Occupational exposure to carcinogens and risk of lung cancer: results from The Netherlands cohort study

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Abstract

Objectives—To investigate risk of lung cancers associated with common established carcinogenic occupational exposures (asbestos, paint dust, polycyclic aromatic hydrocarbons, and welding fumes) in a prospective cohort study among the general population, and to estimate the proportion of lung cancer cases attributable to these occupational exposures.

Methods—A prospective cohort study on diet, other lifestyle factors, job history, and cancer risk that started in 1986 in The Netherlands on 58 279 men, aged 55–69 years. Based on information about job history obtained from a self administered questionnaire, case by case expert assessment was carried out to assign to each study subject a cumulative probability of occupational exposure for each carcinogenic exposure. For analysis, a case-cohort approach was used, in which the person-years at risk were estimated from a randomly selected subcohort (n=1688). After 4.3 years of follow up, 524 lung cancer cases with complete job history were available.

Results—After adjustment for age, each of the other occupational exposures, and for smoking habits and intake of vitamin C, β -carotene, and retinol, significant associations were found between risk of lung cancer and cumulative probability of exposure to asbestos (relative risk (RR) highest/no exposure = 3.49, 95% confidence interval (95% CI) 1.69 to 7.18, trend $P<0.01$) or paint dust (RR highest/no exposure = 2.48, 95% CI 0.88 to 6.97, trend $P<0.01$). The population attributable risks (PARs) for the four exposures based on the multivariately adjusted RRs for ever exposed versus never exposed workers were calculated. The PAR of lifetime occupational exposure to asbestos was calculated to be 11.6%.

Conclusions—This prospective cohort study among the general population showed that occupational exposure to asbestos or paint dust is associated with higher RRs for lung cancer. This study shows that after adjustment for smoking and diet about 11.6% of the cases of lung cancer in men is attributable to lifetime occupational exposure to asbestos.

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Lung cancer is the main cause of cancer mortality and incidence among men in The Netherlands. In the period 1979–90, 37.6% of all fatal cancers in men were diagnosed as lung cancer¹ and in the preceding decade this percentage was 35.9%.² In 1991, 35.5% of all incident cases of cancer diagnosed in the male Dutch population were lung cancer.³ A high proportion of these cases is attributable to past smoking habits. Doll and Peto⁴ have estimated that about 85% of the deaths from lung cancer are attributable to cigarette smoking. Also several chemicals to which workers can be exposed have been identified as agents that increase the risk of lung cancer. Therefore, we studied the association between occupational exposure to carcinogens and risk of lung cancer, after adjustment for smoking habits. The agents and occupations presenting an increased risk for lung cancer to be included in this study were based on the evaluations made by the International Agency for Research on Cancer (IARC). From the update presented by IARC in 1987 two agents asbestos and polycyclic aromatic hydrocarbons (PAHs) were identified to have sufficient evidence of carcinogenicity for the human lung and to which a cross section of the general population was estimated to be often exposed.⁵ Also later IARC monographs were reviewed to see if any other relevant occupations or agents had subsequently been identified. Two occupations met these criteria—namely, painters⁶ and welders.⁷ For welders welding fumes are regarded as the relevant exposure. An IARC Working Group has concluded that there is sufficient evidence of carcinogenicity due to occupational exposure in painters, but not in paint manufacturers.⁶ It was concluded that the relevant exposure in the induction of lung cancer in painters is exposure to paint dust, which is emitted during the removal of old layers of paint and filler.

Therefore, we defined the exposure for painters relative to lung cancer as paint dust (which is always combined with exposure to solvents) instead of exposure to solvents (which is not always combined with exposure to paint dust). So, asbestos, PAHs, welding fumes, and paint dust were selected as the occupational

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risks of lung cancers to be evaluated. Maintenance painters are considered to be definitely exposed to paint dust. Spray painters or construction painters are not considered to be exposed to paint dust.

