

# Quantitative risk assessment for lung cancer after exposure to bitumen fume

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An international cohort of asphalt workers was assembled to study cancer risk after bitumen exposure. This article describes the combination of the exposure assessment with the exposure-response for a quantitative risk assessment for lung cancer mortality within the Dutch component of the study. We identified a retrospective cohort of 3,709 workers with at least one season of employment. Semi-quantitative exposure to bitumen fume was estimated by a job-exposure matrix. Exposure-response relations were fitted by Poisson regression, and excess lifetime risks through age 75 were calculated by a life table method. Working lifetime cumulative exposure to bitumen fume was calculated under different scenarios, representing past and future exposures. For workers with exposures accumulated in the past, excess risks for lung cancer varied from 7.8 to 14.3%. Calculations for future exposures resulted in considerably lower excess risks ranging from 0.6 to 2.6%. The calculated excess risks for lung cancer mortality after working lifetime exposure to bitumen fume depend strongly on when exposure was experienced and to some extent on the exposure-response model chosen, while confounding by smoking cannot be ruled out. Nevertheless, the excess lifetime risk for lung cancer in this Dutch cohort of asphalt workers is above benchmark risks as applied by the Dutch Health Council. Current exposure levels have decreased this risk considerably, but further exposure control may be required. *Toxicology and Industrial Health* 2002; **18**: 417–424.

**Key words:** bitumen; lung cancer; occupational exposure; risk assessment

## Introduction

The International Agency for Research on Cancer (IARC) has assembled a large-scale multi-country cohort of workers from road construction and asphalt mixing companies, to study potential increased risks of cancer, with emphasis on lung cancer (Boffetta and Burstyn, 2003). The study

focused on the possible carcinogenic effects of bitumen fume exposure. Bitumen is used as a binder in asphalt mixes and in roofing applications. Workers are exposed to other agents as well, such as coal tar (now discontinued in Western Europe), silica dust, diesel fume, and asbestos (Burstyn *et al.*, 2000). Bitumen fume is a distillation product of crude oil and contains small quantities of polycyclic aromatic hydrocarbons (PAH), as well as straight chain and cyclic aliphatic hydrocarbons that often contain oxygen, nitrogen and/or sulphur functional groups (Broome, 1973). This retrospective cohort included workers exposed

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to bitumen fume, as well as an unexposed reference group of workers employed in building and ground construction.

Standard categorical analyses with the pooled data showed no clear association between bitumen exposure and risk of lung cancer mortality in the total cohort, but there was an indication for a possible positive association between career-average bitumen fume exposure and lung cancer in a subcohort of workers exclusively employed in road paving. Confounding by exposures to other agents (especially coal tar and tobacco smoke) could not be ruled out, but could also not completely explain the positive association (Boffetta *et al.*, 2003a; Hooiveld *et al.*, 2003). A more refined analysis on exposure-response relations, using data of the Dutch component of the cohort, showed a positive log-linear association of lung cancer mortality with cumulative exposure to bitumen fume (unlagged and 15-years lagged). The association was confirmed by flexible smoothing models (Hooiveld, 2004).

The exposure-response model can be used to calculate the excess risk in the population after a working lifetime exposure; that is the proportion of cases in the exposed group minus the proportion of cases in the unexposed group. It is then assumed that dose delivered during the course of each year (i.e., the integral of the dose rate over the year) is the independent variable for predicting the lifetime risk imposed by exposures in that year, and that risks imposed by each year of exposure are additive and independent (Checkoway *et al.*, 1989).

After publication of the first results on lung cancer risks for workers exposed to bitumen fume (Boffetta *et al.*, 2001; Hooiveld *et al.*, 2003), the Dutch asphalt industry expressed interest in knowing the extent of risks due to exposure in the past and at current exposure levels. This article describes the combination of the exposure assessment with exposure-response modelling to quantify the risks for lung cancer mortality after exposure to bitumen fume. Although the calculations are conditional because they assume a causal relation, they give an indication of the health hazards if bitumen fume did act as a human carcinogen.

