coils. At least four former workers seen by a respirologist were considered to have OA and were no longer at the plant. Early in 1988, a new epoxy resin hardener containing TCPA had been introduced. In our investigation, we attempted to document the extent of TCPA exposure; determine the prevalence of work-related respiratory symptoms; and determine possible exposure measures associated with IgE-mediated sensitization to TCPA.

The facility, which employed approximately 50 employees, manufactured solenoid coils by first, winding copper wire on bobbins. Copper wires are soldered by dipping into heated rosin flux (containing colophony). The epoxy resin containing TCPA is compressed into pills, which are then molded with the solenoid assembly (in the molding machine). Exhaust ventilation for molding presses was not begun until July 1990 and was completed after this survey.

Methods

A. Environment assessment. Air sampling was performed on several occasions for TCPA; concentrations of TCPA on the day of the cross-sectional survey were measured in a number of departments.

Exposure was also classified by: duration of employment and by cumulative TCPA consumption based on records of TCPA purchases by month. This was considered the same for each employee present during that month. In addition, we established 4 exposure groups, listed by decreasing potential for TCPA exposure: 1) molders (n=7); 2) workers who circulated about the plant (such as electrician, maintenance) (6); 3) coil assembly workers (33); and 4) administrative personnel (6).

B. Medical assessment. In July 1990, a cross-sectional evaluation of current employees was performed and consisted of an occupational and medical questionnaire and spirometry performed before and after the shift.
Reported chest symptoms were considered work-related if (i) the onset was after starting at the plant; (ii) there was temporal improvement on weekends and/or vacations; and (iii) it followed certain activities (or exposures) at work. Work-related asthma (WRA) was considered to be present if two or more work-related chest symptoms were reported.

In October 1990, an immunologic survey was conducted; blood specimens were collected for determination by ELISA of serum specific IgE and IgG antibodies to a well-characterized TCPA-human serum albumin (HSA) conjugate. Specific antibody binding greater than 3 S.D. above the mean of the optical density of a non-exposed control group (N=12) was considered elevated.

Results

A. Environment assessment. Results of TCPA exposure data are shown in the Figure; the bars marked with an A refer to area samples; all others are personal. (The dotted bars represent the crimping department in May 1990, finishing in July 90, and office in November 90.) TCPA was detectable throughout the plant, and on a given occasion did not vary considerably between non-office departments. Exposures were markedly lower in July 1990.

B. Medical/epidemiologic assessment. Initial survey: 52 current employees participated in the survey, representing 79% of those eligible. 83% were female, and they had worked an average of 2.5 years at the plant. Work-related wheeze, shortness of breath, and chest tightness were reported by 27%, 29%, and 39% of subjects,

respectively; WRA according to the above definition was present in 35%. In general, wheeze, chest tightness, and WRA were reported most frequently by the mold workers. However, after adjusting for smoking status, the differences between groups in reported work-related symptoms were not statistically significant. The average decline in FEV_1 was greatest in the mold group (-4.1%), and this was significantly different from the change in the office group (+2.5%) ($p=0.0016$ after adjustment for smoking status) while the changes in the other 2 groups were not different from that in the office group ($p > 0.05$).

Immunologic findings: There were 49 samples collected from current employees. Of these, 15 (31%) were positive for TCPA-HSA-specific IgE antibody, and 19 (39%) had specific IgG antibody. As seen in Table 1, the proportion with positive IgE (and IgG) antibody was greatest in Groups 1 and 2 with the most direct exposure, and lower in the coil assembly group; no antibodies were detected in the small office group. With groups 1 and 2 combined, there was a significant trend of increasing proportion having positive antibody status with "greater potential" for TCPA exposure ($p=0.019$ for IgE; $p=0.022$ for IgG).

A separate analysis was performed *among the 35 subjects hired since 1988*, when the new hardeners were introduced. As shown in Table 2, there was an increasing trend in the proportion of those with positive IgE (and IgG) antibody with increasing duration of employment category.

Those positive for specific IgE antibody also tended to be older, and less likely to be current smokers. Duration of employment (on logarithmic scale) was not significantly different between those positive and negative, but *duration of employment since 1988* was significantly longer among those positive ($p = 0.044$). Cumulative consumption of TCPA ranged up to 316,338 pound-months (median 224,480). Mean consumption whether untransformed or log-transformed, was greater among those antibody positive, but only of borderline significance. Among those hired since 1988, those positive for IgE were again somewhat older, and 25% were current smokers compared with 45% of those without antibody ($p=0.123$). Mean duration of employment (log scale) was significantly greater among those IgE positive ($p=0.013$).

The influence of several variables alone and in combination in predicting specific IgE antibody status was examined using logistic regression. Only variables associated with a significant change at the nominal 5% level by the likelihood ratio test in univariate models were included in further models. Models using log-transformed duration of employment provided the best fit. Among all those with serum samples, in univariate analyses, duration of employment (log scale) and older age (older than median vs younger) were not significant, and direct exposure department was of borderline significance. However, duration employed *since 1988* (log scale) and smoking status were significant. Both these latter two variables were also associated with significant change in the likelihood ratio test when included in the model together. A term for the interaction between smoking and duration since 1988 did not contribute significantly. In the final model with both variables, the odds ratio for current smoking was 0.19 (95% CI 0.045, 0.80), and for log duration employed since 1988, the odds ratio (per 1 year) was 2.39 (95% CI 0.93, 6.14).

In logistic regression models *among those hired since 1988*, only the duration of employment was a significant predictor of IgE positivity. The odds ratio for duration of employment (per 1 year) was 4.99 (95% CI 1.14-21.96); it changed moderately when adjusted for direct exposure department (4.05; 95% CI 0.97-16.94), or for department, smoking and age (3.39).

In summary, we have demonstrated specific antibody against TCPA-HSA, as did Venables and colleagues (1985) in the UK. Using the ELISA technique, we found a high overall prevalence of 31% of workers with IgE-mediated sensitization to TCPA. In contrast, specific IgE by RAST was found by Venables (1985) among only 8% of 300 factory workers. Differences in prevalences of serum specific IgE between these two facilities could be attributed to higher exposures at this plant, or to features related to the process. We also found associations between the prevalence of TCPA-HSA specific IgE responses and both exposure status (based on department) and with duration of employment since 1988.

The reduction in TCPA exposure may have resulted in decreased sensitization among new workers. Our observation that new employees hired since July 1990 had not developed IgE-mediated

sensitization to TCPA could be attributed to reduction of TCPA exposure by means of new industrial hygiene measures or to an insufficient exposure period to become sensitized. Prospective follow-up will be required to address this.

In conclusion, several findings are consistent with a role for immunologic and respiratory sensitization to TCPA at the plant. There was a temporal association of the onset of breathing problems with the introduction of the new TCPA hardener. There was a trend to higher prevalence of antibody positivity with duration of employment since the new TCPA hardeners were used. The highest prevalence of antibody positivity occurred in the mold and intermittently exposed groups which were most directly exposed to TCPA. Finally, there has been a marked reduction in reported symptoms and no new cases of OA among newly hired workers at the plant since ventilation was installed and TCPA exposures have been documented to be lower.

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Table 1. Relationship between exposure groups and antibody status, plant A, Ontario, 1990

Antibody Status	No. [% Positive]	Exposure Group[a] 1	2	3	4	p	p(Trend)[b]
IgE	15 (30)	3 (43)	4 (67)	8 (25)	0	0.093	0.019
IgG	19 (38)	4 (57)	4 (67)	11 (34)	0	0.124	0.022
Total Samples	49	7	6	32	4		

[a]**Legend** Exposure Group 1 = Evermold (in year prior to survey); 2 = Utility/maintenance; 3 = Coil assembly; 4 = Office, not in plant. Includes all 49 with antibody determinations.

[b] Exposure groups 1 and 2 combined for trend analysis.

Table 2. Relationship between duration of employment and antibody status among those hired since 1988[a], plant A, Ontario, 1990

Antibody status	Duration of Employment (Years)					
	No.[% Positive]	<0.33	0.33-1.33	>1.33	p	p(Trend)
IgE	12 (33)	0	4 (27)	8 (53)	0.067	0.022
IgG	15 (42)	1 (20)	5 (33)	9 (60)	0.181	0.074
Total samples	35	5	15	15		

[a]Excluding those in group 4 (office)

ASSESSING EFFECT OF DUST EXPOSURE ON LUNG FUNCTION CHANGE IN CHINA COAL MINERS

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It has been recognized for many years that long-term exposure to coal mine dusts can not only lead to Coal Workers' pneumonoconiosis (CWP) but also cause lung function impairment, even on the condition that miners have no CWP.

The aim of the study is to assess the situation of occupational lung function impairment in respiratory physiopathology and to further confirm the epidemiological evidence on the relationship between lung function change and dust exposure in Chinese coal miners. The results will be used as reference data for further formulation of standard of lung function tests and disability evaluation for Chinese coal miners.

2925 coal miners from 4 China coal mines were used as the observed group, who worked underground more than 5 years, aged 21-70 ($X+SD = 47.2+10.7$; 2347 of whom are smokers (80.24%) and 578 nonsmokers (19.76%). 803 subjects who have never been exposed to dust were selected as control group from the same 4 coal mines, with mean age 38.0 (SD=11.5) and 73.47% smoking rate (590 subjects).

During each medical survey, a detailed history concerning respiratory symptoms, occupational history and smoking habits were obtained by occupational doctors. Lung function tests included Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV1), the Ratio between FEV1 to FVC (FEV1/FVC%), Maximal Expiratory Flow-Volume Curves (MEFV), Forced Expiratory Flow between 25-75% of expired FVC ($FEF_{25-75\%}$) and between 75-85% ($FEF_{75-85\%}$), Mean Transit Time (MTT), Part Mean Transit Time (MTT_p), Residual Volume (RV), and Ratio of RV to TLC (RT). The tests were measured using the standardized test

methods. All investigation recordings were on a computer system. Using the SAS program, the data were statistically analyzed by covariance and stepwise regression analysis methods.

The results of investigation shows a remarkedly higher incidence rate of lung function abnormality in observed group, compared with that in controls ($P<0.001$); even after allowance for age and smoking habits, this difference is still significant ($P<0.001$).

The analysis of data tested shows that there is a notable difference in levels of all lung function measurements between the two groups. The levels of VC, FVC, FEV_1, $FEV_2\%$, MEFV, $FEF_{25-75\%}$, $FEF_{75-85\%}$ are significantly lower in observed group than in control group; the measurements of the RV, RT, MTT, MTTP are notably increased in the observed, compared with controls. It might indicate airway obstruction or small airway disease in coal miners.

The results of covariance analysis indicate that the difference in levels of lung function is significant between two groups after age and smoking was adjusted.

Table 1. Incidence of lung function abnormality

Groups	No.	No. of Abnormality	Rate (%)	SR I*	SR II**
Observed:					
Smokers	2347	1062	45.25	-	-
Nonsmokers	578	261	45.16	-	-
Total	2925	1323	45.23	42.73	41.51
Controls:					
Smokers	590	81	13.72	-	-
Nonsmokers	213	17	7.20	-	-
Total	803	98	12.20	17.60	19.14

*SR I: Standardized rate of incidence after age was adjusted.
** SR II: Standardized rate of incidence after age and smoking habits were adjusted.
RR=45.23/12.20=3.68; AR=45.23-12.20=33.03
SRR (I)=42.73/17.60=2.43; SAR (I)=42.73-17.60=25.13
SRR (II)=41.51/19.14=2.17; SAR (II)=41.51-19.14=22.37.

Table 2. Results of covariance analysis of lung function measurements

Variables	F values	Pr > F
FVC	151.87	0.0001
FEV_1	535.05	0.0001
FEV_1/FVC	207.53	0.0001
$FEF_{25-75\%}$	163.73	0.0001
$FE F_{75-85\%}$	57.93	0.0001
V_{25}	138.64	0.0001
V_{50}	574.20	0.0001
$V_{50/25}$	646.78	0.0001
V_{75}	388.18	0.0001
MTT	85.92	0.0001
MTT_{p5}	12.17	0.0001
MTT_{p7}	12.01	0.0001
MTT_{p9}	122.56	0.0001
RV	21.31	0.0001
RT	48.88	0.0001

Stepwise regression analysis of a 8 main lung function measurements revealed strongly inverse relation between the change of lung function and years worked underground in observed group.

Using the models of linear regression listed in Table 3, the levels of lung function impairment of coal miners can be evaluated on the basis of miner's years worked underground.

Table 3. Stepwise regression analysis of years worked underground effect on lung function

Dependent Variable(Y)	a	b	F	Pr>F
FVC (ml)	4432.5983	-39.3095	517.339	0.0001
FEV_1 (ml)	3419.5128	-38.9185	528.413	0.0001
FEV_1/FVC (%)	0.7774	-0.0029	90.165	0.0001
$FEF_{25-75\%}$ (ml/s)	3887.1034	-64.0243	419.376	0.0001
V_{50} (ml/s)	4173.4214	-63.6693	360.224	0.0001
MTT (s)	0.7434	0.0086	30.270	0.0001
RV (ml)	1691.6934	37.5851	5.259	0.0222
RT (%)	29.9601	0.7387	25.175	0.0001

Y=a+bX; X=years worked underground

Table 4 shows some lung function measurements of coal miners with various years worked underground in comparison with controls.

It is indicated that mean values of lung function tests per years is significantly lower in population exposed to dust than in controls.

Table 4. Change of lung function measurements in coal miners and controls

YEARS WORKED		FVC (ml)	FEV_1 (ml)	$FEF_{25-75\%}$ (ml)	V_{50} (ml)	MTT (s)	RT (ml)
5	C*:	4205	3438	3703	4378	0.6737	1688
	O**:	4236	3224	3567	3855	0.7867	1879
	D***:	-31	214	136	523	-0.1128	-192
10	C:	4087	3295	3424	4102	0.7084	1769
	O:	4040	3030	3265	3537	0.8294	2068
	D:	47	265	159	565	-0.121	-299
20	C:	3805	3007	2865	3546	0.7774	1930
	O:	3646	2641	2607	2900	0.9154	2443
	D:	159	366	258	636	-0.1380	-513
40	C:	3378	2432	1747	2435	0.9154	2253
	O:	2860	1863	1326	1627	1.0874	3195
	D:	518	569	421	808	-0.1720	-942
FALL IN	C:	23.62	28.28	55.89	55.51	0.007	16.15
MEAN VALUE	O:	39.31	38.92	64.02	63.67	0.008	37.59
PER YEAR	D:	-15.69	-10.14	-8.13	-8.15	-0.001	-21.44

C*: CONTROL GROUP;
O**: OBSERVED GROUP;
D***=VALUES OF CONTROL GROUP-VALUES OF OBSERVED GROUP

The results presented in this paper have confirmed the observation reported by many studies in Britain, Germany and United States, etc. That long-term coal mine dust exposure may lead to severe impairment of lung function which is sufficient to result in disability, even in the absence of progressive massive fibrosis. Stepwise regression analysis suggests that there is significant relationship between the change of lung function and years worked underground in coal miners who are exposed to coal mine dusts. Since no comparable dust measurements are available in China coalmines, it is difficult to estimate individual's accumulative exposure to dust and to evaluate effects of the quantity of exposure to dust on lung

function. Therefore, the cross-sectional investigation with years worked underground is the only practical and best way to understand true harmful effects of exposure to coalmine dusts on lung function in China coalmines.

Lung function tests are relatively objective and provide quantitative index of impairment in an epidemiology study. It is helpful to investigate dose-effect relationship, to study progression of occupational lung disorder, and to evaluate disability of CWP. But many investigators have recognized that most of the lung function tests show wide intersubject and intergroup variabilities which are very complex. Many factors such as population and measuring techniques may influence the results of the study. In order to avoid to the confusion, it is essential not only to need standardized procedures and quality control techniques of lung function tests, but also to use some convincing and accurate statistical methods such as covariance analysis, logistical regression, and multiple linear regression analysis etc., when interpreting the results of investigation for lung function tests in an epidemiological survey.

Some investigators think that it is important to distinguish smoking effects from those of occupational exposure. But assessing the possible effects of dust exposure in smokers is a complex problem, even if the smoking habits are taken into account when statistical analysis is carried out. Although smoking might influence the change of lung function, there is no evidence that the average effect of dust exposure is altered by smoking in our study.

In conclusion, we suggest that the lung function tests may be included in medical surveillance in China coal industry. Lung function tests should be performed simultaneously while periodical chest radiograph examination is carried out, because chest radiograph alone, we think, is not enough to early and objectively detect occupational pulmonary damage. Clearly, lung function tests would be a helpful index for evaluating coal miners' health level.

MODELLING THE EFFECT OF DIFFERENT TIME VARIABLES ON THE RISK OF DEVELOPING COALWORKERS' PNEUMOCONIOSIS

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In the epidemiological analysis of a disease, time is a fundamental concept, especially whenever the disease process can be broken down into a sequence of multiple spells and/or stages. Coalworkers' pneumoconiosis (CWP), defined by the 12 distinct profusion categories of ILO 1980 [2], forms such a multi-state multi-episode process which can be described on different time scales: time underground (= time since first exposure), calendar time, age, and the duration of disease episodes may be used in a description of the disease dynamics.

Under these circumstances it is natural to define the basic time variable for analysis either as time since first exposure (= non-homogeneous Markov approach, NHM) or as sojourn time in a specified state of the disease (= Semi-Markov approach, SM) [3,4,5,8].

This study's aim is to analyze by Markov- and Semi-Markov methodology the development of CWP in 472 miners of a German hard coal mine, having left the mine in 1974 - 1977, 1980 or 1985 and who worked at least 20 years underground. The miners enter the study with the beginning of their time underground and are traced during their whole working life until retirement from the mine. Total observation time comprises 13877 person-years. All necessary information was compiled for each miner during the regular medical surveys at the mine. 5701 chest radiographs were evaluated independently by at least two physicians according to ILO 1908 [2]. Regression of CWP was not observed. Rate and risk of developing different stages of CWP are analyzed in dependence on individual time data. Some results are given in Table 1 and Table 2.

Table 1. Frequency of transitions and incidence densities [6] in the CWP-Process.

Transition (ILO 1980)	Number at risk	Frequency of transitions / %	Incidence density / $(100\ yr)^{-1}$
0/0 - 0/1	472	44.1	1.7
0/1 - 1/0	208	63.9	19.3
1/0 - 1/1	143	55.2	19.2
1/1 - 1/2	84	47.6	14.6
1/2 - 2/1	42	66.7	21.4
2/1 - 2/2	29	51.7	25.0
0/0 - 1/1	472	17.8	0.6
1/1 - 2/2	84	16.7	3.2

The lowest incidence density is given with 1.7 occurrences per 100 years at risk and describes the intensity of the 0/0-0/1-transition at the start of the process (Table 1). The transition probability estimated by cumulative incidence accordingly is just about 50% for a time underground of 30 years (Table 2). The low transition risk at the beginning of the disease process reflects the long latent period until first signs of CWP are developed. Perhaps this latency phenomenon is caused by an unequal scaling of radiographs using ILO 1980 [10] or by a threshold effect of dust exposure on the disease development [7]

Table 2. Cumulative incidences at risk estimators [6] given by time underground (NHM, Markov model) or given by sojourn time (SM, Semi-Markov Model).

	Cumulative incidence / %			
	NHM - model Time underground		SM - model Sojourn time	
Transition (ILO 1980)	30 yr	35 yr	5 yr	10 yr
0/0 - 0/1	47.4	65.2	0.0	0.9
0/1 - 1/0	97.3	99.5	85.6	94.4
1/0 - 1/1	97.2	99.3	82.9	96.3
1/1 - 1/2	95.7	99.3	68.2	91.8
1/2 - 2/1	97.3	99.9	84.5	90.1
2/1 - 2/2	98.9	99.7	90.5	-
0/0 - 1/1	20.5	31.4	0.0	0.2
1/1 - 2/2	25.1	63.8	7.9	38.5

The incidence density for a transition 1/1-1/2 is lower than the preceding rates 0/1-1/0 and 1/0-1/1 (Table 1). This may be an outcome of the intensified protective procedures which are performed to increase the dust protection of coalminers after developing CWP = 1/1. A comparison of these process intensities by Mantel-Cox tests [1] yields chi^2-values of 2.95 ($p = 0.09$, SM setting) and 2.60 ($p = 0.11$, NHM setting).

After contracting profusion category 1/1, the estimated risk of progressing by one point of ILO 1980 is about 90% given a sojourn time of just 10 years (Table 2). Moreover incidence densities are rising monotonely between CWP = 1/1 and CWP = 2/2 (Table 1). A uniform dust protection holds for miners having developed such stages of CWP.

Results of log-rank tests comparing intensities between CWP = 1/1 and CWP = 2/2 are given in Table 3. The outcome depends substantially on he chosen time basis (NHM setting vs. SM setting). Generalizing this approach Cox models are constructed to the data taking time underground (NHM-time) and sojourn time (SM-time) into account simultaneously (Table 4).

Table 3. Mantel-Cox tests [1] comparing the intensities of CWP-transitions 1/1-1/2, 1/2-2/1, 2/1-2/2 over time underground (NHM model) and sojourn time (SM model). Analysis of 155 risk spells and 83 transitions.

Test for heterogeneity

	chi2	p
NHM model	0.65	0.72
SM model	6.33	0.04

Test for trend

	chi2	p
NHM model	0.41	0.52
SM model	6.33	0.01

Table 4. Sign and p-value of the estimated effect of time-dependent convariables in Cox-models (1); g_1, g_2 and g are indicator variables identifying the kind of transition. Analysis of all CWP-transitions 1/1-1/2, 1/2-2/1, 2/1-2/2 (155 risk spells, 83 transitions).

Generalized test for heterogeneity

	g_1 g_2	sojourn time	age	calendar time
NHM-Cox	+ +	+	-	+
model	0.18	$< 10^{-4}$	0.96	0.19

	g_1 g_2	time underground	age	calendar time
SM-Cox	+ +	+	-	+
model	0.16	0.50	-0.80	0.37

Generalized test for trend

	g	sojourn time	age	calendar time
NHM-Cox	+	+	-	+
model	0.07	$< 10^{-4}$	0.94	0.20

	g	time underground	age	calendar time
SM-Cox	+	+	-	+
model	0.06	0.47	0.79	0.39

Clearly, Table 4 demonstrates the remarkable influence of sojourn time on the risk of progressing ($p < 0.01\%$), whereas the effect of time underground (i.e., time since first exposure) is comparatively small ($p \approx 50\%$). So the disease process appears to be a Semi-Markov process. Age and calendar time are of lesser importance. Tests for heterogeneity and trend give similar results whether based on Markov-Cox models with NHM-time dependent adjustment for sojourn time or based on Semi-Markov Cox models with SM-time dependent adjustment for time underground: there is a borderline significance for a rising process intensity after contracting 1/1 ILO 1980. This finding emphasizes the need for sophisticated modelling in epidemiology to carry out an adequate analysis.

In summary our study on the one side gives hints to a decelerating progression speed just after contracting CWP = 1/1, which may occur due to the onset of an improved individual dust control. On the other side our findings demonstrate that the process is dominated by an "internal" dynamic (sojourn times) with rising intensities between CWSP = 1/1 and CWSP = 2/2. Therefore, the probability of developing 1/1 ILO 1980 during time underground should be minimized by appropriate dust standards in hard coal mining [7, 11]. Special attention should be given to early radiological phenomena (CWP < 1/1) to ensure an adequate epidemiological control of the disease process.

Of course, these results are based on data that describe health outcomes of working conditions in the German coal mining industry about 40 years or 50 years ago, especially if long-term effects are considered. In contrast up-to-date risk assessments should be founded firstly on up-to-date data including gravimetrically measured dust exposure values and secondly on an adequate extrapolation to long-term exposure conditions [9].

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TRENDS IN CLASSIFICATION OF SMALL OPACITY TYPE IN THE COAL WORKER'S X-RAY SURVEILLANCE PROGRAM, 1970-1989

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The objective of this study was to examine trends in the classification of small radiographic opacities in the Coalworkers' X-ray Surveillance Program (CWXSP), a NIOSH-administered medical monitoring program for underground coal miners. Data were restricted to classifications of 15,403 chest radiographs classified as category 1 CWP by 88 B-readers from 1970 to 1989. For films classified under the 1971 ILO U/C system, the predominant type of small opacity was taken as the type with the highest profusion. For films classified under the 1980 ILO system, the predominant type of small opacity was assigned by G-readers. The most striking classification trend observed was a general decrease over time in the proportion of films with a predominance of type p opacities. This decrease occurred largely between 1979 and 1982. Before that time the proportion of category 1 films with predominant type p opacities was fairly stable and averaging above 30%, while after that time the proportion was very stable at about 10%. Type t opacities were the major beneficiary of the reduction in p type opacities, although type q opacities also showed a slight increase over the study period. Proportions of films with a predominance of one of the other three types of small opacities (i.e., r, s, and u) varied little over time. The trend toward a predominance of irregular opacities at the expense of rounded opacities may, in part, relate to a change in the ILO system for classifying radiographs for pneumoconioses, but the trend appears to have begun before the CWXSP adopted the 1980 ILO Classification scheme. The observed trend held when each minor profusion category (1/0, 1/1, and 1/2) was examined separately, when miner tenure was controlled for, and after excluding readings from the seven B-readers who had read the largest numbers of films. The trend also remained evident when the data set was restricted to films from a subset of miners who worked

with high volatile bituminous A coals. In conclusion, a general trend over time for category 1 radiographs from the CWXSP to be classified by B-readers as having a predominance of irregular small opacities at the expense of rounded (especially p) types was noted. Although the change in the ILO classification system has played a role, no definite explanation for the observed trend was found.

THE RELATIONSHIP BETWEEN PNEUMOCONIOSES AND CANCERS

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Introduction

In recent years close attention has been paid to the relationship between pneumoconioses and cancers. So far there has been no clear conclusion. In this paper, all of pneumoconiosis cases in Sichuan Province of China during 1950-1986 were enrolled one by one according to "The Program of the Nationwide Investigation in Pneumoconioses Epidemiology." We have investigated cancers in pneumoconioses so as to ascertain whether the cancer deaths among pneumoconiosis cases is in excess, and whether the dust is carcinogenic. Then, the cancer mortality among pneumoconiosis cases, causes of the total death, the death percentage of cancers among pneumoconiosis cases and the standardized mortality ratios (SMRs) of cancer were calculated.

Subjects and methods

According to the Program of Investigation in Pneumoconiosis Epidemiology, the sex, age, type of work in production, working years, kinds of pneumoconiosis (mainly silicosis, coal workers' pneumoconiosis, asbestosis), time and stage of diagnosis for 48,277 subjects with pneumoconiosis, and the death date and causes for 11,593 death cases among above patients were enrolled in "Pneumoconiosis Case Card." These cases worked in state or collective ownership enterprises of county during 1950-1986 in Sichuan Province were diagnosed by Pneumoconiosis Diagnosis Groups on the basis of "The Chinese Roentgenodiagnostic Criteria of Pneumoconioses (1963)." All data were treated with an IBM computer. The cancer mortality of pneumoconioses, the total death causes of pneumoconioses and the death percentage of cancers among pneumoconiosis cases were analyzed. In addition, using the method of retrospective cohort study, the subjects diagnosed as pneumoconiosis before 1st January 1970, were followed up until 31st

December 1986. Then, the SMRs of cancer were calculated and compared with the data of general population during 1983-1985 in Sichuan Province. The SMRs were tested by Poisson distribution confidence table.

Results

1) The cancer mortality of pneumoconiosis cases during the period of 1950-1986 is shown in Table 1.

Table 1. The cancer mortality in subjects with pneumoconiosis (1950-1986)

Types of pneumoconiosis	Pneumoconiosis grade*									Total		
	I			II			III					
	No. Cancer		Rates (1/10⁵)	No. Cancer		Rates (1/10⁵)	No. Cancer		Rates (1/10⁵)	No. Cancer		Rates (1/10⁵)
Silicosis	7623	137	1797	7886	114	1446	2421	27	1115	17930	278	1550
CWP△	13687	222	1622	12854	184	1431	2530	26	1028	29071	432	1486
Asbestosis	294	10	3401	60	8	13333	5	1	20000	359	19	5292
Other pneumoconiosis	649	20	3082	238	5	2101	30	2	6667	917	27	4938
Total	22253	389	1748	21038	311	1478	4986	56	1123	48277	756	1566

*Grade I and II pneumoconioses are simple pneumoconioses, grade III is complicated pneumoconioses; radiological abnormalities of grade I pneumoconioses roughly correspond to small opacities 1 category profusion in ILO International Classification of Radiographs of the Pneumoconioses, while grade II correspond to 2—3 category profusion.
△CWP = coal workers' pneumoconiosis

Table 1 shows that the cancer mortality of asbestosis is the highest among various types of patients with pneumoconiosis. The total cancer mortality of pneumoconioses is 1,566/1000,000. The mortality of cancers has a dropping trend with the upgrade of pneumoconioses.

2) The total death causes of pneumoconioses and the death percentage of cancers among pneumoconiosis cases.

In all subjects, the four leading death causes are cor pulmonale (25.20%), pneumoconiosis (24.13%), pulmonary tuberculosis (15.70%) and cancers (6.52%) successively.

The death percentage of cancers among pneumoconiosis cases during the period of 1950-1986 is shown in Table 2.

Table 2. The death percentage of cancers among pneumoconiosis cases (1950-1986)

Types of pneumoconiosis	Pneumoconiosis grade									Total		
	I			II			III					
	No.	Cancer	%	No.	Cancer	%	No.	Cancer	%	No.	Cancer	%
Silicosis	1419	137	9.65	2230	114	6.46	1357	27	1.99	5006	278	5.55
CWP	1903	222	11.67	3165	184	5.81	1210	26	2.15	6278	432	6.88
Asbestosis	50	10	20.00	22	8	36.36	5	1	20.00	77	19	24.68
Other pneumoconiosis	150	20	13.33	65	5	7.69	17	2	11.76	232	27	11.64
Total	3522	389	11.04	5482	311	5.67	2589	56	2.16	11593	756	6.52

From Table 2, among the death cases of pneumoconioses, percentage of cancers in asbestosis is the highest.

3) The SMRs for cancer. There are 265,956.5 person-years in pneumoconiosis cohort during the period of 1970-1986 including 92,831.0 in silicosis, 166,232.0 in coal workers' pneumoconiosis and 2,076.5 in asbestosis. In this cohort 441 died of cancers including lung cancer (128), liver cancer (97), esophagus cancer (68) and stomach cancer (51). The SMRs are shown in Table 3.

Table 3 shows that a significant excess of deaths from lung cancer was found among various pneumoconiosis cases, in which the range of SMRs are 1.45-8.00. The risk of lung cancer in asbestosis is higher than that of silicosis or coal workers' pneumoconiosis. The excess of deaths from all cancer and liver cancer was also found among asbestosis.

Table 3. The SMRs of cancer for patients with pneumoconiosis△ (1970-1986)

Types of pneumoconiosis	Obs./Exp. (95% CI)				
	Total cancer	Lung Cancer	Liver cancer	Esophagus cancer	Stomach cancer
Total pneumoco-	0.69	1.86*	0.78	0.48	0.39
niosis cases	(0.63-0.76)	(1.54-2.19)	(0.62-0.93)	(0.37-0.60)	(0.29-0.51)
Silicosis	0.82	2.35*	0.81	0.43	0.43
	(0.70-0.94)	(1.73-2.96)	(0.54-1.07)	(0.25-0.61)	(0.24-0.62)
CWP	0.82	1.45*	0.66	0.55	0.40
	(0.71-0.92)	(1.09-1.82)	(0.48-0.84)	(0.36-0.66)	(0.26-0.55)
Asbestosis	2.45*	8.00*	6.42*	0.00	1.23
	(1.35-3.54)	(1.60-14.40)	(1.66-11.18)		(0.47-2.93)

△ compared with the data of Diseases Supervising and Testing Station in Sichuan Province (1983-1985)
* $P < 0.01$

Discussion

For a long time, a number of circumstantial observations suggest that mineral particles of a variety of types could play a role in the genesis of lung cancer in humans. Churg and Wiggs[1] noted the possible roles of mineral particles in the genesis of lung cancer. There is an important relationship with total number of particles present in lung tissue and smoking is probably a major factor in long-term particle accumulation within the lung. Goldsmith and colleagues[2] regarded that silicosis is the premonitory harm of lung cancer; the fibrosis of lung is the earlier stage symptom of it.

