

# Risk of stomach cancer associated with 12 workplace hazards: analysis of death certificates from 24 states of the United States with the aid of job exposure matrices

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## Abstract

**Objective**—To investigate the risk of gastric cancer associated with 12 workplace exposures suspected or discussed as aetiological agents in previous reports.

**Methods**—A case-control study was conducted based on the death certificates of several million deaths in 24 states of the United States in 1984–96. Overall, the data base included 41 957 deaths from stomach cancer among subjects aged  $\geq 25$  years. These were 20 878 white men, 14 125 white women, 4215 African American men, and 2739 African American women. Two controls for each case were selected from among subjects who died from non-malignant diseases, frequency matched to cases by geographic region, race, sex and 5 year age group. Each three digit occupation and industry code listed in the 1980 United States census was classified for probability and intensity of exposure to asbestos, inorganic dust, metals, lead, polycyclic aromatic hydrocarbons (PAHs), nitrogen oxides, nitrosamines, sulphuric acid, fertilisers, herbicides, other pesticides (including insecticides and fungicides), and wood dust. These job exposure matrices were subsequently applied to the occupation-industry combinations in the death certificates of study subjects, separately by sex and race.

**Results**—Risk of stomach cancer showed a modest association with occupational exposure to inorganic dust (odds ratio (OR)=1.06; 95% confidence interval (95% CI) 1.03 to 1.11) with significant increasing trends by probability and intensity of exposure overall and by cross classification of the two exposure metrics. Workplace exposure to nitrosamines also showed a modest association (OR=1.06; 95% CI 1.01 to 1.11), but the excess risk was even smaller after adjusting for inorganic dust exposure. Risk of gastric cancer was not associated with any of the other workplace exposures considered in this study.

**Conclusions**—Non-differential misclassification of exposure may have caused negative findings in this study, and inorganic dust may be a partial surrogate for exposure to other unknown risk factors. Alternatively, our results suggest that occupational factors contribute little to the aetiology of gastric cancer. Inorganic

**dust might act through non-specific mechanisms, similar to those proposed for salt, aspirin, and heat by other authors.**

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Keywords: stomach; neoplasms; occupational exposure

In a review of occupational risk factors for stomach cancer we suggested that various occupational exposures may cause or contribute to gastric carcinogenesis.<sup>1</sup> Ionising radiation and N-nitroso compounds, either directly or through the formation of free radicals or nucleophilic intermediates, may damage the DNA of the cells of the gastric mucosa, acting as initiators of the carcinogenic process. Other physical agents, such as asbestos and other inorganic dusts, could be irritants to the gastric mucosa and act as cocarcinogens in a way similar to the mechanism proposed for salt, aspirin, and heat.<sup>2,3</sup> These agents cause a superficial gastritis and may increase cell proliferation, thus promoting initiated clones. Dust could also act as a carrier delivering carcinogens to the gastric mucosa. The effectiveness of this mechanism has been experimentally proved in lung carcinogenesis.<sup>4</sup>

A major cause of concern is that most studies of gastric cancer and occupation rely on poor environmental data. Often, only occupational titles are available to imply exposure to suspected gastric carcinogens. Even surrogates for exposure—such as duration of employment—are seldom used to calculate dose-response trends. Besides, small study size has been a limiting factor in interpreting findings. In the absence of industrial hygiene measurements, use of job exposure matrices, which has provided a useful tool in other studies,<sup>5</sup> might be profitable. To test the hypothesis of a role of occupational risk factors in the aetiology of gastric cancer, we established job exposure matrices for 12 suspected gastric carcinogens in the workplace and applied them to the occupation-industry combinations in a large data base including death certificates from 24 states from the United States in 1984–96. Poor detail of the occupational information is still a concern in this study, but both the large size of the study population and the use of already designed job exposure matrices are new contributions.

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### Methods

Since 1984, the National Cancer Institute, the National Institute for Occupational Safety and Health, and the National Center for Health Statistics have supported the coding of occupation and industry titles on death certificates from 24 states from the United States according to the 1980 United States census occupation and industry codes.<sup>6</sup> Details on the data base of death certificates from 24 states of the United States have been reported elsewhere.<sup>7</sup> We extracted data of 41 957 subjects who died from stomach cancer at age  $\geq 25$  from several million death certificates in 1984–96. These were 20 878 white men, 14 125 white women, 4215 African American men, and 2739 African American women. We used a case-control design to evaluate the association of risk of stomach cancer with 12 workplace exposures, separately by sex and race. Two controls for each case were selected from among subjects who died from non-malignant diseases, frequency matched to cases by geographic region, race, sex, and 5 year age group.

