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Cancer Mortality in a Cohort of Male German Iron Foundry Workers

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Background *Observations of an increased incidence of cancers of the upper aero-digestive tract (pharynx, esophagus, larynx, lung) among workers of local German foundries gave rise to concern about a potentially elevated occupational risk of those cancer sites. The purpose of the study was to examine whether occupational exposure in iron foundries increases the risk of cancer.*

Methods *A historical cohort study of 17,708 male German production workers in 37 iron foundries who were first employed in 1950–1985 with a minimum employment period of 1 year was initiated. Employment and occupational histories were collected. Mortality was compared with that of the German general population during 1950–1993 using a new method for computing the SMR when not all causes of death are available (called SMR*).*

Results *Mortality from all causes was elevated to SMR = 115.4 (95% confidence interval (CI) = 111.9–119.1), as was for total cancer (SMR* = 123.8, CI = 102.1–152.6), especially cancers of the lung (SMR* = 163.9, CI = 123.9–223.0) and liver (SMR* = 322.5, CI = 149.5–844.8), and diseases of the respiratory system (SMR* = 147.6, CI = 100.4–221.5). Non-significant elevations of mortality were also found for cancers of the mouth and pharynx (SMR* = 153.5, CI = 82.3–359.8) and larynx (SMR* = 173.1, CI = 85.5–550.5). Mortality from various causes of death was higher among workers with shorter exposure periods than among long-term employees. The elevated mortality persisted for years and decades after termination of employment.*

Conclusions *The results provide further evidence for an increased risk of lung cancer and possibly other cancers of the upper aero-digestive tract among foundry workers. Special attention should be paid to the strongly increased mortality from liver cancer and the mortality pattern among employees having terminated work.* Am. J. Ind. Med. 43:295–305, 2003. © *2003 Wiley-Liss, Inc.*

KEY WORDS: cancer; cohort study; epidemiology; iron foundry; larynx; liver; lung; missing death certificates; mortality; mouth; occupation

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INTRODUCTION

Turner and Grace [1938] reported an excess mortality from cancer of the respiratory and digestive tract among foundry workers in Sheffield which was confirmed in 1950 for the same types of neoplasms, lung, buccal cavity, and pharynx [Swantson, 1950]. Since that time, epidemiological evidence concerning a positive association between working in foundries and subsequent respiratory diseases (malignant and non-malignant) has accumulated, and several

reviews of the literature have been published [Tola, 1980; Palmer and Scott, 1981; IARC, 1984].

In 1986, a working group of the International Agency for Research on Cancer [IARC, 1986] assessed the carcinogenic risk and categorized iron and steel founding in Group 1—''the agent is carcinogenic to humans, giving rise to lung cancer'' [IARC, 1987]. The lung cancer risk found in epidemiological studies was typically elevated to 1.5–2.5-fold. Increased risk from cancer of other sites were also reported, i.e., of the upper digestive system in the USA and UK [Dubrow and Wegman, 1984; Sorahan et al., 1994], colon in Sweden [Chow et al., 1994], and bladder cancer in Denmark [Hansen, 1991; Sherson et al., 1991], without being, however, consistent across different studies and countries.

In the mid-1980s, indications of an increased incidence of cancers of the upper aero-digestive tract (pharynx, larynx, esophagus, lung) among German foundry workers emerged from sporadic reports. The observations gave rise to concern among German occupational health authorities and the metal workers union about a potentially elevated occupational risk not only of lung cancer but also of the less common cancer sites. The relevance of iron and steel founding in German manufacturing, and the large number of materials and technological processes which may be partially different from other countries, made it questionable to refer to negative or inconsistent results of other countries in order to exclude the possibility of an occupation-related increase of cancer risk. At the same time, no epidemiological studies among workers in the German foundry industry were available. Thus, the Employer's Compensation Fund of the Metal Industries initiated and funded a nationwide epidemiological study in order to:

(a) assess risk of cancer from various sites, at different workplaces and different calendar time periods within the companies;
(b) enhance preventive measures in the foundry environment; and
(c) provide quantitative data on cancer risk required to decide about claims for compensation.

