

Dominik H. Pfluger, Christoph E. Minder

Dept. of Social- and Preventive Medicine, University of Berne

## A mortality study of lung cancer among swiss professional drivers: Accounting for the smoking related fraction by a multivariate approach

### Summary

The mortality due to lung cancer among 'chauffeurs', who have a presumably long-term exposure to diesel exhaust fumes, was analysed. As controls, men in industrial occupations of similar socio-economic status were selected. Cases were drawn from the Swiss mortality register for the years 1979–1983. Person-years were obtained using data from the 1980 census records. These two data files were combined by occupation, age class and socio-economic status. Age adjusted incidence rates were calculated applying Poisson regression. To control for tobacco related lung cancer mortality an indirect adjustment was undertaken. Using information about the smoking habits of the people in the occupations under study, smoking-attributable lung cancer mortality was accounted for by incorporating Axelson's technique into multivariate regression modeling. The mortality ratio for lung cancer for chauffeurs with respect to the controls was 2.27, which is significantly in excess of 1: 95% CI (1.99, 2.58). Other tobacco related diagnoses such as bladder cancer, esophageal cancer and ischemic heart diseases showed excess risks as well. After accounting for smoking, a slight but significant increase in lung cancer mortality remained among chauffeurs (mortality ratio 1.48, 95% CI: 1.30, 1.68). In summary, the present results do support the hypothesis that diesel exhaust is a significant cause of lung cancer.

### Introduction

There is increasing concern that exposure to diesel exhaust fumes may be a risk factor for lung cancer. Polycyclic aromatic hydrocarbons from diesel exhaust are known to be both mutagenic and carcinogenic<sup>1-3</sup>. Furthermore, it was shown that inhaled particles from diesel exhaust may result in lung cancer in rats, at least when they

are exposed over a long time to high levels<sup>4</sup>. Occupational epidemiological studies, however, have not yet provided conclusive evidence<sup>5,6</sup>.

In this paper an analysis based on death certificates from the Swiss death register is presented.

The purpose is to demonstrate a method suitable for screening purposes, by which occupational risk can be demonstrated over and

above a possible excess risk associated with smoking. In this particular case, the question asked is whether there remains an excess lung cancer risk among chauffeurs when the smoking habits in this occupational group are taken into account. The method proposed is basically an integration of Axelson's method<sup>7</sup> into the framework of regression modeling.

### Material

#### Death certificates

The occupation 'chauffeur' was considered to involve increased exposure to diesel exhaust. This category comprises a variety of occupations such as truck-, bus- and taxi drivers, which were not distinguishable on the basis of the given information<sup>8</sup>. As a reference population, workers in occupations such as the metal construction, chemical, wood, paper and watch industries were selected. People such as foundry workers, with known occupational risks for lung cancer, were excluded (a detailed list of the occupational codes is available from the authors upon request). The cases were drawn from the Swiss death register for the years 1979–1982 from among

men who had died aged at least 20 years.

As primary outcomes, deaths from malignant neoplasms of the lung or bronchi (= lung cancer), defined according to the International Classification of Diseases, 8th revision (ICD-8: 162)<sup>9</sup>, were selected. Apart from lung cancer, being the target outcome, the following diagnoses were analysed in this study: bladder cancer (ICD-8: 188), cancer of the esophagus (ICD-8: 150) and ischemic heart disease (ICD-8: 410–414). These diagnoses are known to be related to tobacco consumption<sup>10</sup>. They were considered in order to gain additional information about the relative smoking intensity among the study groups. To retrieve as much information as possible, cases were selected irrespective of whether the particular diagnosis was assigned as primary, second or third cause of death on the death certificate.

### Census data

To compute population based death rates we based the estimation of the person-years under observation on the census-data for 1980 as the population at risk. Cases on the death certificates and the risk group from the census data had corresponding occupational codes. In this way, the cases and the population at risk could be combined on the basis of their respective occupational codes and age-classes. The validity of these occupational codes was checked in

earlier studies<sup>11,12</sup>. Using correction factors described in Minder & Beer<sup>12</sup> the numerator-denominator bias resulting from systematic classification error was accounted for.