One occupation and industry is reported on the death certificate. Information on duration

or other characteristics of employment is not available. By applying job exposure matrices to the occupation–industry combinations in the death certificates of study subjects, we evaluated occupational exposure to 12 workplace hazards, that we previously discussed in a review on occupational risk factors for stomach cancer<sup>1</sup>—namely asbestos, inorganic dust, metals, lead, polycyclic aromatic hydrocarbons (PAHs), nitrogen oxides, nitrosamines, sulphuric acid, fertilisers, herbicides, other pesticides (including insecticides and fungicides), and wood dust. An estimate of intensity (none=0, low=1, medium=2, high=3) and probability (none=0, low=1, medium=2, high=3) of exposure to each of the 12 occupational hazards was developed by two authors (MD and PC) for each three digit 1980 United States census occupation and industry code. Intensity of exposure was estimated based upon industrial hygiene and occupational health textbooks,<sup>8,9</sup> computerised exposure data bases (OSHA files, NIOSH inspections data base), unpublished industrial hygiene reports, and personal experience. The probability index was estimated based on the proportion of exposed

Table 1 Risks of stomach cancer by probability of exposure to suspected gastric carcinogens, by sex and race

Exposure	Study group	Unexposed (OR=1) (n)	Probability of exposure (n OR (95% CI))					
			Low	Medium	High			
Asbestos†	WM	16859		4007	0.97 (0.93 to 1.02)	22	1.09 (0.54 to 2.20)	
	AAM	2856		1357	1.08 (0.99 to 1.17)	2	0.78 (0.15 to 4.03)	
	WW	13356		769	1.06 (0.96 to 1.17)	0	—	
	AAW	2538		201	1.19 (0.98 to 1.45)	0	—	
Inorganic dust	WM**	11974	1361	0.98 (0.92 to 1.05)	2666	1.11 (1.05 to 1.17)	4877	1.08 (1.03 to 1.13)
	AAM*	1990	274	1.16 (0.99 to 1.36)	825	1.19 (1.07 to 1.32)	1126	1.08 (0.98 to 1.20)
	WW**	13482	175	1.17 (0.96 to 1.41)	337	1.22 (1.06 to 1.41)	131	1.37 (1.10 to 1.72)
	AAW	2558	28	1.12 (0.70 to 1.79)	71	0.90 (0.67 to 1.20)	82	1.16 (0.87 to 1.55)
Metals	WM	16572	662	1.05 (0.96 to 1.16)	2142	1.04 (0.98 to 1.10)	1502	1.06 (0.99 to 1.13)
	AAM	3473	120	1.08 (0.86 to 1.35)	448	1.01 (0.90 to 1.14)	174	1.08 (0.89 to 1.31)
	WW	13696	67	0.86 (0.65 to 1.15)	292	1.22 (1.05 to 1.41)	70	0.99 (0.74 to 1.32)
	AAW	2678	9	1.41 (0.60 to 3.32)	46	1.14 (0.79 to 1.65)	6	0.95 (0.35 to 2.54)
Lead	WM	17276	1572	1.0 (0.94 to 1.07)	527	1.01 (0.91 to 1.13)	1503	0.92 (0.86 to 0.99)
	AAM	3365	312	1.04 (0.90 to 1.20)	85	0.93 (0.72 to 1.21)	453	1.15 (1.01 to 1.32)
	WW	13753	224	1.01 (0.86 to 1.19)	83	0.90 (0.69 to 1.16)	65	1.53 (1.10 to 2.12)
	AAW	2677	43	1.50 (1.01 to 2.24)	9	1.37 (0.58 to 3.21)	10	1.76 (0.74 to 4.16)