The present article provides the results of the evaluation of the entire cohort focusing on total mortality and cancer. Analyses of other causes of death, specific work areas, calendar time periods, and foundry technologies are still in progress and will be presented in subsequent reports.

MATERIALS AND METHODS

The foundries under investigation were drawn from the compulsory membership of the Employer's Compensation Fund of the Metal Industries (Metall-Berufsgenossenschaften). From this membership, 184 iron foundries met the criteria for the study and were invited to participate. Selection criteria were availability of personnel and technical records of sufficient quality for (a) the identification of potential cohort members, (b) reconstruction of their employment history, and (c) reconstruction of application periods of specific moulding and alloying techniques. Among them, 63 agreed, but only 37 plants in six of the 16 federal states of Germany were able to provide appropriate data with reasonable expenditure of time and money. Among the participating plants, 14 were classified as small (up to 100 workers), 12 as medium (100–250), and 10 as large (more than 250 workers in average during the study period). It was determined that they were representative of the German foundry industry with regard to applied technologies and working conditions. The cohort was defined as German male employees who started work in the foundries between 1 January 1950 and 31 December 1985, and were employed for at least 1 year. Employees who were first employed as white-collar staff and management were excluded, as were pattern-makers, stock, and shipping personnel.

For each individual meeting the inclusion criteria, the following data were extracted from personnel or wage department records: (1) personal data such as name, home address, date of birth, location of birth, health insurance company, and (2) data on employment and occupational history such as date of entrance and termination of employment as well as of specific jobs, qualification and/or occupational titles. Health insurance files, pension files, and other company sources served as control for the completeness of the identification of the cohort members. Foundry experts were asked for additional technical details concerning the foundry process. This occupational information served as a basis for defining ten different foundry work areas with reference to operation (type of manufacturing process, activity) or product (type of materials handled or produced).

Due to this classification, 1,222 cohort members found on the salary list were judged by the experts as not having been exposed to an iron foundry environment because in fact they worked in other buildings, separate stock rooms, or offices. Another 43 exhibited unresolvable implausibilities of data. After these exclusions the study population consisted of 17,708 iron foundry workers.

A mortality follow-up was performed from 1 January 1951 through 31 December 1993. Cohort members were classified as alive if they were actively employed at the end of the follow-up period. For all other members actual vital status was determined from the population registers by tracing the last address of residence. In Germany, registration is mandatory and this allows efficient follow-up. If a cohort member was found to be deceased, place of death and death certificate number were recorded and a copy of the death certificate was requested from the responsible local health office. Since legislation in most German states allows the removal of death certificates after 10 years of storage, therefore, considerable portion of causes of death could not

be obtained for the years before 1980. All causes of death were coded according to the ninth revision of the International Classification of Diseases (ICD) by two trained nosologists from the State Institute of Statistics of Rhine-Palatinate who routinely carry out the coding of deaths from the general population.

Statistical Methods

Analysis of data was carried out by calculation of SMRs using the mortality rates of West-Germany of the years 1952–1995 as reference [Becker and Wahrendorf, 1997]. Because a substantial number of death certificates could not be obtained, a recently developed extension of the SMR-approach to the situation with missing death certificates was applied [Rittgen and Becker, 2000].

This approach uses the fact that the occurrence of cases of death (overall or cause-specific) can be considered as Poisson-distributed events. Because the administrative reasons for non-availability of death certificates are unrelated to the exposures and causes of death of interest, the accessible/missing status can be assumed to be at random, and thus the distribution of the *available* causes of death within given calendar time periods as a random selection of the *unknown total* cause-specific number of deaths. Because the vital status is easily obtainable for each subject from the population files, the total number of all deaths irrespective of the cause is known and allows the estimation of unknown total cause-specific number of deaths through extrapolation by the proportion by which the total number of deaths exceeds the total number of available causes of death. While this estimation is actually straightforward, the crucial step is that the theoretical approach provides confidence limits. Intuitively, they simply adjust the usual Poisson-based confidence limits of the SMR for the additional uncertainty introduced by the proportion of unknown causes of death. This proportion, i.e., unknown number versus total number of deaths, is binomially distributed, and the binomial confidence limits serve for adjustment of the usual confidence limits of the SMR. If all causes of death are known, the proportion is 1 and the binomial confidence limits collapse to this estimator 1 and the generalized SMR becomes identical to the usual SMR.