Doll and Peto¹ have estimated the proportion of cases of lung cancer attributable to occupational exposures in men to be 15%. Other estimates vary from 9.2% to 13%.⁸⁻¹⁰ The population attributable risk (PAR) or aetiological fraction has been defined as the proportion of all cases in the target population attributable to a specific exposure.¹¹ The PARs cannot be estimated solely on the basis of cohort studies of exposed workers, because it is necessary to have information on the prevalence of exposure in the general population. The Netherlands cohort study on diet, lifestyle, job history, and cancer does provide this information for the general population.¹²

Information from this study was used to investigate risk of lung cancers from the four occupational exposures already mentioned. As the intake of β -carotene, vitamin C, and retinol is also related to risk of lung cancer,^{13,14} information about smoking habits and intake of vitamin C, β -carotene, and retinol was used to disentangle possible effects from occupational exposure and possible effects from lifestyle factors. Finally, the corrected rate ratios (RRs) for ever exposed men versus never exposed men were used to estimate the PAR of lung cancer due to occupational exposures.

Materials and methods

COHORT STUDY

The Netherlands cohort study (NLCS) is a prospective cohort study on diet, other lifestyle factors, sociodemographic characteristics, job history, and cancer risk, which started in 1986 among the general population in The Netherlands.¹² In September 1986 340 439 men and women aged 55–69 years were asked to fill in a self administered questionnaire on diet, various lifestyle variables, job history, and other risk factors for cancer (such as socioeconomic status, history of selective medical conditions, family history of cancer, reproductive history, and physical activity). The response rate was 36%, resulting in a male cohort size of 58 279. In earlier studies the representativeness of the 58 279 men has been investigated.¹² Several factors such as demographic variables, smoking, and dietary habits were compared between the cohort and the Dutch general population. It was found for these variables that the cohort was fairly representative for the total Dutch population. Therefore it was concluded that the response rate had not adversely affected determinant distributions in the cohort under investigation.

To achieve a study population free from cancer, prevalent cases of cancer, except skin cancer, were excluded from the cohort at the time of cohort identification (baseline). Prevalent cases were identified by means of specific questions included in the self administered questionnaire.

Follow up for incidence of cancer has been established by periodic record linkage with a

national pathology register (PALGA) and with all regional cancer registries in The Netherlands.¹⁵ Thus cancer cases were identified without any knowledge of the individual exposure status and information on occupational exposure was collected before any knowledge of the disease. This feature of the data collection process effectively eliminates any possibility of information bias.

For data analysis the case cohort approach was used in which cases are derived from the entire cohort, whereas the person-years at risk are estimated for a random sample of 1688 subjects (subcohort). After exclusion of self reported prevalent cancer cases, other than skin cancer, 1630 men remained in the subcohort. The main advantage of this study design is its efficiency as exposure assessment is restricted to the cases and subcohort subjects only.

After the baseline exposure measurement the subcohort has been followed up biennially for information on vital status. No subcohort members were lost to follow up. The cases of lung cancer were diagnosed in the period from September 1986 to December 1990. During 4.3 years of follow up 677 incident cases of lung cancer were detected in the total cohort of 58 279 men. These 677 cases were all identified through PALGA or the regional cancer registries.

EXPOSURE ASSESSMENT

For the exposure assessment by experts information from the baseline questionnaire of the NLCS was used. This information can be best described as a lifetime self reported job history, containing data on job titles, names of the company, type of company, periods, and information about what was being produced at the department. As baseline measurements were collected in September 1986 lifetime job history extended up to that date.

The whole data processing and assessment of exposure probability was done without knowledge of the disease status (case or subcohort) of the subjects. Firstly a list of all jobs in The Netherlands was independently reviewed by an occupational hygienist (IJK) and an occupational epidemiologist (GS). In this first examination all jobs with no potential exposure to lung cancer carcinogens were excluded. Secondly, for a more refined exposure assessment the name of the company, type of company, period, and information about what was being produced in the department was used, as the probability of exposure to some carcinogens may differ between companies and between periods. Therefore, each job title, specified by period and company, was scored separately according to the probability of exposure to the four carcinogens: asbestos, paint dust, PAHs, and welding fumes (particularly stainless steel welding). Four exposure categories were defined: no exposure to the specific carcinogen, possible exposure (probability of exposure estimated to be <30%), probable exposure (probability of exposure 30%–90%), and nearly certain exposure (probability of exposure >90%). In a final review round all the

jobs for which at least one of the two reviewers suspected relevant exposure were reevaluated and a definite probability of exposure was assigned to each of the job titles within the NLCS.

