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Tim H. J. M. Jorna · Paul J. A. Borm · Klaas D. Koiter
Jos J. M. Slangen · Peter Th. Henderson
Emiel F. M. Wouters

Respiratory effects and serum type III procollagen in potato sorters exposed to diatomaceous earth

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Abstract Exposure to diatomaceous earth with low crystalline silica content (< 1%) is rarely reported to cause pneumoconiotic disease, whereas airway obstruction and bronchitis are more frequently reported. We investigated the occurrence of pneumoconiosis and airflow limitation in 172 male workers from 5 potato sorting plants (55 controls, 29 salesmen, 72 currently exposed, and 16 retired exposed) exposed to inorganic dust from former sea terraces (7.7–15.4 mg/m^3), high in diatomaceous earth. The presence of fibrosis was evaluated by chest radiographs (exposed only) and serum levels of type III procollagen (P-III-P) were measured as an estimate of fibrogenetic activity. Lung function was assessed by flow volume curves and impedance measurements. A validated questionnaire was used to record respiratory symptoms. No pneumoconiotic abnormalities were demonstrated by chest radiographs. In line with this finding, serum P-III-P levels were not elevated in exposed workers as compared to controls, suggesting no differences in fibrogenetic activity. In fact, serum P-III-P levels decreased significantly (P < 0.03) with increasing cumulative exposure. Flow volume parameters indicated airflow obstruction, dose-related to (cumulative) dust exposure; the annual decline in forced expiratory flow volume (FEV_1) was estimated at 10.5 ml/year (P < 0.05). Airway obstruction was confirmed by impedance analysis: In the retired group impedance changes were compatible with airway obstruction extending into the peripheral airways. We conclude that this exposure to quartz during potato sorting does not result in an increased risk for pneumoconiosis, but that (prolonged) surveillance in this group is desirable in order to detect early indications of airflow obstruction.

Key words Non-crystalline silica · Pulmonary fibrosis Air flow limitation · Chest X-ray · Spirometry Impedance measurement

P. J. A. Borm
Health Risk Analysis and Toxicology, University of Limburg, PO Box 5800, NL-6202 AZ Maastricht, The Netherlands

K. D. Koiter
Occupational Health Service
Dr Spanjaardweg II, 8025 BT, Zwolle, The Netherlands

J. J. M. Slangen
Department of Epidemiology
University of Limburg, PO Box 5800, NL-6202 AZ Maastricht, The Netherlands

P. Th. Henderson
TNO Medical Biological Laboratory
University of Limburg, PO Box 5800, NL-6202 AZ Maastricht, The Netherlands

T. Jorna (✉) · E. F. M. Wouters
Department of Respiratory Diseases, University of Limburg, PO BOX 5800, 6202 AZ Maastricht, The Netherlands

Introduction

Diatomaceous earth is an amorphous nonfibrous silicate derived from skeletal remains of diatoms that are deposited on marine and lake floors. It contains, in its native form, up to 1% crystalline silica (cristobalite). Calcination at high temperatures (600–1000° C), however, may lead to the formation of up to 60% cristobalite [17]. This calcinated product (Kieselguhr) is used for filtration, insulation, and as a filler and polisher [23]. A recent mortality study showed increased standard mortality ratios in diatomite industry [5]. The increased ratios could be explained by increased rates of lung cancer due to crystalline silica [10] and nonmalignant respiratory disease (excluding infectious diseases and pneumonia). Diatomite pneumoconiosis is rare and has mainly been described in the diatomite-processing industry and in several brewery workers exposed to calcined diatomaceous earth used for filtering purposes [7]. The potential of the unprocessed earth to cause pneumoconiosis is controversial, since some evidence exists that prolonged exposure may result in mild pneumoconiosis [23]. Besides pneumoconiotic effects, the role of dust exposure as a contributive factor in chronic bronchitis symptoms and airflow decrements is well established [2, 9, 24].