Practically, the procedure uses the number c of available causes of death and the knowledge *that* d individuals died as the result from follow-up on the vital status to estimate the true number O* of deaths from specified cause by $O^* = O \times (d/c)$, O being the number of effectively observed cases. With these, the modified SMR* can be computed as usual by $SMR^* = 100 \times O^*/E$, E being the expected number of deaths calculated from the person-years at risk, and reference rates from the general population. The confidence limits can be obtained by dividing the usual confidence limits of the SMR by the respective opposite binomial limits of the proportion p. The tables comprise the effectively observed number of deaths O, the estimated number O*, and the expected number E of cases, from which the SMR* and the confidence limits are computed. However, with O and E the reader can easily calculate the usual SMR and the respective confidence limits himself for comparison.

SMR for overall mortality does not require death certificate information (information about death is available from the population registers) and can, therefore, be evaluated as usual (in the text denoted by the usual abbreviation SMR). Because the availability of the death certificates is better in the more recent years and worse in the more distant past, the calculation of the SMRs* was carried out under subdividing the calendar time into the three periods 1950–1968, 1969–1985, and 1986–1995, calculation of the O* separately and summation of them and the confidence limits as described in Rittgen and Becker [2000].

RESULTS

Table I presents the results of the follow-up. The mean age at starting employment in the foundry industry was 27.0 years, the mean duration of employment was 11 years, the mean period of follow-up was 25.63 years. The study cohort generated a total of 458,732 person-years of follow-up (data not shown).

In Table II, the results of the evaluation regarding groups of causes of death are presented. The total of 3,972 deaths having occurred during the study period contrast to 3441.1 expected from national rates resulting in a significantly increased SMR of 115.4 (CI = 111.9–119.1). SMRs* are also significantly elevated for malignant neoplasms (SMR* = 123.8) and disorders of the respiratory system (SMR* = 147.6).

Table III presents the results for the individual cancer sites. Elevated, statistically confirmed SMRs* were found for liver and intrahepatic bile ducts (SMR* = 322.5) and respiratory and intrathoracic organs (SMR* = 164.2) which is mainly due to an elevated SMR* for cancers of the trachea,

TABLE I. Results of a Follow-Up of German Male Iron Foundry Workers Until December 31, 1993

Follow-up status	Number	Percent
Alive, still employed	2,764	15.6
Alive, retired	9,870	55.7
Deceased	3,972	22.4
Death certificate available	2,896	73.0
Death certificate not available	1,076	27.0
Emigrated	193	1.1
Lost to follow-up	909	5.1
Total	17,708	100.0

TABLE II. Cause-Specific Mortality in a Cohort of German Iron Foundry Workers

Cause of death	ICD-9	O	O*	E	SMR*	95% CI
All causes	001–999	3,972	3,972	3441.1	115.4	111.9–119.1
Infectious diseases	001–139	35	47.8	36.8	129.6	66.1–302.7
Malignant neoplasms	140–208	831	1090.8	881.3	123.8	102.1–152.6
Neoplasms of unspecified nature	210–239	28	40.1	31.4	128.0	59.3–335.2
Endocrine, metabolic, and immunity disorders; disorders of the blood and blood forming organs	240–289	71	100.1	67.4	148.4	80.9–280.9
Mental disorders	290–319	53	69.2	50.1	138.0	74.7–278.2
Nervous system and sensory organs	320–389	35	45.7	52.2	87.5	46.7–214.5
Circulatory system	390–459	1,091	1486.7	1284.5	115.7	96.7–140.5
Respiratory system	460–519	200	274.4	185.9	147.6	100.4–221.5
Digestive system	520–579	187	261.8	263.1	99.5	67.5–149.8
Genitourinary system	580–629	29	39.7	44.1	90.1	44.0–241.4
Skin and subcutaneous tissue	680–739	6	8.1	8.8	92.6	25.1–606.6
Ill defined conditions	780–799	48	62.2	96.0	64.8	36.9–142.0
Accidents, poisonings, violence	800–999	282	444.1	421.3	105.4	74.9–150.0

