

Documentation of ill-health effects of occupational exposure to grain dust through sequential, coherent epidemiologic investigation

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FONN S, BECKLAKE MR. Documentation of ill-health effects of occupational exposure to grain dust through sequential, coherent, epidemiologic investigation. *Scand J Work Environ Health* 1994;20:13–21. This review describes the evolution in epidemiologic methods (study design, outcome, and exposure measurements and target population) in relation to knowledge gained concerning the ill-health effects of exposure to grain dust in the workplace over the past three decades. The clinical conditions associated with grain dust exposure are briefly described. Thereafter the study approaches used to investigate grain-related conditions (clinical studies, workforce-based prevalence studies, prevalence studies including unexposed workers, short-term response to exposure, longitudinal studies, supporting evidence from other research arenas, and studies documenting dose-response relationships) are discussed. The objective is to illustrate the strength of sequential, coherent epidemiologic investigation into the ill effects of a particular work environment on human health.

Key terms: exposure determination, grain dust, lung function change, methodology, respiratory symptoms, review, study design.

Most countries, whether developed or underdeveloped, grow and process their own grain. Hence the potential ill effects of exposure have widespread public health implications. Exposure to grain dust has been known to be associated with disease at least since the 18th century when Ramazzini described respiratory-related disability in grain workers and bakers (1). Grain handling results in the generation of dust from the abrasion of grain kernels, an estimated three to four pounds (1 to 2 kg) of dust being released for each ton (1 short ton = 0.907 metric tons) of grain handled (2). Other contaminants of the dust to which grain workers are exposed include microflora and fungi, mites, inorganic matter and soil dusts, animal matter, and chemicals (pesticides and herbicides used in the industry), depending on season, storage, humidity and many other factors (2).

Grain dust is a superficial irritant of exposed surfaces, and it causes rhinitis, conjunctivitis, and skin lesions ranging from itching to skin rashes. Several acute respiratory conditions have been described in relation to grain dust exposure (2) including (i) asthma with immediate and late reactions on an allergic or nonallergic basis, (ii) grain fever, characterized by acute systemic symptoms, chest tightness and cough,

usually following exposure to high airborne concentrations of dust and attributed to endotoxins or mycotoxins, (iii) extrinsic allergic alveolitis, due to exposure to high levels of fungal spores, in particular *Thermopolyspora polyspora*. Among the chronic conditions attributed to grain dust exposure, chronic bronchitis and chronic airflow limitation are probably the most common and the most important (2, 3). Neither is distinct from the chronic bronchitis and chronic airflow limitation related to exposures to other airborne pollutants, most notably smoking. Evidence that occupational exposures to dusts of inorganic or organic origin are implicated in the genesis of both conditions has accumulated steadily over the past several decades (3–5), and the importance of these conditions may have overtaken that of the traditional occupational fibrotic lung diseases, such as the pneumoconioses, in terms of numbers of individuals affected. In addition, in many work forces, the association between occupational exposures and chronic obstructive airway disease is as strong as the association with smoking (4), a finding which has emerged as a result of improved epidemiologic study design and more sophisticated multivariate analysis techniques to address the confounding effect of smoking with other airborne exposures.

A worker who develops an acute response to grain dust, in particular asthmatic-type responses, is often unable to tolerate the work environment, and there is evidence that such individuals leave this type of employment within a short period after they begin work. For instance a lower prevalence of atopy, as reflected by skin testing, has been shown for grain workers than for workers not exposed to grain dust

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(6–9). This finding suggests that atopic individuals have selected themselves out of the grain industry. An understanding of this phenomenon is important when the findings of research are interpreted, and it has bedeviled cross-sectional studies.

Research approaches used to investigate grain-related conditions

The distribution and determinants of respiratory conditions related to grain dust exposure and their significance has been examined over time with the use of clinical and epidemiologic methods. The overall goal of such research has been to determine whether grain exposure is related to respiratory ill health, and, if so, to determine the nature, cause, and co-determinants of adverse respiratory effects in grain-exposed workers. In this paper we review the evolution in epidemiologic methods (study design, outcome, exposure measurements, and target population) in relation to knowledge gained concerning the ill-health effects of exposure to grain dust in the

workplace over the past three decades. The objective is to illustrate the strength of sequential, coherent epidemiologic investigation into the ill effects of a particular work environment on human health. Many of the studies concern Canadian workers, Canada being one of the world's major wheat producing and exporting countries. Note that the papers we have cited, a selection of which is also listed in tables 1 through 3, have been chosen to illustrate the evolution of study methodology, and they do not constitute a comprehensive review of all material, such as has been published by Chan-Yeung et al (2).