Few data are available about the deleterious respiratory effects of noncalcined diatomaceous earth. Industrial hygiene evaluations in potato sorting in the Netherlands have consistently found elevated dust exposures caused by the diatomaceous earth on the potatoes, grown in former sea terraces.

The main purpose of this cross-sectional study was to determine whether respiratory hazards are present due to the exposure mix, high in diatomaceous dust in potato sorting. To assess pneumoconiotic effects, both chest X-rays and serum type III procollagen (P-III-P) levels, previously suggested to be a sensitive marker of active fibrosis [11], were applied. Flow volume curves and impedance measurements were performed to detect airflow limitation and respiratory symptoms were recorded by means of a questionnaire.

Subjects and methods

Study design and protocol

Male Caucasian workers (n = 174) from 5 potato sorting plants of the same agricultural cooperative in the Netherlands were studied (Table 1), and 172 complete data sets were obtained. The study was conducted in the month of October, just after the potato harvest at peak activity of these plants. Written informed consent was obtained prior to measurements (response rate 88%). Salesmen (n = 29) who experienced short-term exposure during the taxation of the crop (1 h/day on average) were regarded as a separate group. Questionnaires were obtained from 55 office staff (I = controls), 29 salesmen (II = salesmen), 72 blue collar workers (III = currently exposed), and 16 retired blue collar workers (IV = retired exposed). After evaluation of the questionnaire, workers completed three valid measurements of both flow volume curves and impedance using the forced oscillation technique (FOT). The FOT was always performed before registration of flow volume curves to avoid the influence of forced inspiratory maneuvers on the bronchial tonus [19]. A 10-ml blood sample was taken and the serum frozen and stored for determination of serum P-III-P, as previously described [11].

A chest radiograph (± 100 kV, 125 mA) was made in exposed and retired workers only. All radiographs were classified by a panel of three occupational physicians experienced in reading and classifying coal workers' pneumoconiosis according to ILO (International Labour Organization) criteria [8]. Within 2 months after the study all workers were informed individually by the occupational physician (KDK) about the personal outcome of measurements.

Exposure assessment

Stationary monitoring using a continuous dust monitor (Hund TM Data, Meyvis, Bergen op Zoom, NL) based on light diffraction was used to identify main sources and places of exposure. In 1988, job exposure was extensively measured using personal samplers (Casella, cyclone) with at least four (8 h) samples per job. Five different job categories could be distinguished. Total inspirable dust and respirable dust were determined gravimetrically, and silica content of two respirable samples was determined by MT-TNO (Delft, The Netherlands) using a Fourier transform infrared spectrophotometer (Bruker Type 113V, Meyvis, Bergen op Zoom, NL). Assuming homogeneous lognormal distribution of the data, geometric mean and geometric standard deviations were calculated (Table 2). In order to obtain the estimated exposures in units of gram-hours per cubic meter (gh/m^3), the total exposure time was determined as 1200 work hours/year, taking into account the seasonal character of this industrial activity. Job continuity of most workers allowed proper estimation of the individual (cumulative) dose of total dust and of silica exposure from each worker's job history. No data were available on exposure to herbicides, fungicides, or other pollutants.

Lung function measurements

The basis for the impedance measurement was described previously [13]. Briefly, a pseudorandom noise pressure signal containing all harmonics from 4 52 Hz was applied at the mouth by means of a loudspeaker. Recorded random pressure and flow signals were analyzed by spectral analysis techniques and impedance was partitioned into resistance (R) and reactance (X). Of the obtained impedance data, the resistance at 8 Hz ($R8$), at 28 Hz ($R28$), frequency dependence of resistance (FD, the difference between $R28$ and $R8$), the reactance at 8 Hz ($X8$), and the resonant frequency (f_0) were used for analysis. Only measurements with a coherence function ≥ 0.95 were used. $R8$ was chosen because at this frequency usually coherence functions ≥ 0.95 were obtained, which were not always obtained at lower frequencies. Airway obstruction, based on impedance criteria, was considered in this study in the presence of a negative FD concurrent with an increased f_0 (usually ≥ 15 Hz). Three successive measurements, each lasting 8 s were performed in each subject. No active cooperation of the subject was required during the measurement procedure. The apparatus was calibrated daily and all subjects were measured on the same apparatus by the same observer.