O, observed number of cases; O*, estimated number of cases; E, expected number of cases; SMR*, modified SMR (see Materials and Methods); CI, confidence interval.

lung, and bronchus (SMR* = 163.9). Mortality from oral (SMR* = 153.5) and laryngeal cancer (SMR* = 173.1) was also increased, although not statistically significant. Surprisingly low SMRs* were observed for melanoma and multiple myeloma. For all other cancer sites, the observed numbers of cases were comparable to the expected range from the reference.

Table IV shows the SMR calculated according to usual methods for the quoted cancer sites and the overall mortality based on the data confined to the years 1980 and later for which the causes of death have been obtained with a reasonable high completeness. The results confirm the findings of Tables II and III though the point estimates of some causes of death are somewhat lower: for example, total cancer (SMR = 111.1), cancers of the liver (SMR = 210.8), lung cancer (SMR = 151.7).

Deeper insight into the pattern of total cancer mortality with reference to duration of exposure and observation time since first exposure is shown in Table V. If duration of exposure and duration of observation are identical, the cells must represent active employment or recent separation. The cells forming the diagonal from top left to bottom right show mortality of this category of employees. If duration of observation exceeds duration of exposure, the employees must have quit the job during the observation period. The mortality of these 'inactive' employees can be seen in the cells right above the diagonal just described.

The SMRs* along the diagonal depicting mortality among active employment indicate only a modest increase from a slightly decreased level (SMR* = 85.2) to slightly elevated SMRs* (SMR* = 117.4, SMR* = 115.3, SMR* = 102.1, all non-significant). Highest SMRs* occur among inactive subjects after relatively short duration of exposure (first row: SMR* = 137.9, SMR* = 143.0; second row: SMR* = 154.6).

In columns describing the mortality only by duration of exposure, a clear *decline* with increasing duration of exposure exists, indicating that the shorter the employment the higher the SMR*. The highest SMRs* can be observed 10–20 years after termination of employment.

For lung cancer, the same kind of presentation (Table VI) shows that the SMRs* of the main diagonal point to an increasing mortality among the long-term employees. The SMR* begins to rise from an already increased level (SMR* = 117.3) in the first cell to SMR* = 151.2 and 148.2, respectively, for long-term exposure. However, none of these ratios are statistically significant. Again, the columns show a remarkable decline with increasing duration of exposure. Also for lung cancer, the highest SMRs* can be observed 10–20 years after termination of employment (right of the diagonal). As with total cancer, the bottom margin shows increasing SMRs* with increasing duration of observation which are statistically significant for the cells for 20 or more years of observation time.

To address the question whether the high mortality from total cancer and lung cancer among those employees having quit employment is exposure-related or may be due to other, non-related factors, some further analyses were carried out by addressing general mortality and mortality from external causes. General mortality shows a persistent healthy worker effect among the active employees in the main diagonal (Table VII). The highest and clearly significant

TABLE III. Site-Specific Mortality From Cancer in a Cohort of German Iron Foundry Workers