Assuming that the demographic pattern between the occupational categories did not shift substantially during the years 1979–1982, i.e. that efflux and afflux between the age-groups was equal, the corresponding number of *person-years observed* could be estimated by multiplying the census data by 4.

### Data on smoking pattern

As information on smoking habits is not available on death certificates, information from a survey done in 1976 was used to estimate the fraction of lung cancer mortality attributable to smoking<sup>13</sup>. The survey was based on a sample of truck drivers, N = 80, and industrial workers, N = 1260, mainly recruited from the metal construction and machine industries. These 1260 workers were regarded as representative for the occupations in the reference group. Similarly, the job 'truck driver' was considered as representing the smoking habits of the designation 'chauffeur' on the death certificates. However, the description 'chauffeur' represents a wider category and also includes bus- and taxi drivers.

The percentages of the various smoking categories are given in table 1.

### Method

Calculation of age-adjusted risk estimates

#### Poisson regression

The log-linear regression technique was applied to model the risk of lung cancer mortality as a function of 'occupation' and age. As the number of cases was small and the time of observation was large, the number of cases per cell may be modelled by the Poisson distribution. We have tested for that assumption by comparing the number of observed cases per week with the Poisson-expected number. The chisquare-test gave a fairly good fit,  $p > 0.8$ . The procedure is described in detail in<sup>14</sup>. The Poisson regression technique is described in detail elsewhere<sup>15,16</sup>. Since the disease-specific death rates were consistently higher for the chauffeurs for all age classes, it was possible to compare the mortality across ages; that is, to compute an overall age adjusted exposure effect. This analysis was done with the statistical package GLIM<sup>17</sup>. The significance of the variables included was judged using the deviance and the adequacy of the final model was carefully checked<sup>14</sup>.

Accounting for smoking related lung cancer mortality

The Axelson technique is based on two components: the population fractions of the non-smokers, light smokers, heavy smokers and former smokers, respectively, and the

	Cigarettes per day					Pipe/ Cigar	N
	NS	FS	1–9	10–19	> = 20		
truck drivers	24.95	16.3	6.46	14.69	34.08	3.53	80
industrial workers	38.50	13.8	8.68	15.88	11.25	11.88	1260

**Table 1.** Percentages of various smoking categories (Cigarettes per day, pipe or cigar smoker) among truck drivers and industrial workers (NS = Non-Smoker, FS = Former Smoker). Source: FREI, (13).

	Current number of cigarettes/day				
	NS	FS	1–9	10–19	>= 20
Relative risk	1	6.3	4.6	7.5	13.8

**Table 2.** Relative risks of dying from lung cancer for various smoking categories compared to non-smokers. NS: Non-smoker, FS: Former smoker. Source: Tables 20, 21 in: HAMMOND (18).

Age	Chauffeurs		Reference group	
	deaths	N <sub>ij</sub>	deaths	N <sub>ij</sub>
20–24	0	24360	0	151884
25–29	0	26892	0	122212
30–34	1	28516	2	109620
35–39	2	26324	3	93760
40–44	7	21816	14	73968
45–49	16	22012	29	77452
50–54	23	19196	75	77032
55–59	34	15624	128	77032
60–64	53	9200	169	63876
65–69	62	9592	260	76868
70–74	44	7752	304	68568
+75	42	7564	317	74908

