Exhibit 306

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INCREASED RISK OF UROTHELIAL CANCER IN STOCKHOLM DURING 1985–87 AFTER EXPOSURE TO BENZENE AND EXHAUSTS

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In a population-based case-referent study of urothelial cancer in Stockholm during 1985–87, information was obtained from 80% of 320 identified male cases and 79% of 363 selected male referents. Industrial exposures were assessed for each subject by an industrial hygienist on the basis of questionnaire data. Exposure to benzene (any annual dose) gave a relative risk (with 95% confidence interval) of 2.0 (1.0–3.8). The highest risk was seen for a high annual dose. Subjects exposed to both diesel and petrol exhausts (moderate/high annual dose) had a relative risk of 7.1 (0.9–58.8). However, adjusting for benzene changed the relative risk to 5.1 (0.6–43.6). It might be rewarding to consider whether benzene from petrol confounds the associations previously suggested between exhausts and urothelial cancer. Exposure to polychlorinated biphenyls (PCB) gave a relative risk of 3.3 (0.6–18.4).

Many occupations and industries are suspected to be associated with an increased risk of urothelial cancer. But there is no consensus that industry-related chemicals other than aromatic amines are causally linked with the disease (Matanoski and Elliot, 1981; Morrison and Cole, 1982; Alderson, 1986; Monson, 1987; Schulte *et al.*, 1987; BAUS Subcommittee on Industrial Bladder Cancer, 1988).

In a report on a cohort study, we discussed combustion gases from coal as well as creosote and PCB as possible urothelial carcinogens (Steineck *et al.*, 1989). In an evaluation of the epidemiological literature (Steineck *et al.*, 1990*b*), we found evidence supporting an association between certain combustion gases and urothelial cancer, but it is unclear whether this association is due to contaminants of aromatic amines or other agents. Recently, there was a dispute whether an increased risk of urinary bladder cancer among truck drivers was due to exposure to diesel exhausts (Wynder and Miller, 1988; Silverman *et al.*, 1988). Benzene has been linked for a long time to human acute leukaemia (IARC, 1982*b*).

The purpose of the present study was to investigate the association between the above-mentioned, as well as some other, industry-related chemicals and the risk of urothelial cancer.

STUDY BASE AND METHODS

A population-based case-referent study of urothelial cancer was carried out in Stockholm, Sweden. Details in the design and analysis of the study are given in the companion report (Steineck *et al.*, 1990*a*). In short, the study was based on men born between 1911 and 1945 and living in the County of Stockholm for all or part of the observation period 15 September 1985 to 30 November 1987. We attempted to include all incident cases of urothelial cancer and/or squamous-cell carcinoma in the lower urinary tract. Referents were selected by stratified random sampling 4 times during the observation period from a computerized register covering the population of Stockholm. Information on exposure was collected by means of a postal questionnaire and all subjects were contacted in their homes. An estimate of the relative risk, together with a 95% confidence interval, was calculated using the logistic regression analysis method described by Breslow and Day (1980). If not stated otherwise, adjustment was made for year of birth in 3 categories and for smoking (current smoker/former smoker/never smoked).

Two ways of collecting information on occupational history were used. Firstly, the men were requested to specify occupation and industry for all jobs they had held and particulars of their education and military service. They were also asked whether they had ever been engaged/employed in certain specified occupations/industries and whether they had ever been exposed to certain specified chemicals. When relevant, exposure periods and the number of days of exposure per year were indicated. Many men provided additional unstructured information about their work, but no formal documentation was made of this.

An industrial hygienist (N.P.), unaware of the case-referent status, classified subjects as being exposed or unexposed to 38 agents and groups of substances, including 17 exposure categories with aromatic amines. The selection of agents was not systematic. Because of small numbers, the different aromatic amines (4-aminodiphenyl, aniline, aromatic azo pigments, auramine, benzidine, 2-chloroaniline, 2.4-diaminoanisol, 2.4-diaminotoluene, 4-dimethylamino-azobenzene, 8-hydroxyquinoline, magenta, α-naphthylamine, β-naphthylamine, para-aminophenol, paraphenylenediamine, unspecified aromatic amines and unspecified dyes) were combined into a single group in the analysis, as were phenol-related substances (creosote, chlorinated phenols and phenol).

The industrial hygienist used all the information mentioned above, including the unstructured information. He defined the exposure period and rated the "annual dose" as "low", "moderate" or "high" during the defined period, *i.e.*, he appraised the accumulated dose (exposure duration × intensity of exposure) during the course of one average year for the defined exposure period.