MEASUREMENT OF OCCUPATIONAL EXPOSURES

For a measurement of exposure a cumulative probability of exposure (CPE) was calculated, which combines information about the probability of exposure and the duration of possible exposure. Therefore a weight was assigned to each exposure category: no exposure, weight 0; possible exposure, weight 0.15; probable exposure, weight 0.6; and nearly certain exposure, weight 0.95. Each weight corresponds to the midpoint of probability in each exposure category. The CPE was calculated by multiplication of the weight given to each exposure category by the number of years exposed. Subsequently, for each person all weighted exposures were summed up for each of the four carcinogens separately.

DATA ANALYSIS

In the subcohort 1316 of the 1630 men (81%) had completed the self reported job history inventory, whereas 524 of the 677 cases (77%) had done so. For these people the distribution of the CPE was compared between the cases and subcohort. The CPEs to asbestos, PAHs, or welding fumes were divided into four categories (no exposure and tertiles of exposure) and the CPE to paint dust was divided into three categories (no exposure and below and above the median exposure value). These categories were based on the distribution of CPEs in the subcohort. The associations between CPE to occupational carcinogens and covariates were also studied in the subcohort by comparing the prevalence of smoking and by comparing mean values of age, pack-years of smoking, and dietary intake of vitamin C, β -carotene, and retinol between CPE categories. To study the association between CPE to carcinogens and risk of lung cancer, data were analysed according to the case-cohort approach^{16, 17} with the GLIM statistical package.¹⁸ In the multivariate analyses, RRs and 95% confidence intervals (95% CIs) of risk of lung cancer were computed for each of the different occupational exposures, after adjustment for age and after further adjustment for the other three occupational exposures. All these covariates were entered in the model as continuous variables. Additional adjustment was made for smoking habits (never smokers, ex-smokers, current smokers, and pack-years of cigarette smoking) and for dietary intake of vitamin C, β -carotene, and retinol (as continuous variables). Finally, the PAR was calculated, based on the corrected RRs for ever exposed versus never exposed people.

Results

Table 1 shows the distribution of the cumulative probability of exposure to each of the four carcinogens in the case and the subcohort group. Cases were more often exposed to

Table 1 Distribution of exposure categories in male lung cancer cases and subcohort: cumulative probability of exposure*

Exposure	Subcohort (n=1316) †		Cases (n=524) †	
	n	%	n	%
Asbestos:				
0 (no exposure)	1200	91.6	448	86.2
1 Tertile (low)	34	2.6	21	4.0
2 Tertile	38	2.9	18	3.5
3 Tertile (high)	38	2.9	33	6.3
Paint dust:				
0 (no exposure)	1300	98.8	506	96.5
1 low	8	0.6	4	0.8
2 high	8	0.6	14	2.7
PAHs:				
0 (no exposure)	1243	94.9	487	93.5
1 Tertile (low)	21	1.6	10	1.9
2 Tertile	23	1.8	12	2.3
3 Tertile (high)	23	1.8	12	2.3
Welding fumes:				
0 (no exposure)	1169	89.4	457	87.9
1 Tertile (low)	46	3.5	17	3.3
2 Tertile	46	3.5	26	5.0
3 Tertile (high)	47	3.6	20	3.8

*Product of probability (weights 0.15, 0.6, and 0.95) and duration (y) of exposure, approximately divided into tertiles or into two equal categories (paint dust).

