

EXPOSURE TO CEMENT DUST, RELATED OCCUPATIONAL GROUPS AND LARYNGEAL CANCER RISK: RESULTS OF A POPULATION BASED CASE-CONTROL STUDY

Andreas DIETZ^{1,*}, Heribert RAMROTH², Tobias URBAN³, Wolfgang AHRENS⁴ and Heiko BECHER³

¹Department of Otolaryngology, Head and Neck Surgery, University of Heidelberg, Heidelberg, Germany

²Division of Clinical Epidemiology, German Cancer Research Centre, Heidelberg, Germany

³Department of Tropical Hygiene and Public Health, University of Heidelberg, Heidelberg, Germany

⁴Bremen Institute for Prevention Research and Social Medicine (BIPS), Bremen, Germany

A population-based case-control study was performed in the Rhein-Neckar region, Germany, to evaluate occupational risk factors for the development of laryngeal cancer ("Rhein-Neckar-Larynx Study"). Between May 1998 and December 2000, 257 patients (236 males, 21 females), aged 37–80, with histologically confirmed laryngeal cancer, as well as 769 population control persons (702 males, 67 females), were included (1:3 frequency matched by age and sex). History of occupational exposures, as well as other risk factors (tobacco, alcohol), was obtained with face-to-face interviews using a detailed standardized questionnaire. The complete individual work history was assessed. A detailed assessment of work conditions was obtained by job-specific questionnaires (JSQs) for selected jobs known to be associated with exposure to potential laryngeal carcinogens. Estimates for total exposure hours by substance were calculated based on JSQs. Published occupational hygiene data were used to infer semiquantitative scores of exposure intensity for specific job tasks. After adjustment for tobacco and alcohol intake, a significant elevated odds ratios (OR) could be demonstrated for persons that were exposed to cement during their work as building and construction workers. An OR of 2.42 was calculated for workers of the high exposed subgroup (95% confidence interval: 1.14–5.15; $p < 0.001$). Smoking was the main confounding factor because the unadjusted cement OR of 3.20 dropped down to 2.42 after adjustment for tobacco intake. We conclude that there is good evidence for cement dust exposure acting as a tobacco, alcohol and asbestos independent risk factor for laryngeal carcinoma. Our study gives a base for further toxicologic investigations on this topic.

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Squamous cell carcinoma of the larynx (yearly incidence about 10/100,000 in Germany) is the most common malignant tumour of the upper aerodigestive tract in Caucasians. Average prognosis ranges between 80% 5-year survival for glottis, 68% for supraglottis and 53% for subglottis carcinoma.¹ Cure rates for early glottis cancer are nearly 100% but many patients suffer from advanced disease at date of the first diagnosis. Current therapies for advanced tumour stages still includes radical laryngectomy followed by radiotherapy, with severe implications for quality of life in many cases. Therefore, prevention and determination of risk factors is of very high interest.

Tobacco smoking represents a major risk factor for laryngeal cancer, as well as alcohol consumption, which has been consistently demonstrated by a variety of epidemiologic studies.² According to findings from research on genotoxicity and occupational factors, it has been suggested that 10% of all carcinomas in Germany and the US are related to exposure to hazards in the occupational environment.^{3,4} Comprehensive epidemiologic research over the last 40 years has identified certain occupational factors that are associated with the risk for developing laryngeal cancer, such as asbestos,^{5,6} mineral coal products, mineral oil,^{7,8} fossil fuels,⁹ coking plant emissions and other polycyclic aromatic compounds (PAH),¹⁰ ionising radiation, mustard gas, chromium-

VI-compounds, wood dust,^{11,12} nickel compounds, sulfuric acid, isopropylalcohol and bis-chloromethylether² and emissions in the paper-,¹³ textile-,^{14,15} leather-¹⁶ and rubber industries.^{17,18} Finally, painters and varnishers probably have an elevated risk for laryngeal carcinoma. Paints are very heterogeneous compositions containing some carcinogenic hazards, e.g., chromium-VI-compounds.¹⁹