The level of exposure, *i.e.*, the dose per unit time was assessed for asbestos and organic solvents, using an ordinal scale of "low" and "high". Most men were exposed to these agents during the whole year, so we considered "level" more appropriate than "annual dose".

Classification of a subject as "exposed" resulted from an air concentration in the work environment significantly higher than for the general public, or considerable skin contact with liquids of low volatility. Assessment of exposure was based on Swedish (Tidström, 1957) and international data (Kolsch, 1953, 1966; Parmeggiani, 1983), discussions with other Swedish industrial hygienists, and informal contacts with people with experience of industrial processes at the time in question. In the analysis, any exposure after 1981 was ignored, thus allowing for a latency period.

In addition, all men were asked how much time they had

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spent in answering the questionnaire and whether they had used any written documentation, such as a *curriculum vitae,* when pondering their replies.

RESULTS

Information was obtained from 256 cases and 287 referents. Reasons for non-response are shown in Table I. The median year of birth was 1919 for cases and 1921 for referents. As primary localization 5 cases had tumors in the renal pelvis, 5 in the ureter, 243 in the urinary bladder, none in the urethra and 3 at multiple sites.

The mean time spent on answering the questionnaire was 2.6 hr for the cases and 2.8 hr for the referents. Four hours or more were spent by 41/251 (16%) of the cases and 47/280 (17%) of the referents (information lacking from 12 subjects). Written documentation concerning the work-related questions was used by 34/256 (13%) of the cases and 48/287 (18%) of the referents.

Two cases, but no referents, were exposed to a high annual dose of aromatic amines, and they are omitted from all further analyses. The relative risk (with 95% confidence interval) for current smokers was 3.5 (2.2–5.7) and for former smokers 2.0 (1.2–3.3).

Table II shows the estimated relative risk for the substances with regard to which the industrial hygienist classified the men as exposed or not. Among the phenol-related substances, 2 cases but no referents, were exposed to creosote (not shown in table). Most men classified as being exposed to combustion gases from coal were furnace operators, and no association was found with this exposure.

The crude relative risk was 1.9 for benzene and 2.9 for PCB. On adjusting for year of birth in six categories and smoking in seven categories, the relative risk for benzene was 2.0 (1.0–3.9) and for PCB 3.6 (0.6–20.4).

Relative risks with varying ratings of the annual dose were investigated for some exposures judged *a priori* to warrant attention (see opening paragraphs) or suggested in Table II to be of interest (Table III). Many estimates are based on small numbers giving wide confidence intervals. Four cases and 5 referents were exposed to benzene with a moderate annual dose, and 13 cases and 5 referents with a high annual dose. For PCB (not shown in Table III), 3 cases and no referents had been exposed to a moderate/high annual dose. The relative risk depending on the duration and start of exposure to benzene is seen in Table IV. All subjects exposed to petrol were also assigned exposure to benzene. However, 8 cases and 2 referents were assigned exposure to benzene, but not to petrol, giving a relative risk (with 95% confidence interval) of 6.7 (1.3–34.3). These benzene-exposed workers were found, for example, among precision mechanics, bicycle repairmen and rotary printers.

If the analysis was restricted to a moderate/high annual dose (Table V), a 7-fold increased risk was seen after exposure to both diesel and petrol exhausts, and the subjects thus classified are shown in Table VI. The crude relative risk was 8.1, and adjusting for year of birth in six categories and smoking in seven categories gave a relative risk (with 95% confidence interval) of 8.1 (1.0–66.2).

Four cases and one referent exposed to both diesel and petrol exhausts (moderate/high annual dose) were also exposed to benzene (Table VI). Consequently, 3 cases and no referents were exposed to both of the exhausts (moderate/high annual dose), but not to benzene. A regression model including a variable indicating exposure to diesel and petrol exhausts (moderate/high annual dose), benzene (any annual dose), year of birth and smoking gave a relative risk (with 95% confidence interval) for diesel and petrol exhausts of 5.1 (0.6–43.6) and for benzene of 1.8 (0.9–3.9).

No subject assigned exposure to PCB was also classified as being exposed to aromatic amines, benzene or exhausts.

In an overall regression analysis we included vitamin A supplements, fried foods (collapsed variable) and fat (5 categories), found in the companion report (Steineck *et al.*, 1990*a*) to be of interest, along with year of birth (6 categories) and smoking (7 categories). The relative risk (with 95% confidence interval) for benzene was 1.9 (0.9–4.0), for the combination of petrol and diesel exhausts (moderate/high annual dose) 5.0 (0.6–44.4) and for PCB 2.8 (0.5–16.8).