†Numbers may not add up to 1316 or 524 due to missing values for duration of exposure.

asbestos and paint dust than subcohort members. No notable difference in CPE to PAHs or welding fumes was found between cases and subcohort members.

Table 2 shows the association between the CPE and covariates in the subcohort. Differences in mean age between ever exposed and never exposed people were small. The prevalence of smoking was lower in people who were ever exposed to asbestos, PAHs, or welding fumes, than in never exposed people, whereas the prevalence of smoking was higher among people who were ever exposed to paint dust. The mean number of pack-years (for current and ex-smokers) was higher in people who were ever exposed to one of the investigated carcinogens than in those who were never exposed. The mean dietary intake of vitamin C was higher in people who were ever exposed to asbestos and lower among people who were ever exposed to paint dust or PAHs than in never exposed men in the subcohort. The mean intake of β -carotene was also lower among people who were ever exposed to paint dust or PAHs and the mean intake of retinol was only lower in people who were ever exposed to paint dust. Finally, there was a correlation between exposure to asbestos, PAHs, and welding fumes, whereas there was no correlation between exposure to paint dust and exposure to asbestos, PAHs, or welding fumes.

Table 3 shows the results of the case-cohort analyses. After adjustment for age, there was a positive association between CPE to asbestos and risk of lung cancer (trend $P < 0.01$). Men in the highest exposure category had a significantly higher risk of lung cancer than men with no occupational exposure to asbestos (RR 2.66; 95% CI 1.66 to 4.26). There was also a significant positive association between CPE to paint dust and risk of lung cancer (highest exposure/no exposure RR 3.60; 95% CI 1.48 to 8.74; trend $P < 0.01$). No significant association between CPE to PAHs and risk of lung

Table 2 Association between possible confounders and probability of exposure in the subcohort

Probability of exposure	Asbestos		Paint dust		PAHs		Welding fumes	
	Never	Ever	Never	Ever	Never	Ever	Never	Ever
Age (mean y)	61.3	60.7	61.3	61.8	61.3	60.6	61.4	60.3
Current smokers (%)	42.4	35.3	41.5	62.5	42.2	35.6	42.6	35.4
Ex-smokers (%)	47.8	54.3	48.5	37.5	48.0	54.8	47.5	55.8
Pack-years* (mean)	21.9	23.4	22.0	24.3	21.8	27.4	22.0	22.8
Dietary intake of:								
Vitamin C (mean, mg)	99.0	101.6	99.3	96.3	99.6	93.0	99.2	99.8
β -carotene (mean, mg eq vit A)	0.41	0.41	0.41	0.34	0.41	0.38	0.41	0.40
Retinol (mean, mg eq vit A)	0.62	0.63	0.62	0.55	0.62	0.63	0.62	0.63
Exposure to:								
Asbestos (% ever)	—	—	8.9	0	5.5	65.8	1.9	63.9
Paint dust (% ever)	1.3	0	—	—	1.2	1.4	1.4	0
PAHs (% ever)	2.1	41.4	5.5	6.3	—	—	2.6	29.3
Welding fumes (% ever)	4.4	81.0	11.3	0	8.4	58.9	—	—

*Only for current and ex-smokers

Table 3 Rate ratios for lung cancer according to occupational exposures in age adjusted and multivariate analysis