This paper indicated that the mortality of cancers is 1,566/100,000 in pneumoconiosis cases. The death from cancers in the subjects is 6.52 per cent and is ranked as the fourth in total death causes. Above results showed the close relationship between pneumoconioses and cancers. The result of retrospective cohort study for pneumoconioses during 1970-1986 showed that, among all cancer, only lung cancer has association with pneumoconioses. The risk of lung cancer in pneumoconioses was obviously raised. For various pneumoconio-

sis, the risk of lung cancer from asbestosis is the highest (SMR = 8.00, 95% CI 1.60 - 14.40). A significant excess of death was found within all cancer and liver cancer from asbestosis (SMR = 2.45, 95% CI 1.35 - 3.54) for all cancer; SMR = 6.42, 95% CI 1.66 - 11.18 for liver cancer). These results show that there is close relationship between pneumoconioses and lung cancer, and proved further the conclusion that asbestosis can cause human cancers, especially for lung cancer.

But Parkes[3] considered that bronchial carcinoma occasionally occurs in silicotic lungs but there is no evidence of a causal relationship between it and silicosis or siliceous dust. McDonald[4] pointed out that the evidence for the carcinogenicity of crystalline silica to man is indeed limited; although credible, alternative explanations such as chance, bias, or confounding have not been adequately excluded. Recently, Carta et al.[5] didn't find the correlation between lung cancer and severity of the radiological category of silicosis, the type of silica (coal or metalliferous mines, quarries, etc.), or the degree of exposure to silica dust. Some authors did not find any increase in risk of lung cancer either among coal miners or patients with pneumoconiosis.[6-9]

In short, the results of this paper indicate that there is a close relationship between pneumoconioses and lung cancer. So it is highly important to watch over and pay attention to it. Besides, the carcinogenesis of silica and coal dusts to the human lung should be explored further. It must be pointed out that, other environmental or individual factors may act as confounders in the association between silicosis or coal workers' pneumoconiosis and lung cancer.

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A POSSIBLE ROLE FOR GLUTATHIONE TRANSFERASE MU IN SUSCEPTIBILITY TO ASBESTOS RELATED PULMONARY DISEASE

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Summary

Glutathione-S-transferases are Phase II conjugating enzymes that detoxify a variety of electrophilic agents. GST-1, the gene encoding glutathione-S-transferase mu (GST-mu) is polymorphic in the population being deleted in approximately 45% of Caucasians examined to date. This polymorphism was previously reported to be associated with increased susceptibility to smoking-induced lung cancer. We hypothesize that GST-mu deficiency may confer susceptibility to asbestos-induced pulmonary disease, due to a reduced ability of GST-mu deficient cells resident in the lung to detoxify reactive electrophiles associated with asbestos exposure.

In this preliminary study, individuals deficient in GST-mu were more frequently observed in a cohort of workers suffering from non-malignant asbestos-related disease than expected on the basis of the distribution of this genotype in control populations. Although of borderline statistical significance ($p=0.085$) this finding suggests that GST-mu status may be related to susceptibility to asbestos-related pulmonary disease.

Key Words

Asbestos, glutathione-S-transferases, pulmonary disease, susceptibility.

Introduction

While asbestos related disorders are among the most well studied occupational diseases, relatively little is known about host determinants which may affect individual susceptibility to these conditions.

A better understanding of such factors may ultimately lead to improved screening programs to identify individuals at risk of developing pulmonary problems as a result of previous asbestos exposures, may shed light on the mechanisms of asbestos toxicity and may suggest new avenues for therapeutic interventions to ameliorate or prevent the development of asbestos related disease.

The mechanism whereby asbestos leads to pulmonary fibrosis and lung cancers is a matter of debate. One theory implicates asbestos-related oxygen free radicals in the pathogenesis of these diseases (1-5). Alternatively, asbestos fibers may serve to carry other exogenous toxins into pulmonary cells, perhaps enhancing their ability to interact with critical cellular targets (6). The cytotoxic and genotoxic damage caused by electrophilic compounds which result from oxygen free radical generation and/or the metabolism of certain asbestos associated exogenous compounds (e.g., PAH's derived from cigarette smoke) may be involved in the pathogenesis of asbestos induced pulmonary fibrosis and tumorigenesis.

Because many reactive electrophiles are susceptible to glutathione mediated detoxification reactions (7,8), we investigated whether glutathione-S-transferase mu (GST-mu) activity, which is known to be polymorphic in humans, is associated with asbestos induced lung disease. GST-mu is deficient in a high percentage of Caucasians (9-12, 16) and this deficiency has previously been reported to be associated with increased sensitivity to smoking induced lung cancers (9,10). GST-mu deficiency is also associated with increased sensitivity to the induction of genetic damage by mutagens that are known substrates for this enzyme (13). The results of the current study provide preliminary evidence which suggests that individuals deficient in this enzyme may also be susceptible to the development of asbestos related non-malignant pulmonary disease.

Materials and methods

Study population. The study cohort consisted of 87 adult workers, either self-presenting or referred by their primary physicians to the Center for Occupational and Environmental Medicine at the Massachusetts Respiratory Hospital, Braintree, MA. Smoking, medical and occupational histories were recorded. Most subjects had asbestos related diseases (ARD), however, several individuals

without ARD were included to ensure that genotypic analyses were always done blindly.

Diagnostic protocol and criteria. Primary disease classifications included asbestos related pulmonary disease (ARPD) and asbestosis. Diagnoses were based upon physical examination, pulmonary function tests (PFTs), and chest radiography (CXR), all blind as to GST-mu status. Criteria for diagnosis of asbestosis included the presence of interstitial changes on CXR (using the International Labor Office classification, radiographs rated 1/0 or higher), evidence of restrictive changes on PFTs, and/or clinical findings consistent with interstitial disease. The finding of rales on chest auscultation in the absence of other evidence of interstitial disease was not sufficient criteria for the diagnosis of asbestosis.

Exposure classification. As no air or personal sampling data were available, a rough asbestos exposure index, adapted from a protocol previously described (14), was constructed. Briefly, all subjects provided their previous employment histories. Prior to data analysis, all occupations listed were classified as involving either no, low, or high asbestos exposures. These were assigned weights of 0, 1 and 5, respectively. To account for temporal changes in asbestos use, pre-1965 exposures were assigned a relative exposure value of 4, 1972-75 a value of 2, and those occurring after 1972 a value of 1. Summary exposure scores were obtained by multiplying job classification weights by the appropriate temporal weights and summing for all years worked.

GST-mu assay. GST-mu assays were performed, in duplicate, on approximately 2.5 x 10^6 sonicated lymphocytes using radiolabelled trans-stilbene oxide (TSO) (final specific activity 1.5-3 μCi/μM) (Chemsyn Science Laboratories, Lenexa, KA) essentially as previously described (13). Controls, consisting of boiled samples, were included with each assay batch. Background levels ranged from 10-15% of those obtained with samples form GST-mu active individuals. Enzymatic activity was expressed as pmol conjugate formed/min/10^7 cells.

GST-mu polymerase chain reaction (PCR) based assay. A PCR based assay has been developed which allows for the detection of the gene (GST-1) encoding GST-mu activity. This assay is a modifica-

tion of that described by Comstock, et al. (15). Briefly, using appropriate primers, a 273 base pair fragment is amplified from carriers of GST-1. Since the poor metabolizer phenotype is due to a deletion of GST-1 no fragment is amplified from individuals expressing this phenotype. Amplifications were performed on sonicated samples equivalent to approximately 50,000 lymphocytes using TAQ DNA polymerase (Perkins Elmer Cetus, Norwalk, CN). Controls, consisting of known GST-mu positive and GST-mu negative individuals (previously determined by enzymatic analysis), were included in each run.

Statistical analysis. GST-mu status was compared between asbestos related disease groups and control populations (including historical controls) using Chi square (c^2) analysis. Asbestos exposure and smoking histories were compared by GST-mu status by Wilcoxon Rank Sum analysis using the Krushal-Wallis Test (c^2 approximation). Analyses were performed using an established computer software program (Statistical Analysis Software, 604 SAS Institute, Cary, NC).

Results

Study population. 77 Individuals with asbestos related disease and 10 individuals with other pulmonary diseases were enrolled in this study. Summary statistics of the population are presented in Table 1. Disease subjects included 40 individuals (52%) with pleural disease and 37 (48%) with asbestosis. The remaining 10 members of the cohort (11%) had pneumonia, emphysema, or other respiratory complaints with no history of asbestos exposure or asbestos related disease. The distribution of smoking (pack/years) and asbestos exposure (qualitative exposure scores) were compared between GST-mu subgroups using the Wilcoxon Rank Sum test. No significant differences in either smoking ($p = 0.65$) or exposure scores ($p = 0.93$) were observed.

Glutathione transferase-mu status. GST-mu phenotype was determined biochemically, using the TSO-glutathione conjugation assay, on the first 57 individuals enrolled in the study. The GST activities observed in this group ranged from 0-1,864 pmoles product/min/10^7 cells. Twenty-eight exhibited activities of less than 75 pmoles product/minute/10^7 cells, a value within the experimental

error of this assay, and twenty-eight had activities of greater than 200, with only one falling between these values.

In order to compare GST phenotype to genotype, the PCR based assay was employed to determine the presence or absence of the GST-1 gene in all members of the study group. Figure 1 presents a photograph of a representative agarose gel, stained with ethidium bromide, displaying the diagnostic 273 bp PCR generated GST-1 fragment for several individuals previously phenotyped. Excellent overall agreement was observed between the phenotypic and genotypic analyses, with only two discrepancies out the 57 individuals assayed both ways. These two individuals were dropped from the subsequent analysis.

GST-mu status and asbestos disease. Several groups have looked at the distribution of GST-mu within various populations using techniques similar to those relied upon in this investigation. In these studies the prevalence of GST-mu positive (non-deleted) individuals was observed to range from 43% to 59% (Table 2). In a second cohort of Caucasians previously studied in this laboratory, the prevalence of GST-mu positive was 53% (13). In the current study 6 out of the 10 individuals who did not suffer from asbestos related disease were GST-mu positive.

Among those exhibiting asbestos related pulmonary disease in this study, 44 (57%) were GST-mu negative. Although not statistically significant comparisons of the prevalence of GST-mu in this cohort with various control groups (Table 3) suggest that the GST-mu deletion may be over represented among those with asbestos related disease; the prevalence of GST-mu was lower in this cohort than in the entire historical control population presented in Table 2 ($p=0.085$); from that of U.S. historical controls only ($p= 0.147$); and from that of intra-lab controls ($p = 0.187$). No difference in GST-mu status was observed between individuals exhibiting asbestos pleural disease only vs. those with parenchymal asbestosis ($p = 0.87$) (Table 3).

Discussion

Factors which might play important roles in individual susceptibility to asbestos-induced disease include nutritional status, smoking history, and genetic variability in host defense mechanisms. We

have begun to investigate this latter possibility, focusing our initial efforts on glutathione-S-transferase mu, one of the Phase II conjugating enzymes. Glutathione transferases are a complex group of enzymes that mediate a conjugation reaction between an electrophilic substrate and reduced glutathione (7,8). Although GST mediated conjugations can lead to the activation of some compounds, notably the low molecular weight dihaloalkanes, most such reactions lead to a reduction in cytotoxicity and genotoxicity (7,8).

Many Caucasians are deficient in GST-mu type enzymatic activity (9-12). This deficiency appears to result, in most cases, from a homozygous deletion of the GST-1 locus, which encodes GST-mu (17). Individuals deficient in GST-mu have been reported to be at increased risk for smoking-induced lung cancer (9,10) and exhibit an increased sensitivity of peripheral lymphocytes to genotoxicity mediated by trans-stilbene oxide and cigarette smoke (13).

The results presented here suggest that GST-mu status may also be associated with increased susceptibility to asbestos induced lung disease. Individuals genetically deficient in this Phase II detoxifying enzyme were more frequently observed in a cohort of workers suffering from asbestos related interstitial fibrosis and pleural plaques than expected on the basis of the distribution of this genotype in the general population (Tables 2 and 3). Historical controls were used in this analysis because few non-diseased individuals were seen at the enrolling clinic. We believe that the comparison with historical controls is valid since the prevalence of the GST-mu negative phenotype has been quite consistent in previous investigations (Table 2). In fact, it is likely that the historical control populations included at least some individuals suffering from asbestos related disease. This would tend to bias the results from this analysis toward the null hypotheses. None-the-less, we cannot rule out the possibility that the observed effect is due to uncontrolled differences in the populations compared. Confirmation awaits the analysis of a larger cohort of asbestos exposed individuals, which is underway.

The over representation of GST-mu negative individuals among those with ARD did not appear to be due to differences in asbestos exposure or smoking histories. This allows for the possibility that a causal relationship may exist between GST status and ARD. This possibility is consistent with proposed mechanisms of asbestos

toxicity. Reactive electrophilic products resulting from free radical generation or Phase I metabolism of exogenous compounds associated with asbestos fibers (e.g., cigarette smoke, PAHs from ambient air pollution) are likely to be susceptible to Phase II enzymatic conjugation reactions (7,8,18). The cytotoxic damage caused by these reactive electrophiles may, in part, be responsible for asbestos induced pulmonary fibrosis. These products may also be genotoxic, raising the interesting possibility that GST-mu status might be a determinant of susceptibility to asbestos induced lung cancer. Notably, asbestos exposure was not controlled for in the studies reporting an association between GST-mu status and sensitivity to smoking related lung cancer (9,10). It is very likely that the populations studied in these investigations included cases of asbestos related lung cancer. Thus, it will be of great interest to confirm the association suggested herein and to investigate whether it applies to asbestos induced lung cancer as well.

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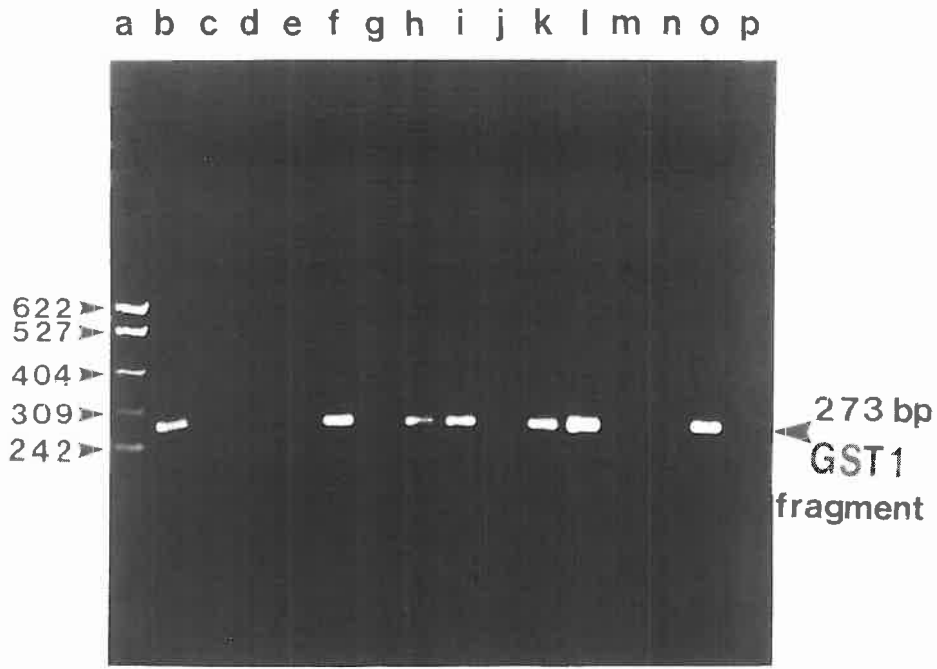

Figure 1. GST1 Genotypic Analysis of 14 Subjects Using a PCR Based Assay. Lane a, MSP1 digested pBR322 DNA (fragment sizes, in base pairs, are indicated to the left); lanes b-p, PCR amplified samples with diagnostic 273 base pair fragment indicated to the right. Lane b, subject 1 (576); lane c, subject 2 (120), lane d, subject 3 (0), lane e, subject 4 (ND); lane f, subject 5 (868); lane g, subject 6 (0), lane h, subject 7 (456), lane i, subject 8 (868); lane j, subject 9 (ND); lane k, subject 10 (ND), lane l, subject 11 (736), lane m, subject 12 (ND); lane n, subject 13 (0); lane o, subject 14 (776), lane p, blank (no cells added). Values in parentheses are GST1 enzymatic activities in pmoles TSO conjugate/min/10 million cells. ND = not determined.

Table 1. Demographics of the study population

N	87
Age	
Mean (yrs)	66 ± 10[1]
Range	42 - 91
GST-1 Status:	
Not deleted (positive)	39
Deleted (negative)	48
Asbestos Exposure	
Mean Exposure Score	67 ± 44[1]
Range	0 - 185
Smoking Status:	
Ever Smoked	68
Never Smoked	17
Unknown	2
Mean Pack-years	40 ± 27
Gender	
Male	86
Female	1

[1]Standard Deviation

Table 2. The prevalence of GST-mu phenotype or genotype in various control populations

	Wiencke 1990 (ref 13)	Seidegard 1990 (ref 9)	Bell 1992 (ref 16)	Smith 1992 (current work)	Heckbert 1992 (ref 19)	Van Poppel 1992 (ref 11)	Zhong 1991 (ref 12)	Seidegard 1986 (ref 10)	Hussey 1987 (ref 20)	Seidegard 1985 (ref 21)
GST-mu positive	24 (53%)	66 (58%)	59 (55%)	6 (60%)	51 (43%)	120 (55%)	131 (58%)	46 (59%)	23 (55%)	115 (46%)
GST-mu negative	21	48	49	4	69	100	94	32	19	133
Population Characteristics										
Nationality	USA	USA	USA	USA	USA	Netherlands	UK	Sweden	UK	Sweden
Mean Age (years)	39 ± 11	60 ± 3	NA	56 ± 9	64	38 ± 9.6	NA	63.5 ± 7.4	NA	NA
Gender (% Male)	42	47	NA	100	NA	100	NA	94	48	NA

NA = not available

Table 3. Comparison of the distribution of GST-1 status by study population

	All ARD[1,2]	Pleural[2] Disease Only	Asbestosis[2]	All Historical Controls	US Historical Controls	Historical Controls from this lab
GST-mu positive[3]	33[4]	18	15	641	206	30
GST-mu negative	44	22	22	569	191	25

[1]Asbestos-related disease
[2]This study
[3]Determined enzymatically and/or with PCR
[4]Number of individuals

Mantel-Haenszel Chi-Square Test Statistics
Pleural Disease Only Compared to Asbestosis; Chi-Square = 0.03; p = 0.87
All Controls (Table 2 all) Compared to ARD; Chi-Square = 2.97; p = 0.085
US Controls (Table 2) Compared to ARD; Chi-Square = 2.105 p = 0.147
Lab Controls (Table 2) Compared to ARD; Chi-Square = 1.744; p = 0.187

EVALUATION OF THE HEALTH STATUS OF WORKERS EXPOSED TO ALIPHATIC AND AROMATIC HYDROCARBONS IN LIGNITE GASIFICATION

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Introduction

A group of workers from the lignite gasification exposed to the combined effect of the aliphatic, polycyclic aromatic hydrocarbons (AH, PAH) carbon monoxide, carbon dioxide, sulphur compounds and phenol derivatives was investigated. Experimental studies demonstrated the carcinogenic potential of some PAH compounds; special emphasis has been placed on 3,4- Benzo/a/pyrene (B/a/P) as a marker of exposure of these industrial risk factors. As long term effects on health, PAH exposure could be responsible for carcinogenic risk in workers at lignite gasification. AH, PAH in association with carbon monoxide determine some nonspecific modifications at the level of the nervous and cardiovascular system; AH and the phenol derivatives have irritative effects on respiratory system. Because of the presence of several chemical compounds in workplace air, the real exposure risk assessment and the health cumulative specific and nonspecific effects evaluation was very difficult, as accordingly their quantitative analyses and identifications were difficult, too; and the health effects could be overlapped. Additionally, we also investigated the non-occupational factors which intervene in workers health status.

Material and methods

Our goal was to characterize to the mentioned compounds; the first step was the air monitoring in the workplaces. To evaluate the air pollution in the workplaces, B/a/P air samples were collected for quantitative analyses. Evaluation of the B/a/P exposure in lignite gasification was performed by the spectrofluorimetric method. The levels of AH, CO and the other compounds were also measured. We have examined 376 workers (aged; $\bar{x} \pm DS = 43.4 \pm 12.0$ years and the time of occupational exposure: $\bar{x} \pm DS = 15.2 \pm 3.9$ years) by applying clinical and laboratory examinations full-history, standardized respiratory symptoms questionnaire, pulmonary

ventilatory tests, EKG, psychologic check-ups, biochemical determinations, prick test screening for peripheric sensitive neuropathy. The survey was carried out during 1985 - 1991 period (three stages).

Also studied was the morbidity prevalence of workers exposed to AH and PAH. The causes of morbidity were coded according to the International Classification of Diseases.

Results and conclusions

1) Dynamics of B/a/P determinations during a three-year study revealed the presence of this compound within the checked working places; the values of wide dispersion were observed in the samples collected. Mean yearly value of 3.4 - B/a/P was 419.91 ± 9.32 ng/m^3. The AH air level in the workplaces was 2.5 times higher compared to MAC (Figure 1).

CHEMICAL	$\bar{x}$ ± DS	MAC
PAH-B/a/P	419,91 ± 9,32 ng/m^3	150 ng/m^3 as soviet legisl.
Total AH C_1 - C_4	2204 ± 96,5 mg/m^3	1000 mg/m^3
Phenol Derivatives	13,5 ± 3,2 mg/m^3	15 mg/m^3
SO_2	5,6 ± 1,4 mg/m^3	15 mg/m^3
CO	34,9 ± 7,5 mg/m^3	50 mg/m^3
CO_2	570 ± 71 mg/m^3	10000 mg/m^3

Figure 1. Workplaces air monitoring

2) The effects of exposure to AH and PAH on health are reported as respiratory, cardiovascular and neurological diseases. Chronic bronchitis was significantly higher in workers (Figure 2) compared to population living nearby the investigated factory. There were also rhythm, ischemic, and conductance types of cardiac troubles ($p < 0.05$) (Figure 3).

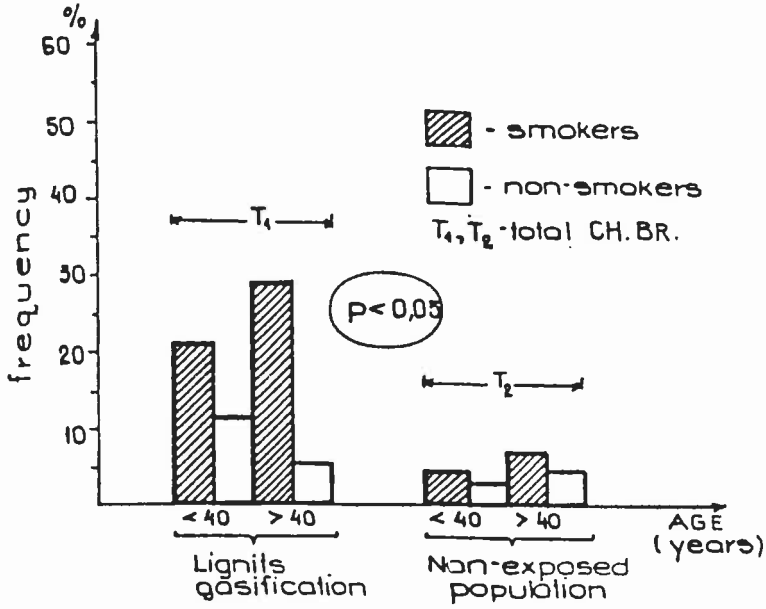

Figure 2. Chronic bronchitis prevalence

	SCOR according to extra risk factors (smoking, heredity, diseases, etc.	HYPERTENSION ARTERIAL	E.K.G. PERTURBANCE	CHOLESTEROLEMIA TOTAL LIPIDEMIA (MG %) $\bar{x} \pm DS$
EXPOSED	95.6	22.4% p>0.05	18.8% p<0.05	220 ± 90 722 ± 177
NON-EXPOSED	90.1	8.7%	1.2%	183 ± 83 699 ± 120

Figure 3. Cardiovascular system

The cardiovascular risk factors in workers and in non-occupational population of polluted area were evaluated with a comparative score method. Health effects evidenced neurological disorders--as well as peripheric sensitive neuropathy which was significantly higher in workers exposed to AH and PAH (Figure 4).

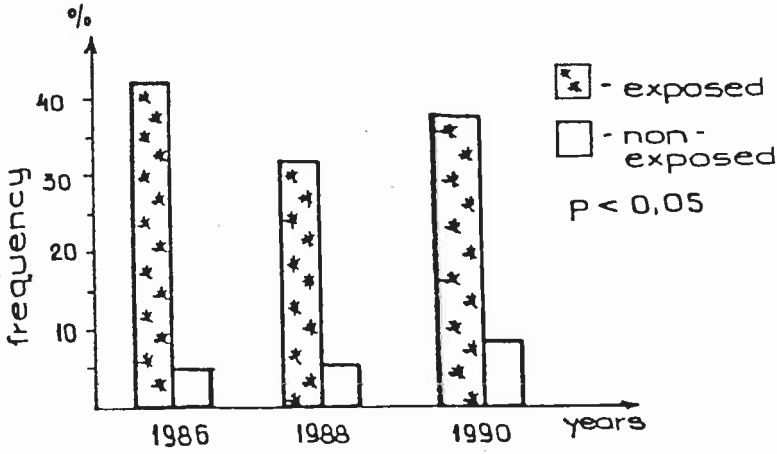

Figure 4. Sensitive neuropathy

3) The morbidity study revealed, that diseases of respiratory system, cardiovascular diseases and diseases of nervous system were placed within the seven first picks of morbidity (Figure 5). No cases of morbidity by cancer of the respiratory system were registered.

The seven first picks of morbidity = (ICD9 CM codes)

1. Accidents (800-999) 26%
2. Respiratory system (460-519) 21%
3. Nervous system + mental disorders (290-389) 17%
4. Skin and subcutaneous tissue (680-709) 10%
5. Musculoskeletal system (710-739) 9%
6. Heart disease + diseases of arteries, veins and other circulatory systems (390-414, 420-429) (440-448) (451-459) 8%
7. Genitourinary system (580-629) 3%
8. Others 6%

Figure 5. Morbidity study

SELF-REPORT WORK INJURY EXPERIENCE OF MINNESOTA HIGH SCHOOL STUDENTS

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The purpose of this study was to describe the incidence and severity of work-related injuries to adolescents. A self-administered questionnaire was completed by 3,054 tenth through twelfth grade students representing public school districts throughout Minnesota. The questionnaire referenced work experience from August 1990 through May 1991. The percentage of working students (57% to 93% of boys and 51% to 92% of girls) was found to increase as grade level increased from tenth through twelfth grade, and varied depending on school district size. Individuals were asked to list up to three activities that described their job. As a group girls most frequently reported working as cashiers (39%, baby-sitters (23%), fast food and short order cooks (17%), and sales clerks (13%). Boys most frequently reported working as fast food and short order cooks (21%), non-construction laborers (20%), farm-agricultural workers (20%), cashiers (17%), and janitors (16%). Comparing responses of working teens from tenth through twelfth grades, report of at least one work-related injury during the ten month reference period decreased from 25/100 to 12/100 for girls and 22/100 to 18/100 for boys. Approximately 5/100 girls and 7/100 boys indicated having restricted their normal activities for more than one day. The most frequently reported injuries were burns, sprains, cuts, and bruises. The cumulative incidence ratio was computed as the incidence of injury among those performing a specific job activity compared to the incidence among those not performing the activity. The highest cumulative incidence ratios in girls were associated with fast food cook, 3.4 (95% C.I.: 1.2, 9.1) in urban and 2.1 (95% C.I.: 1.3, 3.6) in nonurban settings; carhop, 2.2 (95% C.I.: 0.9, 5.1) in urban and 1.9 (95% C.I.: 1.2, 3.1) in nonurban settings; and dishwasher, 1.8 (95% C.I.: 1.1, 3.0) in nonurban settings. In the urban setting, boys appeared to be at equal injury risk regardless of job type.

However, nonurban boys reported somewhat greater risk of injury working as a short order cook, 1.5 (95% C.I. 0.9, 2.4), dishwasher, 1.5 (95% C.I.: 0.9, 2.4), and fast food cook 1.4 (95% C.I.: 0.8, 2.5). The results suggest that modification of the work environment in restaurants could substantially reduce injuries to working teens.

OSTEOARTHRITIS OF THE HIP IN FARMERS

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Osteoarthritis of the hip is a major cause of pain and disability in older people. It has been estimated that in Britain some one in twenty men and women over the age of 60 have symptoms severe enough to warrant hip replacement. The known causes of the disease include developmental deformity of the joint arising from congenital dislocation, slipped femoral epiphysis and Perthes disease; inflammatory arthritis; and various metabolic disorders. Also, the hip may be affected as part of an inherited susceptibility to generalized osteoarthritis. Together, however, these known causes account for only a minority of cases. An important question is whether, as with the knee, mechanical stress on the joint is an important etiological factor.

In recent years evidence has begun to accumulate that farmers are at unusually high risk of hip osteoarthritis.[1-4] Possible explanations include loading of the joint from frequent heavy lifting, and exposure to vibration from driving tractors and other agricultural machinery. Most of the published studies have been based on surgically treated cases, and associations may have been exaggerated if farmers have a lower threshold for obtaining treatment than other occupational groups. This might happen, for example, if the nature of their work meant that they were more handicapped by a given level of symptoms. To obtain a less biased estimate of risk, and to try to identify the aspects of agricultural work responsible for the hazard, we have carried out a cross-sectional survey of farmers and of controls with mainly sedentary jobs.

The study was carried out in the English midlands, and included both upland areas given over mainly to the farming of sheep and dairy and beef cattle, and also lowland areas with dairy and arable farms.

Subjects were identified from an initial screening questionnaire which we sent by post to a random sample of 1231 men aged 60-76 selected from the lists of five rural general practices. Seventy two per cent of subjects replied to the questionnaire which asked for a short occupational history. From this we selected for further study all men who reported ever having worked in farming together with those who said that they had spent all their working lives in office jobs. This subsample was visited at home and interviewed in more detail about occupational history and also about joint symptoms. In particular, we asked the farmers about the types of farm on which they had worked and about specific activities in agriculture. We measured heights and weights and examined hands for the presence of Heberden's nodes. Where subjects reported previous hip replacement for osteoarthritis, we checked their hospital records to confirm the diagnosis. Those subjects who had not undergone hip replacement were invited to attend their local hospital for an A-P pelvic radiograph. Sixty one percent of the subsample agreed to interview and were assessed for osteoarthritis in this way.