**Table 3.** Number of deaths from lung cancer and person-years (N<sub>ij</sub>) observed.

corresponding relative risks. The procedure is described in detail in the Appendix. We used the relative risks derived from the American Cancer Society's study of 1 million men and women<sup>18</sup>, given in table 2. Using these risks with Axelson's procedure we can estimate a relative risk, as it would be if generated solely by the different smoking habits of the two groups considered; that is, it gives the purely tobacco-related relative risk. Our analysis gives a relative risk of 1.53. That is, we would expect the lung cancer mortality rate of chauffeurs to be about 50% higher than that of the reference population, if no further exposure is operating. This relative risk can be used to adjust the observed lung cancer mortality if we re-express the Poisson-process parameter lambda as the

product of the overall disease-specific death rate times the smoking-specific relative risk (=RR<sub>i</sub>). In addition, a correction factor 'c' calculated as 0.69 accounting for the numerator-denominator bias has to be inserted into the model. The expected number μ<sub>ij</sub> of events in occupational category i and age-group j can then be represented as:

$$\mu_{ij} = c_i RR_i N_{ij} \lambda_{ij}$$

i = 1 for chauffeur, 2 for reference group

j = 1, 2, ..., 12 (age-classes)

c<sub>i</sub> = correction factor for occupational misclassification, = 0.69 for chauffeurs, = 1 for reference group  
 RR<sub>i</sub> = relative risk calculated for exposed group (=1.53) as related to the reference (=1)

N<sub>ij</sub> = person-years in occupational group  
 λ<sub>ij</sub> = occupation and age-group specific intensity, to be estimated)

Using the usual logarithmic transformation it follows:

$$\ln(\mu_{ij}) = \ln(c_i RR_i N_{ij}) + x_{ij}'\beta$$

with ln(λ<sub>ij</sub>) replaced by the linear predictor, x<sub>ij</sub>'β, where in the present case β is a parameter vector of length 4 and x<sub>ij</sub>' a 4-dimensional vector of variables (intercept, occupation category, age and age squared).

This estimation can be done with GLIM by using an offset of the first term on the right-hand side of the above formula. An age- and smoking adjusted mortality ratio representing the 'exposure' effect is then obtained by calculating the antilog of the estimated regression coefficient of occupation. This modeling is based on the assumption that smoking does act in a multiplicative way with diesel exhaust with respect to lung cancer. This assumption is in contrast to the finding of a prospective study of Boffetta et al.<sup>19</sup>, suggesting an additive rather than a multiplicative pattern of lung cancer mortality for these two risk factors.

### Results

The number of deaths from lung cancer and the corresponding person-years are shown in table 3.

Without Axelson's procedure

The mortality ratio for lung cancer for chauffeurs with respect to the reference group was 2.27, which is significantly in excess of 1; 95% confidence interval, CI (1.99, 2.58). This calculation is taking into account the correction factor. However, as the other tobacco-related diagnoses such as bladder cancer, esophagus cancer and ischemic heart disease show ratios exceeding 1, as opposed to the

Diagnoses	estimate		95 % CI	adjusted for		
				age	nd-bias	smoking
lung cancer	2.27	1.99	2.58	yes	0.69	no
bladder cancer	2.02	1.36	2.98	yes	0.69	no
esophagus cancer	2.30	1.57	3.38	yes	0.69	no
ischemic heart disease	1.65	1.50	1.82	yes	0.69	no
lung cancer	1.48	1.30	1.68	yes	0.69	yes
lung cancer	1.17	1.03	1.33	yes	0.88	yes

**Table 4.** Mortality ratios adjusted for age, numerator-denominator bias (nd-bias) and smoking for chauffeurs. 95%CI: confidence intervals (lower and upper limits). Two correction factors are used:  $c = 0.69$ ,  $c = 0.88$  ( $c + 2 * SE$ ).

reference group, and about to the same degree as lung cancer mortality does (see table 4), there is no basis for rejecting the concept that the increase in lung cancer mortality is wholly explainable by smoking.

We therefore have to rely on the smoking adjustment.

Using Axelson's procedure

Using the available empirical data on smoking, a mortality ratio of 1.48, 95% CI (1.30, 1.68) is obtained for lung cancer.

## Discussion

Assuming that the method of adjustment for smoking is adequate, and the smoking pattern of the occupations analysed is reflected reliably by the survey data, we can conclude that the observed adjusted excess mortality from lung cancer among chauffeurs can not be explained by smoking alone. Even when using a rather conservative correction factor (i.e. mean+twice its standard error) closer to 1, an excess of lung cancer mortality remains.