Lifetime exposure index †	No of cases in cohort	Person-years in subcohort	RR (95% CI)‡	RR (95% CI)§	RR (95% CI)¶
Asbestos:					
0 (no exposure)	448	5005	1*	1*	1*
1 Tertile (low)	21	141	1.76 (1.02 to 3.03)	1.82 (1.04 to 3.17)	1.59 (0.75 to 3.34)
2 Tertile	18	163	1.26 (0.71 to 2.23)	1.29 (0.73 to 2.30)	0.96 (0.42 to 2.19)
3 Tertile	33	157	2.66 (1.66 to 4.26)	2.72 (1.56 to 4.75)	3.49 (1.69 to 7.18)
Test for trend			23.16 (<0.01)	19.07 (<0.01)	12.72 (<0.01)
χ^2 (P value)					
Paint dust:					
0 (no exposure)	506	5425	1*	1*	1*
1 low	4	33	1.46 (0.43 to 4.97)	1.53 (0.45 to 5.21)	2.29 (0.61 to 8.63)
2 high	14	34	3.60 (1.48 to 8.74)	3.74 (1.53 to 9.11)	2.48 (0.88 to 6.97)
Test for trend			15.58 (<0.01)	16.48 (<0.01)	7.67 (<0.01)
χ^2 (P value)					
PAHs:					
0 (no exposure)	487	5196	1*	1*	1*
1 Tertile (low)	10	86	1.44 (0.67 to 3.09)	1.32 (0.60 to 2.89)	0.53 (0.13 to 2.14)
2 Tertile	12	96	1.61 (0.78 to 3.34)	1.09 (0.49 to 2.40)	0.83 (0.32 to 2.20)
3 Tertile (high)	12	92	1.35 (0.66 to 2.76)	0.63 (0.25 to 1.58)	0.28 (0.09 to 0.89)
Test for trend			3.20 (0.07)	0.56 (0.45)	9.05 (<0.01)
χ^2 (P value)					
Welding fumes:					
0 (no exposure)	457	4884	1*	1*	1*
1 Tertile (low)	17	191	1.06 (0.60 to 1.89)	0.98 (0.55 to 1.76)	0.71 (0.31 to 1.60)
2 Tertile	26	192	1.73 (1.05 to 2.85)	1.16 (0.63 to 2.11)	1.49 (0.72 to 3.07)
3 Tertile (high)	20	191	1.26 (0.73 to 2.18)	1.02 (0.56 to 1.85)	1.01 (0.49 to 2.06)
Test for trend			4.49 (0.03)	0.09 (0.77)	0.10 (0.75)
χ^2 (P value)					

*Reference category.

†Product of probability (weights 0.15, 0.6 and 0.95) $\times$ duration (years) of exposure, approximately divided into tertiles or into two categories (paint dust).

‡Adjusted for age.

§Adjusted for age and other occupational exposures. If information on occupational exposure was lacking for a study subject, that person was excluded from the analysis.

¶Adjusted for age, other occupational exposures, smoking (never/ex/current and pack-years), and intake of vitamin C, β -carotene, and retinol. If information on any variable for which the adjustments were made was lacking, that person was excluded from the analysis.

cancer was found (trend $P=0.07$), but the RRs for the three exposure categories (compared with non-exposed) were all above unity. The risk estimate for the CPE to welding fumes was only significantly different from unity in the middle tertile (RR 1.73, 95% CI 1.05 to 2.85). Nevertheless, the trend test was also significant (trend $P=0.03$).

After adjustment for age and for each of the other occupational exposures, the relative rates of PAHs and welding fumes were greatly diminished. The relative rates of exposure to asbestos and paint dust changed only marginally after adjustment and remained significant (table 3).

After additional adjustment for smoking habits and intake of vitamin C, β -carotene, and retinol, there was still a significant positive

association between the cumulative probability of exposure to asbestos and risk of lung cancer (highest exposure/no exposure RR 3.49; 95% CI 1.69 to 7.18; trend $P<0.01$). There was also a positive association between CPE to paint dust and risk of lung cancer (highest exposure/no exposure RR 2.48; 95% CI 0.88 to 6.97; trend $P<0.01$), but part of the higher age adjusted risk among men in the highest paint dust exposure category seemed to be explained by smoking and intake of vitamin C, β -carotene, and retinol. The cumulative probability of exposure to PAHs became inversely associated with risk of lung cancer after additional adjustment for smoking and intake of vitamin C, β -carotene, and retinol (highest exposure/no exposure RR 0.28; 95% CI 0.09 to 0.89; trend $P<0.01$). The association

between the CPE to welding fumes and risk of lung cancer did not substantially change after additional adjustment.