Table 1 Demographic data of the four groups studied

Parameter (Units)	Group							
	I[a] (n = 55)		II (n = 29)		III (n = 72)		IV (n = 16)	
	$\bar{X}$	(SD)	$\bar{X}$	(SD)	$\bar{X}$	(SD)	$\bar{X}$	(SD)
Age (years)	38.3	(9.4)	44.5	(10.9)	46.4*	(10.9)	63.8**	(6.2)
Length (cm)	184.4	(6.6)	181.2	(5.9)	178.2	(7.0)	175.2*	(6.2)
Weight (kg)	83.6	(9.3)	86.9*	(11.4)	82.7	(8.7)	81.0	(7.7)
Employment (years)	12.4	(9.7)	16.2*	(11.8)	11.8	(8.4)	22.4**	(7.8)
Smokers								
Current	26	(47%)	14	(48%)	36	(50%)	5	(31%)
Past	18	(33%)	12	(42%)	25	(35%)	9	(56%)
Never	11	(20%)	3	(10%)	11	(15%)	2	(13%)
Packyears	9.6	(7.9)	12.2	(9.6)	13.2	(8.9)	16.5*	(8.7)
Cumulative dose (gh/m^3)	–	–	63.2	(77.1)	117.8	(87.4)	199.5	(94.3)

[a] Explanation of groups: I, controls; II, salesmen; III, current exposed; IV, retired exposed. Significantly different from controls (I) at: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ tested by analysis of variance

Table 2 Geometric mean and standard deviation of total dust and respirable free silica exposure among different jobs (*GM* geometric mean, *GSD* geometric standard deviation)

Job	No. of measurements	Total dust exposure (mg/m^3)		Respirable free silica (mg/m^3)	
		GM	GSD	GM	GSD
Sorting	4	6.9	1.9	0.23	1.4
Transport	5	6.9	1.6	0.13	1.7
Loading	4	5.6	1.8	0.20	1.5
Pelleting/package	4	10.8	2.0	0.32	1.9
Reading	4	13.3	1.7	0.35	1.8
Total group	21	8.2	1.9	0.23	1.8

Forced expiratory flow volume (FEV) curves were recorded according to European Community of Coal and Steel (ECCS) criteria using a dry spirometer (Vitalograph P2, Mynhardt, Bunmik, The Netherlands). Three recordings within 5% or a 100-ml range were obtained from each subject. Parameters derived from the flow volume curves were: FVC, FEV_1, FEV_1/FVC ratio, peak expiratory flow (PEF), and maximal midexpiratory flow (MMEF). Flow volume values were expressed as a percentage of the reference values of the ECCS [21] for individual diagnosis. A FEV_1 value less than 80% predicted was considered as a measure of airflow limitation. The spirometer was calibrated at regular intervals and all subjects were measured on the same spirometer. Two spirometric and two FOT measurements failed due to technical problems. FVC, forced vital capacity.

Blood assays

A 10-ml blood sample was obtained from each worker. The serum of the sample was stored at –80°C until analysis of P-III-P. Serum P-III-P levels were assessed using a commercial assay (Behringwerke AG, Marburg, Germany) as described previously [11]. This assay used Fab antibody fragments that binded with equal affinity to the known reactive collagen species col 1 and col 1–3 [22]. This resulted in an inhibition curve whose slope was parallel to the standard [11].

Statistical analysis

Individual dust/silica exposure was expressed as a cumulative measure (g dust) and estimated by multiplying the average time worked in a job times the average exposure for that job category. When a subject had worked in different jobs estimated cumulative exposures were added. Smoking was expressed as packyears (Table 1). Average lung function data for the different groups were tested for significance using analysis of variance (ANOVA). Confounders (age, height, weight, smoking) in lung function measurements were controlled by means of multiple linear regression. In this linear regression, lung function parameters were taken as dependent variables and the confounders and (cumulative) exposure as the independent variables. First the confounders and subsequently the cumulative exposure were put into the model of linear regression. Comparison of the questionnaire data to lung function outcome was done with a multiple logistic regression analysis (BMDP, Berkeley, CA, USA). All procedures, if not stated otherwise, were computed with SPSS-X program (SPSS Inc, Chicago, IL, USA).