Polycyclic aromatic hydrocarbons	WM	14232	1356	1.04 (0.97 to 1.12)	1896	1.06 (1.0 to 1.13)	3394	0.99 (0.95 to 1.05)
	AAM	2815	256	1.02 (0.87 to 1.20)	325	1.02 (0.88 to 1.17)	819	1.01 (0.91 to 1.11)
	WW**	13736	201	1.16 (0.97 to 1.38)	90	1.13 (0.87 to 1.46)	98	1.57 (1.20 to 2.06)
	AAW	2614	33	0.96 (0.63 to 1.46)	13	1.48 (0.72 to 3.02)	79	1.16 (0.87 to 1.56)
Nitrosamines	WM**	16478	792	1.01 (0.93 to 1.10)	2760	1.08 (1.02 to 1.14)	848	1.05 (0.97 to 1.15)
	AAM	3322	163	0.84 (0.70 to 1.02)	567	0.97 (0.86 to 1.09)	163	1.09 (0.89 to 1.32)
	WW**	13810	176	1.09 (0.91 to 1.32)	123	1.40 (1.11 to 1.78)	16	1.42 (0.74 to 2.70)
	AAW	2608	40	1.23 (0.82 to 1.83)	88	1.27 (0.96 to 1.69)	3	1.47 (0.33 to 6.59)
Nitrogen oxides	WM	14794	788	1.04 (0.95 to 1.14)	669	0.98 (0.89 to 1.08)	4627	1.0 (0.96 to 1.05)
	AAM	2835	216	0.99 (0.84 to 1.18)	219	0.98 (0.83 to 1.16)	945	1.03 (0.93 to 1.13)
	WW**	13815	147	1.20 (0.97 to 1.48)	38	1.35 (0.89 to 2.04)	125	1.41 (1.12 to 1.78)
	AAW	2612	37	1.49 (0.97 to 2.29)	8	1.48 (0.59 to 3.70)	82	1.17 (0.88 to 1.56)
Sulphuric acid	WM	15228	4531	1.0 (0.96 to 1.04)	675	1.12 (1.01 to 1.23)	444	0.96 (0.85 to 1.08)
	AAM	2678	1212	1.02 (0.94 to 1.12)	223	1.12 (0.94 to 1.33)	102	1.16 (0.90 to 1.50)
	WW	13128	675	0.91 (0.83 to 1.0)	310	1.02 (0.87 to 1.20)	12	0.87 (0.44 to 1.72)
	AAW	2103	219	1.06 (0.88 to 1.28)	416	0.96 (0.79 to 1.17)	1	2.07 (0.13 to 33.3)
Herbicides	WM	19190	146	1.12 (0.91 to 1.37)	19	0.91 (0.53 to 1.55)	1523	1.06 (0.98 to 1.15)
	AAM	3817	62	1.13 (0.82 to 1.55)	10	0.68 (0.33 to 1.40)	326	0.91 (0.78 to 1.06)
	WW	14062	5	2.05 (0.59 to 7.08)	4	2.10 (0.52 to 8.41)	54	1.71 (1.18 to 2.46)
	AAW	2688	1	0.64 (0.07 to 6.20)	0	—	50	1.25 (0.86 to 1.80)
Other pesticides	WM	18099	1104	0.99 (0.91 to 1.07)	121	1.05 (0.84 to 1.31)	1554	1.04 (0.96 to 1.12)
	AAM	3318	508	1.17 (1.03 to 1.32)	58	0.95 (0.69 to 1.30)	331	0.94 (0.80 to 1.09)
	WW	13930	110	1.41 (1.10 to 1.81)	23	0.87 (0.53 to 1.42)	62	1.78 (1.26 to 2.51)
	AAW	2634	43	0.78 (0.54 to 1.12)	12	0.71 (0.37 to 1.37)	50	1.22 (0.85 to 1.77)
Fertilisers	WM	19058	151	0.90 (0.74 to 1.09)	148	1.30 (1.06 to 1.60)	1521	1.06 (0.98 to 1.15)
	AAM	3760	37	0.76 (0.52 to 1.12)	100	0.95 (0.74 to 1.22)	318	0.89 (0.76 to 1.03)
	WW	14012	48	1.0 (0.70 to 1.41)	7	0.86 (0.36 to 2.08)	58	1.77 (1.23 to 2.53)
	AAW	2648	16	1.28 (0.68 to 2.42)	25	0.97 (0.59 to 1.57)	50	1.27 (0.88 to 1.84)
Wood dust	WM	19107	903	0.96 (0.89 to 1.05)	195	0.91 (0.77 to 1.08)	673	1.0 (0.90 to 1.10)
	AAM	3523	482	1.17 (1.03 to 1.33)	80	0.96 (0.73 to 1.26)	130	0.93 (0.75 to 1.16)
	WW	14022	75	0.91 (0.69 to 1.20)	22	0.71 (0.44 to 1.16)	6	0.84 (0.32 to 2.18)
	AAW	2715	18	0.86 (0.49 to 1.50)	6	1.33 (0.47 to 3.76)	0	—