In addition, the environment of building and construction workers might also cause a higher risk of developing laryngeal carcinoma. In several studies (predominantly case-control studies) significant increased risks (adjusted for tobacco and alcohol effects) were found for construction dust.^{7,20–23} Construction dust contains many different substances, such as asbestos, mineral fibers, sand or metal powders, tar, bitumen and cement dusts. The question of which single agent is responsible for the elevated laryngeal cancer risk remains unanswered, although some studies could identify cement dust as the main candidate. In a German case-control study,²⁴ cement dust was associated with a relative risk (RR) of 2.4, which could be further differentiated into exposure time dependent increased risks (duration of exposure 5–20 years: RR 2.9; 20–40 years: RR 5.5; > 40 years: RR 6.3). After adjustment for tobacco and alcohol (ever exposed) the RR remained significantly elevated at 1.8 ($p = 0.03$). The results from a French case-control study demonstrated that cancer of the supraglottic larynx has been associated with exposure to cement dust (odds ratio [OR] = 4.2; 95% confidence interval [CI] = 1.1–16.4).²⁵ Furthermore, an association between cement dust and gastrointestinal cancer has been shown.²⁶

Despite the obvious need to clarify the role of cement dust as a potential risk factor for laryngeal carcinoma, only a few studies have focused on this issue. Thus, we performed a comprehensive population-based case-control study in Germany. Our study aimed to investigate and narrow down the supposed cement-associated risk for laryngeal cancer (*inter alia*) after adjustment for main confounding factors.

MATERIAL AND METHODS

Our study was conducted in the Rhein-Neckar-Odenwald Region of southwest Germany, with a population of about 2.7 mil-

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*Correspondence to: Universitäts-Hals-Nasen-Ohrenklinik, Im Neuenheimer Feld 400, 69120 Heidelberg 69120, Germany.
Fax: +06-221-566706. E-mail: Andreas_Dietz@med.uni-heidelberg.de

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lion. Within this region between May 1, 1998 and December 31, 2000, nearly all incident cases (response rate 96%) of histologically confirmed squamous cell carcinoma of the larynx (ICD-9-Nr. 161.0–161.9) were recruited ($n = 257$) and frequency matched 1:3 (by age, gender and location) with population controls ($n = 769$) randomly drawn from population registries. Further inclusion criteria were age less than 80 years, German nationality and mental ability for the interview. Cases were recruited at the Department of Otolaryngology, Head and Neck Surgery university hospitals of Heidelberg and Mannheim and town hospitals of Ludwigshafen, Darmstadt and Heilbronn. These hospitals exclusively treat patients with laryngeal cancer within our study region. Local practitioners were additionally contacted to check for possible cases sent to other more distant clinics and to verify complete case ascertainment. The list of population controls was assembled by the town registration offices of our study region and kept at the centre study office. The procedure for drawing population controls from various population registries in our study has been previously described by Ramroth *et al.*²⁷ Altogether, the extent of the control random sample selected by the several registration offices was 32,435 persons. Out of this sample, 1,233 eligible persons were randomly chosen according to the age and sex distribution of the cases. Finally, 769 (response rate: 62.4%) were included in our study, which is rather high considering the fact that blood samples were required by the participants and a special technique of recruitment was performed (e.g., invitation to come to the clinics for interview).

The ages of study participants was between 40 and 75 years. Distribution of sex in cases was 236 men and 21 women. Family status was comparable in cases and controls.

Occupational exposures, as well as other risk factors, were obtained by face-to-face interviews using a detailed standardised questionnaire. Before the start of our study, 5 female interviewers, who were exclusively employed for our study, underwent special questionnaire training. The interview was conducted usually before start of therapy. The interviews of cases and controls were performed predominantly in the hospitals (better facilities for taking blood in controls) mentioned above, and some were conducted in the participant's home. Table I shows the distribution of our study sample.

The assessment of occupational exposure was derived from 3 different sources of the questionnaire: a detailed occupational history of all jobs held for at least 6 months, an exposure check-list for known and suspected carcinogens of the respiratory tract, and 34 job-specific supplementary questionnaires (JSQ) addressing specific exposures in job—or branch of industry—oriented questions. Estimates for lifetime exposure hours by substance were calculated based on JSQs. Published occupational hygiene data were used to infer semi-quantitative scores of exposure intensity for specific job tasks. The quantification procedure was a modification of methods described elsewhere,²⁸ and the performance of this method with respect to asbestos has been evaluated.²⁹ Industries and job titles were coded according to the standard classifications provided by Statistisches Bundesamt (1993)³⁰ and the ILO (1968).³¹ The analysis of the job history was based on these codes, which were grouped into 32 and 21 categories, respectively, on an ever-never-basis and by duration as described before.³²

Additionally a list of agent exposures was checked in every study attendant. Further concentrated attention was paid to consumption of tobacco and alcohol, passive smoking, family health,

nutrition, social status and special personal environmental factors other than occupation.