Cancer site	ICD-9	O	O*	E	SMR*	95% CI
Lip, oral cavity, and pharynx	140–149	36	47.0	30.6	153.5	82.3–359.8
Digestive organs and peritoneum	150–159	245	338.3	293.5	115.3	81.1–166.9
Oesophagus	150	22	24.4	25.2	96.8	54.6–300.7
Stomach	151	70	106.4	92.3	115.3	59.1–222.7
Colon	153	40	51.6	63.0	82.0	45.4–190.3
Rectum	154	35	46.0	36.2	127.0	67.4–300.8
Liver and intrahepatic bile ducts	155	28	40.1	12.4	322.5	149.5–844.8
Gallbladder and extrahepatic gall ducts	156	8	13.0	10.9	119.2	31.6–591.9
Pancreas	157	32	40.4	40.8	99.0	53.6–247.2
Peritoneum and retroperitoneum	158	3	3.8	2.7	141.7	23.2–1702.5
Respiratory and intrathoracic organs	160–165	351	451.0	273.6	164.9	126.1–221.2
Larynx	161	20	24.7	14.3	173.1	85.5–550.5
Trachea, bronchus, lung	162	322	415	253.2	163.9	123.9–223.0
Pleura	163	4	4.8	6.4	75.5	17.0–737.8
Bone, connective tissue, skin, and breast	170–175	10	12.4	23.2	53.3	20.6–258.5
Bone and articular cortilax	170	3	3.8	5.1	74.6	12.2–896.3
Melanoma	172	2	2.7	10.9	24.9	2.2–397.5
Genitourinary organs	179–189	85	103.0	107.1	96.2	63.4–168.5
Prostate	185	39	47.8	48.7	98.1	56.9–226.5
Testis	186	4	4.8	6.3	76.9	17.4–751.6
Bladder	188	23	28.5	27.2	104.7	53.6–309.0
Kidney and other unspecified urinary organs	189	19	21.9	29.6	73.8	38.6–247.3
Other and unspecified sites	190–199	65	86.4	79.7	108.4	62.9–208.1
Brain and unspecified parts of nervous system	191–192	18	24.4	20.9	117.0	51.1–377.6
Thyroid gland	193	2	3.3	2.1	158.2	11.6–2109.6
Lymphatic and haematopoetic tissue	200–208	39	52.7	63.3	83.3	43.8–196.7
Lymphatic system (lympho-, retikulosark., other)	200, 202	15	19.2	16.1	118.9	52.0–452.2
Hodgkin's disease	201	5	7.7	9.6	80.0	16.9–544.7
Multiple myeloma and immunprolif. Neoplasms	203	1	1.1	8.6	12.2	0.3–458.5
Lymphoid leukemia	204	7	8.6	7.3	117.4	38.4–734.7
Myeloid leukaemia	205	5	5.9	12.7	46.1	12.7–383.5
Unspecified leukaemia	208	6	10.3	6.7	153.7	32.9–894.6
Total	140–208	831	1090.8	881.3	123.8	102.1–152.6

O, observed number of cases; O*, estimated number of cases; E, expected number of cases; SMR*, modified SMR (see Materials and Methods); CI, confidence interval.

SMRs* appear again in the cells for the lowest durations of employment and result in an inverse 'exposure–effect relationship' in the right margin.

Table VIII presents data for external causes (ICD 800–999) and indicates that also for these causes the mortality among workers having terminated the employment is elevated and exceeds the SMR* of active employees partially considerably. However, all these elevations are not statistically significant.

Finally, Table IX shows SMR* by duration of exposure and duration of observation (a) for liver cancer which is strongly increased in this study and (b) cancer sites which have been reported in excess in previous studies but did not show relevant elevations in this study (see Table III). The SMRs* for liver cancer indicate a strong and significant increase after 10 years of observation, while an elevation is already visible within the first 10 years of exposure (SMR* = 257.9, non-significant) with a significant maximum increase for 10–19 years of exposure (SMR* = 456.6). For cancers of the upper digestive tract some elevations, though non-significant, can be found; for colon and bladder cancer, no relevant excesses can be identified.

DISCUSSION

The evaluation of the mortality experience of the entire cohort of German male iron foundry workers provided a significantly elevated SMR* for mortality from all causes

TABLE IV. Mortality From Different Causes or Cancer Sites in Iron Foundry Workers Cohort in 1980 and Later

Cause of death	ICD-9	O	E	SMR	95% CI
All causes	001–999	2,665	2144.9	124.3	119.6–129.1
Malignant neoplasms	140–208	687	618.6	111.1	102.9–119.7
Lip, oral cavity, and pharynx	140–149	33	26.3	125.3	86.3–176.0
Liver and intrahepatic bile ducts	155	21	10.0	210.8	130.5–322.3
Respiratory and intrathoracic organs	160–165	301	199.7	150.8	134.2–168.8
Larynx	161	17	10.9	155.6	90.6–249.2
Trachea, bronchus, lung	162	277	182.6	151.7	134.4–170.7
Melanoma	172	1	7.0	14.4	0.4–80.0
Multiple myeloma and immunprolif neoplasms	203	1	6.1	16.3	0.4–90.8
Respiratory system	460–519	159	120.4	132.0	112.3–154.2

O, observed number of cases; E, expected number of cases.