Calculation of the PAR is based on the RRs for ever exposed versus never exposed people, adjusted for age, other exposures (never or ever), smoking, and intake of vitamin C, β -carotene, and retinol (table 4). Because we did not expect a protective effect of exposure to carcinogens, only RRs >1 were used to calculate the PAR—namely, for asbestos and paint dust. The PAR for exposure to asbestos was 11.6% and the PAR for exposure to paint dust was 1.7%.

It is concluded that a substantial proportion (about 11.6%) of all male lung cancer cases in the general Dutch population is attributable to lifetime occupational exposure to asbestos.

Discussion

We have found a positive association between the cumulative probability of exposure to asbestos, paint dust, and welding fumes and risk of lung cancer among men in the general population of The Netherlands. There was no association between the cumulative probability of exposure to PAHs and risk of lung cancer. The positive association between exposure to welding fumes and risk of lung cancer disappeared after additional adjustment for exposure to asbestos, paint dust, and PAHs, whereas the positive associations between asbestos or paint dust and risk of lung cancer remained after additional adjustment for the other exposures. Differences in smoking habits and intake of vitamin C, β -carotene, and retinol could not explain the positive association between exposure to asbestos or paint dust and risk of lung cancer, although the RRs for exposure to paint dust became smaller after adjustment for these lifestyle factors. The PAR for exposure to asbestos was 11.6% and the PAR for exposure to paint dust was 1.7%.

The significant positive association between exposure to asbestos and risk of lung cancer is comparable with results from other studies. In most studies, exposure to asbestos is measured by job title, job history, or job exposure matrix and this information is either categorised as exposed versus non-exposed,¹⁹ as no exposure, possible exposure, and definite exposure,^{20 21} or by means of a lifetime exposure index.^{22 23} In all these studies a significantly positive association

was found after adjustment for smoking habits, with relative risk estimates varying from 2.0²¹ to 4.1.²² In one case-control study²⁴ information about concentrations of asbestos fibre was available and the authors reported a significantly positive association between fibre count and risk of lung cancer. Only one study reported a non-significant positive association between cumulative exposure to asbestos and risk of lung cancer.²⁵

In most studies on the risk of lung cancer in painters, no significantly increased risk was reported,²⁵⁻²⁸ although in all studies the odds ratios were above one. In our study attention was mainly focused on exposure to paint dust instead of exposure to organic solvents and dye products. This may explain the difference between our findings and the results from other studies. Nevertheless, one study on the risk of lung cancer in painters from the Scandinavian countries²⁹ reported significantly higher risk of lung cancers for painters and lacquerers, with risk estimates varying from 1.3 to 1.4.

Studies on PAHs and risk of lung cancer show varying results,^{22 30} probably due to differences in study population. In a cohort study among men who worked for at least one year in a manual job in a large aluminum production factory in Quebec,³⁰ a significant positive association was found between exposure to benzo-a-pyrene (an indicator for PAHs in general) and lung cancer mortality. In a case-control study in Germany²² no significant association was found between exposure to PAHs and incidence of lung cancer, although in this study certain occupations which are associated with exposure to PAHs (metal producing and processing workers and road construction workers) showed significantly increased odds ratios. Finally, in a Norwegian cohort study of workers in the aluminum industry,³¹ it was suggested that the cases could have resulted from exposure to asbestos, rather than from exposure to PAHs. This is partly comparable with our results; the non-significantly increased risk of lung cancer among men exposed to PAHs disappeared after additional adjustment for exposure to asbestos.