Current smokers exposed to benzene had a relative risk (with 95% confidence interval) of 7.5 (2.5–21.4), as compared with "never smokers" not exposed to benzene. Men not exposed to vitamin A supplements and exposed to benzene had a relative risk of 5.8 (1.9–17.7) as compared with men exposed to vitamin A supplements but not to benzene. Men exposed to fried foods (collapsed variable) and benzene had a relative risk of 9.3 (2.6–32.5), as compared with men "unexposed" to fried foods and benzene. Men with a high intake of fat and exposed to benzene had a relative risk of 10.7 (2.2–50.8), as compared with men with a low intake (quintiles 1 and 2) of fat and not exposed to benzene. All analyses were adjusted for year of birth and smoking (when appropriate).

Self-reported employment in certain occupations/industries and exposure to certain chemicals are shown in Table VII. The highest relative risk was seen for employment in the rubber industry. In the paint/varnish manufacturing industry 4 cases and no referents had worked with dusty powder more than 2,000 working days, while no cases and 3 referents had worked with dusty powder 2,000 working days or less. Five cases but no referents had filled car tanks with petrol by hand more than 2,000 working days, while 4 cases and 4 referents had filled car tanks 2,000 working days or less.

DISCUSSION

Misclassification

Some views of misclassification discussed in the companion

TABLE I – NON-RESPONSE AMONG MALE CASES AND REFERENTS IN THE POPULATION-BASED CASE-REFERENT STUDY OF UROTHELIAL CANCER IN STOCKHOLM, SWEDEN, 1985–87

	Cases	Referents
Total number (%) of subjects selected/identified	320 (100%)	363 (100%)
Number (%) of subjects not participating (non-response)		
—refused	28 (9%)	57 (16%)
—disabled	12 (4%)	11 (3%)
—dead	22 (7%)	5 (1%)
—not located	1 (0%)	2 (1%)
—other reason	1 (0%)	1 (0%)
Number (%) of subjects participating	256 (80%)	287 (79%)
Number of subjects significantly exposed to aromatic amines	2	
Number of subjects analyzed	254	287

TABLE II – RELATIVE RISK OF UROTHELIAL CANCER AMONG MEN CLASSIFIED AS EXPOSED BY AN INDUSTRIAL HYGIENIST. THE STOCKHOLM CASE-REFERENT STUDY 1985–87[1]

Exposure	Number of cases	Number of referents	RR	(95% C.I.)
Aromatic amines	6	11	0.6	(0.2–1.7)
Asbestos, white				
low level	46	63	0.7	(0.5–1.2)
high level	3	6	0.6	(0.1–2.0)
Benzene	26	16	2.0	(1.0–3.8)
Carbon black (including printing ink)	14	9	2.0	(0.8–4.9)
Chlorinated aliphatic hydrocarbons	6	11	0.7	(0.2–2.0)
Coal tar	26	27	1.0	(0.6–1.8)
Combustion gases from coal	27	36	0.8	(0.5–1.4)
Combustion gases from oil	10	12	0.9	(0.4–2.3)
Combustion gases from wood	23	22	1.2	(0.6–2.3)
Cutting fluids and cutting oils	46	67	0.7	(0.5–1.1)
Diesel exhausts	25	19	1.7	(0.9–3.3)
Organic solvents, not otherwise specified				
low level	36	52	0.8	(0.5–1.3)
intermediate level	15	22	0.8	(0.4–1.6)
high level	6	8	0.6	(0.2–1.8)
very high level	6	4	1.8	(0.5–6.7)
Passive smoking	107	125	0.9	(0.6–1.2)
Pesticides	5	9	0.8	(0.3–2.7)
Petrol	18	14	1.4	(0.7–2.9)
Petrol exhausts	24	24	1.0	(0.5–1.9)
Polychlorinated biphenyls (PCB)	5	2	3.3	(0.6–18.4)
Soot from coal	20	26	0.8	(0.4–1.5)
Soot from oil	12	20	0.6	(0.3–1.9)
Soot from wood	14	18	0.8	(0.4–1.7)

[1]Number of exposed cases and referents, relative risk (RR) with 95% confidence interval (95% C.I.). Adjusted for year of birth and smoking. Exposure after 1981 was ignored.