(SMR = 115.4; CI = 111.9–119.1), cancer (SMR* = 123.8, CI = 102.1–152.6), especially lung cancer (SMR* = 163.9, CI = 123.9–223.0) and liver cancer (SMR* = 322.5, CI = 149.5–844.8), and diseases of the respiratory system (SMR* = 147.1, CI = 100.4–221.5).

Excess mortality reported from other foundry workers' studies for cancers of the upper digestive system [Dubrow and Wegman, 1984; Sorahan et al., 1994], colon [Chow et al., 1994], and bladder [Hansen, 1991; Sherson et al., 1991] could not be confirmed by this study.

The observation of an increased overall mortality is unusual and in contrast to the general observation of a healthy worker effect among industrial cohorts. However, the finding is consistent with previous studies among foundry workers, which also reported an increased overall mortality [Fletcher, 1986; Sorahan et al., 1994] or an absent healthy worker effect [Sherson and Iversen, 1986; Andjelkovich et al., 1990].

Broken down into combinations of the two components *duration of exposure* and *observation time since first exposure*, the data reveal that a distinct difference exists between long-term exposed employees and employees having terminated employment. Long-term employees do not experience excess mortality. The highest overall mortality occurs in those categories of workers, which represent the relatively shorter exposure times; they cause the excess mortality of the entire cohort.

TABLE V. Mortality Analysis of German Foundry Workers According to Time Since First Exposure and Duration of Exposure: Total Cancer

	Duration of observation (time since first exposure)				
Duration of exposure	**< 10 years**	**10–19 years**	**20–29 years**	**30 + years**	**Total**
< 10 years	40/77.9/91.4	79/120.7/87.5	137/182.2/127.4	161/178.5/131.4	417/558.3/437.7
	85.2	137.9	143.0	135.9	127.5
	31.5–202.4	75.9–283.7	95.1–217.3	104.3–199.6	96.5–173.3
10–19 years		71/120.2/102.4	86/113.2/73.2	56/59.7/54.9	213/290.9/230.5
		117.4	154.6	108.8	126.2
		59.4.2–243.1	93.9–154.6	77.1–212.2	87.5–190.9
20–29 years			73/102.3/88.7	73/78.6/67.3	146/180.9/156.0
			115.3	116.9	115.9
			64.5–214.3	85.1–215.9	79.0–176.1
30 + years				55/58.3/57.1	55/58.3/57.1
				102.1	102.1
				72.6–218.9	72.6–218.9
Total	40/77.9/91.4	150/241.7/189.9	296/398.3/289.4	345/374.3/310.6	831/1090.8/881.3
	85.2	127.3	137.6	120.5	123.8
	31.5–202.4	80.5–209.6	104.7–182.2	99.7–153.5	102.1–152.6

Cell contents: first line, observed/estimated/expected number of cases; second line, SMR*; third line, 95% confidence interval.

TABLE VI. Mortality Analysis According to Time Since First Exposure and Duration of Exposure: Lung Cancer in German Foundry Workers

	Duration of observation (time since first exposure)				
Duration of exposure	**<10 years**	**10–19 years**	**20–29 years**	**30 + years**	**Total**
<10 years	14/25.6/21.8	20/30.8/23.8	59/81.1/36.8	66/73.5/40.0	159/211.5/122.4
	117.3	129.5	220.4	183.7	172.7
	35.0–431.7	51.4–477.7	122.0–398.0	127.5–328.3	113.9–273.1
10–19 years		21/33.5/29.5	33/44.3/21.2	23/24.7/14.9	77/103.3/65.6
		113.6	208.5	165.5	157.6
		44.1–363.5	106.9–454.9	97.9–444.7	92.6–292.5
20–29 years			31/41.1/27.2	29/31.4/19.7	60/72.8/46.8
			151.2	159.7	155.4
			77.5–363.2	98.8–396.2	97.8–285.6
30 + years				26/27.2/18.3	26/27.2/18.3
				148.2	148.2
				92.6–405.7	92.6–405.7
Total	14/25.6/21.8	41/63.7/53.2	123/167.3/85.2	144/156.5/92.9	322/415/253.2
	117.3	119.7	196.2	168.4	163.9
	35.0–431.7	55.3–281.8	130.5–294.5	130.7–242.4	123.9–223.0