\*p<0.05; \*\*p<0.01 test for trend.

†The reference group for subjects exposed to asbestos includes those with a low probability of exposure, due to the difficulty in estimating a baseline exposure. WM=white men; AAM=African American men; WW=white women; AAW=African American women).

workers within a given job title or industry, and the number of occupations or industries coded likewise. To obtain one intensity and one probability score for a given exposure in each study subject, intensity and probability scores associated with the occupation and the industry were considered in two ways: (a) if information on exposure resulted from the occupation regardless of industry—for example, plumber, or welder—we calculated the subject's intensity and probability scores as the square of the occupational score; (b) if industry was the main contributor to exposure assessment—for example, truck driver in the rubber industry, or labourer in the construction industry—then the subject's probability and intensity scores resulted from multiplying the respective score attributed to the occupation code times that attributed to the industry code. The rationale for squaring or multiplying scores in semiquantitative retrospective exposure assessment has been described elsewhere.<sup>10</sup> In the present study, the main scope of this strategy was to have individual scores in the same order of magnitude, whether deriving from occupation

only or from occupation and industry. The final scores of probability and intensity of exposure were further categorised within four levels (none=0, low=1–2, medium=3–4, high=6–9).

Odds ratios (ORs) were estimated by logistic regression, and 95% confidence intervals (95% CIs) with the GEMBO program in the Epicure software. Covariates included in the logistic regression model were age, ethnic origin (American, Hispanic, European, other, unknown), marital status (never married versus ever married), metropolitan versus non-metropolitan residence, and five categories of socioeconomic status based on Green's standardised score for specific occupations.<sup>11</sup> Statistical significance of trends in risk by increasing exposure intensity and probability was tested by assuming covariates as non-categorical, and subtracting from the result of the goodness of fit statistic, obtained when the exposure variable was not included in the logistic regression model, the result of the same statistic with the exposure variable. Under the null hypothesis, this test has a  $\chi^2$

Table 2 Risks of stomach cancer by intensity of exposure to suspected gastric carcinogens groups

Exposure	Study group	Unexposed (OR=1) (n)	Intensity of exposure (n OR (95% CI))					
			Low	Medium	High			
Asbestos†	WM	17783		2764	1.0 (0.95 to 1.04)	431	1.01 (0.90 to 1.14)	
	AAM	3271		848	1.10 (1.0 to 1.20)	96	0.97 (0.76 to 1.24)	
	WW	13912		213	1.07 (0.90 to 1.26)	0	—	
	AAW	2686		51	1.23 (0.86 to 1.75)	2	3.90 (0.35 to 43.1)	
Inorganic dust	WM**	11974	4635	1.05 (1.0 to 1.10)	3002	1.07 (1.01 to 1.12)	1267	1.13 (1.05 to 1.21)
	AAM	1990	1100	1.13 (1.02 to 1.24)	842	1.22 (1.10 to 1.36)	283	0.95 (0.82 to 1.11)
	WW	13482	280	1.37 (1.17 to 1.60)	296	1.23 (1.06 to 1.42)	67	0.88 (0.65 to 1.17)
	AAW	2558	125	0.98 (0.78 to 1.24)	36	1.04 (0.69 to 1.57)	20	1.47 (0.82 to 2.64)