In a review on cancer related to nickel in welders, Langård³² concluded that there was evidence of excess incidence of and mortality from lung cancer in welders with long term welding experience. There was also evidence that stainless steel welders had a slightly higher risk of lung cancer than did mild steel welders. However, exposure to asbestos and smoking are generally major confounders. In a meta-analysis about exposure to stainless steel welding fumes and risk of lung cancer³³ a significant positive association was reported, after adjustment for smoking habits and exposure to asbestos. Only investigations taking smoking and exposure to asbestos into account were included in the meta-analysis, but in two of the five included studies, smoking and exposure to asbestos were based only on assumption. One objective of a case-control study on risk of lung cancer and welding in Germany³⁴ was to assess confounding by exposure to asbestos in what was thought to be a risk associated with

Table 4 Rate ratios and population attributable risks for occupational exposures (non-exposed v ever exposed)

Occupational exposures	Proportion of ever exposed subcohort members*	RR (95% CI)†	PAR‡
Asbestos	0.088	2.49 (1.31 to 4.75)	11.6
Paint dust	0.012	2.46 (1.08 to 5.60)	1.7
PAHs	0.055	0.53 (0.26 to 1.07)	
Welding fumes	0.112	0.86 (0.46 to 1.58)	

*The proportion of ever exposed subcohort members is based on information about the probability of exposure. Information about duration of exposure is not included.

†After adjustment for age, other occupational exposures (never/ever), smoking (never/ex/current and pack-years of cigarette smoking), and intake of vitamin C, β -carotene, and retinol, the following formula was used to calculate the PAR:⁴⁵

$$\frac{p_0 (RR-1)}{p_0 (RR-1)+1}$$

where p_0 is the fraction of exposed subjects in the subcohort.

welding. The authors concluded that some, if not all, of the excess risk of welders may be due to exposure to asbestos, which is compatible with our results. Nevertheless, some types of welding processes in the German study still reached borderline significance after adjustment for exposure to asbestos.

In our study the adjusted relative risks for ever exposed versus never exposed people were used to calculate the PAR due to occupational carcinogens, which was estimated at 11.6% for exposure to asbestos and 1.7% for exposure to paint dust. The actual proportion due to occupational exposure may be higher as the occupational exposures under investigation were restricted to four common exposures. Other occupational exposures, such as exposure to certain heavy metals and bischlo-methylether, were not included, because there was not sufficient evidence for carcinogenicity for the human lung or exposure was not estimated to occur often in the general population. Unlike the relative risk, the PAR depends not only on the strength of the causal relation but also on the prevalence of the risk factors, giving more importance to common moderately hazardous factors than to rare but strong risk factors. Therefore, the contribution of rare exposures to the proportion of lung cancers in men attributable to occupational exposures is considered to be small. Simonato *et al*³⁵ investigated the attributable risk of occupational exposure from studies in which adjustment was made for smoking. They included 16 case-control studies and found a wide variability of attributable risk estimates. When a list of recognised carcinogenic exposures was used for the selection of relevant occupations, the estimates varied between 2.4% and 40%. None of the studies were nationwide and consequently no attributable risks could be computed for the general population.

In our study the attributable risk of occupational exposure to asbestos in the past is 11.6%. Other estimates vary from 6% in the west of Scotland including Glasgow³⁶ and 14% in north eastern Italy (Trieste) for definite exposure to asbestos, and 20% for definite and possible exposure to asbestos,²¹ 16% in Göteborg, Sweden²⁵ and 19% in Helsinki, Finland.²⁴ These differences may be due to differences in exposure assessment but it is more likely that differences in levels of exposure in the study areas, partly due to the degree of industrialisation, may lead to these differences in attributable risk. In our study 8.8% of the subcohort was ever exposed to asbestos, whereas the number of exposed controls in the other studies varied from 17%²⁴ to 37%.²⁵ These percentages are difficult to interpret because of differences in the definition of non-exposure.

Our cohort study has been performed in a large sample of the general population aged 55–69 years at baseline. The follow up period of 4.3 years resulted in 677 men with lung cancer. Job histories were available for 524 cases only. This number is considered to be sufficient, because in general about 400 cases are needed to detect relevant associations.³⁷ The follow up of person-years was 100% complete

and the completeness of cancer follow up was also very high, indicating that selection bias due to loss to follow up is unlikely. The study population originated from 204 municipalities throughout the country. Although the response rate was low (36%), data on demographic variables, smoking, and dietary habits indicated that the response had not adversely affected determinant distributions in the present cohort.¹² Even if the cohort would not have been representative for the total Dutch male population, the calculated RRs should not have been affected under the assumption that the subcohort and the case group were derived from the same subpopulation.