To narrow down data of the individual cement dust exposure, a validation study was performed in exposed cases and controls. A special cement questionnaire asked for ceil techniques; grouts and plaster materials like mortar containing lime, unslaked or slaked lime and gypsum; the way of processing cement-based products on site and the detailed daily direct or indirect cement dust exposure. For every kind of job, associated cement exposure life working hours were calculated by different indices. In case of parallel exposure, the maximum exposure level for a given time period was taken. Rating for cement exposure was done by distinguishing between nonexposure ("0"), middle and high exposure dependent on the median of the controls cement exposure duration.

Another expected confounding factor in analysis of cement associated cancer risk is constituted by asbestos, in particular asbestos cement exposure. For this reason, an exact assessment of exposure to the diverse modifications of asbestos was done. The questionnaire and the JSQs contained the following topics: direct handling/processing of asbestos, using asbestos heat protecting or isolation, contact with asbestos materials and employment in the asbestos industry. Furthermore, asbestos environment was checked in the list of hazardous substances. In consideration of these data, calculation of asbestos life working hours was performed in the same way as was done for cement exposure.

All ORs given are based on a conditional logistic regression model conditioned on a sex \times age classification (5-year age groups).³³ Adjustment for smoking, alcohol consumption and social status was performed as indicated in the tables. To assess the magnitude of confounding, OR estimates with and without adjustment are presented; however, the interpretation of the occupational risks is based on the adjusted values. The statistical software package SAS (PROC PHREG) was used.

Smoking was considered as the cumulative number of cigarettes smoked (pack years [py]; 1 py \cong 20 cigarettes/day for 1 year \cong 7,300 cigarettes). Cigars, cigarillos and pipes were added according to their weight relative to that of cigarettes. It was included as a log-transformed continuous variable ($\log(\text{py} + 1)$). Residual confounding through smoking was minimized by comparing the results using other transformations of the smoking dose, including a categorization into 6 categories (0, > 0–10, > 10–20, > 20–30, > 30–40, > 40 py). The transformation used here gave the best fit and also, in most cases, the maximally reduced estimates for the occupational variables of interest. Time since smoking cessation was included as binary variable "having stopped smoking at least 2 years before diagnosis/before interview." Average daily alcohol consumption was included as a continuous variable.

Daily alcohol consumption was calculated from the alcohol data obtained by the interview (daily, weekly and monthly alcohol consumption 10 years before interview for all common alcoholic beverages), assuming the following ethanol content: beer 5%; wine, fruitwine or sparkling wine 10%; aperitif and liquors 20% and spirits 40%. Average daily alcohol consumption was included as continuous variable in the final model because it gave the best fit. Again, other methods for alcohol adjustment using categories (< 25 g, 20–50 g, 50–75 g, > 75 g ethanol per day) were also investigated. School education was considered as a surrogate variable for social status in 3 levels according to the German educational system (9 years and less "Hauptschule", 10 years "mittlere Reife" and more than 10 years ("(Fach)Hochschulreife").

TABLE I—STUDY SAMPLE (NUMBER OF PARTICIPANTS) AND LOCATION OF INTERVIEW AT THE DEPARTMENTS OF OTOLARYNGOLOGY, HEAD AND NECK SURGERY OF THE TOWN HOSPITALS OF DARMSTADT, HEILBRONN, LUDWIGSHAFEN AND THE UNIVERSITY HOSPITALS OF HEIDELBERG, MANNHEIM

	Darmstadt	Heidelberg	Heilbronn	Ludwigshafen	Mannheim	At home	Sum
Controls	112	234	91	113	4	215	769
Cases	43	61	22	53	78	0	257
Sum	155	295	113	167	82	215	1,026

The scientific nature of our study was explained to all the patients and they gave their informed consent to participate in this investigation. The protocol was approved by the Ethical Committee of the University of Heidelberg.