Cell contents: first line, observed/estimated/expected number of cases; second line, SMR*; third line, 95% confidence interval.

As far as we can see, data on general mortality of other foundry workers' studies have not similarly been broken down so that a comparison of trends is not possible. However, results of other occupational cohort studies and mortality analyses of the effects of employment status (active/inactive) [Sherson and Iversen, 1986] corroborate the findings reported here. Among cohorts of rubber workers [Delzell and Monson, 1981], nuclear facility employees [Gilbert, 1982], or formaldehyde-exposed workers [Stewart et al., 1990], SMRs* for workers who left work relatively early exceeded those for active workers in the plants under study.

It may be speculated that this phenomenon is due to a kind of unhealthy worker effect: those who are unhealthy for any reason leave work earlier and experience a risk of dying

TABLE VII. Mortality Analysis According to Time Since First Exposure and Duration of Exposure: Total Mortality

	Duration of observation (time since first exposure)				
Duration of exposure	**<10 years**	**10–19 years**	**20–29 years**	**30 + years**	**Total**
<10 years	485/522.7	543/390.0	659/480.8	559/419.5	2,246/1813.0
	92.8	139.2	137.1	133.3	123.9
	84.7–101.4	127.8–151.8	126.8–147.9	122.4–144.8	118.8–129.1
10–19 years		389/430.5	367/278.2	253/201.8	1,009/910.5
		90.4	131.9	125.4	110.8
		81.6–99.8	118.8–146.1	110.4–141.8	104.1–117.9
20–29 years			289/318.1	267/228.6	556/546.7
			90.8	116.8	101.7
			80.7–101.9	103.2–131.7	93.4–110.5
30 + years				161/171.0	161/171.0
				94.2	94.2
				80.2–109.9	80.2–109.9
Total	485/522.7	932/820.5	1,315/1077.1	1,240/1020.8	3,972/3441.1
	92.8	113.6	122.1	121.5	115.4
	84.7–101.4	106.4–121.1	115.6–128.9	114.8–128.4	111.9–119.1

Cell contents: first line, observed/expected number of cases; second line, SMR; third line, 95% confidence interval.

TABLE VIII. Mortality Analysis According to Time Since First Exposure and Duration of Exposure: External Causes of Death (Accidents, Poisoning, Violence)

	Duration of observation (time since first exposure)				
Duration of exposure	**< 10 years**	**10–19 years**	**20–29 years**	**30 + years**	**Total**
< 10 years	92/162.1/166.9	48/80.3/62.3	40/54.2/42.8	19/21.8/20.6	199/323.0/292.7
	97.1	128.8	126.6	106.0	110.4
	49.9–184.8	63.7–307.1	78.6–255.4	59.3–301.9	72.1–170.8
10–19 years		32/58.9/61.9	16/22.9/14.2	7/7.8/7.3	55/86.2/83.4
		95.0	161.3	105.9	103.3
		37.2–245.4	69.9–441.0	38.2–541.7	52.0–214.3
20–29 years			15/24.3/28.9	5/5.2/6.7	20/28.4/35.6
			84.1	77.0	79.7
			25.2–246.6	24.1–487.9	27.2–206.8
30 + years				8/8.7/9.6	8/8.7/9.6
				90.0	90.0
				42.9–491.5	42.9–491.5
Total	92/162.1/166.9	80/139.8/124.3	71/100.9/85.9	39/43.2/44.3	282/444.5/421.3
	97.1	112.5	117.4	97.6	105.4
	49.9–184.8	62.3–210.1	69.9–195.2	66.4–196.4	74.9–150.0

Cell contents: first line, observed/estimated/expected number of cases; second line, SMR*; third line, 95% confidence interval.

within the following years which is higher than among those who continue to work in the foundry. Furthermore, the likelihood increases that these persons are exposed in other jobs.