TABLE III – RELATIVE RISK OF UROTHELIAL CANCER ACCORDING TO ESTIMATED ANNUAL DOSE OF CERTAIN INDUSTRY-RELATED EXPOSURES. THE STOCKHOLM CASE-REFERENT STUDY 1985–87[1]

	Annual dose					
	Low		Moderate		High	
	RR	(95% C.I.)	RR	(95% C.I.)	RR	(95% C.I.)
Benzene	1.7	(0.6–5.1)	1.1	(0.3–4.5)	3.0	(1.0–8.7)
Chlorinated aliphatic hydrocarbons	0.8	(0.1–5.7)	0.0		1.2	(0.3–5.2)
Combustion gases from coal	0.9	(0.3–2.2)	0.8	(0.3–2.2)	0.9	(0.4–1.9)
Cutting fluids and cutting oils	0.8	(0.4–1.6)	0.7	(0.4–1.3)	0.9	(0.5–1.7)
Diesel exhausts	1.3	(0.6–3.1)	2.2	(0.7–6.6)	2.9	(0.3–30.0)
Petrol	0.7	(0.2–2.7)	0.9	(0.2–4.3)	2.5	(0.8–7.5)
Petrol exhausts	0.6	(0.3–1.3)	1.4	(0.5–3.7)	3.9	(0.4–35.5)
Printing ink	3.2	(0.4–27.1)	0.5	(0.1–2.1)	3.6	(0.8–12.1)

[1]Relative risk (RR) with 95% confidence interval (95% C.I.). Adjusted for year of birth and smoking. Exposure after 1981 was ignored.

TABLE IV – RELATIVE RISK OF UROTHELIAL CANCER ASSOCIATED WITH DETAILS IN THE EXPOSURE TO BENZENE. THE STOCKHOLM CASE-REFERENT STUDY 1985–87[1]

	Number of cases	Number of referents	RR	(95% C.I.)
Duration				
1–9 years	13	9	1.8	(0.7–4.5)
10+ years	13	7	2.2	(0.8–5.7)
Year of starting				
Before 1942	8	5	2.0	(0.6–6.5)
1942–1961	15	8	2.3	(0.9–5.8)
1962–1981	3	3	1.0	(0.2–5.3)

[1]Relative risk (RR) with a 95% confidence interval (95% C.I.). Adjusted for year of birth and smoking.

TABLE V – RELATIVE RISK OF UROTHELIAL CANCER FOR DIESEL AND PETROL EXHAUSTS (MODERATE/HIGH ANNUAL DOSE), STUDIED SEPARATELY AND TOGETHER. THE STOCKHOLM CASE-REFERENT STUDY 1985–87[1]

	Number of cases	Number of referents	RR	(95% C.I.)
Exhausts				
Both diesel and petrol	7	1	7.1	(0.9–58.8)
Diesel, not petrol	4	5	1.1	(0.3–4.3)
Petrol, not diesel	6	6	1.0	(0.3–3.4)
Neither	247	275	1.0	

[1]Number of exposed cases and referents, relative risk (RR) with 95% confidence interval (95% C.I.). Adjusted for year of birth and smoking. Exposure after 1981 was ignored.

report (Steineck *et al.*, 1990*a*) applies to the present analyses as well. In addition, in considering differential exposure misclassification, a comparison between hygienist-assessed exposure (Table II) and self-reported exposure (Table VII) can be made for printing ink. A higher relative risk and fewer exposed subjects were noted for hygienist-assessed exposure. This may mean that specificity was a problem in self-reported exposure; some subjects tend to report exposures that the hygienist regards as non-significant. There is no indication that this decreased specificity introduced a differential exposure misclassification in the present study. A non-differential exposure misclassification because of decreased specificity would attenuate the relative risk towards 1.0.

The main findings of the study concerning benzene, exhausts and PCB are based on classification of exposure by an industrial hygienist, using the written job history provided by each subject, unaware of case-referent status. No specific questions were asked about benzene from sources other than petrol, or about exhausts and PCB. To try to avoid differences in the quality of the job histories between cases and referents, the

TABLE VI – MEN ASSIGNED EXPOSURE TO BOTH DIESEL AND MOTOR GAS EXHAUSTS WITH A MODERATE OR HIGH ANNUAL DOSE. THE STOCKHOLM CASE-REFERENT STUDY 1985–87[1]