RESULTS

Before presentation of the results regarding environmental risk factors for laryngeal carcinoma, the main confounding factors in our study should be described. Cigarette smoking was the outstanding risk factor for laryngeal carcinoma in the Rhein-Neckar-Larynx Study. Only 2.1% of male and 19.0% of female cases were never smokers compared to 23.8% of male and 53.7% of female controls, respectively. The OR for 0–10 py was 3.9 (95% CI: 1.5–9.7), increasing to 32.8 (95% CI: 15.1–71.0) in the group of heavy smokers (> 40 py) after adjustment for alcohol. Analysis of chronic alcohol consumption showed ORs of up to 2.4 in the highest group consuming more than 75 g alcohol per day (adjusted for tobacco intake, 95% CI: 1.5–3.6). More detailed data about larynx cancer risk associated to tobacco and alcohol of our study are publicized elsewhere. Socioeconomic status, assessed as described in the Material and Methods section, showed differences between cases and controls. Among males, the differences between cases and controls among the first, second and third categories were 87.3% and 62.1%, 6.8% and 15.0% and at least 5.9% and 22.9%, respectively.

Regarding traditional industries, in our study, the group of building and construction workers showed evidence of risk for laryngeal cancer. There were 103 (40.1%) cases and 163 (17.7%) controls who ever had worked as building or construction workers. This industry had an OR of 2.6 without adjustment and 2.2 (95% CI: 1.55–3.14) after adjustment for the confounders tobacco and alcohol. Considering the industry in which employment was longest time of life, building and construction work demonstrated an adjusted larynx carcinoma risk of 1.9 (95% CI: 1.2–3.0).

Further analysis for single substances focused on cement dust. According to the JSQs, 14.8% of male cases and 5.1% of male controls were exposed to cement dust (female cases did not show any exposure to cement dust). With regard to the list of hazardous substances, 23.3% of cases showed cement exposure compared to 14.4% of the controls. Cement exposure duration showed 8.1% of cases compared to 2.7% of controls to be highly exposed with a life working hours account of more than 3,000 hr (Table II).

After adjustment for tobacco, alcohol intake and socioeconomic status, statistically significant elevated ORs could be

demonstrated for persons ever being exposed to cement in their life. Based on categorisation in no, middle and high exposure, no clear dose response was observed. However the calculated ORs are compatible with increasing risk by cement dust exposure. Smoking is the main confounding factor considering the unadjusted cement OR of 3.2 decreasing to 2.4 after tobacco adjustment (Table II).

No exposure to asbestos was reported by 75.0% of male cases and 85.2% of male controls (all female participants were not exposed). All ORs related to the topics of the asbestos-JSQs did not reach significantly elevated levels after adjustment for tobacco and alcohol. The high exposed group of more than 1,000 lifetime working hours included 18.6% of cases and 10% of controls. Without adjustment, the OR for asbestos exposure was 2.1, but after adjustment for tobacco and alcohol, it decreased to 1.3 (95% CI: 0.8–2.1), which was not significant. Thus, we present results without adjustment for asbestos in our analyses.

Eligible for the validation study with the mentioned cement-specific questionnaire were 58 cement dust exposed cases and 106 controls. The cement specific interviews were arranged 2–4 years after the first interview in the clinics. Only 28 cases and 99 controls could be reached for further assessment because of death, loss of contact, etc, and 15 cases and 80 controls accepted a telephone interview to conduct the cement-specific questionnaire.

All 15 cases (100%) classified as exposed in our main study also reported an exposure in the re-interview. However, in controls, only 69/80 (86.3%) confirmed cement dust exposure. Although this difference in proportions is not significant ($p = 0.16$, Fisher exact test), it indicates that exposure to cement in the control group is more likely to have been overestimated than in controls in the original interview. This means that the reported ORs may be underestimated, which emphasizes the assessment of cement dust exposure as relevant risk factor for laryngeal cancer. Distinguishing between exposure to cement and lime or slaked lime, 9/15 (60.0%) of cases and 34/80 (42.5%) of controls were exposed to any kind of lime. Considering the exposure frequency of lime in cases and controls, we observed that a higher percentage of cement-exposed cases also had a lime exposure (60%) compared to controls (48.6%). This indicates that lime exposure may have an additional harmful effect. The data allow an estimation of the OR for lime exposure given cement exposure, yielding an OR of 2.0 (not significant). If high exposure (> 3,000 hr) is considered, the OR is 3.6 (95% CI 1.1–11.9). However numbers are too small to draw definite conclusions. (Table III).