As the PAR is a combination of RRs and the proportion of ever exposed people the calculated PAR will be affected by non-representativeness of the cohort. For example, if the cohort contains a smaller proportion of exposed people than the general population the calculated PAR will be an underestimation of the true PAR. Earlier studies of the cohort indicate that the distribution of educational level in the cohort is different from that in the general Dutch population. Subjects with high levels of education and those with low levels seem to be overrepresented. This may have led to a small overestimation of the PAR. The number of men aged 55–64 years with a high level of education (higher vocational or university) is higher in the subcohort (18%) than in men with the same age in the Dutch population (14%).³⁸ However, the number of men with primary school or lower vocational education was also higher in the subcohort than in the general population (48% *v* 37%). Therefore, the exposure to occupational carcinogens may be higher in the cohort and consequently, the actual PAR of the occupational carcinogens may be lower.

The quality of the exposure assessment strongly affects the outcome of the risk estimate³⁹ and ideally includes both intensity and duration of the occupational exposure for each specific study subject. However, in large population based studies it is almost impossible to obtain this quantitative information. Moreover, in this type of study the range of jobs with potential exposures is large and within given jobs there is a great possible variation of exposures. This makes it even more difficult to identify a clear link between jobs and exposures, compared with industry based studies.⁴⁰ In our study the occupational history of the study subjects was obtained through questionnaires, which did not allow an estimation of the actual exposure concentrations that were experienced in the past. The best estimate was a retrospective exposure assessment in terms of probability of exposure. In general this can be obtained through a job exposure matrix (JEM) or a case by case expert assessment, as was used in this study. The main advantage of this method—compared with a JEM—is that all the available information (job title, type and name of the company, period) is used for the exposure assessment.⁴⁰ Moreover, a JEM may produce greater non-differential misclassification than exposure assessment by experts^{40 41}

because information returned by a JEM is mistakenly taken to relate to individual exposure.⁴¹ However, a JEM will be more reliable, as it will produce the same exposure information for identical basic data.⁴¹ A disadvantage of exposure assessment by experts is the learning phenomenon, because there is no fixed definition of the criteria which are used for the exposure assessment. However, by including a final review round for re-evaluation of all the jobs for which at least one of the two reviewers suspected relevant exposure this phenomenon was minimised. In this final review round a definitive probability of exposure was assigned to each job title.

In case by case expert assessments different measures for exposures are applied. The highest probability of exposure once experienced is often used⁴² and could be directly obtained from our exposure assessment. However, this measure discards the effect of duration of exposure which seemed to be essential in evaluation of exposures to carcinogenic agents.^{39 43 44} To incorporate the effect of duration of exposure we calculated a cumulative probability of exposure for the four carcinogens separately. We also used the highest probability of exposure as the measure of exposure instead of cumulative probability of exposure, which yielded similar results (data not shown).

In most studies on occupational exposure and lung cancer, smoking had no strong confounding effect on this association.^{10 19 20 21} This is comparable with our findings that adjustment for smoking did not substantially change the association between exposure to asbestos and risk of lung cancer. We found no other studies in which adjustment was also made for the intake of vitamin C, β -carotene, and retinol. We also found no studies on risk of lung cancer in painters in which adjustment was made for lifestyle variables. However, it is possible that exposure to paint dust may promote the effect of carcinogens in tobacco smoke.²⁰ In that case smoking should be considered as an effect modifier instead of a confounding factor. Unfortunately, because of the few non-smokers among the male cases of lung cancer, it is not possible to compare the risks associated with exposure between non-smokers and smokers. The unexpected results for PAH after adjustment for smoking and dietary intake of vitamin C, β -carotene, and retinol may be a chance finding. Further research on this subject will be possible after a longer follow up period. As well as the possible interaction between occupational exposure and lifestyle factors, there may be interaction between different occupational exposures.

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