## Methods

### Description of cohort

A detailed description of the Dutch cohort can be found elsewhere (Hooiveld *et al.*, 2003). Minimal differences do exist between this cohort and the Dutch component in the analyses performed by IARC (Boffetta *et al.*, 2003a,b), due to an additional update of the data. Some descriptive statistics are presented in Table 1. Briefly, data were collected in six companies involved in asphalt production and road construction. Personnel records were available since 1969–1984. The first date of employment was in 1927, the last worker entered the cohort in 1998. End of cohort enumeration was August 30, 1999, except for one company where employment records ended due to reorganization on January 1, 1999. We identified 6171 workers. Eleven subjects were excluded because of a missing date of birth and eight subjects were excluded because of missing dates of start of employment. Follow-up for mortality was completed until 31 December 1999.

### Exposure assessment

For each worker, detailed information was abstracted from the personnel files. The information included date of start of employment, date of end of employment, and positions held. Employment records were coded according to a protocol for the international study. From each company, a questionnaire was obtained with information on temporal changes in production characteristics and work organization. The duration of the working season differed from 8 to 12 months per year between jobs, companies and decades. The analyses

**Table 1.** Descriptive statistics for a Dutch cohort of workers in road construction and asphalt mixing companies, 1969–1999.

Statistic	Value
No. in cohort	6171
No. in analysis	3709
No. of deaths	470
No. of lung cancer deaths	72
Mean age at end of follow-up (years) (SD)	50.24 (14.48)
Cumulative exposure to bitumen fume (unit-years)	
Mean (SD)	9.99 (15.90)
Median (range)	3.57 (0–143.30)

SD, standard deviation.

were restricted to workers who had at least one full season of employment at a company ( $n = 3709$  subjects; 60%).

A Road Construction Workers' Exposure Matrix (ROCEM) was constructed based on statistical modelling of 2007 exposure measurements gathered in the participating countries (Burstyn *et al.*, 2000a), expert assessment of relative exposure intensities for jobs and periods without quantitative exposure data, and information on determinants of exposure obtained from company questionnaires. The ROCEM estimates a worker's exposure to bitumen fume and other relevant exposures based on calendar period, country, company and job (Burstyn *et al.*, 2003). Quantitative exposure estimates for bitumen fume (expressed in  $\text{mg}/\text{m}^3$ ) could only be computed for subjects who were exclusively employed in asphalt road paving, since it was not possible to obtain sufficient data to construct predictive models of exposure for other jobs. Semi-quantitative estimates of intensity of bitumen fume and other agents for workers in all job classes in the asphalt industry and building and ground construction were based on the combination of statistical models and expert evaluation of relative exposure intensities between different working conditions. Semi-quantitative cumulative exposure was expressed in exposure intensity unit-years and was based on the combination of job history, length of the working season and ROCEM estimates.

### Exposure-response relation

An analysis of the shape of the quantitative exposure-response for lung cancer mortality (ICD-9 code 162) with workers exclusively employed in road paving was not possible due to small numbers. Many road pavers in the Dutch cohort (43%) had a period of employment as unspecified blue- or white-collar worker as well. Therefore, the exposure-response was analysed with semi-quantitative exposure estimates. A detailed analysis of the exposure-response was described elsewhere (Hooiveld, 2004). Briefly, the NIOSH life table analysis system was used to generate stratum-specific person-years and deaths (Steenland *et al.*, 1998). Cumulative semi-quantitative exposure was classified into 50 categories of equal width, but mid-points of these exposure categories were entered in the model as a continuous variable. A log-linear

Poisson regression model was fitted as following:

$$\text{relative risk (RR)} = \exp(\beta \times \text{exposure}) \quad (1)$$

A more simple approach is to fit a linear regression through the categorical relative risk estimates (Rothman, 1986), in the form of:

$$\text{relative risk} = 1 + (\beta \times \text{exposure}) \quad (2)$$

This approach is often applied in regulatory processes, as it is known to yield conservative estimates. Within the exposure categories, the mean cumulative exposure of the person-time, contributing to that category, was used, and each relative risk estimate was weighted by the inverse of its variance (Checkoway *et al.*, 1989). Details on the categorical model can be found elsewhere (Boffetta *et al.*, 2003a; Hooiveld, 2004). Briefly, exposed subjects were divided into quartiles, each including approximately one fourth of the lung cancer deaths of the international pooled data. We used the same cut points to permit a direct comparison.