Clinical studies

As is often the case, concern over health risks to local workers is first expressed in clinical reports of physicians serving communities in which a high proportion of the population is actively employed in a particular industry (10). In the 1960s and 1970s such reports were published on Canadian prairie elevator workers. The studies documented increased symptoms and impaired lung function and investi-

Table 1. Evolution of research approaches used to investigate the ill-health effects of grain dust exposure: cross sectional studies. (FEV_{1.0} = forced expiratory volume in 1 s, FMEF = forced mid-expiratory flow rate)

Reference	Worksite	Subjects	Outcomes, in addition to symptoms and lung function	Index of exposure	Specific issues addressed and new study features	Findings
doPico, 1977, United States (14)	Lake port elevators	300 exposed	Some antibodies, skin tests	Years	Prevalence of abnormality, immune reactions	Symptoms in 88%, reduced FEV _{1.0} in 37%, symptoms and lung function related to skin reaction
Becklake, 1980, Canada (10)	River port elevators	104 exposed, 39 unexposed	Clinical examination, chest X ray, serum precipitins, skin tests in selected subjects	Membership in work force	Comparison with unexposed workers in same work force	Long-term exposure associated with health effects, influenced by smoking, not related to immunologic status
Mink, 1980, Canada (9)	Lake port elevators	29 nonsmoking exposed, 29 nonsmoking unexposed	Skin tests, bronchial reactivity, serum immunoglobulin E	Membership in work force	Relationship of bronchial reactivity to chronic grain dust exposure	Lung function level higher and prevalence of allergic reactions higher in unexposed workers, bronchial reactivity higher in exposed workers
Dosman, 1980, Canada (18)	Prairie elevators	90 exposed, 90 unexposed nonsmokers		Membership in work force	Effects of grain exposure independent of smoking	Bronchitis five times more frequent, wheezing three times more frequent in grain workers; FMEF also lower
Chan-Yeung, 1980, Canada (7)	Port elevator workers, civic workers, saw mill workers	610 exposed, 136 unexposed, 187 unexposed	Cross-week lung function	Membership in work force, some dust samples	Comparison with other unexposed work forces	Symptoms more frequent in grain workers, FEV _{1.0} change -22 ml in grain workers and +100 ml in others
Cotton, 1982, Canada (17)	Prairie elevators	82 smokers, 82 nonsmokers, all exposed		Membership in work force	Separate consequences of smoking and nonsmoking	Only smoking grain workers demonstrated small airway changes, suggesting synergism
Cotton, 1983, Canada (19)	Prairie elevators	195 nonsmoking grain and reference workers, 195 smoking grain and reference workers		Membership in work force	Interaction of grain and cigarette exposure in selected subjects, stratified by exposure and smoking status	Increased prevalence of respiratory symptoms and decreased lung function associated with either grain exposure or smoking, slightly more pronounced in smokers
doPico, 1984, United States (20)	Lake port elevators	310 exposed, 237 unexposed	Clinical examination	Membership in work force	Interaction of grain and cigarette exposure in multivariate analysis	Effect of grain handling and smoking on symptom prevalence and lung function statistically significant and independent
Chan-Yeung, 1985, Canada (8)	Port elevators	584 exposed	Atopy	Membership in work force	Role of atopy as an effect modifier	Lower prevalence of atopy in grain-exposed workers; healthy worker effect

Table 2. Evolution of research approaches used to investigate the ill-health effects of grain dust exposure: cross-shift and cross-week changes. (FEV_{1.0}=forced expiratory volume in 1 s)