Metals	WM**	16572	1256	1.02 (0.95 to 1.09)	1509	1.04 (0.97 to 1.11)	1541	1.09 (1.02 to 1.16)
	AAM	3473	158	0.96 (0.79 to 1.17)	298	1.13 (0.97 to 1.31)	286	0.99 (0.86 to 1.15)
	WW*	13696	50	0.94 (0.67 to 1.32)	242	1.14 (0.97 to 1.34)	137	1.10 (0.89 to 1.37)
	AAW	2678	7	1.40 (0.53 to 3.68)	25	0.92 (0.57 to 1.49)	29	1.39 (0.86 to 2.25)
Lead	WM	17276	2168	0.96 (0.90 to 1.02)	1144	0.96 (0.89 to 1.04)	290	1.10 (0.95 to 1.27)
	AAM	3365	556	1.10 (0.98 to 1.25)	242	1.11 (0.95 to 1.31)	52	0.81 (0.59 to 1.13)
	WW	13753	170	1.09 (0.90 to 1.31)	165	1.0 (0.83 to 1.21)	37	1.02 (0.68 to 1.51)
	AAW	2677	24	1.82 (1.04 to 3.18)	35	1.39 (0.90 to 2.15)	3	1.25 (0.30 to 5.23)
Polycyclic aromatic hydrocarbons	WM	14232	4047	1.0 (0.95 to 1.04)	1983	1.08 (1.02 to 1.15)	616	1.0 (0.90 to 1.10)
	AAM	2815	855	1.0 (0.91 to 1.10)	320	1.06 (0.92 to 1.23)	225	1.0 (0.84 to 1.18)
	WW	13736	159	1.29 (1.06 to 1.59)	158	1.39 (1.13 to 1.70)	72	0.89 (0.67 to 1.18)
	AAW	2614	85	1.11 (0.84 to 1.46)	21	1.06 (0.63 to 1.81)	19	1.32 (0.73 to 2.37)
Nitrosamines	WM*	16478	433	0.99 (0.88 to 1.12)	3474	1.06 (1.01 to 1.11)	493	1.16 (1.03 to 1.30)
	AAM	3322	48	1.26 (0.87 to 1.82)	666	0.95 (0.85 to 1.05)	179	0.96 (0.79 to 1.15)
	WW	13810	17	1.29 (0.70 to 2.38)	230	1.19 (1.0 to 1.41)	68	1.27 (0.93 to 1.72)
	AAW	2608	0	—	121	1.30 (1.02 to 1.65)	10	1.48 (0.66 to 3.34)
Nitrogen oxides	WM	14794	3636	0.99 (0.94 to 1.04)	1334	1.01 (0.94 to 1.08)	1114	1.05 (0.97 to 1.14)
	AAM	2835	804	1.0 (0.90 to 1.10)	309	1.03 (0.89 to 1.19)	267	1.03 (0.88 to 1.20)
	WW	13815	116	1.50 (1.17 to 1.91)	98	1.28 (1.0 to 1.66)	96	1.12 (0.87 to 1.45)
	AAW*	2612	81	1.18 (0.88 to 1.57)	20	1.38 (0.78 to 2.44)	26	1.54 (0.92 to 2.59)
Sulphuric acid	WM**	15228	4113	0.99 (0.95 to 1.03)	1274	1.03 (0.96 to 1.11)	263	1.23 (1.05 to 1.44)
	AAM	2678	1232	1.04 (0.96 to 1.14)	228	1.05 (0.89 to 1.24)	77	1.11 (0.83 to 1.47)
	WW	13128	565	0.88 (0.79 to 0.98)	419	1.04 (0.91 to 1.19)	13	0.78 (0.41 to 1.49)
	AAW	2103	212	1.09 (0.90 to 1.32)	420	0.96 (0.79 to 1.16)	4	0.55 (0.18 to 1.68)
Herbicides	WM	19190	22	1.11 (0.65 to 1.88)	92	1.17 (0.90 to 1.51)	1574	1.05 (0.97 to 1.14)
	AAM	3817	4	1.07 (0.32 to 3.59)	17	0.88 (0.50 to 1.57)	377	0.93 (0.81 to 1.08)
	WW	14062	2	4.09 (0.37 to 45.6)	8	3.26 (1.07 to 9.99)	53	1.60 (1.11 to 2.31)
	AAW	2688	0	—	1	0.61 (0.06 to 5.85)	50	1.24 (0.86 to 1.78)
Other pesticides	WM	18099	652	1.14 (1.02 to 1.27)	537	0.85 (0.77 to 0.95)	1590	1.08 (1.0 to 1.18)
	AAM	3318	356	1.16 (1.0 to 1.34)	160	1.14 (0.93 to 1.40)	381	0.95 (0.82 to 1.10)
	WW	13930	102	1.40 (1.08 to 1.81)	33	1.22 (0.79 to 1.88)	60	1.51 (1.08 to 2.13)
	AAW	2634	38	0.70 (0.48 to 1.02)	8	0.95 (0.41 to 2.20)	59	1.17 (0.83 to 1.64)
Fertilisers	WM	19058	106	1.17 (0.92 to 1.48)	1529	1.04 (0.96 to 1.13)	185	1.13 (0.94 to 1.36)
	AAM	3760	20	0.81 (0.48 to 1.36)	295	0.85 (0.72 to 0.99)	140	1.0 (0.81 to 1.24)
	WW	14012	12	1.56 (0.73 to 3.34)	92	1.18 (0.90 to 1.54)	9	2.36 (0.91 to 6.15)
	AAW	2648	1	0.60 (0.06 to 5.78)	63	1.23 (0.89 to 1.71)	27	1.09 (0.67 to 1.76)
Wood dust	WM	19107	771	0.98 (0.89 to 1.07)	837	0.98 (0.90 to 1.07)	163	0.88 (0.73 to 1.06)
	AAM	3523	406	1.16 (1.02 to 1.33)	206	1.10 (0.93 to 1.32)	80	0.80 (0.61 to 1.04)
	WW	14022	23	0.83 (0.51 to 1.35)	72	0.89 (0.67 to 1.18)	8	0.69 (0.31 to 1.55)
	AAW	2715	4	0.75 (0.24 to 2.36)	19	0.94 (0.54 to 1.63)	1	0.40 (0.05 to 3.42)