TABLE II – CEMENT DUST EXPOSURE IN CASES AND CONTROLS AND ODDS RATIOS

Cement dust exposure	Cases				Controls				OR ₁	OR ₂	OR ₃	95% CI	p-value
	Male		Female		Male		Female						
	n	(%)	n	(%)	n	(%)	n	(%)					
Assessed by job-specific questionnaires													
Not exposed	201	85.2	21	100.0	666	94.9	66	98.5	1	1	1		
Exposed	35	14.8			36	5.1	1	1.5	3.13*	2.39*	2.04	1.16–3.56	0.01
Assessed by list of hazardous substances													
Not exposed	181	76.7	21		601	85.6	66	98.5	1	1	1		-
Exposed	55	23.3			101	14.4	1	1.5	1.76*	1.45	1.18	0.77–1.81	0.45
Cement exposure rating													
Not exposed (0 h)	201	85.2	21	100.0	666	94.9	66	98.5	1	1	1		
(Lifetime working hours)													
Middle exposed (0–≤3000)	16	6.8			17	2.4			3.10*	2.35*	2.22	1.02–4.84	0.04
High exposed (3000+)	19	8.1			19	2.7			3.17*	2.42*	1.87	0.88–4.01	0.11
Sum	236	100.0	21	100.0	702	100.0	67	100.0					

OR₁, Odds Ratio, stratified for age and gender; OR₂, Odds Ratio, stratified for age and gender, adjusted for tobacco and alcohol intake; OR₃, Odds Ratio, stratified for age and gender, adjusted for tobacco, alcohol intake and socioeconomic status; *, ($p < 0.05$, two side test); 95% CI, 95% confidence interval for OR₃.

TABLE III—VALIDATION STUDY WITH CEMENT SPECIFIC QUESTIONNAIRE IN A SUBGROUP (15 LARYNGEAL CANCER PATIENTS, 80 CONTROLS) OF PARTICIPANTS HAVING BEEN DOCUMENTED AS CEMENT EXPOSED IN THE FIRST INTERVIEW

Exposure to	Cases		Controls	
	n	%	n	%
Cement				
Any cement at work	6	40	40	50
Mixing of cement binder	8	53.3	52	65
Cement processing	7	46.7	20	25
Rating of cement exposure				
No exposure (Life working hours)	0	—	0	—
Middle exposure (≤ 3000 hrs)	6	40	32	40
High exposure (> 3000 hrs)	9	60	38	47.5
Lime ¹				
Not slaked	1	6.7	3	3.8
Slaked	6	40	25	31.2
Slaked in person	5	33.3	10	12.5
Processing of lime plaster	5	33.3	15	18.8
Rating of lime exposure				
No exposure (Life working hours)	6	40	46	57.5
Middle exposure (≤ 3,000 hrs)	1	6.7	17	21.25
High exposure (> 3,000 hrs)	8	53.3	17	21.25
Using only cement	6	40	36	45
Using only lime	0	—	0	—
Using cement and lime	9	60	34	42.5
Using neither cement nor lime	0	—	10	11.5
Sum	15	100%	80	100%

¹Multiple entries possible.

DISCUSSION

The Rhein Neckar Larynx Study, which is partly introduced in this article, is one of the largest population-based case-control studies on laryngeal cancer. One of the important findings in our study was the probability of an independent risk of cement dust for laryngeal cancer. Regarding the tobacco and alcohol adjusted OR of 2.35 in the middle exposed group (0 to ≤ 3,000 lifetime working hours) and 2.42 in the high exposed group (> 3,000 lifetime working hours, Table II), there is a slight dose-response effect. But after adjustment of socioeconomic factors (Table II: OR₃), dose response effects disappeared completely in our sample group. However, further distributions in dose-related groups are not useful due to methodologic reasons, so that validity of our data concerning dose response effects is limited.