Reference	Worksite	Subjects	Outcomes, in addition to symptoms and lung function	Index of exposure	Specific issues addressed or new study features	Findings
Corey, 1982, Canada (21)	Prairie elevator workers	47 exposed, 15 unexposed	-	Dust samples, respirable and total	Acute changes in lung function, dose response relationships	Correlation between baseline lung function and usual dust exposure and within day decrease in flow rates directly related to respirable dust exposure
doPico, 1982, United States (22)	Duluth Superior elevator workers	248 exposed, 192 unexposed	Serum complement levels	Membership in work force, measured dust levels and worker's assessment of dustiness	Comparing measured and worker's dust level assessment; dose-response effect	Referents showed improved lung function over a shift whereas grain workers stayed the same or decreased; association between measured and subjective dust assessment
Yach, 1985, South Africa (25)	Grain mill workers	582 exposed, 153 unexposed	Skin test bronchodilator response	Membership in work force and worker-reported dust exposure	Cross-week change in lung function	FEV _{1.0} decreased in grain workers and increased in unexposed workers; dose-response relationship
James, 1986, Australia (27)	West Australian grain harvest workers	119 exposed	Bronchial challenge and skin tests	Recruited in one employment office for seasonal work, no grain exposure in past 10 months	Investigation of acute effect of cross-season exposure; determination of whether symptoms are related to ventilatory change	Wheezing, chest tightness and breathlessness related to decline in FEV _{1.0}
Fonn, 1993, South Africa (41)	Grain mill workers	305 exposed	-	Worker-reported and measured dust levels	Relationship of exposure measured in two ways to cross-week change in lung function	Worker-reported and measured exposure comparable, either adequate to demonstrate epidemiologic relationships

Table 3. Evolution of research approaches used to investigate the ill-health effects of grain dust exposure: longitudinal studies. (FEV_{1.0}=forced expiratory volume in 1 s)

Reference	Worksite	Subjects	Outcomes, in addition to symptoms and lung function	Index of exposure	Specific issues addressed or new study features	Findings
Warren, 1980, Canada (29)	Prairie elevators	58 exposed	-	Years	First report of longitudinal follow-up (six years) study	High prevalence of symptoms and abnormal lung function in those lost to follow-up, demonstration of healthy worker effect, increased abnormal lung function over the six years
Chan-Yeung, 1981, Canada (30)	Port elevators	396 exposed, 111 unexposed	-	Membership in work force, years	Investigated the relationship between cross-shift change and annual decline in lung function	Annual decline greater in grain workers than in unexposed subjects and related to age, smoking and cross-shift and cross-week change
Tabona, 1984, Canada (31)	Port elevators	267 exposed	Bronchial reactivity	Membership in work force and years, six-year follow-up	Investigated the relationship between cross-shift change and bronchial reactivity to annual decline in lung function	Correlation of cross-week decline in lung function and bronchial hyperreactivity with subsequent decline in lung function; smoking status, skin reactivity and presence of symptoms not significantly correlated with subsequent decline in lung function
Enarson, 1985, Canada (32)	Port elevators	27 cases, 54 referents	-	Membership in work force and dust levels	Nested case-referent study	Cross-week change in FEV _{1.0} , bronchial reactivity and exposure level predicted rapid longitudinal decline in FEV _{1.0} ; skin reactivity and asthma history did not
Broder, 1985, Canada (33)	Port elevators	441 exposed, 180 unexposed	-	Membership in work force	Investigation of workers who had left employment between initial and repeated survey	Similar longitudinal changes in lung function in both groups; grain handlers who left had more symptoms; demonstration of healthy worker effect in longitudinal study

gated their relationship to immunologic markers (10). They led to the involvement of the Canadian Thoracic Society in defining the existing state of knowledge and elaborating research priorities, including the importance of epidemiologic studies.

Cross-sectional studies on work forces

Starting with the 1940s, cross-sectional studies have reported on the prevalence of respiratory symptoms and lung function level of exposed workers; these studies have been well summarized in a recent review (2). Since 1980, surveyors have, for the most part, used the standardized respiratory symptom questionnaire of the American Thoracic Society (11) and adhered to the standards established by the various workshops on standardized lung function monitoring for screening purposes (12, 13). The importance of the standardized methodology is that it allows comparisons to be made across time, within a study, and between studies on comparable work forces.