\*p<0.05; \*\*p<0.01 test for trend.

†The reference group for subjects exposed to asbestos includes those with a low intensity of exposure, due to the difficulty in estimating a baseline exposure.

The number of unexposed subjects differs between the two exposure metrics, as subjects may be attributed to different probabilities of intensity of exposure.

WM=white men; AAM=African American men; WW=white women; AAW=African American women.

Table 3 Risks of stomach cancer by probability and intensity of exposure to asbestos, inorganic dust, metal dust, lead, nitrosamines, nitrogen oxides, PAHs, sulphuric acid, and fertilisers (white men)

Intensity of exposure	Probability of exposure (n OR (95% CI))								Test for trend
	All exposed	Low		Medium		High			
<b>Inorganic dust:</b>									
All levels	8904	1.07 (1.03 to 1.11)	1361	0.98 (0.92 to 1.05)	2666	1.11 (1.05 to 1.17)	4877	1.08 (1.03 to 1.13)	p<0.01
None	11974	1.0	11974	1.0	11974	1.0	11974	1.0	
Low	4635	1.05 (1.0 to 1.10)	971	0.97 (0.90 to 1.06)	1124	1.09 (1.0 to 1.18)	2540	1.08 (1.01 to 1.16)	p<0.01
Medium	3002	1.07 (1.01 to 1.12)	302	1.04 (0.91 to 1.20)	1125	1.13 (1.04 to 1.22)	1575	1.03 (1.0 to 1.10)	NS
High	1267	1.13 (1.05 to 1.21)	88	0.94 (0.73 to 1.22)	417	1.10 (0.97 to 1.25)	762	1.18 (1.08 to 1.30)	p<0.01
p Value test for trend	<0.01		NS		<0.01		<0.01		
<b>Metals:</b>									
All levels	4306	1.05 (1.0 to 1.09)	662	1.05 (0.96 to 1.16)	2142	1.04 (0.98 to 1.10)	1502	1.06 (0.99 to 1.13)	p=NS
None	16572	1.0	16572	1.0	16572	1.0	16572	1.0	
Low	1256	1.02 (0.95 to 1.09)	359	1.06 (0.93 to 1.21)	683	1.0 (0.91 to 1.10)	214	1.01 (0.86 to 1.20)	p=NS
Medium	1509	1.04 (0.97 to 1.11)	268	1.06 (0.91 to 1.23)	857	1.02 (0.94 to 1.11)	384	1.06 (0.94 to 1.21)	p=NS
High	1541	1.09 (1.02 to 1.16)	35	1.01 (0.67 to 1.51)	602	1.12 (1.01 to 1.24)	904	1.07 (0.99 to 1.17)	p<0.05
Test for trend	0.01		NS		0.05		NS		
<b>Nitrosamines:</b>									
All exposed	4400	1.06 (1.01 to 1.11)	792	1.01 (0.93 to 1.10)	2760	1.08 (1.02 to 1.14)	848	1.05 (0.97 to 1.15)	p<0.05
None	16478	1.0	16478	1.0	16478	1.0	16478	1.0	
Low	433	0.99 (0.88 to 1.12)	201	0.94 (0.79 to 1.11)	169	1.05 (0.87 to 1.27)	63	1.06 (0.78 to 1.45)	p=NS
Medium	3474	1.06 (1.01 to 1.11)	487	1.01 (0.90 to 1.13)	2313	1.07 (1.01 to 1.14)	674	1.04 (0.94 to 1.14)	p<0.05
High	493	1.16 (1.03 to 1.30)	104	1.21 (0.95 to 1.54)	278	1.16 (1.0 to 1.35)	111	1.12 (0.89 to 1.41)	p=NS
p Value test for trend	<0.01		NS		<0.01		NS		
<b>Sulphuric acid:</b>									
All levels	5650	1.01 (0.97 to 1.05)	4531	1.0 (0.96 to 1.04)	675	1.12 (1.01 to 1.23)	444	0.96 (0.85 to 1.08)	p=NS
None	15228	1.0	15228	1.0	15228	1.0	15228	1.0	
Low	4113	0.99 (0.95 to 1.03)	3624	0.99 (0.95 to 1.04)	144	1.13 (0.92 to 1.39)	345	0.91 (0.80 to 1.04)	p=NS
Medium	1274	1.03 (0.96 to 1.11)	845	1.04 (0.95 to 1.13)	408	1.05 (0.93 to 1.19)	21	0.79 (0.48 to 1.30)	p=NS
High	263	1.23 (1.05 to 1.44)	62	0.93 (0.68 to 1.26)	123	1.42 (1.12 to 1.79)	78	1.29 (0.97 to 1.72)	p<0.01
p Value test for trend	0.01		NS		<0.05		NS		

n=Number of exposed cases.

distribution with a single degree of freedom, and it probes specifically linear trends in log relative risk with increasing exposure.<sup>12</sup> p Values were two tailed.

## Results

Mean age at death from stomach cancer was lower among men than among women and among African Americans than white people (African American men: 67.3 (SD 13.0); African American women: 71.4 (SD 14.6); white men: 69.4 (SD 12.3); white women: 74.2 (SD 12.8)). Compared with controls, cases were more often married in all four study groups, and they defined their ethnic origin (mainly European, or Hispanic) twice as often as controls among white men and white women. Other variables—such as metropolitan residence and socioeconomic status—did not show a consistent frequency distribution by case-control across the four study groups (not shown in the tables).

Risks by probability of exposure to 12 occupational risk factors combining all levels of exposure are shown in table 1. None of the investigated exposures showed an unequivocal trend in all study groups. Only inorganic dust

Table 4 ORs (95% CI) for stomach cancer associated with any exposure to inorganic dust, metals, nitrosamines, and sulphuric acid adjusted for all the other exposures and by marital and socioeconomic status, and metropolitan residence

Exposure	OR	95% CI
Inorganic dust	1.05	1.0 to 1.10
Metals	1.01	0.96 to 1.07
Nitrosamines	1.04	0.99 to 1.09
Sulphuric acid	0.99	0.95 to 1.03

and nitrosamines were associated with ORs >1.0 for the high probability of exposure category in all four study groups. Two of the four risks associated with high probability of exposure to inorganic dust were significant and another was of borderline significance. Although absolute increases in risk were small, trends for probability of exposure to inorganic dust were significant among white men, white women, and African American men, and for exposure to nitrosamine among white men and white women.