Interestingly, the data of the validation study with cement specific questionnaire in a representative subgroup (15 laryngeal cancer patients, 80 controls) of participants (documented as cement exposed in the first interview: Table III) signified exposure to cement in the group of controls as probably overestimated in the first census. For all 15 cases (100%), cement dust exposure was verified. However, 11 (13.7%) control persons reported no cement exposure after additional assessment. Even though evidence is limited due to the small sample group of the validation study, the findings suggest that OR estimates of cement exposure may gain further significance.

An additional adjustment for asbestos exposure would be possible to exclude possible confounding. Because we did not find a relevant risk for asbestos and laryngeal cancer, OR estimates remain virtually unchanged if we nevertheless perform asbestos adjustment.

Our cement-specific post-assessment allowed us to distinguish between cement and lime; in the 50s and early 60s of the last

century, direct processing of slaked lime in place of Portland cement was very common. In discussion of cement exposure, it therefore has to be considered that lime dust exposure of former times is often lumped together with cement. Especially during slaking of lime, it has to be assumed that strong formation of lime dust takes place. But none of the participants categorized as cement exposed had exclusive contact with lime. Predominant exposure to both materials (lime and cement) was indicated (60% of cases, 42.5% of controls). In the literature, exposure to lime was associated with oesophageal carcinoma.³⁴ In the case of many oropharyngeal and oral cavity cancers in Asia, Africa and Papua New Guinea, it is the alkaline slaked lime in the betel quid that is probably responsible; regarding gastric cancers, it is the reflux of the alkaline duodenal contents into the stomach after alimentation of betel quid.^{35,36} But cancer of the head and neck region associated with lime or slaked lime in builders dust has not been described so far.

One of the most meaningful dues of builder's dust is cement (combined with slaked lime in former years), which might be responsible for elevated carcinoma risk of the larynx, and brings up the question of what the cancer boosting agent in cement (lime) dust could be. Cement (in particular Portland cement, which is mostly used in Europe) is a composition of calcium oxide (62–66%), silicium oxide (19–22%), aluminum trioxide (4–8%) iron oxide (2–5%), magnesium oxide (1–2%) sulphur oxide and alkali oxides that are responsible for the properties of the adhesive agent. Also, small doses of microelements like chromium are found. Above all, chromium-VI-compounds were categorized as human carcinogen by the IARC in 1980.³⁷ Concentration of chromium ranges between 20–100 ppm, partly up to 200 ppm, which allows the expression microelement. The main origin of chromium in cement is clay and lime. Chromium is changed to chromium (VI) after combustion of basic materials. Soluble chromium (VI) is well known as a trigger for allergic cement dermatitis, which is also promoted by the alkali and irritating milieu of water diluted processed cement. Chromium (VI) penetrates the skin more easily than other chromium compounds, like chromium (III). This affected the development of chromium reduced grades of cement in the last decades, due to iron-(II)-sulphate for instance.³⁸ Beside chromium, other microelements like nickel, zinc, lead, titanium, cadmium and arsenic are present in cement dust. These elements do not affect the consistency of cement but their concentration varies because fluctuations in the raw material are described (e.g., arch ledge in stone deposit) and there is increasing combustion of rubber wheel or oil residues in cement fabrication.³⁹ Whether the small dose of chromium (VI) or other elements like arsenic in cement dust are really able to cause cancer of the laryngeal mucous membranes is not yet clear.

Another explanation for the relationship of laryngeal cancer and cement dust exposure could be the strong cement associated alkali reaction. The particles in cement dust ranges between 0.01–200 μm, predominantly between 1 and 50 μm (the fraction of particles smaller than 8 μm is estimated to be 30–50%). Accordingly, sedimentation of inhaled cement dust takes place in the upper and lower aerodigestive tract, particularly in the larynx. After getting wet, it is likely that cement dust causes a strong basic reaction that leads to increased pH-values (12.5–13.0) on the touched mucous membranes of the larynx. This could be a feasible explanation of the advanced susceptibility to several carcinogens like tobacco, PAHs, etc.

In conclusion, our data on exposure to cement dust—merging slaked lime before about 1965 and Portland cement afterwards—shows a tobacco, alcohol and socioeconomic independent, statistically significant elevated risk for laryngeal carcinoma. This risk is also autonomous regarding asbestos and other described risk factors. The Rhein-Neckar-Larynx Study affirmed observations of former studies and singles out cement dust exposure as a more serious candidate for further toxicologic investigations focusing on the development of laryngeal cancer.

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