Subjects were classed as cases of hip osteoarthritis if they had had hip replacement for the disease or if the minimal joint space - (i.e., the shortest distance between the femoral head and the acetabulum) was ≤ 1.5 mm in either hip. In previous studies we have shown that joint space narrowing when measured in this way correlates well with other radiological features of the disease and with symptoms, and shows good repeatability within and between observers.[5]

Among the 250 subjects assessed for hip osteoarthritis, 167 had farmed for more than one year. In our analysis we compared these 167 with 83 controls - 71 office workers and 12 men who had farmed, but for less than 12 months in total.

Table 1 shows the prevalence of osteoarthritis by age in farmers and controls. Two cases were identified among the controls giving a prevalence similar to that recorded in earlier population surveys. In contrast, the prevalence among the farmers was substantially higher, especially in the older age groups. Of 28 cases identified among the farmers, 20 had had hip replacement surgery.

Table 1. Prevalence of hip osteoarthritis by age

	Farmers		Controls	
Age	No. of Cases	Prevalence (%)	No. of cases	Prevalence (%)
60-65	8	13.8	1	2.7
66-70	7	13.0	0	0
71-76	13	23.6	1	5.0

In addition to age, hip osteoarthritis was associated with tall stature, weight in the top third of the distribution for the sample, and with the presence of Heberden's nodes. After adjustment for these potential confounders, the association of hip osteoarthritis with farming persisted. Moreover, there was evidence of a dose-response relation with the highest risk in men who had farmed for more than 10 years (Table 2).

Table 2. Risk of hip osteoarthritis according to duration of farming

	No. of cases	OR (95% CI)
Controls	2	1
1-9 years farming	6	4.5 (0.8-26.3)
≥10 years farming	22	9.3 (1.9-44.5)

To look for an explanation for the hazard, we restricted out attention to the farmers, and examined their risk according to whether or not they had worked in each of a range of different branches of agriculture. None of the types of farming on its own appeared to explain the excess of osteoarthritis in farmers.

Finally we looked at the specific occupational activities reported by the farmers. All but one of the 28 cases of hip osteoarthritis among the farmers reported regularly lifting weights in excess of 25 Kg, but so did 90% of the farmers without the disease. Thus, lifting could

be the explanation for the hazard, but the data do not firmly establish this. In contrast, 8 of the 28 cases had never driven tractors and only 10 had regularly driven tractors at least 4 hours a day. It seems unlikely, therefore, that vibration completely explains the excess, even if it contributes.

Along with other investigations in Sweden and the UK, this study provides strong evidence that hip osteoarthritis is an occupational disease in farmers. The lifetime risk of severe disease in a man who has farmed for more than ten years may be as high as one in five. Manual handling and particularly heavy lifting is the most likely cause, but a contribution from vibration has not yet been excluded.

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LOGGING FATALITIES IN THE UNITED STATES: AN UPDATE

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Forests provide the U.S. population with a variety of products ranging from paper and lumber to chemicals and synthetics, such as rayon. Each of these products originates with the harvesting, skidding, loading and transport of timber by workers in the logging industry. Traditionally, this industry has been one of the most dangerous in the country; the dangers stem from factors which are unique to logging. Trees are typically felled with a chainsaw, requiring loggers to work in close proximity to standing and falling timber. Shifts in weight or wind often cause trees to fall in unexpected directions. Steep terrain, underbrush, uneven footing, powerful equipment, and inclement weather add additional risks for loggers, equipment operators and other workers at logging sites. This study examines the distribution of logging fatalities by cause of death and region of the country using the National Traumatic Occupational Fatality (NTOF) surveillance system maintained by the National Institute for Occupational Safety and Health. NTOF data show that an average of 142 non-managerial logging workers died of work-related injuries each year from 1980 through 1988. Though the Pacific Coast pine/hardwood and the southern pine regions had the most fatalities (38 percent and 37 percent of the total number of U.S. fatalities, respectively), they also have the most logging activity, representing over two-thirds of the nation's timber production. The highest fatality rates were in the central hardwood and the eastern hardwood regions. Fatality rates in the mountain pine, Pacific Coast, plains bottomlands and southern pine regions were intermediate. The lowest fatality rates were in the Lake States pine/hardwood and in the northern hardwood/spruce/fir regions. Logging deaths were slightly higher than average in the 25-to 44-year age group. Logging occupations (e.g., fellers, buckers, choke setters) accounted for 65.6 percent of fatalities in the industry. Truck drivers and miscellaneous laborers represented an additional 11 and 8 percent of the deaths. The leading cause of death was

being struck by falling objects (49.8 percent). Machinery-related (14.5 percent) and motor vehicle related-incidents (14.3 percent) were the next most common causes of death. Differences in forest type and harvesting operations are hypothesized to account for differences in regional fatality rates.

THE REGIONAL RURAL INJURY STUDY (RRIS)-I: A MODEL FOR NATIONAL SURVEILLANCE OF INJURIES IN AGRICULTURE

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Prior to the Regional Rural Injury Study-I (RRIS-I) effort, which has the most comprehensive agricultural population-based information on injuries in the country, there has been no system that could serve as a source for ongoing surveillance data and provide the basis for more specific analytic studies. The specific objectives of the project were to: 1) demonstrate the ability to collect injury data on rural populations in a five state region, based on methodology and tools developed in a previous population-based effort; 2) calculate regional and state-specific injury rates, among other analyses, for both farm and non-farm operation-related injuries (classified as intentional or unintentional) in rural/agricultural areas; 3) apply the results of the study to the planning and development of specific injury prevention and control programs in the region. RRIS-I, conducted in a large regional area involving Minnesota, Wisconsin, North Dakota, South Dakota, and Nebraska, is based on the Olmsted Agricultural Trauma Study (OATS), in which a telephone interview methodology validated telephone-interview injury data against medical records using the (Olmsted County) Rochester Epidemiology Project, an internationally recognized data base. A sophisticated comprehensive computer assisted telephone interview (CATI) system instrument developed for RRIS-I enables efficient data collection including demographic and exposure information on all farm household members, farm operation information, and whether or not any member was injured during 1990. The United States Department of Agriculture National Agricultural Statistics Service's (USDA NASS) Master Sampling Frame of Farm Operations was used to identify a stratified random sample of farming operations from each of five participating states.

A total of 4,136 farm households (13,474 persons) participated in the RRIS-I. Data collection, for two phases, covered a twelve month period of time (January 01-June 30 and July 01-December 31, 1990). The rate for the first six months for farm and non-farm operation-related injuries was 61 and 52 per 1000 persons, respectively. Farm operation-related injuries were more frequent for males than females (88 and 28 per 1000 persons, respectively). The highest rates for farm injuries were among age groups 25-44, 45-64, and 65+, (101, 77, and 54 per 1000 persons, respectively). The lowest rate was 17 per 1000, among those less than 14 years of age. The rates for males, compared with females, were higher in all age groups. In the 25-44 year age groups, the rates were 143 per 1000 persons for males and 54 for females; for ages 45-64, the rates were 120 and 29, respectively, and for ages 65+, they were 75 and 23. Among those less than 14 years of age, the rates were 22 and 8 per 100, respectively. The major source of farming operation-related injuries was animals, accounting for an overall rate of 21 per 1000 persons; for males and females, the rates were 24 and 16 per 1000 persons, respectively. The final phase of the RRIS-I project will include a major regional workshop in which data from this effort will be applied to the development of specific state and regional prevention and control plans. The RRIS-I methodology has been designed to serve as the basis for long term surveillance efforts at the state, regional, and national levels that can significantly impact the agricultural injury problem through ongoing identification of the magnitude of the problem and serve as a basis for analytic efforts. As a result, intervention efforts can be developed from sound scientific data and evaluated for efficacy through the surveillance system.

The primary source of information in this extended abstract is from the report by Gerberich, SG, Gibson RW, French LR, Carr WP, Renier CM, Gunderson PD, Martin FB, True JA, Shutske J, Brademeyer K: The regional rural injury study-I (RRIS-I): A population-based effort, A Report to the Centers for Disease Control, October 1993.

WORK-RELATED ELECTRICAL FATALITIES IN AUSTRALIA, 1982-1984

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Introduction

The first recorded work-related electrical fatality took place in 1879 when a stage carpenter was killed in Lyon, France, by an alternating current of 250 volts from a Siemens dynamo (1). Since then only a limited number of studies of work-related electrical fatalities have been published world-wide. Despite a vast amount of experimental and technical knowledge concerning the hazardous nature of electricity and the knowledge of measures required for electrical safety, electrical fatalities still account for between 4% and 12% of fatalities in the workplace. This paper reports the first detailed study of work-related electrical fatalities in Australia.

Methods

Work-related electrical fatalities were studied as part of a larger investigation of all work-related fatalities which occurred in Australia during the three calendar years 1982, 1983 and 1984 (2). All work-related traumatic deaths in Australia are reported to a coroner, and the study team examined coroners' files throughout Australia to identify the cases which met the study definition of work-related death. Of the 1,738 cases classified as work-related, 1,544 were defined as coming from the employed civilian labor force. Electrical fatalities formed a subset of these cases. For the purposes of this study an electrical fatality was defined as death due to the effects of electricity on the functions of the body. Data for variables were

obtained from the work-related fatalities study and from information provided by the Electrical Supply Association of Australia.

Results and discussion

Ninety five work-related electrical fatalities, out of a total of 1,544 work related fatalities, occurred in members of the employed civilian labor force during the study period. All were male. This represented an incidence of 0.49/100,000 persons (0.79/100,000 males) in the employed civilian labor force. Electricity was the 5th highest cause of work-related fatalities in Australia (2) and was similarly ranked in United States data (3).

The incidence showed a peak in the 25-34 year age range, with the suggestion of a smaller peak above 55 years of age. This is consistent with overseas data (4) but differs markedly from the pattern for all work-related fatalities in Australia, which shows a steady increasing incidence with increasing age (2).

Ninety four percent of workers were performing their normal tasks at the time of the fatal event, suggesting that most of them should have been aware of the electrical hazard. Miners, quarrymen and related workers (8.5/100,000 men), and rural workers (4.5/100,000 men) were the occupational groups with the highest annual electrical fatality incidences. Only 38% of the fatally injured workers were doing work of an electrical nature at the time of their death, which emphasizes the fact that electricity is a hazard in most workplaces.

The greatest number of deaths occurred on farms (22%) and non-construction industrial sites (20%), with overhead powerlines (42%) and fixed wiring (28%) the main sources of current. The main mode of contact with overhead powerlines was via another conductor, such as a crane (18%) or irrigation pipes (10%). Direct contact with the body occurred in 35% of cases involving overhead powerlines. For fatalities involving fixed wiring, contact was usually made with switch boards and control panels (33%), directly with wires because of perished insulation (19%), or via hand tools contacting the wires (15%). Eleven fatalities (12% of the total) involved welding machines and their cords or accessories, with half of these being due to defective cords or accessories.

Where specified, moisture and lack of adequate clothing were contributory factors in almost half the cases. Moisture increases the risks associated with working with electricity because it usually acts as a good conductor of electrical current. Although most clothing does not provide true insulation from electricity, inadequate clothing exposes bare skin to the electrical source. Over half the deaths occurred with domestic voltages (around 240 volts). Residual current devices would probably have prevented 65% of the 55 fatalities not due to aerial powerlines.

Conclusions

This study has established that electricity is a significant cause of work-related death in Australia. Many of these deaths may have been prevented by adequate electrical safety training of the workers involved, use of residual current devices, or placement of overhead powerlines in more appropriate places.

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POPULATION-BASED CASE CONTROL STUDY OF NONFATAL FALLS ON FARMS IN WISCONSIN

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Accounting for one of five injuries and one-third of hospitalized injured persons, falls are the leading cause of all nonfatal injuries in the United States. Nonfatal work-related injuries occur more frequently in farming than in other occupations. While injury rates in other industries have fallen, injury rates in agriculture have increased. Few analytic studies have attempted to identify risk factors for farm injuries. Our objective is to describe the spectrum, circumstances and extent of farmwork-related fall injuries requiring medical attention in a geographically defined rural population. Since March 1990 we have attempted to identify all farm-related unintentional injuries occurring in a geographically defined area in central Wisconsin which includes approximately 1,695 dairy farms. Case reporters include hospital emergency department staff, physicians in clinics, and chiropractors. Study method is case control design, and both types of subjects are interviewed by telephone. Using a random numbers table, controls are selected from a master list of farm operators in the study area. Participation rates exceed 90%. We registered 55 cases of farm falls over 12 months during 1990-91. These represent almost 18% of total farm injuries reported. Of the 55 falls, 11% were hospitalized, and one resulted in permanent disability. Two-thirds of the falls were from one level to a different level, the remainder were on the same level. There were falls from buildings and structures (35%), machines and vehicles (26%), and ladders and scaffolds (9%). In the study area, work-related fall injuries on farms occurred in 61.4 persons per 10,000 farm residents per year. Potential means of reducing the frequency and severity of falls on farms include: provide adequate handholds and footholds for work at elevation; provide energy-absorbing surfaces underneath areas with fall hazards to modify the energy exchange upon impact; improve coefficients of friction of barn and haymow floors and other surfaces as well as soles of shoes; and build haylofts into hills.

FATAL OCCUPATIONAL INJURIES IN QUEBEC 1981 - 1988

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Objective of the study

Estimate the rates of fatal occupational injuries in Quebec for the years 1981-1988 according to sex, age and industrial sector.

Method

The DENOMINATORS were obtained from Statistics Canada, labor force annual average estimates which are based on monthly interviews 48,000 families across Canada. The inclusion criteria were 1) employed persons in Quebec, 2) age 15 and older. The Military personnel and people living on Indian Reservations are not included in Statistics Canada estimates. The standard deviation of these estimates is less than 2%.

The NUMERATORS consisted of all compensated cases of fatal injuries (non-intentional and intentional except suicides) between 1981 and 1988, 15 years and older. Compensation is universal in Quebec except for Federal Government employees. Certain occupations have a lower compensation coverage for their fatalities, due to the self-employment nature of the job. These are farming occupations (coverage around 10%) and truck drivers (coverage around 75%).

Results

The crude death rate for males for the years 1981 to 1988 combined was 9.1 per 100,000 (95% confidence interval (C.I.): 8.6 - 9.7) and for females was 0.5 per 100,000 (95% C.I.: 0.4 - 0.7). The following Figure shows the evolution of death rates in both sexes.

The death rates increased regularly with age. In males under 20 years of age, the death rate was 6.6 per 100,000 (95% C.I.: 4.9 - 8.8) and in males 55 years of age and older it was 11.4 per 100,000

(95% C.I.: 8.9 -14.6). The evolution of death rates for males by industrial sector is shown in Figures 2 and 3. Information previous to 1984 is not shown because the coding scheme was revised in 1984. The only sector that showed a large increase in death rates was Forests Mines and Fishing. The increase was due to the Forests sector which recorded 8 deaths in 1984 and 24 in 1987. The Construction sector showed a steady decline and the sector of Transport Communication and Utilities remained stable. These last two sectors had the largest number of deaths.

Conclusions

1. The crude death rates described in this study compared with those reported by Baker et al. of 6.8 per 100,000 for both sexes (Maryland 1978), by Russel et al. of 11.3 per 100,000 for males (Oklahoma 1985-86), and by Cone et al. of 5.5 per 100,000 for both sexes (California 1983).

2. The crude death rates in females was low but was caused in a larger proportion (17%) than in males (4%) by intentional injuries. This excess is smaller than those reported by Davis et al. (53%) and by Bell et al. (39%) but indicates a priority for prevention.

3. The pattern of higher rates in workers 55 years of age and older was sharper than that observed by Baker et al. The proportion of deaths due to falls was also higher in that age group (17%). A priority should be directed to determining the reasons that put older workers at greater risk.

4. Opposite patterns were observed in the two sectors with the highest death rates. In construction, a steady decline led to a rate in 1988 much lower than that reported by the National Safety Council and by Bell et al. In the primary sectors, the rising rates were largely explained by an increase in the number of deaths in the forests sector.

5. Taking into account the compensation coverage, the two occupations with the largest number of deaths were truck drivers and farmers.

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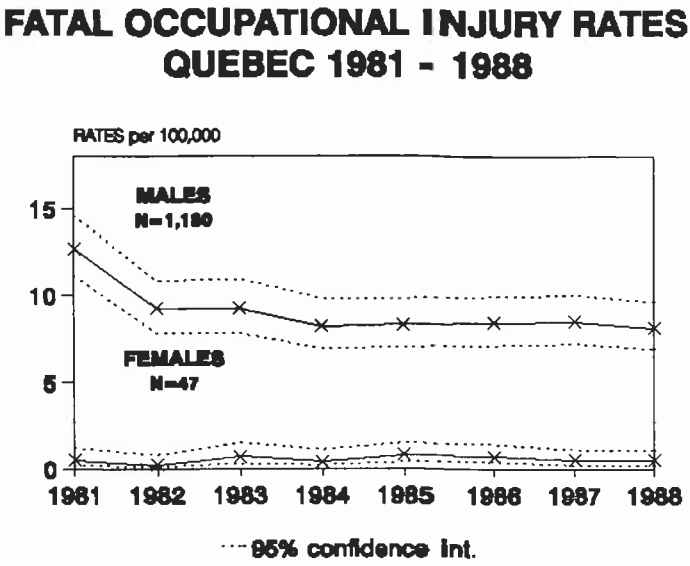

Figure 1. Fatal occupational injury rates Quebec 1981 - 1988

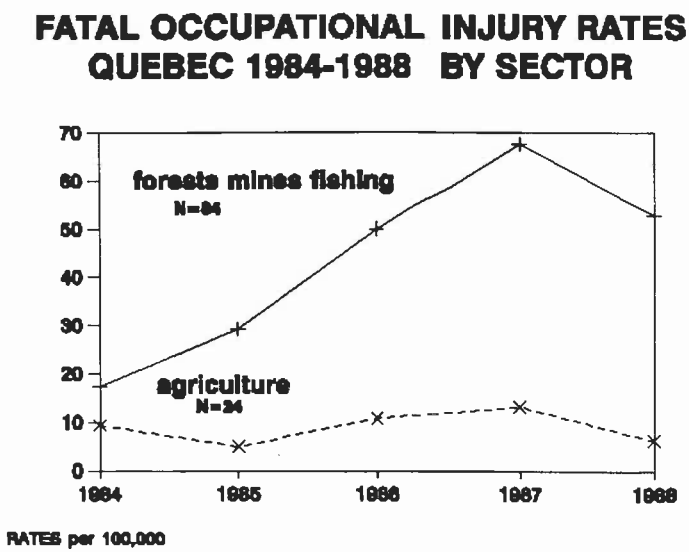

Figure 2. Fatal occupational injury rates Quebec 1984 - 1988 by sector

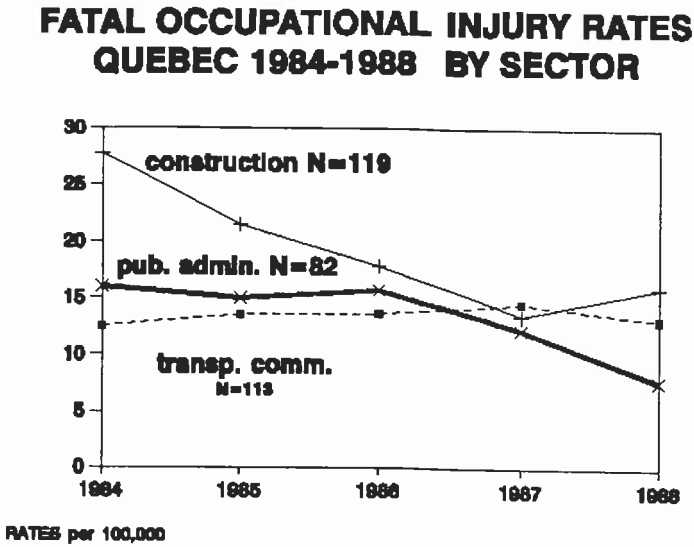

Figure 3. Fatal Occupational injury rates Quebec 1984 - 1988 by sector

PREDICTORS OF SCIATICA IN A FOUR-YEAR FOLLOW-UP AMONG ELDERLY MUNICIPAL EMPLOYEES

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Introduction

In most epidemiologic studies of back disorders, the study base has been cross-sectional. Such a design often leads to selection and information bias, and the question of temporal order in the relationships between the morbidity and the explanatory variables often remains unanswered. Cross-sectional study design rarely permits causal inference, and hence longitudinal studies have been called for to unravel the etiology of back disorders.

In this study, the incidence of sciatica and its predictors was studied in a sample of elderly municipal employees in a four-year follow-up.

Subjects and methods

The subjects consisted of 4863 municipal employees who answered postal questionnaires in 1981 and 1985 who report not having had sciatica prior to year 1981. At the baseline, all subjects were 44-58 years of age and active workers with at least five year experience in their current occupations. The subjects had been selected from 40 occupations that were considered to be physically and/or mentally demanding (Ilmarinen, 1991).

In both cross-sectional studies, information of sciatica was based on the following questions: "Do you at the present have any disease, defect or injury of long duration?" and "Indicate on the following list what kind of diseases or injuries you have at present. Also indicate whether a physician has diagnosed or treated the above disease." As one of the response alternatives there was sciatica diagnosed or treated by a physician.

In the analysis, 72 variables on work (physical and psychological demands, possibilities for development, physical and chemical environment, organization and social environment at work, changes in work stress during the last two years), 34 variables on lifestyle (habits and hobbies, life events in the last half year, living conditions), and 10 variables on life history (physically heavy work, vocational education, change of occupation) were considered as potential predictors. Age, sex, social class and smoking were treated as confounders.

All independent variables whose F-test risk level for predicting sciatica was at most 5 percent were chosen for backward stepwise discriminant analysis. The remaining variable were included in fixed discriminant analysis. Logistic regression modeling was performed using the final reduced set of variables for men and women separately. Risk ratio estimates (RR) and their 95 percent confidence intervals (95% CI) were calculated.

Results

The four-year cumulative incidence of sciatica was 8.7%. The incidence was highest (11.2%) among unskilled workers and lowest (6.2%) among professional or executive workers.

The number of predictors that were included in logistic regression modeling was 13: difficult and uncomfortable work postures; heavy work at the age of 30-39 and at a younger age than 20 years; dry, humid or wet environment; repetitive motions; haste and tight schedule; satisfaction to breaks; starting time for regular work; risk for accidents; need for vocational training; active member in clubs and foundation; severe illness of a family member during the past 6 months; and mentally heavy work.

In women, the significant predictors were heavy physical work at a younger age than 20 year, difficult work postures, and repetitive movements. If all these risk factors were present, RR for sciatica was 4.3 (95% CI 2.9-6.4) in reference to all factors being absent (Figure 1). In men, the significant predictors were difficult postures and mental load at work; RR for sciatica was 2.0 (95% CI 1.3-3.1) for those with high strain from difficult postures and mentally heavy work (Figure 2).

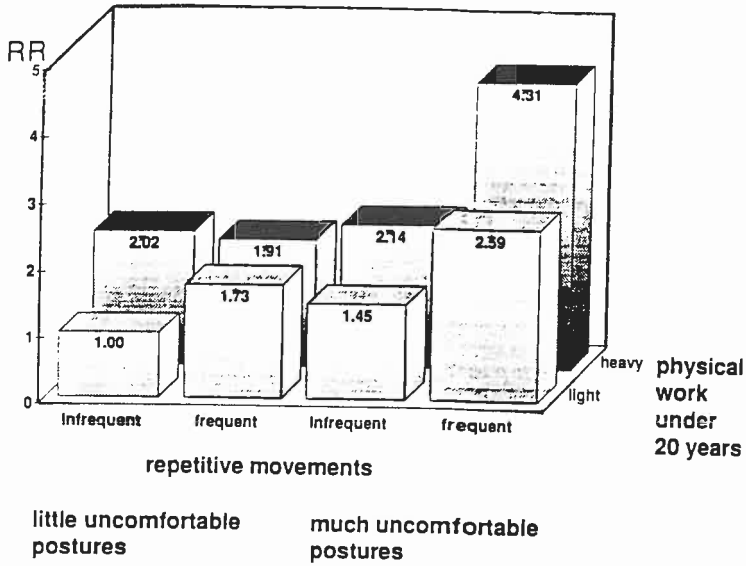

Figure 1. Estimates of risk ratios (RR) for the incidence of sciatica among women (N=2715). Logistic regression analysis

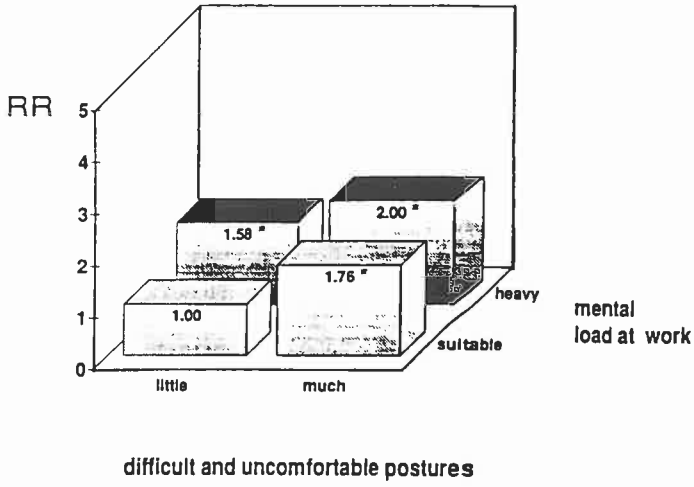

Figure 2. Estimates of risk ratios (RR) for the incidence of sciatica men (N=2112). Logistic regression analysis.

Discussion and conclusions

The results of this study emphasize the role of physical stressors as predictors of sciatica, but also mental stress at work seems to be of importance. The association between physical load and low back disorders have been shown in several earlier studies, both cross-sectional and prospective, and there are also a few prospective studies indicating a relationship between back disorders and psychological stressors (Riihimäki et al., 1989; Bigos et al., 1991). A large number and a broad spectrum of explanatory variables were considered in this study because there was a special interest in social factors. One need to be aware of the problem of multiple comparisons.

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A CASE-CONTROL STUDY OF RISK FACTORS FOR INDUSTRIAL LOW BACK INJURY: THE UTILITY OF PREPLACEMENT SCREENING IN DEFINING HIGH RISK GROUPS

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Introduction

Most orthopedists are well aware of the magnitude of the industrial back pain problem. About 80% of adults will have back pain that interferes with their function at some point during their lives (Kelsey[7]). In 1986, the total compensable cost for all low back pain in the United States was estimated to be 11.1 billion dollars (Webster[18]). Studies from several nations show that, although back injuries account for 15-25% of worker's compensation injuries, they account for 30-40% of the worker's compensation cost (Spengler;[16] Klein[9]).

Because of the enormous costs involved, considerable efforts have been directed at preventing industrial back pain. In industry, personnel departments often hope that preplacement physical examinations will reduce the risk of injuries. However, a study from the Liberty Mutual Insurance Company suggests that this may not be the case (Snook[15]). A recent review of preplacement screening takes a similarly negative view, stating that none of the predictive tests have "sufficient sensitivity or specificity to justify routine usage" (Himmelstein[4]).

However, two risk factors still show some promise in defining high risk groups on preplacement examination: a history of previous back injury and a history of disability. Three studies suggest that a history of previous back injury predicts future back injury. The

increased risk ranges from 1.7 to 16.5 (Venning;[17] Dillane;[3] Daltroy[2]). Among postal workers, those with a previous lumbar laminectomy had an odds ratio of 5.9 for subsequent occupational back injury (Ryan[12]). In addition, our clinical experience at the Postal Service suggested that disabled postal workers, especially disabled veterans, may be at higher risk for industrial back injuries.

To determine whether a preplacement history of previous back injury or of a chronic disability is associated with subsequent on-the-job back injuries, we conducted a case-control study of 154 postal workers with back injuries and 942 controls.

Methods

Population. Our cohort was drawn from among the 8,183 employees hired by the U.S. Postal Service, Boston Management Sectional Center, from 1980 to 1987. Each of these new postal employees underwent a preplacement medical evaluation including a detailed medical history and comprehensive physical examination which was performed by physician assistants or nurse practitioners, specially trained to focus on orthopedic conditions, psychiatric conditions and problems with substance abuse. In each case, the new postal employee filled out a detailed medical history questionnaire and reviewed this history with the physician's assistant. The results of these examinations were compiled by a research assistant, blinded to the identity of cases and controls. The detailed results of the medical examinations were held confidential from management. But because many applicants were concerned about the possibility of being denied employment because of their medical history, they may well have concealed a history of previous back injuries.

Case definition. We defined cases through the computerized records of the Postal Service Injury Compensation Unit. The Federal Employee Compensation Act requires that the Postal Service report all work-related injuries to the Office of Workers Compensation Programs in the Department of Labor; the Injury Compensation Unit gathers all the information to fulfill this reporting requirement. Using an automated system, the Injury Compensation Unit generated a list of all injured employees from 1983 to 1988. A research assistant reviewed the injury compensation files of all these employees. From the medical reports of the treating physician, she identified 154 postal employees who had low back injuries between

1983 and 1988 and who had preplacement physical examinations between 1980 and 1987. Employees who were diagnosed with cervical or thoracic spine injuries were excluded. The injury compensation records did not allow us to diagnose low back pain more precisely.

Controls. From among the postal employees hired from 1980 to 1987, we randomly chose 942 controls who did not have low back injuries between 1983 and 1988. Controls may have had other work-related injuries, including injuries to their cervical or thoracic spines.

Risk factors.

1. **Job classification.** The cohort included postal workers with nine job classifications: letter carrier, postal clerk, mail handler, computer forwarding system clerk, motor vehicle operator, special delivery messenger, mail processor, maintenance worker, and letter sorting machine operator. For the analysis, these classifications were grouped in two categories: the letter carriers, mail handlers, mail processors and motor vehicle operators whose work involves more heavy lifting and pushing and pulling, and the others whose work requires less manual handling.

2. **Gender.** In the general population, females have higher rates of low back pain (Nagi[11]; Biering-Sorensen[1]). However, differing levels of risk within the same occupation have not been noted.

3. **Age.** Younger workers have higher rates of back injury than older workers (Kelsey[6]). In this study, we used the continuous variable, age at the time of the preplacement physical examination.

4. **History of back injury.** On the preplacement medical questionnaire, each new employee was asked about any previous history of back injury. Before the physical examinations, the examiners specifically asked the new employee about any back problems to give them an opportunity to recall any history omitted on the written form. Any low back injury, whether work related or not was included as a positive response. Cervical and thoracic spine injuries were excluded.

5. **Pre-existing disability.** The medical questionnaire asked each new employee whether they carried disability rating from the

Veterans Administration. Because disabled veterans receive hiring preference at the Postal Service, there was an incentive to truthfully report these disabilities. Those with disabilities of greater than 0% were considered disabled.

6. **Quetelet index.** The evidence concerning the association of body weight and low back pain is conflicting (Kelsey[8]). Using measured weights and heights, we calculated the Quetelet index as the weight in kilograms divided by the square of the height in meters. Quetelet index was then characterized as thirty or greater and less than thirty.

7. **History of work-related injury.** The medical questionnaire asked new employees whether they had "ever received compensation or a cash settlement from an employer...for injury or disease." All those who answered yes were considered to have a history of work-related injury.

8. **History of psychiatric disorder.** The medical questionnaire asked new employees whether they "ever had..., at any time, been treated for a psychiatric disorder." All those answering yes were considered to have a previous history of psychiatric disorder. It is likely that there was some under reporting of psychiatric histories.