Results

Exposure

Mean exposure of the total group to total inspirable dust was 9.9 mg/m^3 (n = 21; range: 2.4–21.6 mg/m^3) with highest exposure among readers and those involved in pelleting and packaging (Table 2). The mean exposure was just below the Dutch standard of 10 mg/m^3 for total nuisance dust. Mean respirable dust exposure was 2.21 mg/m^3 (n = 21; range; 0.5–6.7 mg/m^3). The mean respirable silica exposure was 0.27 mg/m^3 (range: 0.09–0.84 mg/m^3) exceeding the Dutch standard of 0.15 mg/m^3. In Table 2 the geometric mean and standard deviations are shown for several jobs in these potato sorting plants.

Table 3 Average results (mean and standard deviation) of flow volume curves, impedance measurements, and serum P-III-P levels in the four groups of workers. *FVC*, forced vital capacity; *FEV*, forced expiratory volume; *PEF*, peak expiratory flow; *MMEF*, maximal midexpiratory flow

Parameter		Group I[a] (n = 55)		II (n = 29)		III (n = 72)		IV (n = 16)	
		$\bar{X}$	(SD)	$\bar{X}$	(SD)	$\bar{X}$	(SD)	$\bar{X}$	(SD)
Spirometry									
FVC	(% predicted)[b]	109.5	(10.9)	110.4	(11.4)	107.3	(11.5)	109.0	(16.4)
FEV_1	(% predicted)	99.0	(11.8)	100.2	(12.5)	93.4*	(15.6)	93.4*	(22.7)
FEV_1/FVC ratio		74.2	(7.2)	74.0	(7.5)	70.4*	(9.3)	66.4*	(8.2)
PEF	(% predicted)	98.8	(13.2)	102.2	(15.5)	93.2*	(17.6)	88.9**	(23.1)
MMEF	(% predicted)	78.5	(21.1)	79.2	(22.2)	67.6**	(24.4)	59.5**	(33.1)
Impedance									
*R*8	(hPa.s/l)	2.26	(0.56)	2.22	(0.57)	2.42*	(0.97)	2.85**	(1.38)
FD	(hPa.s/l)	0.36	(0.37)	0.38	(0.36)	0.21*	(0.63)	–0.28*	(0.87)
*X*8	(hPa.s/l)	0.04	(0.20)	0.05	(0.21)	–0.11*	(0.51)	–0.47*	(1.06)
f_0	(Hz)	8.17	(1.90)	8.16	(1.82)	9.63*	(4.4)	12.62*	(7.9)
Blood									
Serum P-III-P levels		50.9	(9.39)	47.34	(8.01)	46.92	(8.52)	46.04	(9.14)

[a] Explanation of groups: I, controls; II, salesmen; III, currently exposed; IV, retired exposed
[b] Spirometric parameters as percentage predicted of European Community of Coal and Steel (ECCS) reference values [12]
Significantly different from controls (I) at: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ tested by analysis of variance

Table 4 Results of the multiple linear regression (MLR) analysis including smoking, hegiht, age and cumulative exposure as independent variables for the lung function parameters. The MLR was carried out on all workers excluding retired-exposed workers, because of the large differences in age

Lung function parameters	(Units)	R^2 %	β-Exposure	*P* value
FVC	(l)	57	−0.088	0.132
FEV_1	(l)	60	−0.124	0.032
FEV_1/FVC ratio	(%)	24	−0.139	0.079
MMEF	(l/s)	39	−0.117	0.100
FD	(hPa.s/l)	14	−0.089	0.293
*X*8	(hPa.s/l)	16	−0.144	0.084
f_0	(Hz)	19	0.142	0.085