Thus in a 1977 cross-sectional survey of 300 workers who handled grain in a North American lake port, 77% of the workers reported eye symptoms, 64% complained of nasal symptoms, and 88% had one or more respiratory symptoms (14). These symptoms were independent of age and length of employment. Rates tended to be higher among those with one or more positive skin reaction to common allergens, and the differences were significant for wheezing. These findings lead to the hypothesis that the atopic worker is at risk of grain-related respiratory illness. However in this cross-sectional study no unexposed population was investigated. Subsequently, in 1980, the issue of the interaction of smoking and grain dust exposure was addressed in a study of prairie elevator workers (3), for whom a decrease in lung function was found in smoking workers, and the decrease was greater than that in either smokers or grain workers separately. It was concluded that grain workers who smoke are more likely to develop respiratory insult than nonsmoking grain workers or smokers not exposed to grain dust. From these and other studies, it was becoming clear that grain workers were experiencing high rates of respiratory abnormality. However the relationship of these symptoms to work was not clear. Specifically, the interaction of atopy and smoking with grain exposure in the generation of respiratory symptoms and lung function level needed to be addressed.

Cross-sectional studies including unexposed workers

Since 1980, most reported cross-sectional studies have included an unexposed comparison group (table 1). Such comparisons address the question of exposure-response relationships (ie, any versus no exposure), a key element in establishing causality beyond association. These studies also allowed for the comparison of atopy prevalence in exposed and

unexposed work forces. For instance, a study (15) of 103 grain handlers in the port of Montreal and 39 unexposed dock workers showed no relationship between respiratory effects and atopic status in contrast to the findings of an earlier lake port study (16). In another study of lake port workers (9) a higher prevalence of cough, sputum, dyspnea, and wheezing was found in the grain-exposed workers than in the unexposed workers. In addition, although the lung function levels and the prevalence of allergic reactions were higher among the unexposed than among the grain-exposed workers, there was a greater prevalence of nonspecific bronchial reactivity among the grain workers than among the unexposed population. This finding suggested that bronchial hyperreactivity in some grain workers may not be allergic in etiology, and it became clear that respiratory changes were not confined to atopic workers.

Another consequence of the introduction of an unexposed comparison group as a feature of cross-sectional studies on grain workers carried out since 1980 was to provide evidence in support of the strongly held clinical impression that active work forces are essentially survivor populations (7, 8). For instance, it was noted that asthmatic subjects tended to withdraw from work in prairie grain studies and that turnover was rapid among workers in their first two years of employment (3, 17). Similarly atopy was found to be less frequent in a study of west coast port elevator workers than in a nongrain-exposed group of civic workers (7). By the mid-1980s there was thus substantial evidence for a "healthy worker effect" on work forces exposed to grain dust, and it became clear that the nature and frequency of the adverse health effects of grain dust exposure had been underestimated by the cross-sectional design.

Given the dominant role of smoking as a determinant of respiratory health status, an early concern of researchers was to establish whether grain dust exposure had adverse respiratory effects independent of tobacco exposure. One approach was to stratify by smoking status in the analysis. For instance, in the 1980 port of Montreal study (15), comparing dock workers with grain handlers, a higher prevalence of cough and wheezing was only found for the grain handlers who smoked, but a decrease in lung function was evident whether or not they smoked. Another approach was to control for the confounding effects of smoking by selecting for the study only those who did not have exposure to the confounding factor, in this case lifetime nonsmokers. Thus in a comparison of lifetime nonsmoking prairie grain workers with lifetime nonsmoking subjects selected from the same communities, a five times greater prevalence of chronic bronchitis and a three times greater prevalence of wheezing was found for the grain-exposed workers than for those not exposed (18). They also had a lower forced mid-expiratory flow rate and flow rate at 50% of vital capacity (18). These findings strengthened the evidence of the abil-

ity of grain dust to cause respiratory changes in its own right. Other studies yielded evidence of a synergistic relationship between smoking and grain dust exposure (3). For instance, in one study (17) of workers exposed in prairie elevators, there was no difference in the prevalence of respiratory symptoms when these workers were compared with unexposed workers, but a difference in lung function was found for smoking grain workers, a finding suggesting some interaction between smoking and grain dust exposure in the pathogenesis of abnormal lung functions. In a second study of the same working population, matched groups of nonsmokers and smokers, grain exposed and unexposed, were compared (19). An increase in symptoms and decreased lung function were found in the grain workers and in the smokers, but the effects appeared to be additive rather than synergistic. Thus these study approaches allowed researchers to investigate the independent effects and interactive effects of smoking and grain exposure on respiratory health. These findings are in agreement with those of other studies that have demonstrated an effect of grain-dust exposure on respiratory health independently of smoking status.