9. **History of substance abuse.** Postal workers with positive preemployment drug screens have elevated risks for occupational injuries (odds ratio 1.85 for marijuana and cocaine, Zwerling[19]). The medical questionnaire asked new employees whether they had "ever been dependent upon...alcoholic beverages"; whether they had "ever received treatment for...alcoholism"; whether they had "ever been dependent upon...any of the drugs" in a long list of controlled substances; and whether they had "ever been hospitalized or received treatment for the use of drugs." The vast majority of people answering yes to these questions were recovering alcoholics in Alcoholics Anonymous. It is likely that there was significant under reporting both of alcohol abuse and of other substance abuse.

10. **Psychosocial factors.** Psychosocial factors such as psychometric testing and job satisfaction were not available for our cohort.

Analysis. We used logistic regression to determine the associations between low back injuries and the nine risk factors. Following Hosmer and Lemeshow (Hosmer,[5]) we defined our model in four steps. First, because of their established association with low back injury, we included the risk factors: job classification, history of back injury, gender and age, irrespective of their statistical significance in univariate logistic regressions. Second, we performed a univariate logistic regression on each of the remaining risk factors retaining those with likelihood ratio p-values of <0.25, our previously decided cutoff. Third, using the likelihood ratio test and Wald statistic, we compared multivariate logistic regression models containing the variables retained for statistical reasons and all the risk factors mandated by the literature with similar models containing only the variables mandated by the literature. Fourth, we considered twelve potential interactions chosen because of a priori plausibility.

Unless otherwise noted, results are considered statistically significant if $p<0.05$.

All data analyses were performed on an IBM PC AT using PROC LOGISTIC available in SAS (SAS Institute Inc.[13]).

Results

Table 1 describes the cases and controls. The subjects included 285 letter carriers, 276 letter sorting machine operators, 211 clerks, 164 mailhandlers, 57 maintenance workers and smaller numbers of computer forwarding system clerks, mail processors, motor vehicle operators, and special delivery clerks. Subjects ranged in age from 18 to 62 at the time of their examination. Compared with controls, the cases were younger and more likely to have a history of a back injury or of a preexisting disability.

Univariate analysis. Ten risk factors were assessed, one at a time, as described in Table 2. Two risk factors showed highly significant associations with back injury: craft (OR = 2.07) and history of disability (OR = 2.78). In addition, male gender (OR=1.48) and Quetelet index greater than 30 kg/m^2 (OR=1.36) were weakly associated with back injury. Four variables were retained in the model on the basis of established association with back injuries in the literature: craft, history of a back injury, gender and age of preemployment screening. In addition, Quetelet index and history

of disability were retained for further review because their p values for the univariate logistic regression were less than 0.25.

Using the methods outlined by Schlesselman[14] (equation 6.10), we calculated the power of this study as 80% assuming that the number of cases is 154, that the prevalence of prior back injuries among the controls is 8.4%, that there are 6.12 controls for each case, and that there is a relative risk of 2.0 for cases relative to controls.

Multivariate analysis. To determine which variables to include in our final model, we compared multivariate logistic regression models containing the four factors mandated by the previous literature: job classification, history of back injury, gender and age with models containing those variables and, in addition, either history of disability or Quetelet index. Using the likelihood ratio test and Wald statistic, we retained the history of disability variable but not the Quetelet index. Finally, we tested twelve potential interactions and found none of them to be significant at the 0.05 level. Thus, our final multivariate model included: age, gender, job classification (craft), history of back injury, and history of disability.

Table 3 shows the results of this final logistic regression model. The strongest association is between the history of disability and having a back injury (OR = 2.90). As expected, job classification was also associated with the risk of back injury (OR = 1.91). Age was inversely correlated with the risk of back injury. Surprisingly, the history of a previous back injury on preplacement examination was not associated with back injury in this study.

Discussion

Our study has two results of special interest. First, in spite of the large literature suggesting an association between a history of back pain and subsequent back injuries, we found no association between a history of back problems on a preplacement examination and subsequent occupational back injuries. Second, we found that a history of a chronic disability on preplacement examination was associated with subsequent occupational back injury.

Before discussing these results, we must first consider two possible sources of bias in our study. In most case-control studies, recall bias is a serious problem. One of the strengths of our study design was to avoid this problem by nesting our case-control study in a cohort

that was followed prospectively. Specifically, the information on the preplacement evaluations was collected before the employee began work, before any injury could occur. In addition, the research assistant extracted these data from the medical records blinded to the identity of cases and controls. Thus, differential recall between cases and controls was not possible.

A second possible bias is misclassification. Since the computer system we used to identify cases was implemented in 1983, we were not able to identify occupational low back injuries that occurred between 1980 and 1982. They may well have been misclassified as controls artifactually lowering our point estimates. However, making a few assumptions, we can assure ourselves that this bias was small. If we assume that injuries occurred with the same frequency from 1980 to 1982 as in later years, we would expect 77 low back injuries from 1980 to 1982. Random sampling would select about 9 of these for our control group. If we assume that these 9 "false controls" were typical of the other cases, we can recalculate the crude odds ratios of the associations between the risk factors and subsequent occupational back injuries. These calculations show that the strength of the association between a history of back injury and a subsequent occupational back injury increased by 0.5% - from 1.31 to 1.32. The strength of the association between a pre-existing disability and a subsequent occupational back injury increased by 1.4% - from 2.90 to 2.94. Thus, misclassification bias was of no practical significance.

If bias does not explain why a preplacement history of low back injury was not an important risk factor for low back injury in our cohort, we must look further. The contrast, between our results (OR = 1.3) and those of Daltroy[2] (OR = 16.5), is even more striking because both studies were performed on postal workers in Boston. In fact, 44 (29%) of our cases were also cases in Daltroy's study, representing 19% of his cohort. The most likely explanation for the difference lies in the way the history of low back injury was obtained. In Daltroy's study, a history of low back injury was defined as a worker's compensation claim of back injury at the Postal Service within three years prior to the index injury. In our study, a history of low back injury was defined as any low back injury reported on the preplacement medical history form. Thus, it may be that more recent back injuries (within three years) are more potent

predictors of recurrent back injuries. However, this is not likely to be the entire story, since a study of a random sample of adult Danes (Biering-Sorensen[1]) showed an odds ratio of 8.4 for recurrent back pain among those with a positive lifetime history. We suspect that the rest of the explanation lies in the underreporting of previous back injuries on preplacement examinations. Only 8.4% of our subjects reported a previous back injury, a significantly lower percentage than one would expect from population based studies. This underreporting occurred even though the Postal Service in Boston is known to fire employees who falsify their preplacement medical examination. In view of this apparent significant underreporting, it is unlikely that a patient-reported history of prior back injury on preplacement examination can be used to identify high risk workers who would need special accommodation.

In contrast, a history of chronic disability, here defined by a disability pension from the Veteran's Administration, was a significant risk factor for occupational back injuries. This confirmed our clinical suspicion. Only ten of the disabled veterans had any disability related to their back. Twenty had disabilities of the upper extremities; forty-three of them had disabilities of the lower extremities; twenty-eight had psychiatric disabilities; sixty-five had other disabilities which are not defined in our data set. Table 4 shows that the odds ratios for the risk of back injuries were elevated for each of the disability categories: back, 4.16; lower extremity, 2.48; upper extremity, 2.07; psychiatric, 2.53; and other, 1.93. Of those with disabilities, 53% carried ratings of 10% disabled. The rest carried ratings of 20% or more disabled. The crude odds ratios showed both those with less severe and those with more severe disabilities were at equal risk for subsequent back injuries.

There is little in the existing literature to explain these findings. A recent study from a shipyard (Moll van Charante[10]) showed that workers with hearing loss greater than 20 decibels had a risk of injury of 1.90 compared to workers without hearing loss. Our results may indicate that a wider variety of disabilities put workers at risk of secondary injury in attempting to compensate for their impairment. Alternatively, involvement in one federal compensation system (a veteran's administration disability system) may make it more likely for an employee to file for another type of federal compensation (Worker's Compensation). Our study can not

differentiate between these possibilities. Whatever the explanation, the passage of the American's Disabilities Act will lead to greater integration of disabled Americans into the work force. Our findings suggest that we need to carefully consider how we accommodate these workers in order to avoid secondary injuries and disabilities.

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Table 1. General description of cases and control

Variables	Cases Number (%)	Controls Number (%)
Total in study	154 (100.0)	942(100.0)
Craft (heavy)	96 (62.3)	417(44.3)
History of a back injury	19 (12.3)	79(8.4)
History of a injury on the job	11 (7.1)	71(7.5)
History of psychiatric disorders	8 (5.2)	38(4.0)
Gender (male)	116 (75.3)	635(67.4)
History of substance abuse	7 (4.5)	49(5.2)
Quetelet index ($\geq$30Kg/m^2)	30 (19.5)	142(15.1)
History of disability	48 (31.2)	132(14.0)
Mean age at pre-employment screening (years)	29.8 (sd=7.4)	31.0(sd=8.4)

Table 2. Univariate logistic regression models

Variable	Odds ratio (95% CI)	-2 Log-likelihood	Likelihood Ratio Test (p-value)
Intercept		889.71	
Craft (heavy)	2.07 (1.46, 2.95)	872.49	17.22 (<0.001)
History of a back injury	1.54 (0.90, 2.62)	887.38	2.34 (0.127)
Gender (male)	1.48 (1.00, 2.18)	885.72	3.99 (0.046)
Age at pre-employment screening (10 years)	0.98 (0.96, 1.00)	886.75	2.96 (0.085)
Quetelet index ($\geq$30 kg/m^2)	1.36 (0.88, 2.11)	887.86	1.85 (0.174)
History of disability	2.78 (1.89, 4.09)	865.20	24.52 (<0.001)
History of work-related injury	0.94 (0.49, 1.82)	889.68	0.03 (0.862)
History of psychiatric disorder	1.30 (0.60, 2.85)	889.29	0.42 (0.518)
History of substance abuse	0.87 (0.39, 1.95)	889.59	0.12 (0.728)

Table 3. Multiple logistic regression model

Variable	Odds ratio	95% CI	p-value (Wald-statistic)
Craft (heavy)	1.91	1.32 - 2.76	<0.001
History of back injury	1.31	0.75 - 2.30	0.340
Gender (male)	0.96	0.62 - 1.49	0.866
Age at pre-employment screening (10 yrs)	0.70	0.56 - 0.89	0.004
History of disability	2.90	1.88 - 4.48	<0.001

Table 4. Associations between various disabilities and subsequent occupational back injuries

Disability	Number Disabled	Odds Ratio	Test Based Confidence Interval (95%)	P-Value (Fisher exact 2-tailed)
Back	10	4.16	(1.28, 13.52)	0.039
Lower Extremity	43	2.48	(1.27, 4.84)	0.007
Upper Extremity	20	2.07	(0.76, 5.65)	0.137
Psychiatric	28	2.53	(1.12, 5.70)	0.046
Other	65	1.93	(1.06, 3.51)	0.031

INCREASED RISK OF MYOCARDIAL INFARCTION AMONG BUS DRIVERS IN URBAN AREAS

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A number of studies have been previously carried out in order to investigate cardiovascular disease in bus drivers. These studies, of which some are Swedish, have indicated that bus drivers have an increased risk of developing coronary heart disease. In general, these previous studies have focused on urban bus drivers. The aim of the present study was to investigate mortality, overall and from specific causes, for male bus drivers in Sweden compared to that of other employed men. Furthermore the aim was to investigate the incidence of myocardial infarction among Swedish bus drivers, compared to that of other employed men.

Three substudies were carried out. In the first substudy, mortality overall and from specific causes was investigated. The population defined by the Swedish 1970 census was followed with respect to mortality for the period 1971-86. Deaths were identified by linkage of the census data to the National Cause of Death Register. The cause specific mortality among 9,446 male bus drivers was compared to that among other employed men. The results indicated that bus drivers in the counties where the two largest cities of Sweden are situated (Stockholm and Göteborg and Bohus counties) had a 50%-60% increased mortality from myocardial infarction, compared to other employed men in these counties. No increased mortality from lung cancer, cancer (all sites combined), or from all causes combined, was observed for these drivers. For bus drivers in other parts of Sweden (predominantly rural areas) no increased mortality from myocardial infarction, cancer (all sites combined), or from any cause was found compared to other employed men.

In the second substudy, the relative risk of developing a first myocardial infarction among bus drivers, compared to that among other employed men, was studied by case-referent methods. The study base comprised the population in five Swedish counties during

the period 1976-81/84. Incident cases of myocardial infarction in the study base were identified by combining information on hospital discharges and deaths. Information about occupation was obtained from the 1970 Swedish census as well as from the 1975 census. Among the bus drivers, 90 cases were identified. The results indicated a 60% increased incidence of myocardial infarction for bus drivers in Stockholm County, compared to other employed men in this county. In the other four predominantly rural counties, no increased incidence of myocardial infarction was observed among bus drivers.

In the third substudy, mortality from all causes combined and for specific causes, as well as incidence of myocardial infarction, were investigated among urban bus drivers employed at the Stockholm Transport during the 1970s. The results were in agreement with the first two substudies. Thus, mortality from as well as incidence of myocardial infarction were elevated for bus drivers at Stockholm Transport, compared to other men in Stockholm County. This was found particularly among the middle-aged drivers. For drivers 55-64 years of age, mortality from myocardial infarction was twofold that for other employed men in Stockholm of this age. For drivers older than 65 years of age, no increased risk of developing myocardial infarction was indicated.

The results of the different substudies of the present investigation may have been influenced by a misclassification of occupation and disease. It is reasonable to assume, however, that misclassification of occupation was unrelated to developing a myocardial infarction, thereby introducing a non-differential misclassification. Correspondingly, the misclassification of disease probably was similar for bus drivers and for other employed men. Therefore, it is likely that a misclassification of occupation and disease tended to bias the relative risk estimates towards the null value. A positive health selection into the bus driver occupation may have been present which would tend to result in underestimates of the relative risk of myocardial infarction among the bus drivers. It seems reasonable to conclude that bus drivers in the urban counties of Stockholm and Göteborg had an increased risk of developing myocardial infarction, compared to other employed men in these counties.

An increased risk of myocardial infarction among urban bus drivers may be caused by a number of factors. These factors include differences with respect to life style factors such as smoking and dietary habits, as well as work environment factors. Work environment factors of possible importance are job strain, irregular working hours, automobile exhausts, and noise.

CARDIOVASCULAR DISEASES AMONG FOUNDRY WORKERS EXPOSED TO CARBON MONOXIDE

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In 1972 carbon monoxide (CO) was measured in 52 iron, 10 steel, and 5 copper alloy foundries. The threshold limit value for CO (50 cm^3/m^3) was exceeded in 72% of the iron foundries, in 9% of the steel foundries, and in 20% of the copper alloy foundries. The blood carboxyhemoglobin content of iron foundry workers exceeded 6% COHb in 71% of the smokers and in 28% of the nonsmokers.

The aim of the present study was to investigate long-term effects of CO exposure on foundry workers' morbidity and mortality from cardiovascular diseases (CVD).

The study population comprised (1) a cohort of 2,857 men hired in 1950-1972 by 20 Finnish foundries, and (2) 931 men who were still active in 1972 an exposed for at least 4.2 years and who took part in the health examination in 1973; 653 of them were also members of the cohort. Mortality and morbidity of the study groups were followed up to the end of 1987.

During the follow-up of the cohort (from 1950 to 1987) 255 cardiovascular deaths occurred, whereas 283.5 were expected based on national rates. The number of deaths due to ischemic heart disease was 183 (202.8 expected). Also this time only small differences were found between the carbon monoxide categories. Probably, the explanation was the lack of the data on smoking habits and complete occupational histories. On the contrary, the analysis of morbidity from cardiovascular diseases revealed differences: the age-standardized incidence rate of free medication for hypertension was 4.7 among workers whose exposure time was less than one year and who were not exposed to CO, and 9.4 among those who were regularly exposed to CO for at least 5 years ($p < .01$); among iron

foundry workers the rates were 4.7 and 9.9 ($p < 0.1$) (Table 1). Also incidence rates of free medication for all cardiovascular diseases showed statistically significant differences between the extreme study exposure categories ($p < .001$).

Table 1. Free medication for hypertension in 1964-87 by CO exposure in the cohort of 2,857 foundry workers

CO Exposure	IHD ID/1,000 p-years		
	Period of exposure, years		
	<1	3 - 5	>5
Regular	3.2	7.0	9.4
Occasional	3.9	3.8	8.0
No	4.7	4.2	6.3
Total	4.5	4.7	7.6

In the follow-up of the *health examined group* (from 1973 to 1987) the age-standardized incidence rate of free medication for hypertension was 9.1 among nonsmokers not exposed to CO and 21.4 among CO-exposed smokers ($p < 0.5$); the difference originated in the iron foundry workers for whom the rates were 8.1 and 24.0 ($p < .05$). Also the differences between nonexposed nonsmokers and exposed ex-smokers were statistically significant (Figure 1). For the

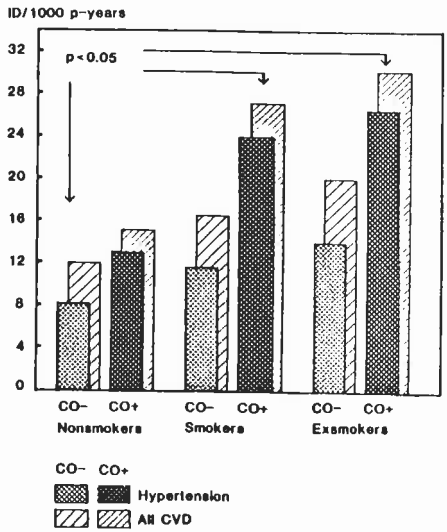

Figure 1. Incidence of free medication for hypertension and all cardiovascular diseases in 1973-87 among 458 iron foundry workers who were health examined in 1972.

iron foundry workers, the effect of CO only showed a rate ratio of 1.6 among nonsmokers and 2.1 among smokers. The effect of smoking only gave a rate ratio of 1.4 for workers not exposed to CO and 1.9 for the exposed workers. The combined effect of CO exposure and smoking showed a rate ratio of 3.0. For all cardiovascular diseases similar differences were found between the CO exposure and smoking categories.

The age-standardized mortality rate for cardiovascular diseases was 1.9 for nonsmokers without CO exposure and 9.2 for those with both exposures ($p < .025$) (Figure 2). This difference was caused by IHDs, for which the corresponding rates were 1.9 and 7.3. Analysis of mortality from ischemic heart disease among the workers with mild or severe angina pectoris in 1973 showed the highest incidence rate for CO-exposed smokers.

Altogether, the results indicate that CO exposure increases the risk of cardiovascular morbidity and mortality. It has been shown elsewhere that even low levels of carboxyhemoglobin interfere with cardiovascular function in patients who already have a reduced capacity to deliver oxygen to the heart. The pathologic manifesta-

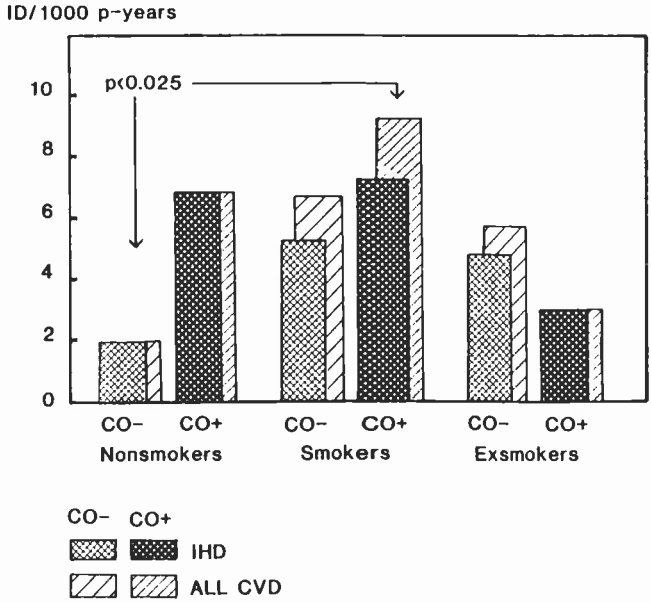

Figure 2. Mortality from IHD and all CVD in 1973-87 among 931 foundry workers who were health examined in 1972.

tions of CO exposure may have been caused by reduced oxygen delivery to the heart, or by the chemical effects of CO on myocardial cell function, or by accelerated atherosclerosis and coronary lipid deposition due to chronic arterial hypoxia related to carboxyhemoglobin (COHb).

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CASE-CONTROL STUDY REGARDING MYOCARDIAL INFARCTION, SHIFTWORK AND OCCUPATIONAL EXPOSURE TO NOISE

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For the practice of workside prevention of myocardial infarction (MI), it is not only important to know which occupational stressors are likely to put an individual on higher risk of suffering myocardial infarction, but it is also useful to identify high-risk-associated variables, which can define particular occupational groups that should receive special attention in the prevention of myocardial infarction.

In an attempt to scrutinize such occupational stressors that also could be obtained objectively, that means apart from the subjects' own judgement, this paper focuses on shiftwork and occupational exposure to noise, and to some extent on high temperature at the workplace, of which only subjective judgement could be obtained.

Materials and methods

We conducted a case-control study of 65 patients with first MI between 1986 and 1988, of which complete data about risk-factors, psychosocial and occupational variables and laboratory analysis could be obtained. These 65 patients were part of a total of 110 cases of MI or acute death due to coronary heart attack which occurred in 20,000 employees of a metalworking plant during the time period mentioned above. Controls were obtained from the company's register and matched for age, length of employment, sex and nationality. Data were collected using a questionnaire, clinical examination and laboratory analysis of blood samples, regarding lipid metabolism.

Laboratory analysis as well as statistical computing were carried out at the Department of Clinical Chemistry, University of Munich (Prof. Dr. D. Seidel). Statistical analysis had to address the usage

of matched pairs. Univariate analysis of discreet variables was proven using a likelihood-ratio-chi^2-test, comparisons of mean-values were tested using a t-test for observations in matched pairs, and interactions were tested using a chi^2 -test. The variables with considerable influence in univariate analysis were simultaneously tested using a logistic regression procedure. Significance of the results obtained, was proven utilizing likelihood chi^2-test. Computing of multivariate variables was done utilizing EGRET (by Statistics and Epidemiology Research Corporation, Seattle, Washington).

The correctness of questionnaires regarding the shift-rhythm was proven to be in full agreement with company-registers. Regarding noise, the workers were asked whether industrial noise was perceived to be stressful (sub.noise). Reports of each participant's working history were analyzed by the company's noise-level-expert and judged using the data available in his reports (obj.noise). Regarding high temperature at the workplace, not enough objective data were available for a clearcut judgement, so we had to stick to the data obtained from the questionnaire.

Results

Table 1. Relation between shift work variables and MI

Variable	OR	CI 95%	p
Currently 3 shifts	3.60	1.43-9.09	0.007
Currently 2 shifts	1.75	0.74-4.13	0.201
History of 3 shifts	1.75	0.74-4.13	0.201
History of 2 shifts	1.00	-	-

Table 1 gives the relation between shiftwork variables and MI. Shiftwork including nightwork (3-shift work) has the highest OR 3.60 on a significant p-value. Shiftwork not including nightwork (2-shift work), lifetime 3-shift work and lifetime 2-shift work have considerably lower ORs and do not gain significance.

Table 2. Relations between the variables regarding occupational noise exposure and MI

Variable	OR	CI 95%	p
Subj. Noise	1.64	0.78-3.44	0.194
Obj. Noise	2.00	0.77-5.23	0.157

Table 2 gives the relations between the variables regarding occupational noise exposure and MI. Neither subj. noise , nor obj. noise reaches a significant p-value. The length of lifetime-exposure to occupational noise does also fail to reach a significant p-value, so does the length of lifetime exposure to shiftwork.

Further work-related variables with a significant relation to MI are: high temperature at the workplace (OR 3.25;p=0.002), lack of time (OR=2.78; p=0.006) and overwork (OR 7.33; p<0.001). These work-related variables and the variables of psychological stress, such as lack of support (OR=3.67; p=0.033) and lack of approval (OR=2.57; p=0.028) were combined to a job-strain-score reaching a highly significant relation to MI.

Also the generally acknowledged risk factors for CHD and some psychosocial variable yielded significant associations with MI.

Analysis of interactions shows that smoking is the most important confounder for the relation of shiftwork and MI. History of metabolic lipid disorder, subj. noise overwork and high temperature at the workplace are significantly related to 3-shiftwork, too. It is remarkable that obj. noise has no significant interaction to 3-shift work. An interaction of hyperlipemia is laboratory analysis and 3-shift work is not detectable.

For the reason of minimalizing bias influence, the LDL/HDL-Chol. ratio measured by means of laboratory analysis instead of the questionnaire data was used as a parameter for the lipidmetabolism in the multivariate analysis.

Multiple logistic regression procedure sets the hyperlipemia on the top of the risk factor list.

Table 3. Results from the multiple logistic regression procedure

Variable	Chi^2	p	OR	CI 95%
LDL/HDL	26	<0.0001	6.8	2.0-23
Job-Stress Score	19	<0.0001	21	2.8-154
Smoking	6.9	0.009	5.9	1.3-27.4
3-Shift Work	5.2	0.02	5.3	1.1-24.7

Table 3 gives results from the multiple logistic regression procedure. Regarding a 5%-level of significance, 3-shift work's impact to the discrimination of MI-patients and controls is significant. If work-strain score as a possibly biased variable is excluded, 3-shift work is no longer significant. There is a kind of competition between 3-shiftwork and hypertension for the ranks behind hyperlipemia and smoking. Only if smoking is additionally excluded, does 3-shift work get a higher rank in the model and is highly significant.

If the variables 3-shift work, noise exposure and heat exposure are combined and computed as a pseudo-continuously distributed variable, the logistic regression procedure yields the results given by Table 4.

Table 4. Logistic regression procedure results

Variable	OR	p
LDL/HDL	3.2	<0.001
Combined Variable (SNT)	2.7	0.018
Smoking	2.3	0.10

With an OR of 2.7 and p=0.018, it is stronger than smoking and positioned between hyperlipemia and smoking. The combined variable is stronger in its contribution to the discrimination of MI-patients and controls than its single parts.

Discussion

Shiftwork including nightwork may act as a partly independent risk factor for MI, although it is to a large extent confounded by smoking.

Comparable to other studies, especially from Sweden and Austria (Alfredsson 1982, Alfredsson 1985, Knutsson 1986, Koller 1983), our results show that shiftwork including nightwork is a good discriminator of MI-patients and controls. Part of this effect may be independent, but most of it depends on a considerably elevated portion of smokers in 3-shift workers.

Some other authors could not detect an elevated risk for MI among shiftworkers (Thiis-Evensen 1958, Angersbach 1980). This may be

due to the fact that shiftwork is usually combined with other workrelated stressors such as noise, overwork and heat, as confirmed by our results. And those combined effects may be different in different industries. Moreover there may be a selection of personnel lacking health consciousness in shiftworkers, which could be different if regarding different professions and different levels of education. In the plant examined in this paper, 3-shift workers are mostly unskilled or semi-skilled workers, whereas the highly skilled maintenance workers and toolmakers mainly worked in a 2-shift-rhythm.

The high prevalence of smoking among 3-shift workers may be partly due to selection, on the other hand there could also be a enhancing effect of nightwork on smoking.

Regarding noise exposure, no significant impact of current exposure (obj. noise), current annoyance (subj. noise) or lifetime exposure to occupational noise on the discrimination of MI-patients and controls could be detected. This stands in good accordance with the literature regarding noise-effects on the cardiovascular system, that until now an effect regarding MI could not be proven (Kryter 1985), although there might be an effect regarding hypertension.

The variable high temperature at the workplace could not be obtained objectively, that means apart from the participants personal judgement. Therefore it may be possible that reduced heat tolerance during symptomatic phases of coronary heart disease of patients prior to myocardial infarction could bias our results. But considering the acute cardiovascular effect of heat exposure, an effect of high temperature at the workplace on the incidence of MI is plausible.

High temperature at the workplace, shiftwork and noise exposure are also working conditions that can be easily detected and that, except shiftwork, do define groups of workers already subjected to special preventive examinations. If these working conditions are combined in a single variable, this TSN-variable has a significant impact on the discrimination of MI-patients and controls in our study. It is also stronger than smoking and stronger than its single parts.

The distribution of the relative incidence of MI in different departments of the plant, based on 96 blue collar MI-incidence cases

in three years (a part of those participated in our study), shows a significant excess incidence for MI in the company's foundry. The foundry belongs to the transmission operating part of the plant and produces transmission boxes made of aluminum in a pressure-founding process. Carbon monoxide measures were within the limits, but most of the foundry workers have to deal with a combination of high temperature, 3-shift work and occupational noise (>90dB(A)).

We conclude that preventive examinations of 3-shift workers and workers enduring high temperature should include risk-factor screening and treatment regarding generally acknowledged risk-factors for MI. Prevention programs should particularly focus on shiftworkers and on departments with a combination of workrelated stressors-- high temperature, shiftwork and occupational noise.

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SHEEP - STOCKHOLM HEART EPIDEMIOLOGY PROGRAM: STUDY DESIGN

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Background

Most multifactorial studies of coronary heart disease so far have been prospective in their design - e.g., the Framingham Study, the Multiple Risk Factor Interventional Trial (MRFIT), the MONICA study, the North Karelia Project, and several others.

Using a prospective study design, baseline values of exposure can be ascertained in the beginning of the follow up period, i.e., before the outcome is known, and later related to the outcomes under study. Thus, recall bias is avoided. Such a prospective approach is only valid for exposure factors that are truly constant over time, however, e.g., genetically determined characteristics. Since the follow up period usually is several years, information on other exposure factors has to be collected retrospectively when the outcome occurs, also with this design. The crucial point is then rather to apply reliable techniques to collect the exposure information retrospectively. In relation to coronary heart disease, many risk factors of current interest are extraneous and thus of nongenetic origin. Some potential risk factors, such as certain occupational exposures, may also have a long latency period. Both these conditions urge data to be collected retrospectively. We believe that a well designed, well conducted, and large enough case-referent study is the most efficient

way to increase the knowledge about the absolute and relative effect of a number of potential risk factors for coronary heart disease, such as exposure to "job strain"(1), shift work (2), combustion products (3), and unemployment (4), also in relation to the recognized risk factors: smoking, hypertension, and elevated serum lipid levels. Such a design will also permit studies of possible interaction between different component causes of coronary heart disease, given valid exposure information and a sufficient number of persons with multiple exposures. These and other considerations led us to initiate a study of causes of acute myocardial infarction (AMI), using the case-referent design. The study, *SHEEP - Stockholm Heart Epidemiology Program*, combines several disciplines: cardiology, epidemiology, occupational health, social medicine, and nutrition. It also involves the cardiology units at each of the ten emergency hospitals that together cover the county of Stockholm, Sweden.

Study design

Cases and referents. The study population comprises all residents in the Stockholm county, aged 45-69 years, and who are Swedish citizens. So defined, the study population consists of approximately 600,000 persons. All persons from the study population who experience a clinically diagnosed first event of acute myocardial infarction (ICD 410) during 1992 - 1993 are defined as cases. With the current incidence, we expect almost 2300 cases during the recruitment period, of which 550 will be women. Approximately 40% of the AMI events will be fatal and 900 of the cases will die from their infarction, most of them very shortly after onset of the infarction. One referent is chosen for each case; the referent should be of the same sex and age but is otherwise chosen randomly from the study population. The referents should be free of clinically diagnosed AMI, but no other restrictions are applied. If a referent refuses to participate, a second (or third) referent is included in the study. This is to maximize the information gained in the study. All referents ever included will be kept in the study, however, to permit basic comparisons between responders and non-responders to appreciate certain potential bias. All referents are alive, also those who are referents to deceased cases.