R^2, Percentage of variance explained by the model; β, slope due to cumulative exposure to silica-containing total dust

Table 5 Results of multiple logistic regression analysis studying the relation between the data of the questionnaire, lung function parameters, and confounders

	Lung function parameter*		Confounder
	n	$\chi < 10\%$	
Cough	34	*R*8, f_0	Packyears, age
Phleghm	32	–	Cumulative dose
Chronic bronchitis	24	FEV_1	Cumulative dose
Short of breath	20	*X*8, f_0	–
Wheezing	34	f_0	Packyears, age
Asthmatic attacks	8	FEV_1	Age

* Statistical significance was tested using the X-test on two different levels ($P < 0.1$; $P < 0.05$)
[a] Explanation of paramters: *R*8 = resistance at 8 Hz, *X*8 = reactance at 8 Hz, f_0 = resonant frequency

Respiratory effects.

On the chest radiographs no irregular densities could be observed and, in consequence, the radiographs were classified 0/0 according to the ILO criteria. In line with this finding serum P-III-P levels were similar in the control and exposed groups (Table 3). In all exposed groups, however, serum P-III-P levels tended to be lower. Cumulative exposure was significantly ($P \leq 0.03$) inversely related to serum P-III-P levels after adjustment for packyears smoking. Flow volume values adjusted for differences in age and length were expressed as percentage predicted (Table 3). All spirometric parameters, except FVC, were significantly lower in currently exposed workers (group III) than in controls. Differences were even more pronounced when parameters were compared to data from retired workers (group IV). The FOT outcome showed that *R*8, FD, *X*8 and f_o were statistically significantly different in group III compared with the control group. Again, differences were more pronounced when controls were compared with group IV. The comparison of salesman (group II) to controls did not reveal significant differences in lung function data.

Airflow limitation ($FEV_1 \leq 80\%$) was observed in 23 subjects (Table 3), resulting in an incidence rate of 23/172 (13.4%). Impedance criteria indicative for airway obstruction (FD < 0 concurrently with an increase in f_o) were found in 15 subjects, or 8.7%, of the studied population. Cumulative dust exposure in the 16 workers with $FEV_1 \leq 80\%$ from group III and IV was significantly higher compared to workers without airflow limitation (223.4 vs 112.5 gh/m^3; $P \leq 0.001$).

The effect of exposure on lung function was further analyzed by multiple linear regression analysis after adjustment for smoking, height, and age (Table 4). Retired exposed workers were not included in this analysis because of the higher age and the lack of proper controls for this group. Results of this analysis for the separate lung function parameters are listed in Table 4. These results show that only FEV_1, significantly differs between controls and currently exposed. The decrease in FEV_1 (in group III) due to dust exposure was found to be 124 ml/11.8 years of employment (10.5 ml/year). This is equivalent to 1.0 ml/ghr per cubic meter. No interaction between smoking and cumulative exposure was found.

Complaints of cough, phlegm, chronic bronchitis (productive cough for 3 months in 2 subsequent years), shorteness of breath, wheezing, and asthmatic attacks were related to aberrations in each lung function parameter, dust exposure and personal characteristics (age, length, smoking) using multiple logistic regression (Table 5). Complaints of phleghms (19%) and chronic bronchitis (14%) in this population were positively related ($P < 0.05$) to cumulative dose. Asthmatic attacks were reported by eight subjects (4.6%) and positively related to age ($P < 0.10$). Cough and wheezing were positively related to smoking ($P < 0.10$). Most symptoms, even cough, were related to FOT parameters (f_0, *R*8 and *X*8), whereas FEV_1 was related to chronic bronchitis and asthmatic attacks.

Discussion

To the best of our knowledge, the present paper is the first to describe respiratory effects in the potato sorting industry. Among workers in this industry, airflow obstruction manifested by significant changes in spirometric and impedance parameters was demonstrated. These changes occurred in the absence of radiological evidence of pneumoconiosis. Furthermore, FEV_1 was significantly related to cumulative dust exposure while impedance parameters were more markedly related to airway complaints. These results might be corroborated by "healthy worker" influences since exposed workers are seasonal laborers, i.e., in case of ill health they are less likely to be rehired in the next season.