Subsequently, as multivariate methods of analysis evolved, they were used to explore these relationships. For instance, in a study of workers exposed to grain in lake port elevators and unexposed civic workers in the Lake Superior area, the prevalence of chronic bronchitis was significantly higher for grain-exposed workers than for unexposed workers (20). Dyspnea, chest tightness, and wheezing were also found to be more common among the grain-exposed workers. Chronic bronchitis and wheezing were related to both smoking history and grain dust exposure. The odds of grain exposed workers' exhibiting the symptoms of chronic bronchitis and wheezing were 4.4 and 4.8, respectively, irrespective of smoking status, while the odds of smokers' exhibiting the symptoms of chronic bronchitis or wheezing was 2.9 and 1.9, respectively, irrespective of grain exposure. Thus multivariate analysis was able to provide a numerical description of the effect of grain exposure and smoking on respiratory symptoms. In this study no relationship between lung function level and length of employment was demonstrated, and therefore the researchers interpreted the result as evidence of a "healthy worker effect."

Thus, from these cross-sectional studies, evidence was forthcoming to suggest that grain-dust exposure, independent of smoking, was related to respiratory symptoms and change in lung function.

Short-term responses to exposure

As part of the thrust to establish exposure-response relationships, acute changes in lung function over a week or a shift were studied in several work forces, often as part of cross-sectional prevalence studies, with or without unexposed comparison groups, com-

ing either from within the same work force or from other work forces selected because they were not exposed to grain or, in some instances, any obvious workplace pollution (table 2).

For instance, in a study of three Vancouver work forces (port grain elevator workers, saw mill workers, and civic workers) (7), one of the first studies to measure short-term changes in lung function, forced vital capacity (FVC) and forced expiratory volume in 1 s ($FEV_{1.0}$) decreased over 1 d, as well as over one workweek, whereas in the other two work forces these lung function parameters increased over the same period. A subsequent study (21) on Canadian lake port workers who were examined on Monday, Wednesday, and Friday found that FVC and $FEV_{1.0}$ decreased on Wednesday when compared with the corresponding values on Monday, but there was no decrease in lung function in the afternoon compared with the morning measurement. The results were interpreted as providing some evidence for the reversibility of lung function changes related to grain exposure. Likewise studies in lake port grain workers in the United States (22) showed cross-shift decreases in lung function, whereas civic workers not exposed showed increases in lung function over the workshift, a finding independent of age or smoking status. In a subsequent study these cross-shift changes in lung function were shown to be dose-related to exposure levels when workers were stratified according to whether exposure levels were greater or less than $5 \text{ mg} \cdot \text{m}^{-3}$ (23). Studies on Canadian port elevator workers (24) also showed dose-related changes in lung function over a shift.

Changes in lung function over the workweek have also been reported for grain workers from other parts of the world. For instance, in a South African study of grain mill workers and factory workers at sea level, lung functions for both the grain-exposed and nongrain-exposed populations were similar (25). However, the grain workers demonstrated a decrease in $FEV_{1.0}$ and forced mid-expiratory flow rate, while the factory workers demonstrated an increase in these parameters over the workweek. A 10% decrease in $FEV_{1.0}$ was seen in 23% of the grain-exposed population and in only 9% of the unexposed population. Neither atopic status nor smoking status was related to this change in lung function of the study population over the week. In another South African study (26), conducted in the Johannesburg area [approximately 6000 feet (1829 m) above sea level], a decline in lung function over the workweek was seen in those workers exposed to high concentrations of grain dust as assessed by the measurement of airborne grain dust in milligrams per cubic meter in comparison with a rise in function over the workweek in those in the low-exposure category. An Australian study (27) reported a decrease in lung function measured at the beginning of the employment season compared with the end of the season. The change was significantly associated with work-re-

lated breathlessness but not with skin reactivity to allergens.

In summary, several studies in different work forces in different parts of the world have established that grain-dust exposure is associated with short-term decreases in lung function measured over the work-shift, workweek, or work season. There is also evidence to suggest an exposure-response relationship between cross-shift or cross-week changes and subsequent chronic airflow limitation. In a review of occupational asthma (28) the measurement of cross-shift change in lung function was considered good evidence of the work relatedness of this respiratory change. However the relationship of short-term lung function changes to the long-term health of grain workers can only be elucidated by longitudinal studies.