The cases are identified from the combination of three sources: the cardiology units at the ten emergency hospitals in the Stockholm county, the computerized hospital discharge register, and the cause

of death registry, kept by Statistics Sweden. More than 90% of the hospitalized cases of AMI are treated in the cardiology units at the emergency hospitals. Specially appointed staff at these units report *SHEEP* cases on admission. Hospitalized cases treated elsewhere are identified through the hospital discharge register. The fatal cases, who die before admission to hospital, are identified by special routines, set up for *SHEEP* at the Statistics Sweden. The referents are identified from the computerized register of the county population.

Consensus on diagnostic criteria and a high autopsy rate among deceased cases result in a consistent (and high) specificity of the diagnosis. Eligible referents are checked for history of myocardial infarction in the hospital discharge register. Before ultimately including a referent, anamnestic information is also requested.

Exposure information. The exposure information is mainly collected by a questionnaire, but non-fatal cases and their referents are also subjected to certain biomedical examination. For the fatal cases, the questionnaires are sent to the spouse, or secondly-- to a close relative.

Most questions in the questionnaire are based on previously published and evaluated questions/questionnaires. The questionnaire is filled out at home and mailed to the project. If needed, project personnel complete any missing answers in the questionnaire during a telephone call with the respondent.

Occupational exposures. Each case and referent is also asked to give a history of occupations and jobs. Based on this history, certain chemical exposures can be inferred by applying specially constructed job-exposure matrices. Quantitative exposure information on combustion products, especially motor vehicle exhaust, organic solvents, nitrate esters, and lead is collected by direct questions. The questionnaire also deals rather extensively with psychosocial factors in the working environment with focus on the perceived conditions during the last five years. Two main hypotheses will be tested. One concerns the "demand-control" model suggested by Karasek and Theorell (1). According to this model, exposure to "job strain", that is working under high psychological demands but with a small decision or control latitude, can increase the risk of myocardial infarction. The other hypothesis is of German origin. Siegrist and

coworkers (5) have reported an association between "lack of social reward" and increased risk of myocardial infarction. This hypothesis will also be tested in *SHEEP* by questions describing "need for control" and "immersion." Levels of work related physical activity are assessed on a semi quantitative scale and also as perceived effort on a Borg scale.

Non-occupational environmental exposures. As previously indicated, *SHEEP* is a multi-disciplinary study and investigates several risk factors in addition to occupational exposures. The scales, used to assess aspects on social network and on social support, are developed in Sweden or adapted to Swedish conditions from internationally published scales (6). Sleeping disturbances and exposure to stressful "life events" during the last year are also investigated by special sets of questions, which have been used in previous Swedish population studies (7,8). The dietary habits during the last twelve months are penetrated by a set of food-frequency questions. Off work physical activity including household work and exercise habits, tobacco exposure, including passive smoking and snuff use, coffee consumption, and alcohol habits are mapped from the age of 15 and onward, as averages across ten year periods.

Biomedical data. The medical history includes questions on cardio- and cerebrovascular symptoms, diabetes, and medication, also for the parents and children of cases and referents. The nonfatal cases and their referents are also subjected to a small biomedical examination including blood pressure, height, weight, and waist/hip measurement. Blood samples are drawn for analyses of serum lipids and certain hemostatic factors. Current medication is assessed and all women are asked about their use of oral contraceptives and about hormone substitution treatment.

Expected statistical power of the study

Using the conventional values for significance level (5%) and statistical power (80%) of the epidemiological analyses, we have estimated the lowest detectable levels of excess risks, under the assumption of 80% response rate among both cases and referents. (The actual response rates during the first year of the study were 91% for the cases and 76% for the referents.) Some such relative risks are shown in Table 1. The percentage column gives the approximate prevalence of different exposures in the study

population. The large number of cases will give the potential to identify also rather small excess risks and, further, to study interaction/effect modification between different risk factors.

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Table 1. Estimated lowest detectable relative risks (OR) in the *SHEEP* study*

Exposure	Prevalence	Approximate Relative Risk	
		The whole study	Women only
"Job strain"	18%	1.3	1.6
Combustion products	8%	1.4	
Sedentary (work + leisure)	9%	1.4	1.8
	5%	1.6	3.1
	1%	2.3	4.4

*Assumed: 80% response rate among both cases and referents: for the whole study (2300 cases, 2300 referents), and for the women only (550 cases, 550 referents), respectively. Significance level: a=5%, statistical power: (1-β) = 80%

THE RELATIONSHIP BETWEEN JOB STRAIN, AMBULATORY BLOOD PRESSURE AND HYPERTENSION

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During the past decade, attention has focused on the possible role of work-related stress in the etiology of cardiovascular disease and high blood pressure. A model of occupational stress developed by Karasek and colleagues posits that "job strain" (jobs characterized by high psychological workload demands and low "decision latitude") may play a role in the development of these diseases. Decision latitude is an operationalization of the concept of control and is defined as the combination of job decision-making authority and use of skills on the job. Karasek argues that exposure to highly demanding work situations in which the individual does not have the resources or control to manage such demands results in biological arousal, mediated by increases in catecholamines and blood pressure, contributing ultimately to the development of cardiovascular disease. In addition, job strain (also known as having a "high strain" job) may lead to unhealthy coping behaviors, such as smoking, that contribute to cardiovascular disease (1).

Over the past 13 years, 36 studies on job strain and heart disease or heart disease risk factors have been published. These studies, which have been conducted in Sweden, the U.S., Finland, Denmark, Australia, and Japan, provide strong evidence that job strain is a risk factor for heart disease (2). Of the 15 heart disease studies, 13 showed clear associations between job strain and heart disease. More importantly, seven of the eight cohort studies showed strong positive associations.

In the 21 studies of risk factors for heart disease, the following patterns were seen. Three studies found no association between job strain and serum cholesterol. Two studies found a link between job strain and smoking, while two did not. (One of the negative studies, however, did show higher rates of smoking at lower levels of job

decision latitude.) Of eight studies of blood pressure measured in a clinical setting, only one found a significant association. However, of the nine studies where an ambulatory (portable) blood pressure monitor was worn during a workday, five showed strong positive associations between job strain and blood pressure, while the other four provided mixed results. Since ambulatory blood pressure is both more reliable (since there is no observer bias, and the number of readings is increased) and more valid (since blood pressure is measured during a person's normal daily activities) than casual measures of blood pressure, we feel confident in placing more emphasis on the ambulatory blood pressure results. Two of the five positive ambulatory blood pressure studies are described in more detail below.

An ongoing prospective cohort study of healthy employed men and women in New York City, aged 30-60, was begun in 1986 at Cornell University Medical College. A nested case-control study design, which included 262 men from 8 worksites, in a wide variety of white-collar and blue-collar job titles, was implemented as part of the first wave of data collection. Eligible cases (N=85) had diastolic blood pressure (DBP) above 85 mm Hg at both screening and recruitment, or were taking antihypertensive medication, while controls (N=177) had DBP less than or equal to 85 mm Hg at both screening and recruitment. All participants wore a 24-hour ambulatory blood pressure monitor, completed detailed psychosocial and health questionnaires (including the Karasek Job Content Questionnaire), received a medical examination, and provided blood and urine samples. Other known risk factors for hypertension were evaluated. In the first wave of the study, participants exposed to job strain (21% of the sample) were at significantly increased risk of hypertension (being a case), controlling for other possible risk factors (age, race, body mass index, Type A behavior, alcohol use, smoking, 24-hour urine sodium, education) as well as potential confounders of the association (physical exertion level of the job and worksite) (3).

Risk factors for hypertension - Cornell worksite study (N=262)

Risk Factor*	Odds Ratio (95% C.I.)	p
AGE 51-60 (vs. 30-40)	11.4 (4.3-30.4)	<.0001
AGE 41-50 (vs. 30-40)	6.4 (2.6-15.7)	<.0001
ALCOHOL	3.0 (1.4-6.3)	.005
JOB STRAIN	2.9 (1.3-6.6)	.011
BMI	1.3 (1.1-1.5)	.0009
RACE (non-white)	1.7 (0.6-5.3)	NS
SMOKING	1.5 (0.7-3.3)	NS
PHYSICAL EXERTION	1.1 (0.7-1.8)	NS
TYPE A BEHAVIOR	1.1 (0.5-2.2)	NS
EDUCATION	1.0 (0.8-1.2)	NS
URINE SODIUM	1.0 (1.0-1.0)	NS

Risk estimates reflect the independent effect of each variable, controlling for all other variables in the model. The full model was computed by unconditional logistic regression. Worksite was also controlled for, coded as seven dummy variables.

The same sample was analyzed utilizing mean ambulatory blood pressure as the outcome rather than case-control status (4). Using ANCOVA, job strain was associated with an elevation in work systolic blood pressure (SBP) of 6.8 mm Hg (p=.002) and in work DBP of 2.8 mm Hg (p=.03) after adjusting for the same potential risk factors and confounders. This effect persisted to home and sleep blood pressures, indicating that job strain is associated with a generalized and persistent arousal beyond the immediate work situation. Job strain was also associated with an increase in left ventricular mass index (LVMI) of 9.7 g/m^2 (p=.001).

These participants and 22 additional men eligible for the cohort study have been followed for three years. Of the 284 eligible men, 195 were alive, could be located, and agreed to participate in the follow-up. Analysis of cohort data displayed a pattern of blood pressure change consistent with the initial case-control and cross-sectional findings. Workers exposed to job strain at both waves of data collection (N=15) had a significantly greater increase in work ambulatory DBP (+3.8 mm Hg, P=.02) controlling for the covariates listed above, than the reference group (no exposure at

either wave, N=138), whose mean DBP changed minimally over 3 years. A similar pattern emerged for work SBP. The group that moved from job strain to no job strain experienced a drop in adjusted DBP over time (N=25, DBP=-1.5 mm HG), while, conversely, the group that moved from no strain to job strain experienced a rise in adjusted DBP (N=17, DBP =+0.9 mm Hg). Differences in work DBP across the 4 exposure groups were significant (P=.04). A similar pattern emerged for work SBP.

These associations are now being tested over a 6-year period. In addition, 90 women are now included in the cohort study. Analysis is continuing of the main effects of demographic variables, such as gender, race, age, and socioeconomic status, and their possible interaction with job strain. In addition, several new tests are being added to the Cornell study. One is for urinary catecholamines and cortisol, to better assess the biological mechanisms involved in blood pressure elevation, and another is an ultrasound procedure to measure the extent of atherosclerosis in the carotid artery. Aside from associations between job strain and standard coronary risk factors, other hypothesized pathways by which job strain might affect CVD are an increase in the mass of the left ventricle (LVMI), an increase in the speed of coronary atherosclerosis through mechanisms such as coagulation, and the precipitation of myocardial infarction or arrhythmias among vulnerable persons with underlying heart disease.

In addition, the current study only assessed current exposure to job strain, which cannot adequately reflect interpersonal differences in cumulative exposure. Some older study participants with high blood pressure may have worked for years in high strain jobs, but were eventually promoted (to a job with more authority and/or skills), and were therefore classified as "not exposed" in this analysis. In theory, a measure of cumulative exposure would provide a more rigorous test of the job strain hypothesis. While the cross-sectional age-strain interaction (the apparent lack of effect among the 30-40 year olds in the study) suggests an induction period of at least a decade, preliminary cohort findings, stratified by age group, suggest that blood pressure increases occurred over three years even in the youngest group. Therefore, complete work histories are now being collected from study participants.

Previously, attempts were made to construct a more "objective" measure of exposure by imputing to individuals the national averages of job characteristics for their job title. However, this strategy results in substantial misclassification due to within-occupation heterogeneity, and a loss of statistical power for detecting job strain effects. Such a technique might be more effectively applied within a workplace, by averaging people's ratings of job characteristics across a job title. Other strategies need to be developed to obtain more objective measures of job stressors, for example, by looking at other features of the work environment that may be correlated with job strain (such as involuntary overtime, low education required by the job, sexual harassment, conflict with supervisors or coworkers, assembly-line work, electronic monitoring, short cycle time work, etc.).

It has also been suggested that the typical measures of job demands and job decision latitude need revision and possible expansion. For example, levels of workers' influence, not just on their task, but higher level influence at the group, department or company level, either individually by workers or collectively, also need to be examined.

With the help of work by Jeffrey Johnson, Ellen Hall and Tores Theorell, a third major psychosocial job factor has been added to the job strain model -- social support from coworkers and supervisors, or lack of social isolation -- which is hypothesized to be protective against illness (5). Such measures need to be analyzed in the current study and in future studies, as well as other job characteristics such as physical exertion, job security, and chemical and physical hazards (e.g., lead, carbon monoxide, solvents, noise). Some participants' blood lead levels will be measured in the Cornell study to examine whether lead is possibly a confounder or effect modifier in the job strain-blood pressure relationship.

Finally, while most studies of the effect of job strain have focused on cardiovascular disease and psychological distress outcomes, several recent studies have also been conducted showing an effect of job strain on adverse pregnancy outcomes such as low birth weight, spontaneous abortion, and pregnancy-induced hypertension. In addition, repetitive, short cycle time work, which is a predictor of the development of cumulative trauma disorders (CTDs) is similar in

concept to job strain. (The stress of electronic monitoring has also been recently linked to CTD symptoms.) Therefore, we recommend the use of the job strain assessment instrument not just in studies of cardiovascular disease and hypertension, but any occupational health study involving ergonomics, psychological strain, reproductive health outcomes, or other possible stress-related outcomes.

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ADJUSTMENT FOR SMOKING, ALCOHOL CONSUMPTION, AND SOCIOECONOMIC STATUS IN THE CALIFORNIA OCCUPATIONAL MORTALITY STUDY

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This paper presents methods for adjusting for smoking, alcohol, and socioeconomic status in death certificate-based occupational mortality surveillance. The methods were applied in the California Occupational Mortality Study, a statewide study of rates based on 180,000 deaths and census estimates of occupations. For each occupation, levels of smoking, alcohol consumption, and socioeconomic status were estimated using National Health Interview Survey and U.S. Census data and an empirical Bayes procedure to improve the stability of smoking and alcohol estimates for small occupations. Expected death rates for occupations were calculated by modeling rates as a function of age, smoking, alcohol, and socioeconomic status with Poisson regression.

The effects of adjustments were usually moderate and in the expected direction, with the adjusted relative risks (RR) being generally closer to 1.0 than the unadjusted estimates. After adjustment, elevated risks were identified in several occupations, including agricultural occupations in which there was excess mortality from injury in all agricultural occupations combined ($RR = 1.60$, $p < 0.05$) and excess mortality from chronic obstructive pulmonary disease in farmers ($RR = 1.65$, $p < 0.05$). Physicians and dentists had very high rates of suicide (adjusted $RR = 2.12$, $p < 0.05$).

Many occupations were identified that had high levels of smoking or drinking and correspondingly high unadjusted mortality from diseases related to these factors. Such occupations could be considered in the targeting of preventive intervention programs. The following male

occupations had high estimated levels of smoking and significant excess mortality from respiratory and cardiovascular diseases: construction workers, truck drivers, roofers, operating engineers, bartenders, and waiters. Occupations with high estimated levels of alcohol consumption and significant excess mortality from cirrhosis and other liver diseases or cancer of the lip, oral cavity, or pharynx were: bartenders, cooks, helpers and laborers, performing artists, stone masons, roofers, and waiters.

OCCUPATIONAL IMPAIRMENT AND DISABILITY AMONG APPLICANTS FOR SOCIAL SECURITY DISABILITY BENEFITS IN PENNSYLVANIA

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Introduction

A potential source of data on work-related impairment and disability, as yet not widely utilized, is the federal Social Security Disability Insurance (SSDI) benefit program. For many workers with occupationally caused illnesses and injuries, SSDI serves as an alternative or back-up benefit system for workers' compensation. Therefore, it is potentially an important data base for occupational health surveillance.

Each state can designate a "state agency" responsible for reviewing applications and making disability determinations. In Pennsylvania, claimants for SSDI benefits apply to the Bureau of Disability Determination (BDD) in the Department of Labor and Industry. In principle, the records of this Bureau can serve as a source of information on the impaired and disabled population, potentially including information on workplace causes of impairment and disability.

To assess the extent of workplace-related disease and injury among SSDI applicants, we carried out an analysis of such information contained in BDD records for two months in 1990. This study was conducted as part of a larger report on occupational disease and injury in Pennsylvania.

Methods

SSDI benefits are awarded based on the presence and degree of functional impairment, rather than on etiology. Hence, the disability application form does not specifically request information on the work-relatedness of an individual's medical condition. However, the

application does ask how the applicant's condition affects his/her ability to work, and it inquires into past jobs including job title, type of business, and dates worked as far back as 15 years from the time of application for benefits. Using these data, it is possible to make judgments about whether the applicant's previous employment could plausibly have contributed to current impairment and disability.

Since this information is not routinely abstracted onto Social Security data tapes, we could not readily assess the proportion of past disability applicants in Pennsylvania with work-related problems. As an alternative approach, we reviewed 240 consecutive first-time applications assigned to a single BDD claims examiner (LG). The applications were processed in the Harrisburg branch (one of three) of the BDD during the two-month period from February through March, 1990. Two occupational physicians (EB, HF) independently reviewed each case and made determinations of work-relatedness; there was concurrence on all cases. We considered a case to have a work-related component if there was a clear statement of a workplace illness or injury associated with the impairment, or if the applicant had worked at an occupation with a high likelihood of exposures known or suspected to contribute to the condition of interest (e.g., lung cancer in a welder).

Based on the results of this analysis, we extrapolated the results to Pennsylvania, to estimate the annual number of new disability cases statewide that are occupationally related. To do this, we obtained an estimate of the total number of SSDI applicants for 1990, excluding disabled children, psychiatric cases, and widows. (It was necessary to use an estimate, because no data were available that excluded these categories of applicants from the total.) Next, because the probability of a disease being occupationally related varies by organ system involved, we stratified these applicants by organ system, based on the distribution of applications submitted to the Harrisburg BDD office. This distribution was derived from a random sample of cases evaluated in the Harrisburg office, compiled during a 1990 quality assurance evaluation (LG, unpublished data). We then multiplied the number of estimated applicant cases in each organ system category by the probability of being occupationally related and disabled, as derived from our study sample. Finally, we summed the results from each organ system category to generate a

total number of estimated occupationally-related disabled cases receiving SSDI benefits in Pennsylvania in 1990.

Results

Of the 240 SSDI applicants we reviewed, 166 (69%) were awarded SSDI benefits, and 74 (31%) were denied these benefits. A total of 27 applicants (11%) had potentially work-related conditions. These included 14 of the 166 who received SSDI benefits (8%) and 13 of the 74 whose claims were denied (18%).

The distribution in our study sample differed from the overall profile seen in the Harrisburg BDD office, since cases are not randomly assigned to claims examiners. For this reason, results on disability and work-relatedness are stratified by organ system.

The proportion of applicants receiving SSDI benefits ranges from zero (skin) to 86.5% (multiple organ system), and the proportion of these found to be work-related ranges from zero in several categories to 100% in the neoplastic and neurologic categories (based on six cases and one case, respectively).

The age distribution of our sample did not differ from the age distribution of the quality assurance sample, and the proportion of cases that were occupational did not vary with age.

When we extrapolated our results to an estimated 71,680 SSDI applicants in Pennsylvania in 1990, excluding disabled children, psychiatric patients, and widows (H. Thorkelson, BDD, personal communication), we projected 5,076 new SSDI beneficiaries with an occupationally-related disability.

Although we did not prospectively abstract information on whether applicants had applied for workers' compensation (WC) benefits, we were retroactively able to obtain information on three of the lung cancer patients who we concurred had a potential work-related component. None had filed for WC benefits.

Discussion

The study results indicate that a substantial number of applicants for SSDI benefits in Pennsylvania, and by inference nationally, are likely

to be suffering from an impairment caused or exacerbated by prior workplace exposures. The neoplastic disease category merits specific discussion. Of the 59 disability applicants with cancer, we concluded that six (10.2%) had some work-related etiologic component. This proportion is consistent with estimates published elsewhere of the annual incidence of work-related cancers. Our finding of 10.2% is probably conservatively biased, because information on occupation was abstracted from a disability application form that does not elicit a full occupational history. With more complete information, more associations between past employment and current cancer might emerge.

Our analysis was based on a small convenience sample from one reviewer's files in one branch of the BDD. As a result, the distribution by organ system in our sample differed from other examiners and BDD branches and was a potential bias. However, since our analysis was stratified by organ system, the major potential effect on our analysis is the impact on the robustness of the point estimates for each organ system.

Musculoskeletal cases were the most prevalent in our sample despite being underepresented (based on the quality assurance sample used for comparison). In fact, 40% (11/27) of cases judged to have a work-related component were musculoskeletal in origin, and 30% (11/37) of applicants in this category had a work-related component. Moreover, in our statewide projections of work-related impairment and disability, we used the percentage distribution of applicants in the quality assurance sample which was representative of the distribution of applicants in all three BDD branches. Consequently, our estimates are unlikely to underestimate the total number of work-related cases and awarded claims statewide.

The other major source of potential bias in our sample was age. However the age distributions of our sample and the quality assurance sample were similar, making it unlikely that age affected our projected estimates of work-related disease and injury.

Currently, state agencies responsible for conducting disability determinations do not review applications with an eye toward identifying those claimants as sentinel events who may be suffering from an occupational disease or injury. But because these agencies

receive a thorough medical history and at least a sketchy work history from each applicant, they are well-positioned to identify claimants (and their co-workers) with potentially work-related impairments. These disability determination agencies could, then, set in motion a variety of follow-up activities directed at both the claimant and the claimant's former employer(s). These activities could potentially benefit the claimant, other similarly exposed workers and the Social Security Trust Fund.

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ANNUAL INCIDENCE AND RISK FACTORS OF NEEDLE-STICK INJURIES AMONG NURSES IN A UNIVERSITY HOSPITAL

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The objective of this study was to determine the annual incidence rate and risk factors of needle stick injuries among nurses. In May of 1991, 998 nurses of a university hospital were asked to fill out a structured questionnaire regarding the annual frequencies and mechanisms of their needle stick injuries. 863 (86.5%) responded, and a random sample of 85 of them were asked to refill the same questionnaire. The reliability calculated by Kappa value was 66.7%. The results showed that the annual incidence rate of needle stick injuries was 75.2% in the previous year. If only considering contaminated needles, there were 44.4% during the previous year. The annual incidence rates of needle stick were higher during the preparation of medication (59.8%), cardiopulmonary resuscitation (34.9%), and cleaning the table (33.5%); while mechanisms of such injuries showed that 58.6% happened during the recapping of needles, 36.5% happened during the removing of needles. Only 17 nurses with needle stick injuries went for HBIG (hepatitis-B immune globulin) injection. We concluded that the needle and its cap need to be redesigned to avoid such injuries, and that nurses should be provided with adequate education and training to prevent adverse effects from needle sticks.

SURVEILLANCE OF OCCUPATIONAL SKIN DISEASE IN THE UNITED KINGDOM: THE OCC-DERM PROJECT

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Occupational dermatoses are common and they may lead to severe and lasting disability. However, there have been few attempts to develop a systematic method for assessing frequency, type of disease and the agent responsible. Incidence rates by industry have been reported for the US[1] and Denmark[2] but studies of agents have been based largely on patients seen at one or more special clinics,[3,4] or on compensated cases.[5]

In September 1989 the Health and Safety Executive commissioned the British Association of Dermatologists to pilot a surveillance scheme for occupational skin disease. The work, to be carried out under the supervision of the British Contact Dermatitis Group, sought to answer the question "Is it possible to establish an effective national information and early reporting scheme system for occupational skin disease?" The scheme has much in common with the SWORD project[6] for occupational respiratory disease which is also funded by the Health and Safety Executive.

The pilot scheme, which will run until January 1993, includes 17 centers located in major cities throughout the UK. The participating dermatologists agreed to report, at three month intervals, all new cases thought to be due to occupational exposure. Each center completed a reporting card giving diagnosis, date of birth, sex, type of work and suspected agents. The occupations reported were coded using the three figure occupational codes devised for the UK census.[7] Suspected substances were classified on a "chemically defined substance code" developed by the funding agency for its own use. Denominator data on sex, age and occupation were obtained from the Labor Force Survey,[8] a household survey conducted by the Office of Population, Censuses and Surveys.

During the first two years of the pilot study, August 1990 - July 1992, 2861 cases were reported; of these 96% were contact dermatitis, and the rest of this report is limited to such cases.

In men, the most frequent occupations were metal working and maintenance fitters (7.7%), laborers in making and processing industries (7.0%) and machine tool operatives (6.1%). Among the women, the most frequent were hairdressers (16.6%), cleaners and domestics (8.4%) and nurses (7.9%). The agents commonly reported included, for men, non-specific irritants (11.2%), petroleum oils (11.1%) and rubber (8.1%). For women, nickel (24.9%) accounted for more cases than any other agent, followed by non-specific irritants (15.6%) and hairdressing chemicals (12.4%). Comparison with Labor Force Survey data suggested that women under 30 years were over-represented among the cases (27% of women observed, 14% expected), while six occupational groups had reporting rates at least 10 times that expected: these were machine tool operatives, printers, florists, hairdressers, spinners and laborers in making and processing.

This project has now been funded for a further three years, and has been extended to include all consultant dermatologists in the UK.

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OCCUPATIONAL MORTALITY IN ITALY: A RECORD-LINKAGE BASED SURVEILLANCE SYSTEM

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A national surveillance program of occupational mortality is being implemented in Italy. It is based on record-linkage procedures among databases containing individual information about work histories and health outcomes. Such surveillance systems represent a major improvement in terms of efficiency and validity, in comparison with more traditional occupational mortality analyses based only on death certificates. On the other hand, the feasibility of record-linkage depends on the availability of suitable keys for linkage and on the confidentiality rules in effect in a given country.

This paper describes the main features of the available databases and of the record-linkage procedures, along with some examples of finding from an occupational mortality analysis based on a linkage between census records and death certificates.

The databases providing information on the occupational history of a person include: Census (every 10 years, economically active population, 258 job titles and 545 industry codes), pension fund (complete work history back to 1974, employees in the private industry, 12 titles, 545 industry codes), tax return (yearly back to 1978, economically active population, 9 professional titles, 280 industry titles), workers' compensation (occupational diseases and work injuries back to 1937, economically active population, 473 job titles, 240 industry codes, 51 occupational exposures). Information on causes of death (ICD 8th and 9th) is available from the National Death Index (created in 1969, anonymous data) and from the Regional Death Indexes (implemented in a few Regions since 1985, covering 50% of Italian deaths with individual identification data).

Three different sets of variables are needed for the record linkage. A first set consists of the personal identification number, which is

available in the tax return file and may be automatically created on the basis of the personal identificators available in the Regional Death Indexes. A second set of variables, consisting of the household number and the date of birth, allows one to link census and mortality records (both at the National and at the Regional level). The third set of key-variables consists of surname, name, date and place of birth, and allows one to match both the pension fund and the workers' compensation records with the Regional Death Indexes.

Two databases are ready for an epidemiologic analysis of mortality among economically active individuals at 1981 census: The Torino Longitudinal Study - TLS - (10,798 deaths, follow-up 1981-89, Standardized Mortality Ratio analysis), and the National Mortality Cross-sectional Study - NMCS - (15, 734 deaths, 6 month follow-up 1981-82, Mortality Odds Ratio analysis). Two examples of results are illustrated.

The mortality pattern among male drivers of motor vehicles shows significant excess for lung cancer (NMCS: MOR 1.28, 95% CL 1.02-1.61; TLS: SMR 1.43, 95% CL 0.95-2.09) and for traffic accidents (NMCS: MOR 1.54, 95% CL 1.22-1.96; TLS: SMR 1.46, 95% CL 0.52-3.09); and the mortality pattern for male agriculture workers in NMCS includes significant decreases of mortality for lung cancer (MOR 0.74, 95% CL 0.62-0.88) and ischemic heart diseases (MOR 0.83, 95% CL 0.71-0.96); while significant excess for stomach cancer (MOR 1.38, 95% CL 1.08-1.77), work injuries (MOR 2.11, 95% CL 1.66-2.68) and suicides (MOR 1.96, 95% CL 1.50-2.56).

INEFFECTIVE WORKPLACE SURVEILLANCE IN A STEEL FOUNDRY, CONNECTICUT, 1984-1990

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Background

In October 1991, separate community sources reported two cases of disabling lung disease among air arc operators in one Connecticut foundry to the Connecticut Department of Health Services. The health department initiated an investigation of the foundry's workforce and learned that the National Institute of Occupational Safety and Health (NIOSH) had investigated this steel foundry in 1979 as part of its Health Hazard Evaluation program. The NIOSH review of annual medical surveillance data collected in 1979 detected previously unrecognized chest radiographic findings indicative of pneumoconiosis in 4 (3%) of 117 employees. Their industrial hygiene evaluation of the workplace identified excess silica in the foundry's grinding, molding, and shakeout areas and an excess of a variety of metal fumes in the air arc booth. At that time, NIOSH recommended that the foundry improve its medical surveillance program; implement an Occupational Safety and Health Administration-approved respirator program; institute engineering controls to improve ventilation; and perform repeated environmental monitoring. While investigating the two sentinel cases from 1991, we assessed the usefulness of the foundry's workplace surveillance system for detecting and preventing occupational lung disease.

Methods

For the period 1984 through 1990, we evaluated the basic components of the foundry's surveillance system for both hazard

exposures and health outcomes. The following surveillance system components were reviewed:

- the collection of surveillance data,
- the analysis of these data,
- the dissemination of information derived from surveillance data, and
- the application of this information to the workplace for the purpose of disease prevention.

Medical surveillance data collected from workers in 1984, 1985, 1986, 1989, and 1990 were abstracted and reviewed. Medical surveillance was not conducted in 1987 and 1988. We interviewed the medical subcontractor who conducted medical surveillance from 1984 through 1990 to determine the procedures for conducting and evaluating the foundry's medical surveillance program.

Because of our initial concern with occupational lung disease, we reviewed chest radiographic data and pulmonary function data. Pulmonary function test data are not presented because of the variable quality of those data. The medical subcontractor's chest radiographic interpretations were reviewed over time and for the group of workers evaluated in 1990.

Results

Health Outcome Surveillance Evaluation Annual medical examinations were required of all current employees of the foundry. However, only 82% to 92% of eligible workers were in medical surveillance between 1984 and 1990. Annual medical examinations included a respiratory disease questionnaire, a chest radiograph (CXR), pulmonary function testing, and an audiogram. For our evaluation, pneumoconiosis, as demonstrated by CXR, was the event under medical surveillance.

Between 1984 and 1986, the foundry's medical subcontractor did not interpret the surveillance CXRs according to International Labour Office (ILO) criteria for the classification of radiographs of pneumoconioses. Instead, a descriptive interpretation was provided.

In 1989 and 1990, NIOSH-certified B-readers reviewed the annual CXRs according to ILO criteria. The B-readers were different in

each of these years. Additionally, the medical subcontractor considered lung parenchymal profusions up to and including 1/2 to be "mildly abnormal." These profusion criteria are much less sensitive than those used in many pneumoconiosis surveillance programs.

The medical subcontractor did notify individual workers of the type of medical follow-up needed. However, no assessment was made of what the workers did with the medical information given to them. The medical subcontractor also provided medical data to the foundry's management, but did not summarize the clinical features of workers with abnormal CXRs. Because the medical subcontractor was not provided with workplace exposure information, characterization of the workers with abnormal CXRs according to potential job-specific exposures was not possible. The foundry's analysis of the annual and cumulative medical surveillance data, if it existed, was not available for our review.

Hazard Exposure Surveillance Evaluation No industrial hygiene data were available for the period 1984-1990. No quantitative industrial hygiene evaluation of this foundry appeared to have been conducted since 1982.