In further analyses we calculated age- and smoking-adjusted mortality ratios for the following occupa-

tions: dredging machine operators (occupational code 634)<sup>8</sup>, and gas station attendants (679), applying exactly the same adjustments. The following mortality ratios were obtained: 2.46, 95% CI (1.93, 3.14) for dredging machine operators, 2.56, 95% CI (1.33, 4.92) for gas station attendants. These results seem to support the hypothesis that occupational exposure to diesel exhaust increases the risk of lung cancer. Dredging machine operators might be expected to have a high exposure, as they often stay in the same place, surrounded by accumulated exhaust fumes. Gas station attendants are continually exposed to heavy concentrations of exhaust fumes.

For dredging machine operators, an alternative explanation of generally high cancer rates is their belonging to the group of construction workers – a group with high risks of various cancers. For gas station attendants, on the other hand, exposure is not restricted mainly to diesel fumes, but rather to all types of exhausts.

In conclusion, the present results give some evidence for an excess of lung cancer risk from an occupational exposure to diesel exhaust. This is in line with another recent finding: in a case-control study<sup>20</sup>, significantly increased relative

odds for exposed workers were obtained after controlling for smoking and asbestos exposure. Moreover, a dose-response relationship between 'diesel-years' and the incidence of lung cancer was shown at least for workers aged at 64 years or less, giving further support to the hypothesis that there is a hazardous effect. However, other recent studies<sup>19,21</sup> give only weak evidence for such an etiologic association.

## Appendix

Axelson's procedure to account for differences in smoking habits

The overall mortality rate of lung cancer can be expressed as a weighted mean of the rates among the diverse smoking categories  $l$ , ( $l = 1, 2, \dots, m$ ) and the non-smokers,  $l = 0$ , where the weights are just the fractions of these categories in the study groups.

If the effect of smoking is known in terms of a relative risk with respect to non-smokers, the overall mortality rate from lung cancer can be expressed in the following way:

$$\lambda = \sum_{l=0}^m p_l RR_l \lambda_0$$

where the term  $RR_l \lambda_0$  represents the mortality rate for category  $l$ .

Rearranging the terms, the equation can be rewritten as:

$$\frac{\lambda}{\lambda_0} = \sum_{l=0}^m p_l RR_l$$

The term on the right hand side represents the smoking induced relative mortality rate from lung cancer of the group investigated compared to non-smokers.

By computing such a decomposition for the exposed and non-exposed groups, two factors are obtained. By calculating the ratio

between them, we finally obtain a rate ratio (RR) which represents the relation of the overall rates among the exposed to that among the non-exposed group, as we expect it based on the smoking habits of the two groups only. Based on our data (Table 1 and 2) we obtain the following figures: for the chauffeurs a relative mortality of 7.54 compared to non-smokers is calculated; for the reference group we obtain a relative mortality of 4.94. Thus, the RR calculated is 1.53 (7.54/4.94), which was subsequently used in the regression. Pipe and cigar smokers were classified as having the same relative risks as light cigarettes smokers, e.g. 1–9 cigarettes per day, since it is known that at least Swiss cigar and pipe smokers experience a lung cancer mortality comparable to cigarette smokers<sup>22</sup>.

### Zusammenfassung

#### **Die Sterblichkeit an Lungenkrebs bei Schweizer Chauffeuren: Berücksichtigung des rauchenbedingten Anteils mittels eines Regressionsansatzes**