All Poisson regression models were fitted using SAS PROC GENMOD (SAS, 1999). Regression coefficients with 95% Wald confidence intervals were calculated, controlling for age (ten five-year groups), calendar period at end of follow-up (before 1975, 1975–1979, 1980–1984, 1985–1989, and 1990 or later), and time since first employment (less than 10, 10–20, and 20 or more years). Models were fitted with and without a 15-year lag period.

### Exposure scenarios for working lifetime cumulative exposure

Working lifetime cumulative quantitative exposure to bitumen fume was calculated for a Dutch road paver starting at age 20 and working for 45 years till age 65, according to three different scenarios about past (A) and future (B and C) exposures (see Figure 1).

In the first scenario (A), we used the model that was developed to assess exposure to bitumen fume for the international cohort (Burstyn *et al.*, 2000b). In this model, exposure intensity depends on time period and production characteristics. Predictions were generated for the most common type of paving with hot mix asphalt. Median of quantitative long-term eight-hour-shift time-weighted average exposures among pavers were calculated as

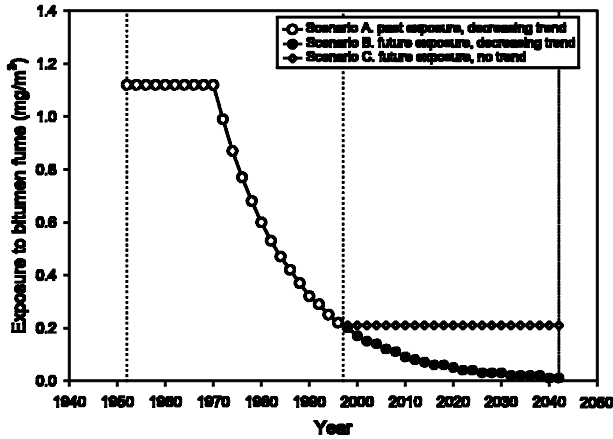


Figure 1. Three different scenarios for calculating working lifetime cumulative exposure to bitumen fume for a Dutch asphalt paver.

following:

$$\text{exposure}(\text{mg}/\text{m}^3) = \exp[(0.062 \times \text{years since 1997}) + \text{intercept} + \frac{1}{2} \times_{\text{ww}} \hat{S}^2] \quad (3)$$

where  $\text{intercept} = -2.10$  and  $\frac{1}{2} \times_{\text{ww}} \hat{S}^2 = 0.54$  ( $_{\text{ww}} \hat{S}^2$  is the estimate of residual logarithmic within-worker variance in bitumen fume exposure).

The predicted average quantitative exposure in a certain year was adjusted for the duration of the paving season, which was on average nine months before 1975 and ten months thereafter, according to information from company questionnaires. Working lifetime cumulative exposure started at age 20 in 1952 and ended at age 65 in 1997.

In the two scenarios addressing future exposure levels (B and C), working lifetime cumulative exposure started at age 20 in 1997 and ended at age 65 in 2042, with an average duration of the working season of ten months. In scenario B, we assumed that a similar decreasing trend in exposure would continue in the future. In scenario C, we assumed that exposure levels will remain constant in the coming years.