Surveillance CXR Interpretation Following our review of the foundry's surveillance of workplace hazards and worker's health, we reviewed the CXR data available from medical surveillance. For the period 1984 - 1986, we defined an abnormal CXR as one with an interstitial lung parenchymal pattern, since ILO interpretations of CXRs were not performed by the medical subcontractor during this period. In 1989 and 1990, the medical subcontractor did follow ILO criteria when interpreting CXRs. For this period, we defined an abnormal CXR as one with lung parenchymal round and/or irregular opacities in any or all lung fields with a profusion of 1/0 or greater by ILO criteria. The prevalence of workers with an abnormal screening CXR was <5% for 1984-1986 and 1989 versus 43% (34/79) in 1990.

For 1990, workers at increased risk for abnormal CXRs included those >= 40 years old (56%[24/43] versus 29%[10/35]; RR=2.0, 95% confidence interval [CI]=1.1,3.5) and those with duration of employment >= 10 years (65%[22/34] versus 22%[7/32]; RR=3.0,

95% CI=1.5,6.0). The rate of abnormal CXRs was significantly higher among chippers and grinders than among all other workers (67%[14/21] versus 35%[18/51]; RR=1.9, 95% CI=1.1,3.0) and was independent of age or duration of employment. Ethnicity, smoking history, and history of respiratory disease did not increase the risk of having abnormal CXRs. The single index case screened during this period had a normal CXR.

Discussion

Effective workplace surveillance requires ongoing, systematic monitoring of both health outcomes and hazard exposures. Linkage of annual and longitudinal workplace medical surveillance data to workplace hazard exposure data is required to evaluate whether adverse health outcomes are associated with workplace exposures and to identify the materials and processes toward which primary prevention measures (e.g., engineering controls to reduce worker exposures) should be directed.

The foundry implemented the 1979 NIOSH recommendations incompletely and inconsistently. This foundry and its medical subcontractor were committed to annual medical surveillance of foundry workers, but they failed to follow-up on workers who had been notified of possible adverse health effects; failed to respond to the increase in the prevalence of workers with abnormal CXRs in 1990; and failed to link medical data to the assessment of workplace hazards.

While the foundry's management suggested that some engineering controls were implemented between 1984 and 1990, their effectiveness is not known since hazard exposure data were absent. After 1982, the NIOSH recommendation for routine hazard exposure surveillance was ignored.

Conclusion

Summary health outcome surveillance data from the foundry had not been reviewed, analyzed, and reported prior to our investigation. This surveillance system failed to indicate the presence of a problem with both the reported lung disease in the screened air arc operator and the increased prevalence of abnormal CXRs among chippers and grinders. During 1984-1990, potentially hazardous exposures could

not be targeted for intervention because the foundry lacked information on hazard exposures in the workplace for this period. Additional investigation is required to determine whether occupational lung disease exists among workers in this foundry.

Recommendations

Following our evaluation of the foundry's workplace surveillance system, we initially recommended that the reasons for the high prevalence of workers with abnormal CXRs in 1990 be further assessed. This assessment should include the interpretation of all 1984-1990 CXRs following ILO criteria, and further medical assessment of all workers with abnormal CXRs. Additionally, an industrial hygiene evaluation of the chipping and grinding operations should be conducted.

More general recommendations include the following:

- A comprehensive hazard surveillance program involving periodic analyses of aggregate findings should be established and maintained.
- The foundry should continue to perform annual medical surveillance, similarly involving period analyses of aggregate findings.
- Medical and hazard surveillance data should be linked and analyzed to determine the risk factors for adverse health outcomes.
- Medical and industrial hygiene consultants should be required to coordinate their systematic evaluations of the workforce and the workplace.
- In addition to notifying workers of abnormal surveillance findings and of overexposures, employers should follow-up on persons with abnormal findings to determine their medical significance.

EPIDEMIOLOGIC SURVEILLANCE FOR OCCUPATIONAL LEAD POISONING IN WASHINGTON STATE USING WORKERS' COMPENSATION AND OTHER SOURCES OF DATA: ANALYSIS AND RECOMMENDATIONS

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Lead poisoning of workers continues to occur despite a large body of literature on its prevention. Improved surveillance of the problem can lead to needed prevention activities. We tested the usefulness of workers' compensation data for surveillance of lead poisoning in Washington State using a sentinel event model, and investigated the feasibility of using several other data sources for surveillance.

We performed a detailed record review of the 146 claims filed for lead poisoning or related procedures between 1983-1990; of these only 45 were actually associated with lead. Only 10 claims filed in 1989-90 were identified with blood lead levels (BLLs) at least 40 μg/dl or zinc protoporphyrin levels greater than 100 μg/100ml, and we determined the work location of each case (six of the claims were related to transient construction operations). Worksite air sampling and biomonitoring at the four remaining locations demonstrated significant exposure in other workers. We compared these worksites to similar operations in which no claims had been filed and found even greater exposures/BLLs at these referent worksites. It is apparent that while workers' compensation records may contribute sentinel events, they give a very incomplete picture of the extent of occupational lead poisoning.

We also tested the feasibility of surveillance using clinical laboratory reporting, hospital discharge records, mandated toxic substance use records, and industrial hygiene laboratory records. Each of these potentially contribute additional cases of lead poisoning or worksites with the potential for poisoning, but each source also had significant drawbacks. The major problem found was the lack of biomonitoring performed by employers exposing workers to lead, with the result

that over-exposed workers are not captured by any existing surveillance system.

We conclude that a successful epidemiologic surveillance system for occupational lead poisoning must have three components: 1) Laboratory reporting of all elevated BLLs to a central tracking center; 2) Maintenance of a list of all employers who potentially expose workers to lead ("lead users list"); 3) Mandated biomonitoring by all employers on the lead users list. Existing data sources can be used to supplement this system and improve the quality of the lead users list. This surveillance loop, linked with case follow-up and intervention activities, should enable a marked reduction in the occurrence of occupational lead poisoning.

ORGANIZATIONAL CORRELATES OF WORK-RELATED DISABILITY

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We have conducted a study of organizational factors in relation to Workers' Compensation Lost Time Frequency Rates (LTFR). We selected nearly 1000 workplaces in eight "Rate Groups" (industrial groupings), stratified by size (50-99, >100 employees) and LTFR (3 categories). Each was sent a survey: 3 booklets to management, aimed at the senior manager, human resources manager, and management co-chair of the Joint Health and Safety Committee (JHSC), and one booklet for the worker co-chair of the JHSC. Some questions were identical in both the management and worker questionnaires.

Questions explored several areas: basic data on the workplace; management organization, culture and philosophy; management approaches and attitudes to occupational health and safety (OHS); labor approaches to the workplace and OHS; labor-management relations and joint approaches to OHS; indicators and perceptions of physical risk; and financial performance.

In a second phase of the study, we conducted several detailed interviews at a small number of workplaces in our sample. We wanted to explore areas that could not be addressed in a mail questionnaire and examine other questions arising from the survey.

Overall, we received at least one completed booklet from 54% of our sample and all 4 booklets from 44% -- an excellent response in this type of survey. A brief telephone interview with a sample non-responders obtained a 75% response from management and answers were very similar to those from the mail survey. It was more difficult to contact the worker co-chair by telephone and differences from the mail responses are attributed to this. The mail survey

response was similar for each of the LTFR categories, and we believe comparisons between them are valid.

Variables significantly associated with higher LTFR included employee turnover, unionization, grievance rate, low training of labor members of JHSC, work refusals in the last 3 years. Lower LTFR were related to delegation of authority by management, a high degree of worker autonomy/participation, encouragement of career commitment, OHS defined in managers' job descriptions and included in their annual appraisals, and the provision of group safety incentives. The study is discussed in the context of some limitations, including the use of compensation claim rates as measures of safety performance. Interpretations are assisted by the broader understanding of some issues that we gained in the Phase II interviews.

LOST TIME INJURY RATES IN THE U.S. CONSTRUCTION INDUSTRY, 1975-1990

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Introduction

The construction industry in the United States has the highest incidence rate of lost time injuries of all industries in the U.S. It is more than twice the national average for private sector employers and about 30% higher than the lost time injury rate in manufacturing. As of 1990, the construction industry employed over 5 million people or about 5% of the private sector labor force. Lost time injuries among construction workers, however, account for 10.6% of all lost time injuries.[1]

Purpose

The purpose of this investigation is to determine whether there has been progress in reducing either the incidence rate or the number of days lost for lost time injuries in the construction industry. We evaluate trends in lost time injury incidence rates and average days lost in the construction industry and compare injury rates by SIC codes.

Data source, methods

Numbers employed, lost-time injury rates, and days lost rates for two and three digit Standard Industrial Classification (SIC) codes were obtained for the period from 1975 to 1990 from *Occupational Injuries and Illnesses in the United States by Industry*, published annually by the Bureau of Labor Statistics (BLS). (Table 1) These reports are based on information obtained from a random sample of about 10,000 private sector employers in the U.S. All rates are crude estimates; industry-wide rates are estimated from this sample and rates are not adjusted for known correlates of injury rates such as worker age and experience. Data from 1971 to 1974 were not used because it was tabulated differently than the data from 1975 to the present. Data for 1985 were not available.

A lost time injury is defined by BLS as " . . cases which involve days away from work, or days of restricted activity, or both." The lost time injury incidence rate is the total number of lost time injuries per 200,000 hours worked. Lost workdays ". . are the number of work-days (consecutive or not) on which the employee would have worked but could not because of occupational injury or illness." We calculated the average number of days lost per lost time injury by dividing the lost work-day rate by the lost time injury incidence rate.

The SIC coding system is a hierarchical numerical coding system that classifies all employers into classes defined by common products, commodities, or services. Its principal purpose is to monitor economic performance and not occupational injuries. At the two digit level, the construction industry is classified into three classes: SIC 15, building construction, SIC 16, non-building construction, and SIC 17, special trades. These are further subclassified at the three digit level as shown in Table 2.

To investigate trends in both lost time injury incidence rates and average days lost, we performed simple linear regressions of these two variables on years for the three major sectors of the construction industry for the period 1975-1990. At the three digit level, we identified the three highest injury incidence rates for each year.

Findings

Lost time injury incidence rates for all three sectors of the construction industry have increased from around 5 to more than 6 lost-time injuries per 200,000 hours worked over the period from 1975 to 1990 (Figure 1, Table 3). Similarly, average days lost per lost time injury have increased from a low of 16 days in 1979 to a high of 23 days in 1990 (Figure 2, Table 4). All trends are significant statistically.

Sectors of the industry that have consistently higher lost time injury rates are SIC 176 (roofing, siding, and sheet metal work) which had the highest rate for each year and SIC 174 (masonry, stonework, and plastering), which was second highest for half of the years (Table 1). The SIC code with the third highest injury rate varied from year to year but almost always occurred in one of the subgroups of SIC 17 (special trade contractors).

Discussion, conclusions

Both lost time injury incidence rates and the average number of days lost per lost time injury in the construction industry have increased during the period from 1975 to 1990. The highest lost time injury rates almost always occurred among special trade contractors with roofing, siding, and sheet metal work consistently reporting the highest injury rates.

We conclude that whatever efforts have been made during this period to reduce the risk of lost-time occupational injuries in the construction industry have not been successful. Intervention in some form is necessary to reduce the risk of injury. Additional investigation is needed to identify opportunities to prevent injury, for the industry as a whole and particularly in SIC 176 and 174.

Reference

1. U.S. Department of Labor, Bureau of Labor Statistics. Occupational Injuries and Illnesses in the United States by Industry, 1990. Bulletin 2399. Washington, DC: U.S. Government Printing Office, April, 1992

Table 1. Lost time injury incidence rates for the construction industry, 1975-1990

SIC Year:	1975	76	77	78	79	80	81	82	83
15	5.0	5.1	5.6	6.2	6.7	6.4	6.1	5.9	6.1
152		4.6	5.5	5.9	6.0	5.7	5.5	5.1	5.7
153		3.2	4.7	6.2	6.8	5.2	5.1	4.5	4.2
154		6.0	5.8	6.6	7.4	7.2	6.7	6.6	6.7
16	5.8	5.4	5.6	6.2	6.6	6.2	5.9	5.8	6.1
161	5.1	5.2	5.3	5.7	6.2	6.1	5.7	5.5	5.8
162	6.4	5.5	5.7	6.4	6.8	6.3	6.0	5.9	6.2
17	5.4	5.5	6.0	6.5	6.9	6.6	6.5	6.1	6.3
171	4.6	5.0	5.4	5.8	6.1	5.8	5.9	5.5	5.8
172	3.6	4.5	4.4	4.6	5.1	5.0	4.8	4.6	4.9
173	4.1	4.2	4.4	4.7	5.3	5.1	5.1	5.0	5.2
174	5.5	5.5	7.1	7.3	7.6	7.6	7.4	6.7	7.1
175	5.6	5.4	7.2	7.2	7.4	6.9	6.3	6.3	7.0
176	10.0	9.4	9.7	11.7	12.0	11.2	10.2	10.2	10.2
177	5.6	6.4	6.3	6.6	6.8	6.9	6.7	5.9	6.9
178	6.6	6.6	7.0	6.5	8.5	8.4	7.1	6.3	5.7
179	6.3	6.1	6.2	7.1	7.5	7.3	7.4	6.9	6.4

continued on next page

Table 1 continued. Lost time injury incidence rates for the construction industry, 1975-1990

SIC Year:	1984	85	86	87	88	89	90
15	6.9		6.6	6.4	6.4	6.4	6.3
152	6.2		6.3	5.5	5.8	6.0	6.0
153	5.7		4.6	4.9	3.8	3.5	2.6
154	7.6		7.1	7.6	7.3	7.1	6.9
16	6.3		6.3	6.3	6.9	6.4	6.2
161	6.3		5.8	6.2	6.6	6.4	6.4
162	6.4		6.5	6.4	7.0	6.5	6.1
17	7.0		7.1	7.0	6.9	6.8	6.8
171	6.3		6.4	6.8	6.2	6.2	6.5
172	5.4		5.1	4.4	5.2	4.8	5.2
173	5.4		5.9	5.3	5.4	5.3	5.2
174	8.5		8.6	8.3	8.5	8.2	8.6
175	7.8		7.3	8.0	7.0	7.0	6.9
176	11.5		10.9	10.8	11.0	9.9	9.6
177	7.1		7.2	6.9	7.1	6.9	7.1
178	7.3		5.1	6.8	6.9	7.5	6.9
179	7.1		7.3	7.2	7.1	7.6	7.0

Table 2. Regression of lost time injury incidence rates on years for SIC 15, 16, and 17

SIC		Description
15		General building contractors
	151	Residential building construction
	152	Operative builders
	153	Non-residential building construction
16		Heavy construction, except buildings
	161	Highway and street construction
	162	Heavy construction, except highway
17		Special trade contractors
	171	Plumbing, heating, air conditioning
	172	Painting and paper hanging
	173	Electrical work
	174	Masonry, stonework, and plastering
	175	Carpentry and floor work
	176	Roofing, siding, and sheet metal work
	177	Concrete work
	178	Water well drilling
	179	Miscellaneous special trade contractors

Table 3. Regression of lost time injury incidence rates on years for SIC 15, 16, and 17

SIC	Slope	r^2	t	p
15	0.071	0.411	3.01	= 0.01
16	0.499	0.400	2.95	< 0.02
17	0.082	0.560	4.07	< 0.01

t with 13 d.f., tests the null hypothesis that the slope = 0.00

Table 4. Regression of average days lost per lost time injury on years for SIC 15, 16, and 17

SIC	Slope	r^2	t	p
15	0.250	0.564	4.10	< 0.01
16	0.301	0.584	4.27	< 0.01
17	0.220	0.587	4.30	< 0.01

t with 13 d.f., tests the null hypothesis that the slope = 0.00

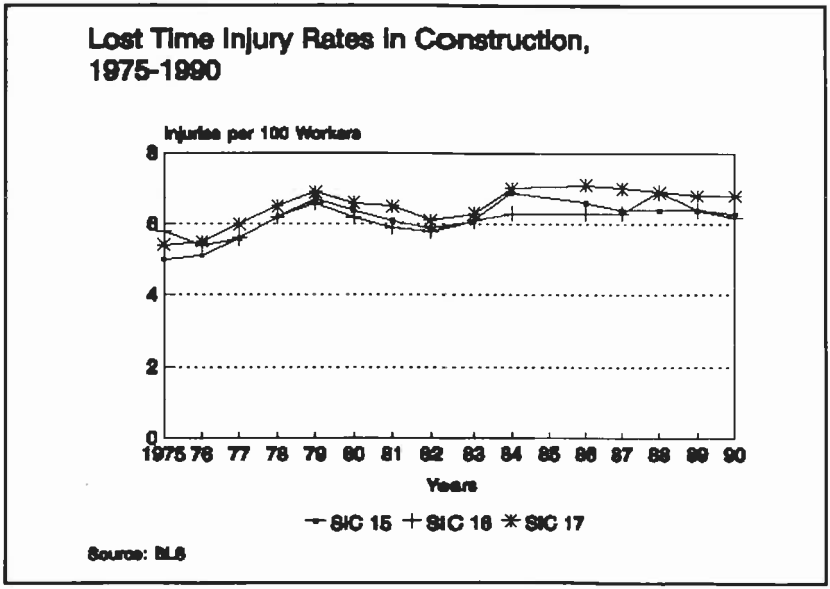

Figure 1. Lost time injury rates, 1975-1990

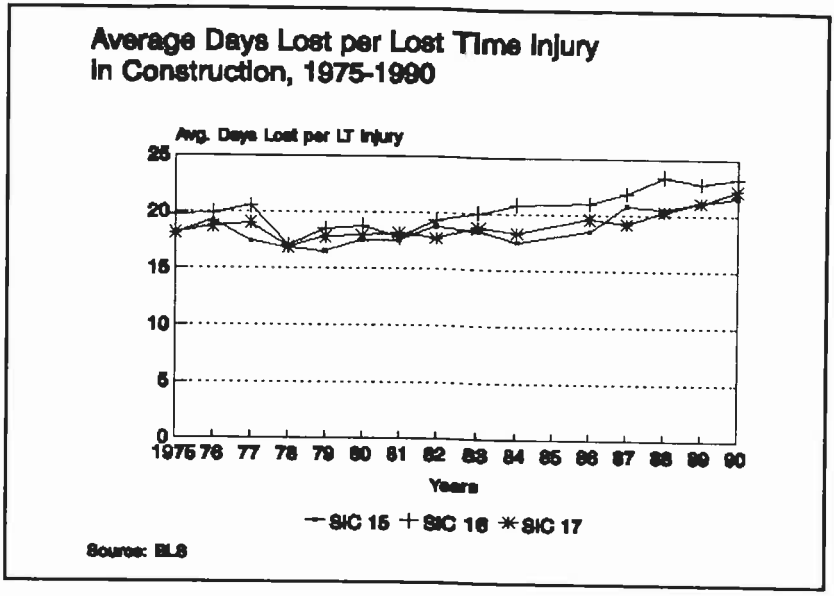

Figure 2. Days lost per lost time injury, 1975-1990

LIVER AND KIDNEY FUNCTION IN HOUSE PAINTERS WITH LONG-TERM EXPOSURE TO ORGANIC SOLVENTS

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Cross-sectional studies of active workers have indicated an effect of organic solvent exposure on urinary albumin levels, serum bile acids, and rarely, on serum liver enzymes. The objective of this study was to determine if tests of liver and kidney damage were affected among house painters with long-term, previously heavy, solvent exposure.

The study group was selected from the painters and carpenters who had been members in their respective trade unions for at least 10 years before 1970 and who were born 1925 or later.

148 painters and 85 carpenters who had performed psychometric conscription tests were invited to a clinical examination, regardless of their current exposure status. 135 painters and 71 carpenters participated. Blood and urine samples were obtained in the morning after one night's fasting. Serum activities, or levels, of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), bilirubin, cholic acid, chenodeoxy cholic acid, and the fraction of total transferrin with isoelectric pint 5.7 were used as tests of liver function. Urinary albumin was used as an index of glomerular function.

The participants were interviewed concerning their solvent exposure and potential confounding factors (age, alcohol consumption, obesity, drugs affecting liver function). Cumulative solvent exposure, frequency of episodes feeling high, and the solvent exposure during the last year were considered as exposure estimates. The data were analyzed with multiple linear regression and logistic regression with the results adjusted for potential confounders.

There was a significant relationship between cumulative solvent exposure and ALP serum activities ($p=0.03$). There was no relationship between any exposure estimate and any of the other outcome variables.

The increasing ALP activities with increasing cumulative solvent exposure may indicate minor changes in liver function due to solvent exposure since ALP previously has been suggested a useful indicator of mild hepatic injury due to environmental agents. However, all other outcome variables were unaffected by solvent exposure and it seems that long-term, heavy exposure to paint solvents, in most workers, has a low potential to cause chronic liver damage or glomerular damage in the kidneys.

GLOMERULONEPHRITIS AND SOLVENT EXPOSURE: PRELIMINARY RESULTS OF A CASE-CONTROL STUDY OF 298 BIOPSY PROVED CASES

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Since 1972, when Beirne published thirteen cases of Goodpasture's syndrome, six of whom had been heavily exposed to fuel or solvent vapors,[1] several cases of rapidly progressive glomerulonephritis,[2] some cases of membranous glomerulonephritis[3,4] and one case of Ig A nephropathy[5] have been reported among subjects exposed to solvents. Detailed analysis of these case histories reveals widely differing exposures insofar as the type of solvents and the level and duration of exposure, which varied from a few hours to more than twenty years. Thus, although some of these case histories suggest an association between exposure and disease occurrence, they do not provide evidence for a causal relationship.

Since Goodpasture's syndrome is a very rare disease, all epidemiological case control studies[6-18] -- with the exception of one study[19] -- concern primarily all other types of glomerulonephritis. Ten of these studies show a significant increase of odds-ratios, from two to five for all glomerulonephritis related to solvent exposure;[10-18] the other four are negative, with odds-ratios very close to one.[6-9] Most of these studies, however, have methodological weaknesses related to their definition of cases, exposure evaluation, choice of control population and sample size.[20,21]

The purpose of this study was to evaluate the relationship between solvent exposure and glomerulonephritis and to provide an accurate description of the occupations, solvent categories and histological types involved.

Materials and methods

Cases were identified from the list of all patients with histologically proven glomerulonephritis (GN) -- both by light and electron microscopy and immunofluorescence -- diagnosed from January 1985 to February 1991 in the pathology departments of five hospitals in the Paris area. The following histological types were considered:

- Membranous glomerulonephritis (MGN=82);
- Nephrotic syndrome with either minimal change nephritis or focal and segmental glomerulosclerosis and hyalinosis (MCN/FSH=100);
- Ig A nephropathy or Berger's disease (Ig A N = 116).

The study was limited to patients aged 18 or older and living in metropolitan France at the time of their biopsy. Patients with secondary GN due to systemic diseases (diabetes, lupus, malignancies, cirrhosis, rheumatoid purpura) were excluded.

In each hospital, controls were selected in five different departments which treated a wide variety of pathologies and whose populations were very comparable to those of the nephrology wards with respect to social class. Subjects with a history of nephritis, renal failure of any etiology, proteinuria, bladder or renal cancer and those admitted for a work-related accident were excluded. Controls were marched for sex, date of birth (within five years), national origin (French or foreign) and place of residence (Paris area or provinces).

Subjects were recruited between November 1988 and March 1991. To increase the likelihood that case patients would participate in the study, outpatients were interviewed at their own convenience, after visiting the nephrologist (68%) or by telephone (13%); other case patients were interviewed in the hospital (19%).

For exposure evaluation, subjects were asked about their lifetime occupational histories, using a standard questionnaire devised with the help of chemists and industrial hygiene experts. For each occupation held at least 6 months, subjects were asked about solvent exposure and working condition, using a detailed list of all materials or processes in which solvents may be found. These were named as they are known to workers, in order to increase reporting. Industrial activity was coded according to the international standard industrial classification and occupation according to the International standard classification of occupations. Job periods were reviewed blindly with

respect to case-control status by the experts who helped compile the questionnaire. For each period, they assessed type of solvents (halogenated, oxygenated or hydrocarbon), probability, level and frequency of exposure. Painting, gluing and metal decreasing were the types of operation classified in the high exposure level, whereas the cleaning of small parts (e.g., metallic or electronic) and housecleaning activities were classified in the low exposure level. Information was also recorded about subjects' personal characteristics, alcohol and tobacco consumption, drug and medical history.

Potential duration of exposure to risk factors was made comparable between the two groups by studying, for the case patients, only those job periods prior to the first clinical signs of disease, and, for the control subjects, only the corresponding periods, i.e., those periods until they reached the ages at which their matched case patients first became ill. Comparisons of solvent exposure were made:
(1) between cases taken as a whole and controls, adjusting for sex, "age at GN onset" and hospital; (2) between each histological type and all of the controls, according to sex and adjusting for "age at GN onset" and hospital. Adjusted odd-ratios were calculated using a logistic regression model.

Results

Matching for age, sex, national origin and place of residence resulted in a close comparability between cases and controls regarding their social category (Table 1).

Mean age was 51±16 years for MGN cases, 44±18 for MCN/FSH and 38±14 for Ig A N. The male-female ratio was 1.3, 1.2 and 3.3 respectively. Patients from Southern Europe were more numerous among Ig A N cases than among the other two groups. Histological types did not differ according to social category.

There were 15 job categories in which more than 10% of the subjects who worked in them were considered by experts to have been exposed to solvents at a high level, that is, more than 2 hours/week at a high level: no significant increase of risk was observed in these categories. In particular, there was no significant excess of painters, woodworkers, machinery fitters and mechanics or printers among the cases (OR = 0.9, 2.0, 1.4, 0.5, respectively).

Nor did analysis by sex and histological type show an excess of any job.

Thirty percent of male control subjects and 13% of the females had been exposed to solvents during their occupational life, but only 13% and 2%, respectively, had been exposed more than 2 h/week at a high level. Table 2 shows the principal results for men.

Subjects exposed to any solvent showed no excess among the cases, considered either as a whole or by histological type; nor was a significant excess of any of the studied solvent categories found among cases as a whole, as compared to controls. When only the highest exposures were considered, odds-ratios of IgA N were significantly elevated for exposure to oxygenated solvents and aromatic solvents (OR=5.6, 95% CI 1.5-21.2).

No increase of GN risk was observed among women with any solvent category nor for any histological type.

Conclusion

In this study comparing 298 cases of histologically well-defined GN and 298 controls with special attention given to exposure evaluation, we did not confirm an overall association between organic solvent exposure and the occurrence of GN. Nor did we observe any association between overall solvent exposure and any of the histological types considered, including MGN which has twice been found to be related to such exposure.[6,13] These results were true when exposure was defined broadly (a prevalence of 30% among males) and narrowly (a prevalence of 13%).

We found significant relationships between Ig A nephritis and both oxygenated and aromatic solvent exposures, but this result must be regarded cautiously. Among types of glomerulonephritis, only Goodpasture's syndrome and MGN have been related to solvent exposure; MGN has also been clearly shown to be related to mercury exposure and medical uses such as gold salts. Ig A nephropathy, however, has never been related to any toxic exposure, with the exception of a single case report. Nonetheless, since Ig A N is the most frequent histological type of GN in most countries and is a major cause of end stage renal failure, our results should be tested

in other populations, despite the meager support in the literature for a causal relationship between solvent exposure and this type of GN.

Analysis will be continued by comparing the relationship between solvent exposure and GN according to the state of the renal function in order to determine if solvents play a role in the prognosis of the disease. Comparison according HLA phenotype of the subjects will also be performed, since genetic factors are well-known determinants for the onset of MGN.

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Table 1. Description of the population

	Cases (298)	Controls (298)	p
Male	64%	64%	ns
Mean age (± sd)	43 ± 17	44 ± 16	ns
Foreigners	23%	23%	ns
Social category			
Professional and managerial workers	21%	19%	
Clerical, sales and service workers	46%	47%	ns
Agricultural and production workers	28%	30%	
Never employed	6%	6%	

Table 2. Odds-ratio of GN for solvent exposure

MEN ONLY	Controls (190)	Cases (190)	MGN (47)	MCN/FSH (54)	Ig A N (89)
Exposure to any solvent:					
none	70%	1	1	1	1
<2h/week or low level	17%	0.9 (0.5-1.7)	1.3 (0.6-3.1)	1.3 (0.6-3.0)	0.6 (0.3-1.4)
>2h/week and high level	13%	1.0 (0.6-1.9	0.8 (0.3-2.2)	0.9 (0.4-2.4)	1.3 (0.6-2.8)
Exposure > 2h/week and high level to:					
halogenated solvents	6%	0.6 (0.2-1.5)	0.9 (0.2-3.6)	0.2 (0.0-2.0)	0.6 (0.2-2.2)
oxygenated solvents	5%	1.3 (0.5-3.2)	0.7 (0.1-3.6)	1.0 (0.0-2.6)	3.1 (1.0-9.1)
hydrocarbons (aromatic+aliphatic)	11%	1.0 (0.5-2.1)	0.7 (0.2-2.3)	0.9 (0.3-2.6)	1.5 (0.6-3.4)

OCCUPATIONAL NOISE EXPOSURE AND NOISE-INDUCED HEARING LOSS: AN EPIDEMIOLOGICAL STUDY IN CHINA COAL MINERS

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Noise is an occupational hazard in coal mines. There are about 2 million workers exposed to noise in our country's coal mines. Currently, because most of the mines have not adopted efficacious noise control measures, coal miners are exposed to noise at high intensity and for extended periods, so the hazard is very serious. The aim of the study was to assess the extent of the occupational noise hazard in China coal mines and, more specifically, to look for the epidemiological evidence on the relationship between occupational noise exposure and noise deafness in Chinese coal miners.

1502 coal miners with noise exposure who worked underground in five Chinese coal mines were the observed group--ages 24 to 79 years old, with an average age of 46.7; the working years were 5 to 43, with an average of 20.9 years. 130 subjects from the same five coal mines who never had occupational noise exposure were selected as the control group. Their ages were from 20-66 years, with an average age of 40.4. All study subjects were male, and before going to the mine, none had had an explosion history, ototoxic medical history, various ear disease, or history of dizziness.

Hearing was measured with B.K., DANPLAX AS 72 audiometry, and was calibrated before using. According to the standardized examination program, the observed group was examined medically including hearing, after being away from noise for 12-16 hours. The following frequencies were included: 0.5, 1, 3, 4, 6 and 8 kHz.

According to WHO noise-induced grades (class) standardizing, the speech frequency average (0.5+ 1 kHz + 2 kHz /3) was as mainly grades. Before the data was analyzed, the hearing threshold values

were corrected for age. All data were recorded in a computer system and the statistics were carried out using the SAS program.

The statistical analysis showed that the hearing threshold at each frequency tested was remarkably higher in the miners exposed to noise than in the control group. The difference was significant with the T test ($P<0.001$) (Table 1). Factors such as age, smoking, drinking and injury may influence and change the hearing threshold, so the covariance was analyzed. The results showed that after the factor for age was eliminated, the hearing threshold at each frequency for each miner exposed to noise was still higher than in the control group, and was still statistically significant.

The general incidence rate of hearing damage in the observed group was 48.2%-- 31.30 times more than in the control group (1.54%). With age standardization, the incidence of hearing damage in the observed was 45.14% and 2.81% in the controls with a risk of 16.06. This suggested that the risk for noise-induced coal miners was over 1.6 times that of the control, and was highly statistically significant ($p<0.001$) (Table 2).