Die Sterblichkeit an Lungenkrebs bei Schweizer Chauffeuren wurde analysiert, um die Hypothese der kanzerogenen Wirkung von Diesel-Abgasen zu untersuchen. Es wurde angenommen, dass Chauffeure durch ihre berufliche Tätigkeit langzeit-exponiert gegenüber Diesel-Abgasen sind. Als Kontrollen wurden Berufe aus verschiedenen industriellen Bereichen mit ähnlichem sozio-ökonomischem Status verwendet. Die Todesfälle wurden anhand der Schweizerischen Sterbestatistik im Zeitraum 1979–1982 erhoben. Daten der Volkszählung von 1980 wurden benutzt, um bevölkerungsbezogene Risiken zu berechnen. Altersstandardisierte Raten wurden mit log-linearen Poisson-Regressionsmodellen gerechnet. Die Sterblichkeit an Lungenkrebs bedingt durch Tabakkonsum wurde auf indirekte Art korrigiert, indem Angaben zum Raucherverhalten der untersuchten Berufe berücksichtigt und mit Axelson's Methode in das Poisson-Modell integriert wurden. Das relative Risiko (RR) für Lungenkrebs bei Chauffeuren in Bezug zur Vergleichsgruppe beträgt 2.27. Die Erhöhung ist signifikant (95%-Vertrauensintervall: 1.99–2.58). Andere rauchenbezogene Diagnosen wie Blasen- und Speiseröhrenkrebs sowie ischämische Herzkrankheiten zeigten ebenfalls erhöhte Risiken. Nach Kontrolle des rauchenbedingten Anteils war die Sterblichkeit an Lungenkrebs immer noch signifikant erhöht, RR: 1.48, 95% VI: 1.30–1.68. Zusammengefasst unterstützen die vorliegenden Resultate die Hypothese, wonach Dieselabgase zu erhöhter Lungenkrebssterblichkeit führen.

**Résumé****Etude de mortalité par cancer du poumon chez les chauffeurs suisses – ajustement en fonction du tabagisme de manière indirecte**

Afin d'examiner l'hypothèse d'un effet cancérigène des gaz d'échappement des moteurs diesel, les taux de mortalité par cancer du poumon chez les chauffeurs suisses ont été analysés. Nous avons supposé que par leurs activités professionnelles les chauffeurs étaient exposés à long-terme aux gaz d'échappement des moteurs diesel. Des professions du secteur industriel correspondant à une position socio-économique similaire ont constitué le groupe témoin. Les cas de décès furent tirés du registre suisse de mortalité pour les années 1979–1982. Le recensement de 1980 a été utilisé pour calculer le risque de mortalité par rapport à la population générale en estimant les années de personne pour la période 1979–1982. Le risque ajusté en fonction de l'âge a été calculé au moyen de la régression de Poisson (modèle log-linéaire). L'ajustement en fonction du tabagisme a été fait de manière indirecte, en utilisant des données sur les habitudes tabagiques des professions incluses dans cette étude et en appliquant la méthode d'Axelson au modèle de régression. Nous avons observé un risque relatif (RR) de décès par cancer du poumon chez les chauffeurs de 2.27 (intervalle de confiance à 95%: 1.99, 2.58). De même, l'analyse des taux de mortalité par des autres affections liées au tabagisme comme cancer de vessie, cancer de l'oesophage et des maladies ischémiques du cœur a mis en évidence des risques élevés chez les chauffeurs. Après ajustement en fonction du tabagisme, nous avons observé une augmentation faible mais significative de la mortalité par cancer du poumon chez les chauffeurs: RR: 1.48, intervalle de confiance à 95% dl 1.30 à 1.68. En résumé, ces résultats confirment l'hypothèse que les gaz d'échappement des moteurs diesel ont un effet cancérigène.