Because the exposure-response models were fitted with semi-quantitative exposure estimates, we had to transform the working lifetime cumulative quantitative exposure into semi-quantitative estimates. Although cumulative quantitative and semi-quantitative exposure estimates as experienced by the cohort members were not directly related, the correlation was high (Pearson correlation coefficient = 0.99,  $P < 0.0001$ ). Linear regression showed a strong association between quantitative

and semi-quantitative estimates among road pavers ( $\beta = 3.31$ , standard error = 0.03,  $R^2 = 0.99$ ). We therefore used the regression coefficient to transform the calculated working-lifetime cumulative quantitative exposures into the units of the semi-quantitative exposures.

### Calculation of excess risk

The calculation of working-lifetime risk was based on an actuarial method which accounts for the effects of competing causes of death, as proposed by Gail (1975). For each exposure scenario A, B, and C, we calculated an excess lifetime risk through age 75, assuming 45 years of exposure beginning at age 20 and ending at age 65:

$$\text{excess risk} = \sum_{i=20}^{74} (RR_i - 1) \times q_1(i) \times \exp \left[ - \sum_{j=20}^i \{ (RR_j - 1) \times q_1(j) + q_a(j) \} \right] \quad (4)$$

where:

- $q_1$  lung cancer male mortality rate in Dutch population
- $q_a$  all-cause male mortality rate in Dutch population
- $RR_i$  and  $RR_j$  age-specific rate ratio estimate for exposed versus nonexposed
- $i$  and  $j$  index age

We used mortality rates for the Netherlands, 1990–1998, obtained from the World Health Organization mortality databank.  $RR_i$  and  $RR_j$  were obtained from the different exposure-response relations.

### Results

Figure 2 presents different exposure-response relations. In addition to the log-linear, power, categorical and cubic spline models, a linear regression model was fitted. The estimated linear regression coefficient for cumulative exposure to bitumen fume was 0.023 (95% CI = -0.002, 0.049) and decreased to 0.017 (95% CI = -0.018, 0.052) after including a 15-year lag.

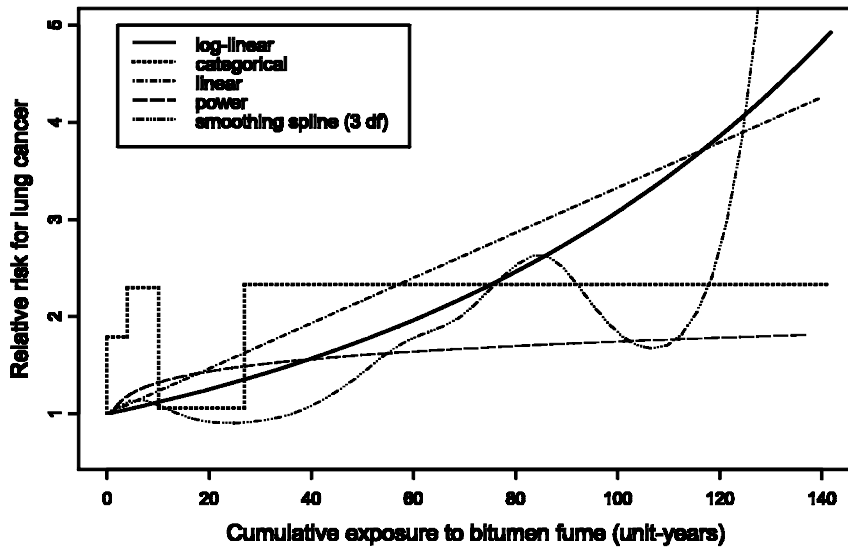


Figure 2. Exposure-response relations for bitumen fume and relative risk for lung cancer mortality in a Dutch cohort of workers in road construction and asphalt mixing companies, 1969–1999. Log-linear, categorical, power, and cubic spline models adapted from Hooiveld (2004).

Working lifetime cumulative exposures were calculated according to the three different exposure scenarios. For scenario A, using past exposures as experienced by the cohort members, lifetime cumulative exposure at the age of 65 was 24.97 mg/m<sup>3</sup>-year. Scenarios B (decreasing trend will remain in future exposures) and C (future exposure with no decreasing trend) resulted in significant lower lifetime cumulative exposures (2.73 and 6.09 mg/m<sup>3</sup>-year respectively). The quantitative estimates were transformed to semi-quantitative estimates of 82.64 (scenario A), 9.05 (scenario B) and 20.17 (scenario C) unit-years (Table 2). These working lifetime cumulative exposures were within the range of exposures experienced by the cohort members (0–143.30 unit-years).