There was a difference in the incidence rate of hearing damage in the observed group, based on the type of work performed. The highest incidence rate was for rock drilling; the lowest incidence rate was for transference. The order of the incidence rates from high to low was rock drilling > motor and power > cutting coal > explosion > auxiliary transference. The measured noise levels in the mines also showed this same order. The analysis showed a close relationship between the level of occupational hearing damage and the occupational noise exposure level.

Logistic regression was used to analyze the relation between hearing change and 5 non-occupational risk factors (age, smoking, drinking, blood pressure, and injury of the head), and 2 occupational risk factors (exposure noise working years and type of work). Results are shown in Table 3.

Table 3 shows that besides age having a significant effect on hearing change, work years and type of work were also risk factors for hearing loss. The influence of other factors was not significant.

Loss of hearing forecast analysis was carried out with the two linear regression equations of age influence on hearing loss in observed Y = (a) 5.49 + (b) 0.5335 (dB); and in controls Y = (a) 9.73 + (b) 0.12889 (dB). The difference of hearing change was significant in each year's groups between the two groups.

The results showed that the hearing threshold level at 30 years in the exposed group was approximately equal to the hearing threshold at 60 years in the control group. Only at 40 years may one arrive at the up limit of abnormal hearing threshold. Above 60 years may be mid-level damage. Multiple linear regression analysis showed that there was a relationship between hearing threshold change and exposure noise years (shown in Table 4). Using the regression equation in Table 4, the forecast of hearing damage was analyzed for Chinese coal miners (Table 5).

The results showed that if the miner's exposure to noise was less than 5 years, the hearing loss possibly may be about 30 dB at 6.0 kHz; the appearance of hearing loss at 6.0 kHz was the earliest. The time for attaining the abnormal limit was progressively longer at 4.O kHz, 3.O kHz and at the speech frequency. It was found that for exposure to noise at work for about 10 years, the hearing threshold at the speech frequency was below the extra low limits of the normal field (25dB). But the hearing threshold of 4.O kHz and 6.O kHz have exceeded the normal field of high frequency (30 dB). If noise exposure continues for an extra 20 years, the speech frequency change may appear as abnormal hearing. The results may suggest that there was a high risk of population for hearing loss in coal miners with over 10 working years of noise exposure. They should have their health supervised in order to find hearing damage early, and adopt hearing protective measures.

Table 1. Hearing test results of the two groups (x+SD dB)

Group	N(ears)	SF*	3kHz	4kHz	6kHz	8kHz
Observed	3004	28.79 +13.35	38.94 20.36	49.71 21.16	52.58 21.73	47.35 23.87
Control	260	14.75 +5.16	17.45 9.79	20.61 11.65	24.67 13.95	20.63 12.38
Difference		14.04	21.09	24.10	27.91	26.62
T		35.1	30.05	29.39	29.38	30.25
P		<0.001	<0.001	<0.001	<0.001	<0.001

* SF=speech frequency

Table 2. The incidence of various grades of hearing loss

Groups	N	Normal	I	II	III	IV	V	Total
Observed	1502	778	545	128	40	10	1	724
	%	51.80	36.28	8.52	2.66	0.66	0.07	48.20
Control	130	128	2	0	0	0	0	2
	%	98.46	1.54	0.0	0.0	0.0	0.0	1.54

X=105.49 P<0.001

Table 3. Likelihood analysis of factors affecting hearing change

Source	X value	P
Intercept	17.65	0.0000
Age	86.31	0.0000
Work year	83.21	0.0000
BP	0.63	0.4266
Drinking	0.87	0.3498
Smoking	0.12	0.7310
Work kind	54.43	0.0000
	711.53	0.0006

Table 4. Multiple regression analysis of the effect of working years on hearing threshold change (dB)

Index	a	b	F	P
Speech average	18.57	0.44	269.73	<0.0001
3.0 kHz	18.66	0.90	505.743	<0.0001
4 kHz	23.82	0.92	480.85	<0.0001
6 kHz	28.13	0.98	505.85	<0.0001

Table 5. Forecast analysis of hearing loss in coal miners

Index	Working years to attain abnormal limit*	Hearing threshold at various working years		
		10	20	30
Speech frequency	14.16	22.97	27.37	31.77
3.0 kHz	12.60	27.66	36.66	45.66
4.0 kHz	6.72	33.02	42.22	51.42
6.0 kHz	<5.00	37.73	47.74	57.53

* Abnormal limit of speech frequency average=25DB
Abnormal limit of high frequency average =30DB

MORTALITY OF PAINT PRODUCTION WORKERS. RE-ANALYSIS AFTER ASSESSMENT OF EXPOSURE TO SOLVENTS

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A cohort mortality study of employees at one of the largest coatings and paints industry in Italy has been re-examined.

1614 male workers employed for at least four months since the beginning of operations were followed-up during the period 1948-1987. Vital status ascertainment was 96.4% complete. The cohort experience was 35,970 person-years and less than 20% of the members died during the study period (287 deaths). Standardized Mortality Ratios were estimated: the age and calendar time mortality rates of the corresponding population of a nearby town were used to compute expected deaths.

The plant is a paint manufacturing plant operational since 1948 which has undergone the evolution of coating and resin technology, engineering and industrial hygiene, with a shift from nitrocellulose and oil based paints to synthetic coatings where acrylic, epoxy, polyurethane, and melamine resins gradually took a predominant role up to the introduction of water based paints and electrodeposition paints in the 80's.

Exposure was complex, involving hundred of different chemicals. Solvents should be considered first. Napthas, toluene, xylene, butanols and acetates made up 50% of solvent consumption (benzene per se was discontinued in the mid fifties). Different kinds of resins were manufactured inside the plant; the far largest quantity being represented by alkidic, epoxy-acrylic, and melamine based polymers. Numerous pigments were used, too. The yearly consumption of chromates was around 100 tons. Azo-dyes and lead-compounds were used in smaller quantities.

More than 150 individual jobs were identified through the company records. Individual job histories were available for all but 81 workers. Quantitative levels of exposure were not available at the time of the first analysis and after examining individual job histories and technological changes in production processes workers were classified on a qualitative scale (not exposed; solvents only; solvents and resins; solvents, resins and pigments). All workers in production had a significant exposure to solvents. Clerical workers and workers with unknown job histories were not considered in the analysis.

Previous analyses (1) showed suggestive increases of hematologic neoplasms and cirrhosis among workers exposed to solvents, and an excess of oesophagus cancer (based on 2 cases only, however) was seen among those exposed to solvents and resins. No relevant pattern or trend emerged as regards duration of employment, years since first employment, year of and age at first employment.

Data on measurements of solvent air concentrations during the period 1978-1987 were recently made available. This made possible a re-evaluation of the exposure history of the cohort with a focus on solvents, using cumulative indexes and a semi-quantitative scale instead of the qualitative one used before.

753 samples (area samples, personal, short term exposure level or 8 hour weighted average samples) were collected during the period, mainly after 1980. Personal samples of at least 180 minutes duration were considered most representative of workday weighted exposure and were used in this analysis.

Availability of measurements and knowledge of production processes made it possible to subdivide the factory into 14 departments. Alternatively 17 jobs were identified. They clearly had a broader meaning and did not completely cover all the 150 individual jobs considered before.

Though individual solvent measurements were available the total solvent mixture measurement was preferred in the analyses because more than one solvent was used at the same time and primary focus was not on a specific solvent.

All measurements were below limit values throughout the time period covered by hygiene monitoring and, on the whole, the average values of solvent mixture were exponentially decreasing with time.

In order to obtain an estimate of the cumulative exposure to solvents for each worker's employment period, the following steps were considered.

Using total solvent mixture measurement derived from personal samples of at least 180 minutes, duration mean levels of exposure were computed for each job and department. These values were used for ranking jobs and departments. Exposure decrements over time were evaluated using linear and non-linear regression models and the decrements were assumed to follow the same trends for all job/department exposures. The ranking between more-less exposed jobs/departments was considered constant over time. For the time periods prior to 1978 quantitative estimate of exposure were obtained combining regression models and industrial hygiene considerations assigning arbitrary weights to relevant technological changes and range unplausible exposures (only values encompassed between 0 and 4 times the reference threshold limits were considered plausible). The period covered by the study was subdivided into time segments and an exposure score (based on estimated solvent mean values) was assigned to each combination of time and job (or department). Cumulative and weighted cumulative exposure indices were then computed for each worker according to standard formulae. All exposure indices by job and by department were well correlated ($r > 0.7$), and in this re-analysis, data by department were used for its greater representativeness. Quartiles were considered for groupings.

Epidemiologic analysis has been performed via Standardized Mortality Ratios and Poisson regression techniques (with both internal and external standard), controlling for age, calendar period, years since first exposure (2). If we consider a measure of effect (be it a Relative Risk or a Standardized Mortality Ratio) these analyses gave similar results but confidence intervals were in general larger when we used an internal comparison. SMRs are presented for comparability with previous analysis.

Results for major causes of death and for cancers of specific sites are presented in Table 1. No relevant trend or pattern according to increasing levels of cumulative exposure to solvents is visible. Cirrhosis of the liver in the second quartile of cumulative exposure is the only statistically significant excess observed, while relevant deficits were found for cardiovascular death in the fourth quartile and for all cancer in the third.

Table 1. Results for major causes of death and for cancers of specific sites.

Cause of death		CUMULATIVE EXPOSURE (quartiles) 1	2	3	4	Total
All Causes	Obs	55	67	48	58	228
	SMR	80	125	92	82	93
All Cancer	Obs	18	16	8	19	61
	SMR	84	93	47*	86	79
Digestive	Obs	7	4	3	6	20
	SMR	105	74	58	83	82
Oesophagus	Obs	1	2	0	1	4
	SMR	193	493	0	180	224
Stomach	Obs	2	1	1	3	7
	SMR	77	46	48	105	73
Rectum	Obs	2	0	1	1	4
	SMR	130	0	80	62	71
Larnyx	Obs	1	1	0	0	2
	SMR	92	110	0	0	50
Lung	Obs	4	4	2	6	16
	SMR	56	70	35	83	62
Bladder/Kidney	Obs	1	1	0	2	4
	SMR	106	148	0	195	120
Hematologic	Obs	1	2	1	0	4
	SMR	69	165	85	0	78
Cardiovascular Disease	Obs	24	18	20	10	72
	SMR	94	95	108	35*	79
Ischemic Heart Disease	Obs	11	5	9	3	28
	SMR	84	51	91	21*	60
Respiratory Disease	Obs	0	5	2	5	12
	SMR	0	189	85	122	95
Digestive Disease	Obs	6	8	1	9	24
	SMR	102	165	21	152	112
Cirrhosis	Obs	4	8	0	6	18
	SMR	93	226*	0	138	115
Accident	Obs	3	5	6	3	17
	SMR	59	111	132	86	97

*$p < 0.05$

Results that emerged in the previous analysis were not confirmed. Neither oesophageal cancer nor hematologic neoplasm or cirrhosis revealed any specific pattern or cluster. On the whole, the use of quantitative, or semiquantitative information on exposure to solvents was not able to enlighten SMRs which were elevated in the previous analysis.

Many factors might come to mind in order to explain these findings. Small observed numbers and the reference population used are commonly listed first, and this is true also for the present study, but we want to concentrate and call attention to exposure evaluation because it is the only factor which differed in the two analyses.

Hygiene monitoring which began in late seventies was directed to specific targets and was accompanied by technological changes and preventive measures so that the picture emerging from quantitative measurements might simply reflect the current exposure conditions, conditions which indicated low levels of exposure to solvents.

Reconstruction of exposure in the past was based on assumptions that are questionable, mainly because it is rarely the case that the ranking among departments or jobs and the composition of the mixture during time are constant. Job and department categorization required making many decisions and the specificity of such categorization can be problematic, particularly in connection with the availability of measurements which are not equally widespread all over the factory. In addition, it should be noted that differences in job or department ranking, particularly for intermediate ranks, are more artificial than real, being based on low levels of exposure. Also the statistical models used, the weights assigned to technological changes, and the plausible values chosen could be questioned.

Peak exposures, though absent in recent years, are not accounted for in this analysis. They might have played a significant role mainly in the fifties and sixties. Also the quantitative evaluation of exposure may be reassessed using not only personal sample measurements, but also all types of sample measurements available, and also focusing on some specific solvent.

Exposure conditions are complex, encompassing many different chemicals and processes, and the use of solvent quantitative

measurements could be an oversimplification. Solvents were a common exposure in the production departments and, though many operations involving other chemicals were preformed in closed systems, they might not be necessarily the most relevant exposure and also other toxic agents must be taken into account. This observation becomes more important if we consider that excesses observed for some specific causes of death are based on a limited number of cases.

As a final remark the SMR value in the category of lowest exposure in each of the exposure classification schemes (qualitative and quantitative) is presented in Figure 1. Each dot in the scatter represents the values for a specific cause of death. As can be clearly seen from the figure, even in this simplified situation, the level of disagreement was very high.

In conclusion, this re-analysis demonstrates, once again, the difficulties in tackling exposure evaluation in epidemiological studies, even when some quantitative measurements are available. In particular, we call attention to the many steps involved in the process of grouping exposures on a semiquantitative scale and suggest that different ways of looking at exposure might result in different pictures of the risk.

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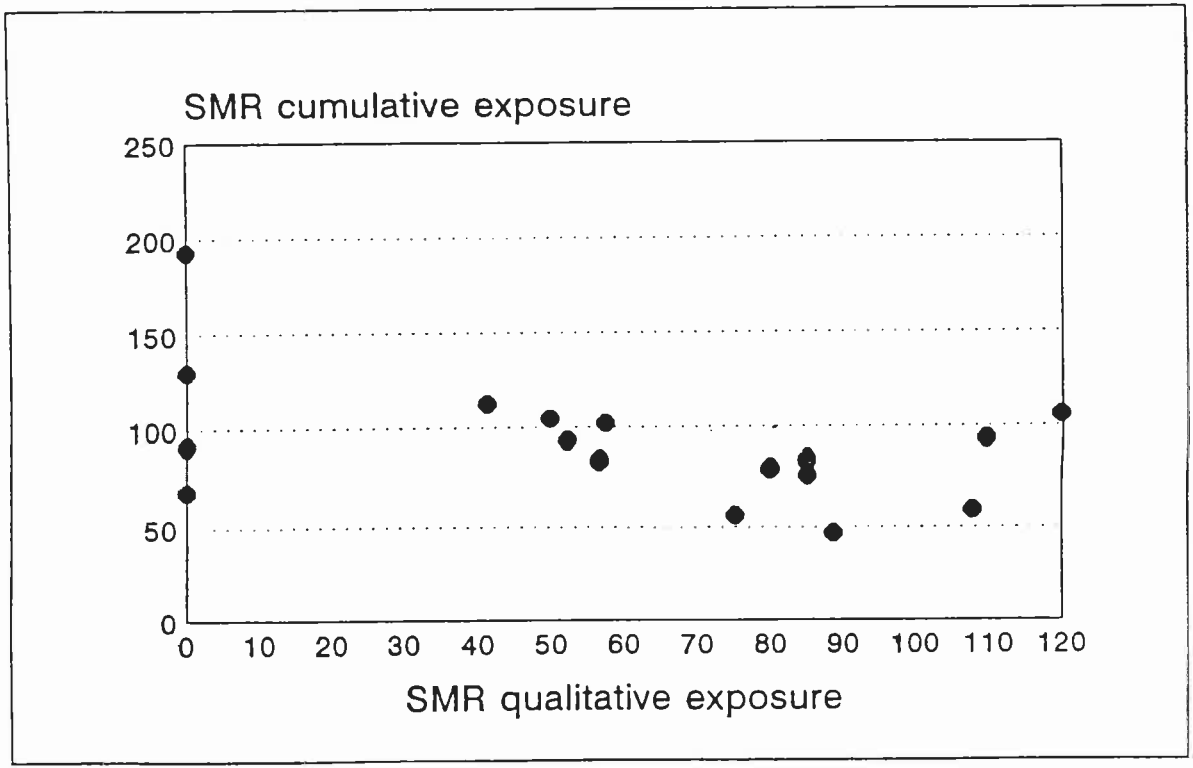

Figure 1. SMR value in the category of lowest exposure in each of the exposure classification schemes (qualitative and quantitative.

PSYCHOSOCIAL STRESSORS AT WORK AND MUSCULOSKELETAL PROBLEMS - A STUDY ON A REPRESENTATIVE SAMPLE OF THE DUTCH WORKING POPULATION

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Introduction

It has often been demonstrated that psychosocial stressors at work are related to depressive symptoms and psychological dysfunctioning (e.g., 1, 2) and to health behaviors like medicine use, doctors' visits and sickness absenteeism (e.g., 1,3). Psychosocial stressors at work have also been found to be related to other diseases. Recently more attention is given to the relationship between psychosocial stressors at work and musculoskeletal problems (4). The relationship between psychosocial stressors and psychological dysfunctioning, as well as the relationship between psychosocial problems and musculoskeletal problems are especially interesting, since these two health problems constitute the main reasons for disablement in two thirds of the population diagnosed as disabled for work in the Netherlands (5). In other countries as well, psychological dysfunctioning and especially musculoskeletal problems (back pain) are considered to be important problems, associated with poor well being, use of medical care and restriction of activities or absenteeism at work(6). Although the relationship between psychosocial stressors and psychological (dys)functioning has been studied extensively and models of stress and indicators of psychological health have been constituted (1), research on the relationship between psychosocial stressors and musculoskeletal problems has been limited. Positive evidence for a relationship between psychosocial stressors at work and musculoskeletal problems will, however, provide interesting options for preventive actions to save costs by a reduction in complaints, absenteeism and perhaps even disability not only due to psychological dysfunctioning but due to musculoskeletal problems as well.

A recent review shows that studies on the relationship between psychosocial stressors and musculoskeletal problems are very heterogeneous, both with respect to the independent variable and the outcome variable (4). No clear picture exists as to which psychosocial stressors are most strongly related to musculoskeletal problems. It is also not clear whether the relationships are causal, and how specific the relationships are with respect to the type of musculoskeletal problem: back pain or other musculoskeletal problems; chronic or acute effects; and whether non-work activities like sports participation confound the relationship. Several mechanisms have been proposed. Psychological and physiological explanations have been put forward, suggesting that either psychosocial load might change the perception of pain (7) or might induce physiological changes that might result in musculoskeletal problems (4). A methodological explanation might, however, apply as well (4). Although there might be a direct relationship between psychosocial stressors (e.g., work pace and monotony) and musculoskeletal problems, the relationship might well be confounded by physical stressors such as static load or repetitive work.

In the present study, a cross-sectional analysis was performed on a representative sample of the Dutch working population. The study is descriptive in nature and aims to determine the relationship between psychosocial stressors at work and several indicators of health, including both psychosomatic complaints, health behaviors and acute and more chronic musculoskeletal problems. The study aims to study both the specificity of the relationship between psychosocial stressors at work and health outcomes and to gain insight in the influence of physical load on this relationship, adjusting for several confounding personal characteristics as well.

Materials and methods

Secondary analyses were performed on data of the National Work and Living Condition Survey, administered by the Central Bureau of Statistics (CBS) to a representative sample of the working population in the Netherlands, from 1977 to 1986 (on a three-yearly basis). The total sample consists of 5865 employees in the age of 18 to 65 years. To improve the reliability of the results, the three samples gathered in the period of 1977 to 1986 were pooled together. This was considered to be justified since the interrelations of the different variables were found to be stable across the years. In the Survey,

information was gathered on the work of the employees (occupation and stressors), health and several personal characteristics (sex, age, education and sports participation), which may act as possible confounders in the relationships of psychosocial stressor and health, especially musculoskeletal problems.

The relationships between stressors and health indicators were tested with multiple logistic regression analyses. Since the independency of the stressors at work was not empirically established, first a factor analysis (Varimax rotation) was performed on these stressors to identify possible underlying stressor dimensions. It was expected that a factor analysis would identify dimensions which would have theoretical relevance. Although, from a theoretical perspective, the regressions of the dimensions to be extracted on the health indicators were considered potentially interesting, information would be lost by aggregating stressor-information and the variance which could be explained by the dimensions would probably be less than that to be explained by single stressors in the survey. Because of this, the regression analyses were performed on both single stressors and underlying dimensions of stress risk.

Results

The factor analysis on the stressors resulted in 3 independent factors, explaining 45% of the variance of the individual stressors:
1) work pace (Eigenvalue = 1.02); 2) intellectual discretion (consisting of monotonous work, poor possibilities for personal development, poor fit between the actual work and education or experience level and poor promotional prospects) (Eigenvalue = 1.62; Cronbach α = .55; factor loadings range from .56 to .77); and 3) physical stressors (heavy physical work, bad smell at work, dirty work, noise at work, dangerous work) (Eigenvalue = 2.27; Cronbach α = .63; factor loadings range from .59 to .71).

Table 1. Estimated odds ratios of the individual risk factors on the different health indicators. Between brackets the 95% confidence intervals. The odds ratios indicate the health risk associated with the independent variable as opposed to the situation in which this variable is absent, adjusting for all other variables in the logistic model, including sex, age, education and sports participation.

Variable	Psychosomatic symptoms	Back Complaints	Muscle/joint complaints	(Chronic) back problems
Work pace:				
High work pace	1.50 (1.32-1.70)	1.21 (1.06-1.39)	1.29 (1.12-1.49)	1.20 (.93-1.54)
Intellectual discretion:				
Monotonous work	1.61 (1.34-1.95)	1.35 (1.10-1.64)	1.32 (1.08-1.62)	1.29 (.92-1.82)
No good development	.98 (.84-1.30)	1.00 (.86-1.17)	1.04 (.88-1.21)	1.15 (.87-1.51)
Poor fit work-education	1.23 (1.07-1.42)	1.13 (.97-1.31)	1.19 (1.02-1.39)	1.21 (.92-1.59)
Poor promotional prosp.	1.14 (.99-1.32)	1.05 (.86-1.23)	1.04 (.89-1.22)	1.23 (.89-1.69)
Physical stressors:				
Physical heavy work	1.32 (1.12-1.56)	1.62 (1.36-1.91)	1.61 (1.35-1.92)	1.36 (1.00-1.85)
Noise	1.23 (1.06-1.44)	1.10 (.93-1.29)	1.25 (1.06-1.47)	.99 (.73-1.35)
Dirty work	.91 (.76-1.08)	1.22 (1.02-1.46)	.93 (.77-1.12)	1.09 (.78-1.52)
Bad smell work	1.40 (1.13-1.74)	1.19 (.95-1.50)	1.38 (1.10-1.74)	1.59 (1.08-2.34)
Dangerous work	1.27 (1.02-1.58)	1.19 (.95-1.50)	1.28 (1.01-1.61)	1.22 (.80-1.85)

Table 2. Estimated odds ratios of the psychosocial risk dimensions on the different health indicators. Between brackets the 95% confidence intervals. The odds ratios indicate the health risk associated with the level of the independent variable as opposed to the situation in which this independent variable is absent, when adjusting for all other variables in the logistic model (including sex, age, education and sports participation).

Variable	Psychosomatic symptoms	Back complaints	Muscle/joint complaints	(Chronic) back problems
Work pace:				
High work pace	1.53 (1.34-1.72)	1.25 (1.09-1.43)	1.33 (1.15-1.52)	1.21 (.94-1.56)
Intellectual discretion:				
0 stressors	1.00	1.00	1.00	1.00
1 stressor	1.06 (.89-1.26)	.92 (.76-1.11)	1.00 (.82-1.21)	.99 (.66-1.47)
2 stressors	1.28 (1.06-1.54)	1.11 (.91-1.36)	1.16 (.94-1.42)	1.33 (.88-2.00)
3 stressors	1.37 (1.11-1.69)	1.19 (.95-1.49)	1.25 (.99-1.57)	1.44 (.93-2.30)
4 stressors	2.19 (1.64-2.95)	1.47 (1.08-1.99)	1.67 (1.22-2.29)	2.10 (1.24-3.58)
Physical stressors:				
0 stressors	1.00	1.00	1.00	1.00
1 stressor	1.18 (1.01-2.95)	1.05 (.88-1.25)	1.25 (1.05-1.48)	1.35 (.98-1.85)
2 stressors	1.55 (1.27-1.87)	1.50 (1.22-1.84)	1.47 (1.19-1.82)	1.47 (1.01-2.13)
3 stressors	1.39 (1.08-1.80)	1.60 (1.23-2.09)	1.63 (1.24-2.13)	1.54 (.95-2.50)
4 stressors	2.15 (1.55-2.98)	3.03 (2.19-4.20)	3.37 (2.42-4.70)	1.76 (.95-3.26)
5 stressors	2.64 (1.64-4.25)	3.90 (2.43-6.27)	2.78 (1.70-4.55)	4.34 (2.18-8.64)

The factors, identified by factor analysis, have theoretical relevance since they do well accommodate the dimensions of the "job demands - decision latitude" model of Karasek (1), since work pace can be considered a job demand, whereas intellectual (skill) discretion is an aspect of decision latitude. The odds ratios and 95% confidence intervals for the individual stressors on each of the health indicators, estimated on the basis of the multiple logistic regression analyses, are presented in Table 1. In Table 2, the estimated odds ratios and confidence intervals are presented for the three risk dimensions which resulted from the factor analysis.

Conclusions

1. High work pace and poor intellectual discretion, especially monotony, on the job are found to be related to psychosomatic health and musculoskeletal problems, including acute and more chronic back pain.

2. It is found that the odds ratios for indicating the relationship between intellectual discretion and all health indicators (psychosomatic complaints as well) are reduced as soon as physical stressors are entered into the model. The associations do, however, remain significant (see Tables 1 and 2). Odds ratios which indicate the association between intellectual discretion and (chronic) back pain drop from 2.81 to 2.47 when the physical stressor dimension is entered, and drop further to 2.10 when personal characteristics are entered into the model as well. Odds ratios indicating the relationship between intellectual discretion and psychosomatic symptoms drop from 3.13 to 2.84 when physical stressors are entered into the model, and drop further to 2.19 when personal characteristics are entered as well.

3. The strength of the associations found for psychosocial stressors and musculoskeletal problems are comparable to those found between psychosocial stressors and psychosomatic complaints. None of the odds ratios found in this study are, however, very large.

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WORK COMPLAINTS AND PHYSICAL WORKLOAD DURING PREGNANCY

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Introduction

During pregnancy a lot of changes are occurring in the female body (Zuspan, 1986). In order to detect signs that could indicate a disturbance in the balance between workload and working capacity during pregnancy, we conducted a prospective follow-up study on a sample of 117 pregnant nurses, 81 pregnant clerical workers and 122 non-pregnant nurses. In this way we were able to ascertain the proportion of the problems of the pregnant nurses caused by the pregnancy itself and the proportion of the problems caused by the physical workload.

Materials and methods

Monthly the nurses and the clerical workers have been asked to keep a diary of their working day, in which they had to note down how many minutes or how many times out of every hour they spent walking, standing, lifting, stooping or squatting during an eight-hour working day under normal conditions that were not accommodated due to pregnancy. Under these circumstances, fifty percent of the nurses and eighty percent of the clerical workers were able to do this. By means of a monthly questionnaire from the seventeenth week of pregnancy up to delivery, we collected data pertaining to the problems with physical workload.

For purposes of analysis of the problems with physical workload, the pregnant nurses were matched individually with a pregnant clerical worker and a non-pregnant nurse. For the pairs of nurses we used the matching criteria: hospital ward and shift schedule. For both types of pairs we used age, number of management tasks, number of working hours and number of children. This gave us 71 pairs of pregnant nurses and pregnant clerical workers and 71 pairs of pregnant nurses and non-pregnant nurses.

Results

Between nurses and clerical workers there exists a considerable difference with regard to their physical workload (Figure 1). During a working day over fifty percent of the nurses lifted objects weighing 5 kg or more at least ten times, stooped or squatted twenty-five or more times, stood for two hours or more and spent three or more hours walking. Daily over eighty percent of the nurses lifted objects weighing 5 kg or more three or more times, stooped or squatted ten or more times, stood for one hour or more and walked for two hours or more. Every day almost all nurses lifted in less than optimal circumstances.

Of the pregnant clerical workers ten percent lifted objects weighing 5 kg or more ten or more times daily and stooped or squatted at least twenty-five times a day. Twenty-five percent of them lifted the above mentioned objects three or more times daily and stooped or squatted ten or more times per day. The clerical workers did not stand for more than one hour and a half and walk for more than two hours a day. Eighty percent stood for between ten minutes and one hour and a half and walked for between half an hour and two hours a day.

Almost all clerical workers sat for at least four hours a day, whereas only five percent of the nurses did so.

Due to their changed working capacity more pregnant nurses experienced their physical workload significantly as more tiring. At the end of the seventh month of pregnancy for the pregnant nurses lifting, stooping or squatting, standing and walking was four times as difficult when compared to the pregnant clerical workers. Working posture was more than five times as difficult. In both groups the difficulty with these physical aspects increased significantly during pregnancy (Figure 2).

Compared to the non-pregnant nurses for the pregnant nurses lifting was more than twice as difficult, stooping or squatting was six times as difficult, working posture was four times as difficult and standing and walking was three times as difficult. During the observation period difficulty with walking increased significantly in the non-pregnant nurses.

Comparing the pregnant nurses to both reference-groups together, it becomes clear that the combination of physical workload and pregnancy is causing the difficulty with each of the physical aspects during pregnancy. This combination of combined exposure is leading to a synergistic effect (Dormolen, 1990).

These results suggest that present adaptations in the workplace are insufficient to prevent disturbances in the balance between workload and working capacity. To facilitate a more equal participation at work for pregnant employees with a physical workload, compared to non-pregnant employees with the same physical workload and compared to pregnant employees without a physical workload, more suitable and more earlier job adaptations seem to be necessary.

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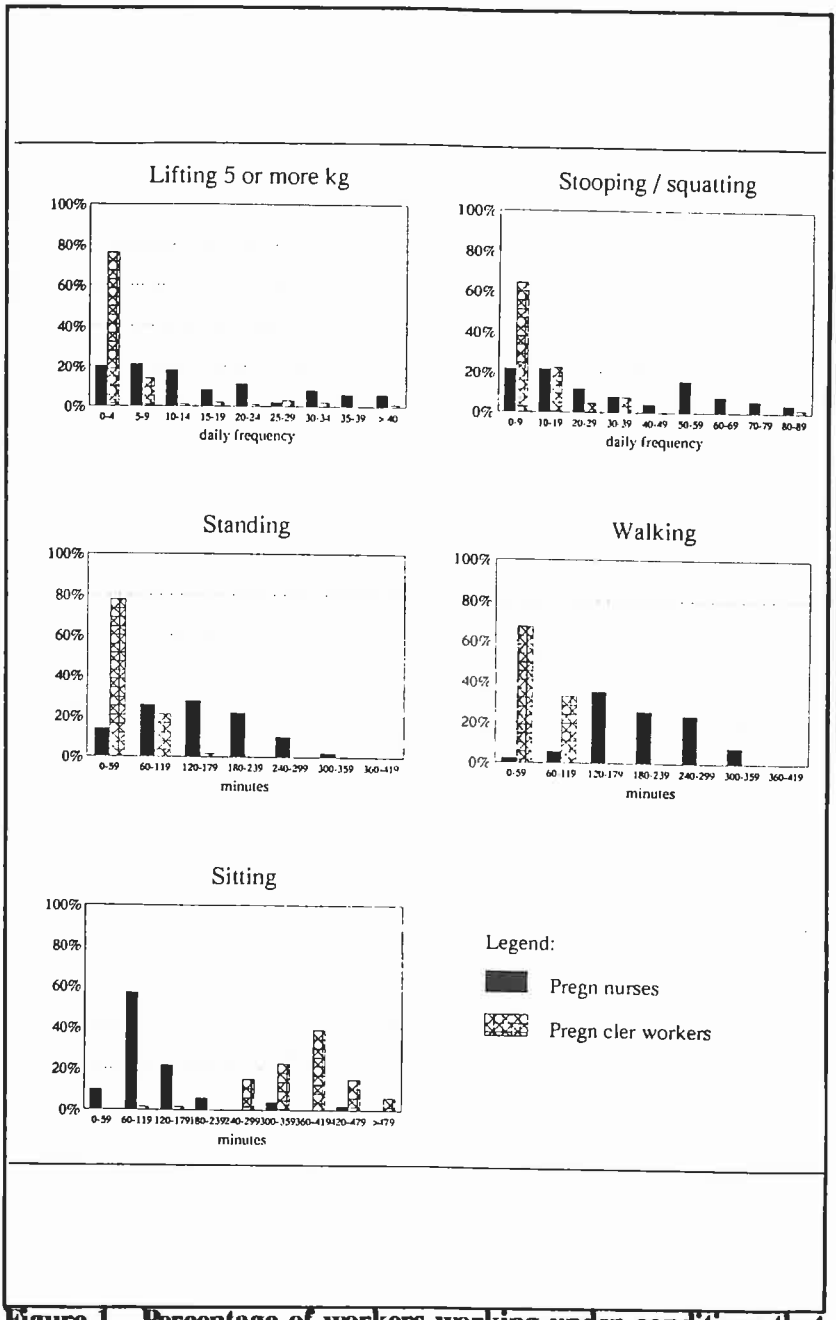

Figure 1. Percentage of workers working under conditions that were not accommodated due to pregnancy divided to the maximal degree of workload per day resulting of physical aspects of the work.