Evidence for a relationship between inorganic dust exposure and airflow obstruction is reported in various cross-sectional and longitudinal studies in coal workers. Airflow obstruction in coal workers was related to cumulative exposure to respirable dust, irrespective of the presence of pneumoconiosis, smoking habits or concurrent bronchitic symptoms. Subjects with airflow limitation had a significantly higher cumulative exposure than subjects without airflow limitation. Decreases in FEV_1 were markedly consistent among different studies in British and US coal miners and varied between –0.49 and –0.76 ml/ghr per cubic meter respirable coal dust [15, 16, 18]. We have calculated a decrease in FEV_1 (in group III) of 1.0 ml/ghr per cubic meter due to respirable noncalcined diatomaceous earth exposure.

When FEV_1 was dependent on the active cooperation of the study subject, airflow obstruction was confirmed in the present study by significant changes in impedance parameters, assessed by the technique of forced oscillations. No active cooperation of the subjects is required for this procedure [18]. Resistance versus frequency and reactance versus frequency curves in the group of exposed workers showed frequency dependence of resistance and a decrease in reactance values, resulting in an increase in resonant frequency. These curves were explained by airway obstruction extending into the peripheral airways [20].

Although exposure to respirable free silica was above its threshold limit value (TLV) no irregular densities on the chest radiographs were observed. In the present study, whether procollagen type III-N terminal peptide (P-III-P) was used as a marker to detect fibrogenic activity possibly indicative for pneumoconiosis. P-III-P is released during synthesis of type III collagen as a result of N-terminal cleavage of type III procollagen [12, 14]. Areas of active fibrosis show an increase in the proportion of type III to type I collagen [2, 12, 14]. Thus, serum P-III-P levels can be considered as a potentially important marker of active fibrosis. Measurement of P-III-P in serum and bronchoalveolar lavage has provided insight into several pulmonary interstitial diseases [23], including silicosis [12], asbestosis [5], and coal workers' pneumoconiosis [11]. But even in the absence of X-ray-detectable fibrosis several investigators have reported increases in serum P-III-P levels in individuals exposed to inorganic dust such as silica or asbestos. In this study, serum P-III-P levels were within the normal range in the absence of radiographic evidence of pneumoconiosis. Serum levels did not differ between exposed groups and controls. To our surprise serum P-III-P levels showed a significant decrease with increasing cumulative exposure, indicating slightly lower fibrogenetic activity. The meaning of these findings is unclear, but two factors might be involved. Firstly, amorphous silica might protect against silica fibrosis. The data suggest an adaptation of serum P-III-P production with increasing exposure to diatomaceous dust in this population. Secondly, interruption of work during the summer might allow clearance of dust from the lungs.

The analysis of questionnaire data showed that dust exposure was significantly related to complaints of productive cough and chronic bronchitis. A marked increase in the percentage distributions of chronic bronchitis with increasing exposure to dust for both smokers and nonsmokers was reported earlier after coal dust exposure [17]. Comparison of questionnaire data to lung function outcome suggests that the FOT is a sensitive tool to detect and objectify airway complaints, such as cough, shortness of breath, and wheezing.

In conclusion, this study shows that this semiagricultural working population is not at an increased risk to develop pneumoconiosis. The main respiratory effect of the dust, mainly generated from clay adhering to incoming potatoes, observed was airflow limitation with or without chronic bronchitis. Unfortunately, our data do not allow discrimination between the effects of total dust and respirable silica and the contribution of exposure to diatomaceous earth, organic dust, growth inhibiting agents, and herbicides as possible contaminants of the harvested potatoes. Although our data do not allow a conclusion about a causal role of the specific agent(s), results derived from FVC flow volume curves and complaints are well in line with data obtained after other forms of inorganic dust exposure. Therefore, prolonged surveillance to assess the harmful nonpneumoconiotic effects associated this type of dust dust exposure is desirable.

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