Longitudinal studies

The strength of longitudinal studies (table 3) of work forces lies in their ability to clarify time relationships; their weakness is the result of the difficulty of achieving satisfactory follow-up rates. One of the earlier longitudinal studies on grain workers was that of Warren & Manfreda (29), who reported a six-year follow-up of 68 Manitoba grain elevator workers. In this study, 19% of the original work force had changed jobs, and these workers were found to have a higher prevalence of symptoms, as well as abnormal lung function. In those workers who were retested after the six-year period, more were found to have abnormal lung function findings ($FEV_{1.0}/FVC = <70\%$). Although only a small group of workers was followed, the findings are nonetheless interesting and have subsequently been confirmed by other reports, in particular a coherent series of interrelated papers based on research with port elevator workers in the Vancouver area, conducted by a research team headed by Chan-Yeung et al (30–32). A two-year follow-up of grain-exposed workers and reference civic workers showed that respiratory symptoms increased over the two years in the grain-exposed workers, but not in the civic workers, and the annual decline in $FEV_{1.0}$ was also greater in the grain workers. In addition, the annual decline in $FEV_{1.0}$ was found to be significantly related to the cross-shift and cross-week changes in lung function recorded in the earlier study. These findings suggest that acute changes in lung function predict or lead to irreversible airflow limitation. In 1984, a six-year follow-up of these workers (31) confirmed that the change in lung function over one week was a significant predictor of subsequent annual decline in $FEV_{1.0}$. Neither atopic status nor the initial lung function level was related to this annual decline in $FEV_{1.0}$. Nor, surprisingly, was smoking status. Methacholine challenge, used to define bronchial hyperreactivity, was also found to be a significant predictor of annual decline in $FEV_{1.0}$. In a further analysis of these data, using a nested case-referent design within the follow-

up cohort (32), a rapid decline in $FEV_{1.0}$ (defined as a decrease of greater than 100 ml in $FEV_{1.0}$ per year) was found to be related to the level of grain-dust exposure, and a greater than 4% decrease in $FEV_{1.0}$ over the workweek and bronchial hyperreactivity were significant predictors of accelerated annual lung function decline. These effects were demonstrable for exposure levels greater than $4 \text{ mg} \cdot \text{m}^{-3}$.

In contrast to these findings, a four-year follow-up study of lake port workers (33) found no difference in the prevalence of symptoms between the two surveys and no difference in the lung function level. However not exactly the same subjects were retested. There was also a higher prevalence of eye irritation, shortness of breath, and cough, but no difference in the lung function level, in those who had left compared with those who had remained in the same employment. These findings were interpreted, correctly in our view, as evidence of a "healthy worker effect." The authors warned researchers that in longitudinal studies the "healthy worker effect" is likely to attenuate the exposure-response relationship in studies of grain workers. The fact that a selected healthy group of workers is available for long-term follow-up was recently underlined; the authors went on to question the usefulness of longitudinal studies, given their expense and difficulty, in assessing exposure-related health hazards since this relationship has been demonstrable with the use of cross-sectional data (34).

There is consistency in the findings of the follow-up studies indicating that acute cross-shift changes in lung function are of clinical importance and also in the evidence suggesting that cross-shift changes predict long-term irreversible obstructive airway disease (35).

Supporting evidence from other research arenas

In the nonoccupational setting, attention has also been given to early markers of chronic obstructive airway disease. For instance, in one analysis (36), a decrease in $FEV_{1.0}$ was the most important risk factor, other than age and cigarette smoking, for the future development of chronic obstructive airway disease. In addition, a reduction of $FEV_{1.0}$, as well as other measures of ventilatory function, has been shown to be associated with increased mortality and morbidity (37). Again, in one study (38) of the bronchodilator response of patients with chronic obstructive airway disease, the greater the degree of airway responsiveness to bronchodilators, the more rapid the decline in both FVC and $FEV_{1.0}$ over time. Other researchers (39) have reported that a low $FEV_{1.0}$ predicts a more rapid decline in $FEV_{1.0}$ and that this predictor is more reliable if the change in $FEV_{1.0}$ is taken into account. Thus the finding that short-term change in $FEV_{1.0}$ predicts long-term decline in lung function is not an isolated finding for workers exposed to grain dust, nor is it confined to one study design or one method of defining acute response to grain-dust

exposure. The demonstration of cross-shift changes in lung function becomes more significant in light of the findings of the longitudinal studies on both grain workers and other populations in which early indicators of obstructive lung disease have been studied.