The excess risks for lung cancer mortality at age 75 after working lifetime exposure were estimated using the linear and log-linear exposure-response models (Table 2). For workers with exposures accumulated in the past (scenario A), excess risks varied from 7.79 to 14.31%. The highest excess risk of 14.31% (95% CI = 1.83, 39.34) was obtained with the log-linear model including a 15-year latency period.

Assuming a decreasing trend in future exposure to bitumen fume (scenario B), excess risks for lung cancer mortality decreased, ranging from 0.63% (95% CI = 0.10, 1.19) to 1.23% (95% CI = -0.11, 2.55). Assuming current exposure levels remained

constant (scenario C), the estimated excess risk lowered to a range from 1.41% (95% CI = 0.22, 2.82) to 2.60% (95% CI = -0.24, 5.34).

Background cumulative lifetime risk of dying from lung cancer in the Netherlands by age 75 is 6.80% (Netherlands Cancer Registry, 1997). The Health Council of The Netherlands calculates concentrations at benchmark excess risks for ‘dangerous’ and ‘safe’ industries of respectively 0.4% and 0.004% over 40 years (DECOS, 1995). These figures are based on annual risks of 1 per 10 000 and 1 per 1 000 000 extra deaths due to a certain environmental factor. Although our working lifetime cumulative exposures were estimated for a slightly longer period of 45 years, the estimated values were above these limits in all three exposure scenarios. Calculations with 40 years of exposure did not change the results.

## Discussion

We used exposure-response models obtained from a Dutch cohort of road construction and asphalt mixing companies to estimate excess risks for lung cancer mortality after working lifetime exposure to bitumen fume. Under the assumption of a causal relation, the excess risks at age 75 ranged from 0.63 to 14.31%, which are above the benchmark excess risks applied by the Dutch Health Council.

**Table 2.** Cumulative semi-quantitative exposure (unit-years) to bitumen fume after working lifetime exposure, and excess risk for lung cancer mortality at age 75 in a Dutch cohort of workers in road construction and asphalt mixing companies, 1969–1999.

Exposure scenario	Cumulative exposure at age 75 (unit-years)	Linear exposure-response model		Log linear exposure-response model	
		RR at age 75	Excess risk (%) at age 75 (95% CI)	RR at age 75	Excess risk (%) at age 75 (95% CI)
A. Past, decreasing trend					
No lag	82.64	2.92	10.41 (– 1.03, 20.19)	2.53	8.33 (0.98, 21.70)
15-years lagged	79.14	2.41	7.79 (– 8.97, 21.30)	3.77	14.31 (1.83, 39.34)
B. Future, decreasing trend					
No lag	9.05	1.21	1.23 (– 0.11, 2.55)	1.11	0.63 (0.10, 1.19)
15-years lagged	8.83	1.15	0.90 (– 0.95, 2.71)	1.16	0.91 (0.18, 1.73)
C. Future, no trend					
No lag	20.17	1.47	2.60 (– 0.24, 5.34)	1.25	1.41 (0.22, 2.82)
15-years lagged	17.93	1.34	1.92 (– 2.03, 5.67)	1.38	2.11 (0.39, 4.25)

RR, relative risk; CI, confidence interval.

The calculations on excess risks are heavily dependent on the model chosen. Since it is unknown what the real model is (the fitted models are only representing the current dataset), we used different models and presented a range of risk estimates. The fitted linear relative risk model through the weighted means of the exposure categories is not the same as an additive model, but only assumes that there is a linear association between cumulative exposure and lung cancer risk. Although the linear model is perhaps not always the biologically relevant or empirically the best fitted model, it is a generally accepted model in quantitative risk assessment because it is considered conservative (Moolgavkar *et al.*, 1999). The linear regression model resulted in a statistically significant regression coefficient for (lagged) cumulative exposure to bitumen fume. This regression coefficient has to be considered as a crude estimate of the exposure-response relation.