**References**

- 1 Kotin P, Falk H, Thomas M. Aromatic hydrocarbons. Arch ind Hlth 1955; 11:113–120.
- 2 Lewtas J. Evaluation of the mutagenicity and carcinogenicity of motor vehicle emissions in short-term bioassays. Env Hlth Per 1983; 47:141–152.
- 3 Wei E, Shu H. Nitroaromatic carcinogens in Diesel soot: a review of laboratory findings. AJIH 1983; 9: 1085–1088.
- 4 Mauderly JL, Jones RK, McClelland RO, Henderson RF. Carcinogenicity of Diesel exhaust inhaled chronically by rats (abstract). Am Rex Respir Dis 1986; 133:A86.
- 5 Schenker M. Diesel exhaust – an occupational carcinogen. J Occup Med 1980; 22 (1):41–46.
- 6 Steenland K. National Institute for Occupational Safety and Health, Cincinnati, Ohio. Lung cancer and Diesel exhaust: a review. Am J Ind Med 1986; 10 (2):177–189.
- 7 Axelson O. Aspects of confounding in occupational health. Scand J Work Env Health 1978; 4:85–89.
- 8 Klassifikation der Berufe für die Schlüsselung der Statistikkarten der Bevölkerungsbewegung, Eidg. Statistisches Amt, Bern 1979.
- 9 Internationale Klassifikation der Krankheiten und Todesursachen, ergänzt für den schweizerischen Gebrauch ab 1969. Eidg. Statistisches Amt, Bern 1979.
- 10 The Health Consequences of Smoking. Cancer and Chronic Lung Cancer in the workplace. A Report of the Surgeon General U.S. Department of Health and Human Sciences. Public Health Service. Rockville Maryland, 1985
- 11 Beer V, Greusing Th, Minder ChE. Berufsbezogene sozio-ökonomische Gruppen für die Schweiz: sozialwissenschaftliche Untersuchungen zur Validität. Sozial- und Präventivmedizin 1986; 31:274–280
- 12 Minder, ChE, Beer-Porizek V. Cancer mortality of Swiss men by occu-

- pation, 1979–1982. Scand J Work Environ Health, 1992; 18 suppl 3: 27p
- 13 *Frei A.* Gesundheitszustand, Leistungsprofil und Lebensgewohnheiten des Lastwagenchauffeurs. Inaugural-Dissertation, Institut für Sozial- und Präventivmedizin der Universität Zürich. ADAG-Administration & Druck AG, 1986.
- 14 *Pfluger DH.* A mortality study of lung cancer among Swiss chauffeurs – accounting for smoking related fraction by a multivariate approach. Unpublished postgraduate thesis, Université de Neuchâtel, 1993.
- 15 *Breslow NE, Lubin J, March P, et al.* Multiplicative models and cohort analysis. J Am Stat Assoc 1983; 78:1–12.
- 16 *Breslow NE, Day NE.* Statistical methods in cancer research, Volume II, The design and analysis of cohort studies (IARC Scientific publications No. 82) Lyon, International Agency for Research on Cancer, 1987.
- 17 *Baker RJ, Nelder JA.* Generalized linear interactive modeling (GLIM) System. Release 3. Oxford, Numerical Algorithms Groups, 1978.
- 18 *Hammond E.* Smoking in relation to the death rates of one million men and women. In Haenszel W (ed.) “Epidemiological study of cancer and other chronic disease”, NCI Monograph 19, MD: NCI Bethesda 1966; 127–204
- 19 *Boffetta P, Stellman SD, Garfinkel L.* Diesel exhaust exposure and mortality among males in the American Cancer Society prospective study. Am J Ind Med 1988; 14:403–415
- 20 *Garshick E, Schenker MB, Munoz A, Segal M, Smith TJ, Woskie SR, et al.* A case-control study of lung cancer and Diesel exhaust exposure in railroad workers. Am Rev Respir Dis 1987; 135 (6): 1242–1248
- 21 *Boffetta P, Harris RE, Wynder EL.* Case-control study on occupational exposure to Diesel exhaust and lung cancer risk. Am J Ind Med 1990; 17:577–591
- 22 *Gsell O, Abelin T.* Cigar and pipe smoking in relation to lung cancer and excess mortality. J Nat Cancer Inst 1972; 48 (4):1795–1803.

---

### Acknowledgements

We thank Theodor Abelin und Yadolah Dodge for their helpful comments. This research was supported by the Swiss National Research Fund, Grant-Nr. 3.968-0.87.

---

### Address for correspondence

Dominik H. Pfluger, lic phil. nat.  
Dept. of Social- and  
Preventive Medicine  
University of Berne  
Finkenhubelweg 11  
CH-3012 Berne/Switzerland