Studies documenting exposure-response relationships

Dose-response relationships are a key element in establishing the harmful effects of exposure to an agent in the fields of pharmacology and toxicology. Dose in these circumstances is defined as the amount of agent delivered to, and remaining in contact with, the target organ for a sufficient length of time to evoke an effect. In occupational epidemiology, exposure is the only practical substitute for dose, and exposure-response relationships (with exposure characterized categorically as any versus none) are used to establish the occurrence of adverse health effects, while exposure-response relationships (with exposure characterized as a continuous or ordinal variable) provide information useful for public health purposes, in particular for determining appropriate environmental control levels. The preceding discussion indicates the consistency with which adverse respiratory effects have been demonstrated with the use of categorical exposure indices (ie, any versus no exposure) (3, 6–8, 15–23, 25). Several studies provided some evidence from quantitative environmental measurements of the exposure levels associated with detectable adverse respiratory effects in grain workers (23, 26, 32). Researchers have also used duration of employment as a proxy for exposure (40). In addition, clear relationships between exposure, assessed subjectively by the worker, and both symptoms and lung function level have been demonstrated in two studies of workers in different South African grain mills; these findings point to the usefulness of qualitative exposure measurements for this purpose (25, 41). However, only recently has a systematic study of exposure-response relationships, using quantitative industrial hygiene measurements of exposure, been reported (42). The study, incorporating information from the extensive data on Vancouver grain elevator workers, used 781 personal air samples representing 20 job titles over the 15-year study period to construct a job-time matrix for average dust exposure. This study provides some of the strongest evidence to date of chronic adverse effects of exposure on lung function, exposure-associated effects having been demonstrable at levels as low as $4 \text{ mg} \cdot \text{m}^{-3}$. Confirmation in other work forces would further strengthen the evidence for a causal association. In addition, the first planned study to investigate survival in the industry from the time of recruitment was recently published by Zejda et al (43). After four years only one-third of the subjects who originally underwent an initial employment examination were still at work, and the short-term (an-

nual) lung function loss was negatively related to the number of years a worker remained in the industry. Thus those who left after one year had an annual FEV_{1.0} loss of function of 224 ml, whereas for those who left after three years the corresponding value was 71 ml.

Synthesis

An appreciation of the relationship of grain-dust exposure and respiratory health has developed through the rational application of epidemiologic methods. Initially cross-sectional studies indicated an apparent increase in respiratory symptoms and other health indicators among grain-exposed workers. This finding was confirmed by the use of more sophisticated study approaches in which exposed workers were compared with unexposed individuals, either from within the same work force or from other unexposed work forces, and exposure-response relationships were established by contrasting those with any exposure versus those with no exposure. The demonstration of acute cross-shift changes in lung function supported the evidence for grain-related ill-health effects. Further evidence of exposure-response relationships was obtained in longitudinal studies which demonstrated a relationship between acute cross-shift or cross-week changes in FEV_{1.0} and long-term lung function loss. Supportive evidence from nongrain-related research added weight to this argument. Finally, the documentation of exposure-response relationships for lung function deficit, first using subjective (qualitative) exposure estimates and subsequently quantitative industrial hygiene measurements, completes the documentation generally required to establish associations as causal.

To date, no use has been made of experimental studies, for instance, in the form of a randomized control trial, to assess the effect of an acute intervention, such as decreasing exposure in a given workplace over a short period, such as a week or a month. To achieve this situation, the cooperation of employers in conjunction with organized workers would be needed. While the evidence to date strongly suggests that efforts to control grain-dust exposure should be undertaken, a demonstration study of the expected associated health benefits is now clearly indicated, rather than further documentation of the problem. Moreover, positive results from a short-term intervention study would provide additional ammunition for the argument for control levels below $4 \text{ mg} \cdot \text{m}^{-3}$, the level suggested on the basis of the best available data to date (42).

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