Table 2 shows risks by intensity of exposure to the same 12 occupational risk factors. High intensity exposure to the risk factors was rare among women. However, a significant positive trend in at least one study group was found for inorganic dust, metals, nitrosamines, nitrogen oxides, and sulphuric acid. Again, although absolute risk increases were small, the significant trends by intensity of exposure to inorganic dust and nitrosamines among white men replicated similar findings that used probability of exposure.

Patterns of increasing risk of stomach cancer by probability within intensity category and vice versa were explored for inorganic dust, metals, nitrosamines, and sulphuric acid (table 3). Although excess risks were quite small, trends by probability of exposure to inorganic dust were significant in low and high categories of intensity, and trends by intensity of exposure were significant for subjects classified in the medium and high probability of exposure. Results were less consistent for metals, nitrosamines, and sulphuric acid. No such pattern was found for exposure to the other workplace

Table 5 Risks of stomach cancer by probability and intensity of exposure to inorganic dust among subjects unexposed to metals and nitrosamines (white men)

Intensity of exposure	Probability of exposure (n OR (95% CI))						p Value test for trend
	Low		Medium		High		
Inorganic dust:							
Unexposed	10955	1.0	10955	1.0	10955	1.0	
Low	701	0.93 (0.84 to 1.02)	705	1.23 (1.10 to 1.38)	180	0.96 (0.80 to 1.15)	NS
Medium	59	0.94 (0.69 to 1.28)	293	1.13 (0.97 to 1.30)	680	1.01 (0.91 to 1.12)	NS
High	13	1.14 (0.58 to 2.24)	59	1.10 (0.80 to 1.51)	359	1.20 (1.04 to 1.38)	<0.01
p Value test for trend	NS		NS		<0.05		

hazards considered in this study. To see whether reciprocal confounding was responsible for some of the observed associations, we combined all categories of exposure and fitted a model with the basic variables plus exposure to inorganic dust, metals, nitrosamines, and sulphuric acid to reciprocally adjust the respective risk estimates. As reported in table 4, this analysis resulted in a very modest increase in risk of stomach cancer for exposure to inorganic dust and to nitrosamines, but no excess risk was associated with ever exposure to metals and sulphuric acid.

Cross tabulation of probability and intensity of exposure to inorganic dust among workers unexposed to metals and to nitrosamines showed significantly positive trends by probability in the high intensity category and by intensity in the high probability category (table 5). The analysis of such a risk pattern among subjects with isolated exposure to metals or to nitrosamines did not provide interpretable results due to small numbers and empty cells.

Among white men, the most numerous occupation contributing to the excess risk associated with high probability and high intensity of exposure to inorganic dust was mining machine operators represented by 1.34% cases and 1.25% controls. Other less numerous contributing occupations were: plasterers (0.05% cases and 0.04% controls), concrete and terrazzo finishers (0.12% cases and 0.07% controls), mining occupations not elsewhere classified (0.10% cases and 0.09% controls), excavating and loading machine operators (0.04% cases and 0.03% controls), and crushing and grinding machine operators (two cases and no controls). In the same study group, the most represented industry contributing to the excess risk of stomach cancer in the high probability and high intensity of exposure to inorganic dust was mining and quarrying (1.49% cases and 1.35% controls). Coal mining, metal mining, and non-metallic mining and quarrying contributed equally to the modest excess risk. Other contributing industries were: construction (0.21% cases and 0.13% controls), and structural clay products (three cases and three controls).

### Discussion

In this large case-control study based on death certificates from 24 states from the United States we found a modest association of risk of stomach cancer with occupational exposure to inorganic dust. Although the increase in risk was tiny, increasing trends were calculated by

probability and intensity of exposure overall and by cross classification of the two exposure metrics. Other suspected risk factors for gastric cancer did not show the same association or showed a even weaker association after adjustment for exposure to inorganic dust. Our data do not provide information about whether ingestion of generic inorganic dust or specific dust components play a part in gastric carcinogenesis. Therefore, one possible explanation for our findings is that exposure to inorganic dust may have behaved as a partial surrogate for exposure to other unknown risk factors. Alternatively, dusty workplace environments could play a non-specific role in gastric carcinogenesis. If the association were confirmed with exposure to generic inorganic dust, a plausible explanation would be that physical properties of dust might be important, by causing local irritation or absorbing gastric carcinogens on its surface and delivering them to the target cells in the gastric mucosa. Such a mechanism was experimentally proved long ago in lung carcinogenesis.<sup>4</sup>