The working lifetime cumulative exposure to bitumen fume was calculated under three different scenarios, but they all did not take into account the higher exposures related to mastic paving or recycling activities, or the lower exposures from oil gravel paving (Burstyn *et al.*, 2000b). However, according to information on company questionnaires, oil gravel was not used and mastic paving was limited to less than 1% of road paving activities. An increased exposure to bitumen fumes was observed after the introduction of recycling activities in the 1980s (Burstyn and Kromhout, 2000). However, this was mainly due to hot re-paving of coal-tar containing road materials.

Nowadays, coal-tar containing asphalt is treated as hazardous waste and is recycled differently than tar-free asphalt (CROW, 1997). Recycling activities in future are therefore expected to have little impact on exposure levels to bitumen fume, and subsequently the excess risks.

We assumed the obtained exposure-response models based on semi-quantitative exposure estimates, could be used for risk evaluation after transformation of working lifetime cumulative quantitative exposure estimates into semi-quantitative estimates. Although the correlation between them was high in this cohort, it may well vary from sector to sector in the asphalt industry. Repeating the exposure-response analyses with quantitative estimates from the pooled international cohort would not solve this problem, because considerable uncertainty was expected in absolute values of exposure concentrations predicted by quantitative exposure models for bitumen fume (Burstyn *et al.*, 2002).

Smoking, a potential confounder when studying lung cancer, could affect the results on different levels. First, as a confounding factor on the exposure-response models. Direct adjustment for smoking in these models was not possible, since information on smoking habits was not systematically collected. However, we did have information on smoking for part of the cohort (1138 workers, 31%). A previous paper (Hooiveld *et al.*, 2003) on the possible effect of confounding by smoking, showed that smoking was positively associated with cumulative semi-quantitative exposure to bitumen fume. Indirect adjustment for

confounding by smoking (Axelson and Steenland, 1988), using information about the strength of the association between smoking and lung cancer, reduced the observed relative risks in the categorical analyses by 10–20%. Using these smoking-adjusted relative risks and a linear exposure-response model, the excess risks decreased by 30%. Including a 15-year latency period resulted in 10% lower estimations of the excess risks. These estimates were still above benchmark risks of the Dutch Health Council.

We used general population mortality rates for the calculation of excess risks and therefore assumed that smoking habits in our population of asphalt workers were comparable with the general population. However, the prevalence of smokers in the subcohort of workers of whom we obtained information on smoking habits was 75% (Hooiveld *et al.*, 2003), compared to 55% smokers in the general male population (Stivoro, 2000). Lower excess risks would have been obtained when using reference rates based on a distribution of smokers and nonsmokers that is comparable to the distribution found in our subcohort (assuming that the subcohort is representative for the whole Dutch cohort).

Occupational bitumen exposure is one of many PAH sources and may contribute little to overall PAH exposure, especially in the lifetime heavy smokers (Burgaz *et al.*, 1992). Thus, assuming that approximately 10% of the lung cancer cases are due to nonsmoking factors and using this proportion of the calculated excess risks, the range among different exposure scenarios and exposure-response models will become 0.06–1.4%. This is still above the benchmark excess risk of 0.004% as applied by the Dutch Health Council, and for workers with exposures experienced in the past decades also above 0.4%.

In conclusion, the calculated excess risks depended on the exposure history and on the exposure-response model selected. In addition, confounding by smoking cannot be ruled out. Nevertheless, although the risk to the individual worker seems low in most scenarios, the excess lifetime risks for lung cancer in this cohort of Dutch asphalt workers is above benchmark values used in standard setting by the Dutch Health Council. Current exposure levels have decreased

these risks considerably, but additional exposure control might be necessary in the future.

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