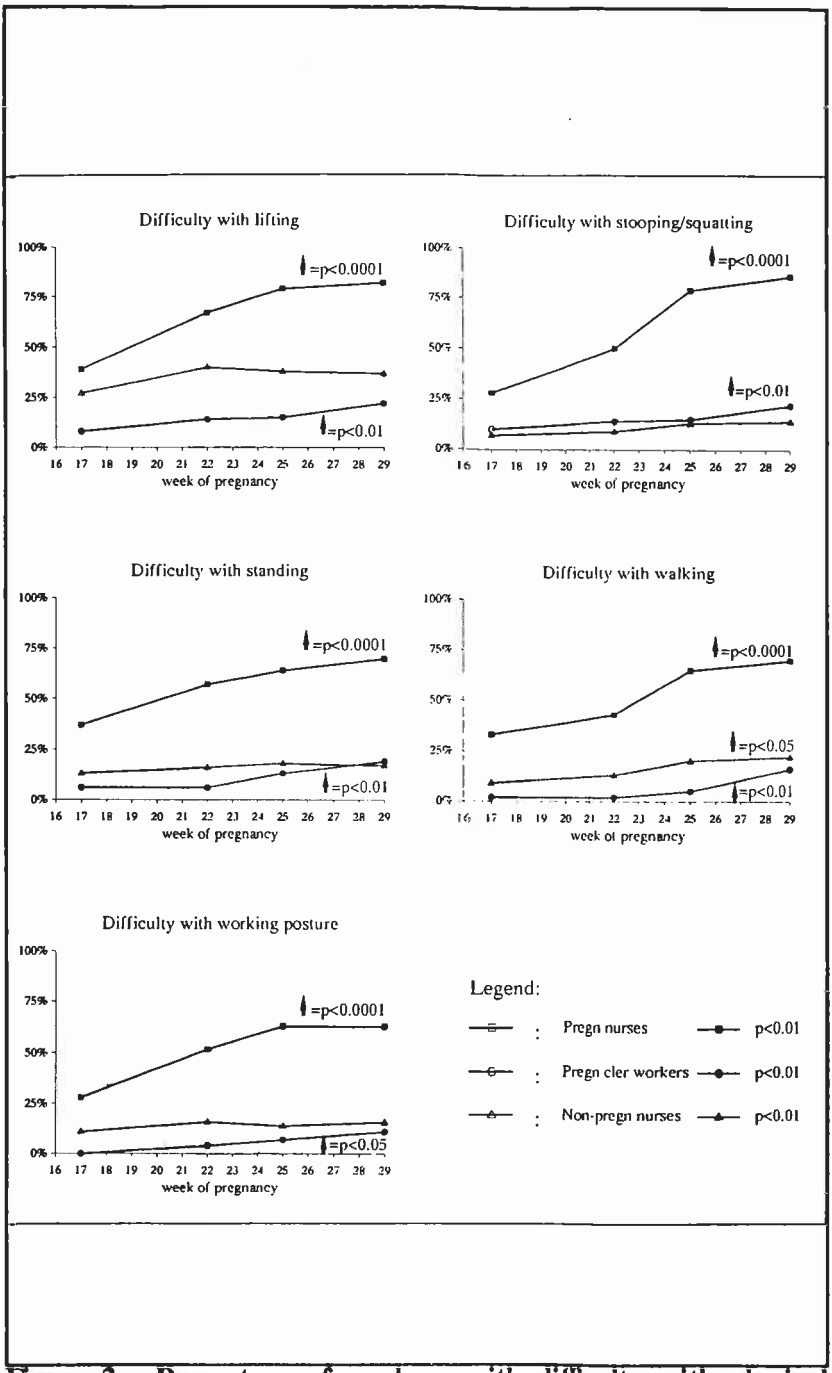

Figure 2. Percentage of workers with difficulty with physical aspects of work during 17th till the 30th week of pregnancy.

TEMPORARY HEARING THRESHOLD LEVELS IN AN IRON AND STEEL FACTORY IN NIGERIA

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Introduction

A study of the temporary hearing threshold shift of 132 men exposed to noise level between 66 and 120 dBA in a 20 year old Iron and Steel Factory was undertaken as part of continuing baseline assessment of the impact of industrialization on the health of Nigerian workers. Noise levels in developing country industries are excessive on account of: (i) the lack of noise abatement regulations and;[1-5] (ii) the use of obsolete machinery usually dumped there from the developed countries.[6]

Materials and method

The factory investigated derived its materials from metal scraps and antibodies. It had a monthly production of 6000 metric tons of reinforced round bars and single angle bars used in construction industry.

The operations in the factory's Electrical Furnace were characterized by noise, intense heat, and ultraviolet radiation. Those at the Rolling Mill were characterized by noise. The factory workers had no protective devices against the occupational assaults - no ear muffs, no reflective clothing. Only few wore the eye goggles provided.

Between 15 and 24 noise level measurements were taken at each of the three work locations in the factory including the Administrative Block, using Bruel Kjear Precision 2232 sound level meter.

A study questionnaire eliciting information on medical, occupational and drug history was administered to all the subjects.

The hearing of the subjects was assessed, with the use of Damplex A563 air conductance audiometer, at the following frequencies 0.25, 0.5, 1, 2, 4, 8, kHz. The audiograms were taken at least 18 hours after cessation of exposure and before commencement of morning shift.

Only subjects in the morning shifts were selected for the study. The subjects consisted of 44 from the Rolling Mill, 36 from the Electrical Furnace and 52 from the Administrative Block. All the workers were invited for the study - and only those available during the period of the study were assessed.

Results

The mean ages of the three exposure groups were not significantly different. The noise level ranges in the three work areas were: 4 - 71 dBA at the Administrative Block, 86 - 95 dBA at the Electrical Furnace and 96 - 120 dBA at the Rolling Mill.

The mean hearing threshold (left ear) of the subjects in the three work locations are shown in Table 1. The subjects at the Rolling Mill which recorded the highest noise level, had the highest hearing threshold at the critical frequency of 4.0 kHz. The hearing threshold of this group was significantly ($p < 0.001$) higher than those of the subjects in either the Electrical Furnace or the Administrative Block.

When hearing threshold at 4 kHz was regressed against age and duration of employment for the Rolling Mill sub-group, the following regression equation was obtained. It was also found that duration of employment (DE) alone accounted for 21.1 and the 25.2 percent variation in hearing threshold.

$$THTL = 8.8 + 1.2\ DE\ (Yr) + 0.43\ Age\ (Yrs.)$$
$$R2 = 0.25;\ F = 3.21$$

For the Electrical Furnace group, duration of employment alone accounted for 20.3 of the 21.5 percent variation in hearing threshold and the corresponding regression equation was:

$$THTL = 19.4 + 0.59DE + 0.15\ Age$$
$$R = 21.5;\ F = 2.0$$

The hearing threshold of the subjects was not influenced by previous occupational noise exposure but by current tenure at the Iron and Steel Factory.

Discussion and conclusion

This study has shown that exposure to continuous noise level of 86 - 120 dBA for an average of 12 hours per day for six days a week has adverse effects on the hearing threshold of unprotected workers in an Iron and Steel Factory. The severity of the impact increased significantly with duration of employment which factor alone accounted for over 21 of the 25 percent variation observed in the hearing threshold of the factory workers.

All the 90 subjects in both the Electrical Furnace and Rolling Mill Work areas had average threshold exceeding 25 dBA at the critical frequencies of 1, 2, 4 kHz indicating hearing impairment by WHO criteria.[7] The study suggests urgent measures be taken to protect the health of industrial workers if gains made in controlling traditional diseases are not to be eroded.

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Table 1. The mean hearing threshold levels (left ear) at different frequencies for study subjects

LOCATION	No	0.25kHz	0.5kHz	1.0kHz	2.0kHz	4.0kHz	8.0kHz
ADMINI-STRATION	52	41.4 +8.6	29.3 +7.6	20.0 +4.4	14.6 +5.4	16.8* +5.4	14.6 +9.3
ROLLING MILL(RM)	44	43.5 +6.5	42.3 +10.3	28.3 +8.8	25.3 +13.2	40.0* +20.3	28.9 +14.5
ELECTRICAL FURNACE(EF)	36	45.4 +8.7	45.3 +9.9	33.8 +11.5	26.3 +9.2	28.6 +9.6	26.6 +11.7

* At 4kHz P 0.0001.
RM.EF

A CROSS-NATIONAL COMPARISON OF THE OPERATING CHARACTERISTICS OF JOB STRESS AND MENTAL HEALTH MEASURES BETWEEN JAPAN AND THE UNITED STATES

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The purpose of this research was to serve as a pilot study to validate research methodologies and the measures for a larger cross-national study on job stress between Japan and the U.S. The objective of the larger study will be to test various models of the role of job control in the relationship between job stressors and indicators of emotional and behavioral dysfunction after controlling for individual and psychosocial factors that also might play a role in the relationship. The samples for the pilot study were from Japanese-owned semiconductor factories located in the U.S. (n=184; males=81%; mean age=33 yrs) and in Japan (n=473; males=82%; mean age=30 yrs). The research follows closely the NIOSH model and guidelines for studying job stress. The measures include: job control (i.e., the NIOSH measure modified to reflect a sense of control at both an individual and collective level); other sources of job stress (i.e., quantitative job overload, job future ambiguity, under-utilization of abilities, job role ambiguity, and job/non-job role conflict); individual and psychosocial factors (e.g., sociodemographic factors, sense of mastery, centrality of one's job, social support, and life stress other than job); job characteristics (e.g., job status, environmental exposure, and type of shift work); and dependent measures of well-being and dysfunctional behavior (i.e., health conditions, sick days, use of medical care, alcohol and tobacco usage, life satisfaction including job, family and leisure satisfaction, depression, and anxiety). Detailed item analyses of all items in the questionnaire were performed which included cross-national comparisons of: missing data, response tendencies, and internal consistency reliability of composite indexes. Higher rates of missing

data (i.e., about double) on a majority of the job stress and mental health measures were observed among the Japanese compared to the U.S. Workers. Inspection of individual items identified differences that may signal culturally sensitive items, e.g., on an item inquiring about "being a failure in life" in the depression scale, there was 16 times the rate of missing data among the Japanese compared to the U.S. workers. As to response tendencies, the data did not show that the Japanese tended to express emotional distress somatically as has been suggested in the literature. While the pattern of responses on the mental health measures were similar between the Japanese and U.S. workers, there was a tendency among the Japanese to choose the exact midrange response choice on the items forming the job stress measures. The internal consistency reliability of the composite measures of job stress and mental health indicated that the measures tended to be somewhat more reliable among the U.S. workers. While many of differences on Cronbach's alpha were negligible, several of the scales showed differences of between 11 to 24 points. Measures of job future ambiguity, job overload, social support (boss/marital or live-in partner/and friend support), job satisfaction, and alcoholism were substantially less reliable among the Japanese compared to the U.S. workers.

THE EFFECT OF PSYCHOSOCIAL WORK STRESS ON MUSCULOSKELETAL DISORDERS IN HEALTH CARE

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Abstract

A study is carried out among five professional groups (n= 2194) from 34 intramural health care institutions in the Netherlands, to elucidate the relationship between psychosocial work stress and back pain. The conclusions are: 1) physical work load and psychosocial job demands each have an independent heightening effect on back pain, 2) job control has in independent lowering effect on back pain, 3) personal characteristics (age, education, working week, shift work) do not have an effect on back pain.

The research question

It is widely recognized that musculoskeletal disorders of employees may be caused by a large variety of factors, of which heavy physical work load, some non-work activities (sports, gardening, smoking, etc.) and some constitutional aspects of the employee (age, sex, physical condition) are the most accepted (Hildebrandt, 1987). The impact of work-related psychosocial stressors on musculoskeletal problems, however, has not received much attention in research (Theorell et al., 1991; Bongers et al., 1993, in press).

Method

To elucidate the relationship between psychosocial work stress and musculoskeletal disorders, a study was carried out on data of 8702 employees of 34 health care institutions in the Netherlands (8 general hospitals, 7 mental hospitals, 5 homes for mentally retarded and 14 nursing homes). The employees had completed a questionnaire on their work and health (mostly dichotomous answer-categories: yes vs. no), as well as on personal characteristics.

The dependent variable in the study was: Do you regularly have low back pain? Though the study was focused on the relationship

between psychosocial work stress and musculoskeletal problems, **three independent variables/scales** were used (viz. Physical Work Load, next to Psychosocial Job Demands and Job Control). These scales were constructed from the questionnaire items as follows.

Physical work load was based on two questions: Do you often have to work standing-up for a prolonged period? Do you often have to walk during your work for a prolonged period? The reliability of coefficient Cronbach's Alpha of this Physical Work Load scale was 0.75 (this coefficient may have a value between 0 and 1; the higher this value, the higher the inter-correlation between the items of which the scale is constructed). The scores on the two dichotomous questions were added per employee. Then two employee-groups were formed by a median split of the scores on two added questions. Finally, every employee was given a 1 or a 2 (a low or a high level of physical work load).

Psychosocial job demands was based on four questions: Are you working regularly under time pressure? Is there a shortage of personnel in your department? Are there any possibilities for interrupting your work? Is your work hindered by unexpected situations? Cronbach's Alpha reliability coefficient of the Psychosocial Job Demands scale was 0.57. Again, the employees were divided into two groups by a median split of the added scores and every employee was given a 1 or a 2 (a low or a high level of demands).

The third independent variable was **job control**, which was composed of seven questions: Do you have work with sufficient autonomy? Are you sufficiently informed about what is going on in your institution? Does your supervisor sufficiently pay attention to what you say? Is there sufficient consultation with your colleagues and your supervisor about work? Do you (not) find your work too simple? Is there sufficient variety in your work? Is your work usually interesting? The reliability coefficient of this Job Control scale was 0.68. Here, the same procedure was applied as to the other two independent variables, so that every employee finally got a 1 or a 2 (a low or a high level of job control).

Finally, **four control variables** were used in the analysis: Age (in 3 categories: 15-25 years, 26-30 years and 31-65 years), Length of

working week (also in 3 categories: 2-24 hours, 25-36 hours and 37-40 hours per week), Level of education (in 3 categories: lower, middle and higher education) and Shiftwork or daywork (2 categories).

Logistic regression analyses were applied to test the effect of the work and personal variables on low back pain. To exclude the influence of sex and profession too, these analyses were carried out separately for the five largest professional groups of female employees (nurses, nursing aides, household personnel, kitchen personnel and ergotherapists). The final research population is 3059 female employees from 34 institutions. Because of missing values, the population on which the logistic regression analyses were applied became 2194 employees.

Table 1 shows the means and standard-deviations of the eight variables in the study as well as their empirical minimum and maximum values.

Table 1. Means and standard-deviations of the variables in the study (n=3059)

		N	Mean	s.d.	minimum	maximum
1.	Physical work load (low-high)	2871	1.47	.50	1	2
2.	Psychosocial job demands (low-high)	2798	1.52	.50	1	2
3.	Job control (low-high)	2531	1.58	.49	1	2
4.	Age (young-old)	3042	1.90	.84	1	3
5.	Level of education (low-high)	3038	1.92	.57	1	3
6.	Length of working week (short-long)	3024	2.17	.83	1	3
7.	Shift work (yes-no)	3046	1.65	.48	1	2
8.	Low back pain (yes-no)	3016	1.62	.49	1	2

The employees under study are relatively young (74 percent is 30 years or younger and only 26 percent is older), highly educated (only 17 percent has a lower education), working part-time (24 percent works 24 hours per week or less and only 24 percent works 36-40 hours per week), and working frequently in shifts (35 percent). Finally, Table 1 shows that 38 percent of the employees under study report to have low back pain regularly (since the mean score is 1.62).

Table 2. Results of the logistic regression analyses with low back pain as the dependent variable (Odds ratios)

	Nurses (n=1060)	Nursing aides (n=544)	Household personnel (n=262)	Kitchen personnel (n=173)	Ergo-therapists (n=202)	All five professions (n+2241)
1. Physical work load						
(high vs. low)	1.87**	1.41*	1.53	2.35*	2.13*	1.68**
2. Psychosocial job demands						
(high vs. low)	1.60**	2.26**	2.05*	1.73	1.10	1.77**
3. Job control						
(low vs. high)	1.44**	1.55**	1.25	1.52	1.21	1.36**
4. Age						
(31-65 vs. 15-25 years)	.66*	.87	1.60	2.43*	.91	.90
(26-30 vs. 15-25 years)	.88	.96	1.13	2.56*	.86	1.01
5. Level of education						
(higher vs. lower)	.83	.42	.26	1.37	6.52	.94
(middle vs. lower)	1.10	.43	.30	1.29	1.18	1.04
6. Length of work week						
(37-40 vs. 2-24 hours)	1.00	.94	.85	1.48	.85	1.02
(25-36 vs. 2-24 hours)	.83	.63*	.57	2.15	1.95	.85
7. Shift work						
(yes vs. no)	1.27	1.52	.24**	1.23	3.70	1.28*

* = p<05 and ** = p<01

Results

The results of the logistic regression analyses per professional group, with low back pain as the dependent variable, are shown in Table 2.

Conclusions and discussion

The three main conclusions of our study are: 1) Physical Work Load and Psychosocial Job Demands each have an independent heightening effect on back pain, 2) Job Control has an independent lowering effect on back pain, 3) Personal characteristics (age, education, working week, shift work) are not related to back pain.

The impact of physical work load was expected and is in accordance with many earlier studies. As far as the psychosocial work stressors are concerned, the study by Theorell et al., (1991) includes parts which are very comparable with ours. They showed that high levels of job demands significantly correlate with back, neck and shoulder problems.

Interpretations of the impact of stressors (psychosocial job demands and job control) on musculoskeletal disorders are discussed by Bongers et al., (1993, in press). According to them, three alternative hypotheses regarding the impact of stressors on musculoskeletal problems should be studied: 1) stressors coincide with high levels of physical work load, 2) stressors increase the muscle tension and lead to the development of musculoskeletal symptoms, 3) stressors increase the perception of poor health in general, symptoms of musculoskeletal problems included.

The results of our empirical study do not exclude the validity of the second and third hypothesis. But they are no confirmation for the first hypothesis, because it is shown in our study that the stressors do have a significant effect on musculoskeletal disorders, even when this relation is controlled for the effect of some important aspects of physical work load (having to work standing-up and having to walk during work for a prolonged period).

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INCREASED LEAD ABSORPTION CAUSED BY WORKING NEXT TO A LEAD RECYCLING FACTORY

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Our series of studies found out that workers at a lead recycling plant in Taiwan suffered from lead poisoning. Air and soil outside the plant were seriously contaminated by lead. The objective of this study was to determine whether workers at a factory adjacent to the lead recycling plant were affected by lead contamination. 41 out of 45 workers of a forging factory next to the lead recycling plant were enrolled as the exposed group. A comparison group of 51 workers was selected from another forging factory about 20 km away. Each subject was interviewed regarding his life style, work history and residence, and was drawn blood for lead measurement by graphite furnace atomic absorption spectrometry. The results showed that the two groups were compatible for age, sex and smoking patterns. Blood lead of the exposed group was significantly higher than that of the comparison group (Mean $\pm$ SD:20.4 $\pm$ 9.4 ug/dl vs. 5.9 $\pm$ 2.9 ug/dl). The difference persisted after stratification control by sex and working zones. Blood lead levels were lower among exposed workers who were employed less than 2 months than those employed longer. There was no difference among exposed workers at different outdoor working zones. 5 months after the improvement of pollution control and decrease of production volume in the lead factory, 31 exposed workers were retested for blood lead. The blood lead of outdoor workers had an average decrease of 4.2 ug/dl while that of indoor workers showed no significant difference. We concluded that the changes of blood lead level among exposed workers were caused by lead contamination generated by its neighboring lead recycling plant.

IMPACT OF UNLEADED GASOLINE REGULATION ON BLOOD LEAD LEVELS OF WORKERS IN MUFFLER SHOPS

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Introduction

In 1984, the Saskatchewan Department of Labour published a report which revealed that muffler shop workers could be overexposed to lead. In that study, excessive airborne lead concentrations were measured in the general air of the workshops as well as in adjoining office areas. Oxyacethylene torch cutting of exhaust components of vehicles employing leaded gasoline appeared to be the major source of lead exposure.

In order to evaluate the situation on its territory, the Community Health Department of Sacre-Coeur Hospital (Montreal) conducted a first survey, in March 1986. The objective of the survey was to assess environmental lead exposure and blood lead levels of workers employed in muffler repair shops.

Methods

Study population According to the Quebec Occupational Health and Safety Commission, nine shops whose main activity was muffler sale and repair were operating in the territory. The shops employed 49 workers among which 38 agreed to participate to the survey (77.6%). For the purpose in the study, the workers were categorized in two groups: muffler installers and others (mechanics and service personnel).

Environmental evaluation The environmental evaluation was divided into three parts: air sampling, fumes and dusts analysis.

Air sampling included long- and short-term evaluation of personal exposure, and long-term measurement of lead in the work environment. Personal exposure was evaluated with personal devices

worn at the breathing zone. Lead concentrations were measured in the fumes generated by Oxyacethylene torch cutting operations as well as in dusts found on different surfaces. The type of gasoline used by vehicles on which mufflers were either installed or repaired was also recorded.

Environmental evaluation was performed by four technicians in industrial hygiene who used standardized procedures.

Blood lead levels A sample of blood was taken from each participant by venipuncture. Blood lead concentration was measured. Blood sampling took place the same day as the environmental evaluation.

Questionnaire A short questionnaire was completed, for each participant, by an occupational health nurse. Data were collected on age, seniority, smoking, work habits and personal hygiene.

Analysis Arithmetic as well as geometric means were computed. Paired and unpaired t-tests were performed using SAS and EPISTAT software packages.

Results

Environmental lead exposure As expected, the average lead concentration measured at the breathing zone was higher for muffler installers with a value of 0.09 $\mu g/mc.^3$ In this job category, three out of thirteen samples had lead concentration in excess of 0.15 $\mu g/m.^3$

During the cutting of an exhaust system, an average airborne lead concentration of 0.49 $\mu g/m^3$ was measured at the breathing zone, for vehicles which burned leaded gasoline, compared with a non detectable level for vehicles using unleaded gasoline. In the first category, leaded gasoline, four out of ten samples had lead concentration higher than 0.45 $\mu g/m.^3$

During the cutting activities, lead concentrations as high as 760.0 $\mu g/m^3$ were measured in the resultant plume. For leaded gasoline, the average lead concentration was 163.0 $\mu g/m^3$ compared with 4.5 $\mu g/m_3$ for unleaded gasoline.

In the general work environment, average airborne lead concentrations were two times higher in the workshop than in the office area. In the workshop, the airborne lead contamination was approximately ten times less than the personal installers' lead exposures.

Lead concentrations in dusts were slightly elevated in the storing area with an average of 60.0 mcg/100 cm^2, as well as in the working area, with an average of 30.0 mcg/100 cm^2.

Blood lead levels Installers and other workers were comparable for age (mean: 30.6 years vs. 32.9), seniority (mean: 8.2 years vs 7.0) and smoking habits (66.7% smokers vs. 63.6%). They differ significantly for their mean blood lead levels. The 27 installers had a geometric mean blood lead level of 35.0 μg/dL (range 23.8 μg/dL to 59.0 μg/dL) compared to 22.4 μg/dL for the 11 other workers (range 12.2 μg/dL to 3.2 μg/dL). The difference was statistically significant ($p < 0.001$).

Six installers, 22.2%, had blood lead levels equal to or higher than 40.0 μg/dL. Even if none of the eleven other workers had blood lead levels equal to or higher than 40.0 μg/dL, 63.6% had values that ranged between 20.0 and 39.9 μg/dL.

As far as personal habits are concerned, 55% of the installers and 66% of the other workers said that they used to eat their lunch in the shop while 15% of the installers said that they did not wash their hands before they eat. No significant difference was found in the mean blood lead levels of workers according to their eating habits. The same observation was made for their smoking habits.

Discussion

The results of this survey showed that muffler shop workers, especially the installers, were exposed to lead in their workplace. Oxyacethylene torch cutting of exhaust systems on vehicles using leaded gasoline appeared to be the main source of exposure. Mechanics and service personnel were also exposed to non negligible levels of lead as shown by their mean blood lead level, 23.6 μg/dL, which was nearly twice as high as what was recorded in a sample of Quebec workers.

The differences in mean blood lead levels between installers and other workers could not be explained by differences in age, seniority or personal habits. Even though no questions were asked on other sources of lead exposures (hobbies, for example), we do not believe that this lack of information could explain by itself the differences measured between the two groups. There remained a major source of lead exposure in the workplace which justified that preventive measures should be implemented. In that sense, workers and employers were informed on environmental as well as personal protective measures. The necessity for good personal hygiene was also reinforced.

1990 Survey

In order to evaluate the impact of the 1986 intervention, blood lead levels of workers were measured in April 1990. 29 workers participated to this second survey, for a participation rate of 63.0%. Only eight workers participated to both surveys.

The 24 installers and the 5 other workers were comparable for age and seniority. Even though the geometric mean blood lead level of the other worker group (8.9 μg/dL) was smaller than that of the installers (14.8 μg/dL), the difference was not statistically significant.

The comparison of blood lead levels measured in 1986 and 1990 shows that in both groups, there has been a significant decrease. The mean blood lead level went from 35.0 μg/dL to 14.8 μg/dL ($p < 0.001$), in the installer group, and from 23.6 μg/dL to 8.9 μg/dL ($p = 0.01$) in the other group.

Six installers participated in both surveys. Their mean blood lead level dropped significantly from 40.7 μg/dL in 1986 to 21.2 μg/dL in 1990 ($p < 0.001$). Only two non-installers participated to both surveys. Their mean blood lead level went from 27.1 μg/dL in 1986 to 13.4 μg/dL in 1990.

A visit to the workplace, in 1990, revealed that no environmental and personal protective measures had been implemented in the shops. Therefore we believe that the significant drop in blood lead levels could be attributed mainly to the important decrease of leaded gasoline use between 1986 and 1990. In fact, in Canada, leaded gasoline use had been banished by federal regulation in December 1990.

A RETROSPECTIVE COHORT STUDY ON THE RELATIONSHIPS BETWEEN METHYLMERCURY EXPOSURE AND HEALTH INDICES OF THE INHABITANTS IN JAPAN

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There have been two outbreaks of methylmercury poisoning in Japan, caused by intake of fish and shellfish contaminated by methylmercury compounds discharged from chemical plants: The first case was found in 1965 in Minamata City, facing the Yatsushiro Sea, and therefore the disease was designated as Minamata Disease; the second outbreak was seen in 1965 along the Agano River in Niigata.

To clarify a dose-response relationship between methylmercury exposure and health indices of inhabitants, a retrospective cohort study was conducted. Hair was used for assessing the dose of methylmercury taken through the diet. The mercury concentration levels in the hair, collected from the subjects in Minamata (1960-1963) and Niigata (1965), were measured by a dithizone procedure.

Effects of the mercury levels on the mortality of the recognized patients in Minamata were examined by Cox's proportional hazards regression analysis adopting sex and age as covariates. The total number of subjects was 902, among which 178 died. Results indicate that the mortality rate increased with the mercury level. For example, among subjects with same sex and age, the relative risk of subjects with mercury level over 100 ppm to those with 5-20 ppm was estimated to be 1.3, which suggests that the exposure to methylmercury may have increased the risk of death.

Among the 1,191 subjects whose hair mercury concentration was determined in 1965 in Niigata, a total of 134 cases developed the

typical symptom and were officially diagnosed as Minamata Disease patients by the end of 1990. The results of dose-response analysis on these data indicated that the threshold dose is estimated to be 40-70 ppm by the hockey-stick model. It is also suggested that the dose-response may be modified by age at exposure.

NASAL SEPTUM LESIONS CAUSED BY CHROMIUM EXPOSURE AMONG CHROMIUM ELECTROPLATING WORKERS

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One case of nasal septum perforation was found on a chromium electroplating worker who suffered from epistaxis during this work. To determine the etiology and prevalence of nasal septum lesions, we conducted a survey of 7 chromium electroplating factories and examined 79 workers. 40 workers from 3 aluminum electroplating factories were also enrolled as the reference group. Every worker was thoroughly examined by an otorhinolaryngologist. A questionnaire interview regarding symptoms of upper respiratory tract, past medical history, life style, and work history was also conducted. 118 out of 119 workers received blood tests of alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin/globulin (A/G) ratio, blood urea nitrogen (BUN), creatinine (Cr), urine test of n-acetyl-d-glucosaminindase (NAG), and venereal disease research laboratory test. Urine samples of these workers were taken at end-of-shift at end-of-workweek. Air chromium concentrations were measured by taking area sampling for 4-6 hours. Concentrations of urine chromium and air chromium were determined by graphite furnace atomic absorption spectrometry. After field observation and chromium measurements, we divided chromium electroplating into 3 different exposure zones: workers directly dealing with electroplating tanks (n=31), other processes workers (n=29), office workers and drivers (n=19). Among the 79 chromium electroplating workers, there were 16 cases with nasal septum perforation, 4 with scar formation, and 31 with ulceration. No worker from aluminum electroplating factories had any nasal septum abnormalities. Air and urine concentrations of chromium for the three exposure zones were 0.7-168.3 ug/m3 and 3.1-36.3 ug/gm creatinine; 0.5-39.7 ug/m3 and 0.7-6.4 ug/gm creatinine; 0.3-4.4 ug/m3 and 0.3-6.1 ug/gm creatinine, respectively; while those of the reference group were 0.04-0.2 ug/m3 and 0.08-0.4 ug/gm creatinine.

There were no statistical differences among different groups of workers for ALT, AST, A/G ratio, BUN, Cr, and urine NAG. All tests of VDRL were negative for all surveyed workers. There was a consistent trend between the degree of chromium exposure and signs and symptoms related to nose, throat, and skin. The severity of nasal septum lesions was associated with lifetime index of chromium exposures (air concentration x duration of work). We conclude that signs and symptoms of nasal septum among chromium electroplating workers were caused by the exposure of chromium, and immediate improvement of occupational hygiene should be started.

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