Year of birth	Occupational title	Industrial category	Period	Annual Dose		
				Diesel exhausts	Petrol exhausts	Benzene/ petrol
	Cases					
1916	Process worker	Petrochemical industry	1950–56	Mod[1]	Mod	—
	Construction worker	Road construction	1956–63	Mod	—	—
1919	Chauffeur	Transport	1940–69	Mod	Mod	Mod
	Chauffeur	Transport	1969–83	Mod	Mod	—
1921	Chauffeur	Wholesale	1949–50	Mod	Mod	—
	Taxicab driver	Transport	1950–55	Mod	Mod	—
	Chauffeur	Wholesale	1955–70	Mod	Mod	—
	Petrol station worker	Petrol station	1970–80	—	—	High
1921	Taxicab driver	Transport	1969–86	Mod	Mod	—
1931	Chauffeur	Transport	1952–54	Mod	Mod	—
	Taxicab driver	Transport	1974–87	Mod	Mod	—
1933	Petrol station worker	Petrol station/auto repair shop	1959–85	High	High	High
1937	Mechanic	Auto repair	1951–53	—	High	High
	Forklift driver	Petrochemical industry	1954–56	—	Mod	—
	Chauffeur	Brick manufacturing	1958–59	Mod	—	—
	Forklift driver	Mechanic industries	1959–60	—	Mod	—
	Lorry driver and construction worker	Road construction	1963–86	Mod	—	—
	Referent					
1939	Lumberjack	Forestry	1954–57	—	Mod	—
	Lorry driver	Wholesale	1957–60	Mod	—	—
	Lorry driver	Petrochemical industry	1960–61	Mod	—	High
	Lorry driver	Construction	1961–68	Mod	—	—

[1]Mod = Moderate.

TABLE VII – RELATIVE RISK OF UROTHELIAL CANCER AMONG MEN WITH SELF-REPORTED EXPOSURE TO CERTAIN OCCUPATIONS/ INDUSTRIES/CHEMICALS. THE STOCKHOLM CASE-REFERENT STUDY 1985–87[1]

	Number of cases	Number of referents	RR	(95% C.I.)
Occupation/industry				
Dry cleaner	2	2	1.2	(0.2–9.2)
Petrol station/ automobile repair	17	15	1.3	(0.6–2.8)
Hairdresser	1	2	0.4	(0.0–4.7)
Health care	7	10	0.8	(0.3–2.3)
Laboratory	5	11	0.7	(0.2–2.1)
Painter	4	12	0.4	(0.1–1.2)
Paint/varnish industry	4	7	0.6	(0.2–2.1)
Plastics industry	4	5	0.8	(0.2–3.2)
Railway	8	19	0.4	(0.2–1.0)
Rubber industry	9	3	3.1	(0.8–11.9)
Shoe or leather industry	0	2	0.0	
Chemicals				
Asbestos	35	54	0.7	(0.4–1.1)
Combustion gases from coal, coke or wood	53	59	1.0	(0.7–1.6)
Cutting fluids and cutting oils	37	48	0.8	(0.5–1.4)
Passive smoking	114	130	1.0	(0.7–1.4)
Pesticides	14	23	0.7	(0.4–1.4)
Printing ink	22	19	1.4	(0.7–2.6)
Solvents	57	70	0.9	(0.6–1.3)
Soot	42	45	1.0	(0.6–1.6)
Tar, asphalt	19	26	0.9	(0.5–1.7)
Any other chemical	29	30	1.1	(0.6–2.9)

[1]Number of exposed cases and referents, relative risk (RR) with 95% confidence interval (95% C.I.). Adjusted for year of birth and smoking.

questionnaire was answered in the home by all subjects, and they were unaware of the investigation.

We chose "annual dose" as a parameter for the dosage of an agent. A subject exposed to an agent at a high level for a few working days a year is rated as being exposed to a "low annual dose", as is a subject exposed to a low level during many working days. This dosage-parameter could be inappropriate, and introduce an exposure misclassification that distorts the dose-response relationships obtained. There are certainly many alternative dosage parameters, and it is difficult to judge which is the most appropriate biologically.

Confounding

Certain aromatic amines are firmly held to be causative factors of urothelial cancer (IARC, 1973), and it is essential before interpreting increased risks of urothelial cancer as causal to consider a possible distortion by aromatic amines. Thus, to avoid any possibility of spurious influence of aromatic amines, we omitted from the analysis all subjects (2 cases) exposed to a high annual dose of aromatic amines and verified that none of the men exposed to benzene, exhausts and PCB were assessed to be exposed to aromatic amines at lower doses.