Previous case-control studies have reported an association between occupational exposure to dust and stomach cancer,<sup>5 13-15</sup> not explained by ethnicity<sup>13</sup> or diet.<sup>5</sup> Results were less consistent for a role of specific dusts. A case-control study based on the Los Angeles County cancer registry found the greatest increase in risk of cancer of the antrum or pylorus for exposure to mineral dust.<sup>14</sup> The association was also found in an Italian multi-centre case-control study of 640 histologically confirmed male cases of stomach cancer,<sup>5</sup> although no attempt was made to investigate subsites in more detail. In a large multicancer site, multifactor case-control study in Montreal, Canada, silica was the only inorganic dust,<sup>15</sup> and wood the only organic dust<sup>13</sup> to show a positive association with stomach cancer. Disentangling exposure to silica from other inorganic dust would require additional information on workplaces and possibly industrial hygiene measurements, which was not the case in the present study. On the other hand, we did not find an association with wood dust, the only organic dust we tested, and trends associated with exposure to metals (which included dust and fumes) were less consistent than with the more generic category of inorganic dust (including also metal dust). Exposure to lead was not associated with a risk of stomach cancer, and adjustment for exposure to inorganic dust weakened the positive association found with nitrosamines. Cross

tabulation of probability and intensity of isolated exposure to nitrosamines did not provide further clues, because of small numbers and empty cells. Endogenous synthesis of nitrosamines from dietary precursors was suggested as the crucial event in gastric carcinogenesis.<sup>2</sup> Exposure to nitrosamine precursors or to preformed nitrosamines in the work environment was also suggested as a possible explanation for the repeatedly found increase in risk of gastric cancer in industries where such exposures may occur.<sup>1</sup> Further study including monitoring of exposure to nitrosamines in the work environment and in biological fluids of exposed workers are warranted.

Occupational exposures in agriculture, such as to herbicides, other pesticides, and fertilisers, were not associated with a risk of gastric cancer in this study. A review of cancer among farmers suggested a possible increase in risk of stomach cancer.<sup>16</sup> The epidemiological evidence for this seems to be conflicting,<sup>1</sup> and confounding by rural residence was suggested as a possible explanation.<sup>5</sup>

Limitations in this study are mainly related to the poor occupational information that may be extracted from death certificates and the insufficient specificity of the coding system. Use of the most prevalent occupation and industry in the working history of each person as reported in the death certificate may result in important loss of information on exposures experienced in other jobs, mainly among short term workers who usually experience the highest workplace exposures.<sup>17</sup> Besides, the three digit census code of occupations and industries may incorporate very heterogeneous workplace conditions within the same code, which prevents a reliable classification of exposure. Although this characteristic was considered in classifying occupations and industries by probability of exposure, a substantial amount of non-differential misclassification could have affected our results, which could have lowered the association between stomach cancer and occupational exposure to inorganic dust.<sup>18</sup>

Among possible confounders, ethnic origin, marital status, and socioeconomic status were included in the logistic regression model. As rural residence is another important confounder in occupational studies of stomach cancer,<sup>5</sup> but an urban or rural characterisation of residence was not available from the death certificates, we used metropolitan versus non-metropolitan residence as a surrogate. Region of residence was controlled for by matching cases and controls. The analysis was conducted separately by race and sex groups. As controlling for diet was not possible, residual confounding may have biased our findings in cases of important differences in dietary habits associated with the occupational exposures considered in this study.

Gastric cancer risk is reportedly correlated with low educational level and low socioeconomic status.<sup>1 19 20</sup> Therefore, risks associated with exposures typical of occupations classified in the lower socioeconomic groups, such as inorganic dust, might have been affected as

well. Low socioeconomic status was not associated with stomach cancer risk in our study, which was conducted using a death certificate data-base. This source of information is not suitable to evaluate the association between low socioeconomic status and mortality from specific diseases, as bias can result from a more accurate definition of the cause of death and a lower mortality from all causes among the wealthier socioeconomic groups. As a consequence, in our study, when socioeconomic status was not included as a covariate in the logistic regression model to adjust risk estimates, risks associated with intensity and probability of exposure to inorganic dust were 1.0 or very close to unity, and no positive trend was found (not shown in the tables). On the other hand, risk associated with high probability of exposure to inorganic dust was increased in three out of four socioeconomic groups comprising exposed cases (lowest socioeconomic status: 1.12; second lowest socioeconomic status: 1.11; medium socioeconomic status: 0.89; medium to high socioeconomic status: no cases; highest socioeconomic status: 1.08), although linear increases with probability of exposure were found only in the two lowest socioeconomic groups. Odds ratios for high intensity exposure to inorganic dust were increased in three socioeconomic groups (no cases and no controls were classified in this cell among the medium to high and the highest socioeconomic status category), and linear increases in risk with intensity of exposure were found in the second lowest and medium socioeconomic status (not shown in the tables). Therefore, low socioeconomic status was not an explanation for the modest increase in risk of stomach cancer associated with exposure to inorganic dust found in our study.

In conclusion, our results confirm previous reports of an association between occupational exposure to inorganic dust and risk of stomach cancer. Further research is warranted to explore mechanisms and dose-response relations possibly with measurements of environmental dust.

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