The changes in estimates from the crude relative risk on adjusting for year of birth and smoking was small for benzene, and away from unity for PCB, indicating that confounding from these factors could not explain the increased risks. For the combination of petrol and diesel exhausts, the relative risk on adjusting for year of birth and smoking in 9 strata was lower than the crude relative risk, while using 54 strata led to a higher relative risk. The reason for this discrepancy in changes of estimates is probably a lack of precision due to small numbers.

Benzene

We found a significantly increased risk after exposure to benzene. Although based on small numbers, the results indicate that the highest annual dose gives the highest risk, and that the exposure has to start more than two decades before the observation period if it is to have an effect. The increased risk applied to benzene due to exposure from petrol but was more pronounced for benzene from sources other than petrol. The results are consistent with an effect modification between smoking, intake of vitamin A supplements, fried foods and fat, respectively, and benzene.

In a cohort study we observed a small increase in the risk of

urinary bladder cancer after exposure to benzene, but a relative risk below unity for petrol (Steineck *et al.*, 1989). Wong (1987) observed 2 cases of urinary bladder cancer among workers exposed 5–14 years to benzene and also 2 cases among workers exposed 15 years or more, giving a relative risk of 1.7 and 1.3. No case of urinary bladder cancer was found among those exposed for less than 5 years. All four cases had an induction-latency period of at least 20 years.

Certain groups employed in the rubber industry have an increased risk of urothelial cancer (IARC, 1982*a*). Since the work of Veys (1969), this risk has generally been considered to be due to contaminants of β-naphthylamine in anti-oxidants (removed from the market in UK in 1949). Another explanation could, however, be exposure to benzene. Benzene warrants further attention as a possible risk factor for urothelial cancer.

Diesel and petrol exhausts

Since the observation by Howe *et al.* (1980) of an increased risk of urinary bladder cancer after exposure to "diesel and traffic fumes", many jobs involving exposure to exhausts have been reported to increase the risk of urothelial cancer. For example, Silverman *et al.* (1986) noted a relative risk (with 95% confidence interval) of 1.5 (1.1–2.0) for usual occupation as a truck driver or deliveryman, of 6.3 (1.6–29.3) for usual occupation as a taxicab driver or chauffeur and of 1.5 (0.6–3.9) for usual occupation as a bus driver. Others (Wynder *et al.*, 1985; Siemiatycki *et al.*, 1988) suggest that there is no association between urothelial cancer and exposure to diesel exhausts.

If a transport-related occupation is considered as increasing the risk of urothelial cancer, exhausts, but also benzene/petrol, might be the responsible agent(s), as already mentioned. Several jobs involving exposure to exhausts also involve exposure to benzene/petrol. Moreover, as seen in the present study (Table VI), a subject having an exhaust-related job may have had or may afterwards take another job related to transport which involves exposure to benzene/petrol. We obtained a change in the estimate of the relative risk on adjusting the relative risks of exhausts for benzene (see "Results"), and benzene may have confounded the association for exhausts. It might be rewarding to consider whether benzene/petrol distorts the previously suggested associations (*e.g.*, Silverman *et al.*, 1986) between exhausts and urothelial cancer.

PCB

In a cohort study, we found an association between exposure to PCB and urothelial cancer (Steineck *et al.*, 1989). In a literature review (Steineck *et al.*, 1990*b*), however, we found little data on the association. The increased risk for PCB in the present study was based on small numbers and could be due to statistical variability. Furthermore, electricians assigned exposure to PCB may also be exposed to electromagnetic fields. Hence this exposure is a potential confounder, although we know of no data illustrating a possible relationship to urothelial cancer.

Combustion gases/soot from coal

Coal-carbonizing workers (Doll *et al.*, 1972), aluminium production workers (Thériault *et al.*, 1984) and chimney sweeps (Gustavsson *et al.*, 1988), all exposed to certain combustion gases, have an increased risk of urinary bladder cancer. Polycyclic aromatic hydrocarbons, a constituent of combustion gases/soot, have been linked to the disease (Bonassi *et al.*, 1989). No association with combustion gases was found, however, in the present study. One explanation could be that the validity problems mentioned above bias the relative risk. Another possibility, as discussed in our review (Steineck *et al.*, 1990*b*), is varying constituents and exposure levels of the combustion gases for different groups of workers.

Aromatic amines

Our primary concern for aromatic amines was the possibility that these agents would confound associations for other agents. Hence, in the classification of exposure to aromatic amines, we emphasized sensitivity over specificity when there was little documentation of a possible exposure in a certain job. This may have introduced a non-differential exposure misclassification when studying the aromatic amines *per se* which thereby attenuated the relative risk. We observed a relative risk below unity for aromatic amines.

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