A more specific explanation could be that unskilled persons are found at 'dirty' workplaces in a higher proportion, and that they are simultaneously those employees who tend to change jobs more frequently. Thus, due to particularly high exposure, 'short-term' employees might experience a higher workplace-related risk than long-term employees.

Thirdly, it may be speculated that employees who change workplaces more frequently may have lifestyles with higher risks for various causes of death.

The fact that mortality from different causes including external causes are consistently elevated decades after quitting employment in the foundries provides some support to the consideration of socio-ecocomic conditions in this group. This does not exclude that the other alternatives may contribute to the explanation of the observed pattern of risk. However, the increased mortality from cancers of particular interest among the former foundry workers cannot fully be interpreted as exposure-related.

A limitation of the study is that we had to restrict the analysis for the time being to the German nationals of a total cohort of foundry workers; 39% were foreign workers, which caused major problems in follow-up. As long as the foreigners live and die in Germany, they can be followed-up regularly as described above, however, only relatively few live in this way. Because many of them leave the country again, it may be speculated that those who suffer from serious illnesses return to their countries of origin and might preferentially die there. Cooperation with the official institutions of those native countries which is necessary for follow-up, has not yet been established, but efforts are underway so that the mortality experience of the whole cohort will be considered in a later analysis. It must be noted that these migrant workers sometimes hold the more hazardous jobs.

A further limitation of the study is that smoking histories were not available. An increased prevalence of cigarette smoking within this cohort, compared with the national average, could explain some of the observed increases in lung cancer risk. Such an explanation has been put forward for workers of an iron foundry in the United States [Andjelkovich et al., 1990]. Therefore, we tried to assess the proportion of excess mortality from lung cancer, which might likely be attributable to smoking, although data on smoking in occupational groups are scarce in Germany and the reliability is questionable. We applied the approach of Axelson [1988] using for the general population the following subdivisions and proportions taken from a report of the Federal Statistical Office of a microcensus in 1978 [Statistisches Bundesamt, 1978]: non-smokers (36.3%), ex-smokers (20.8%), moderate smokers (27.3%), and heavy smokers (10.1%). For the foundry workers, only three categories are available, also derived from the 1978 microcensus data [Borgers and Menzel, 1984]: non-smokers (29%), moderate smokers (50%), and heavy smokers (21%). Ex-smokers, moderate smokers, and heavy smokers have been considered having relative risks of RR = 4, RR = 15,

TABLE IX. Mortality Analysis According to Duration of Exposure and Duration of Observation for Cancers of the Upper Digestive Tract, Colon, Liver, and Bladder

Cause of death and parameter of interest	Years of exposure or observation			
	0–<10	10–19	20–29	30+
Upper digestive tract (ICD-9 140–149, 150, 151)				
Duration of exposure	63/86.2/75.6	37/54.0/38.6	21/28.1/24.7	7/8.1/9.4
	114.0	140.0	113.8	86.1
	64.0–235.5	67.6–344.5	52.7–294.4	30.0–525.8
Duration of observation	7/15.8/17.2	37/62.6/34.7	42/54.6/49.4	42/46.0/46.9
	91.9	180.5	110.5	98.0
	16.3–448.1	75.1–442.1	61.3–215.3	64.5–191.0
Colon (ICD-9 153)				
Duration of exposure	19/23.9/30.0	9/13.2/17.0	11/12.8/11.7	1/1.0/4.2
	79.4	77.5	109.2	24.6
	38.1–268.1	24.3–385.6	46.7–396.5	0.6–718.7
Duration of observation	3/3.0/4.8	5/10.2/12.6	15/20.6/21	17/17.8/24.5
	62.5	81.0	98.0	72.7
	12.9–943.6	12.8–502.1	40.0–276.5	40.3–195.8
Liver (ICD-9 155)				
Duration of exposure	11/15.4/6.0	9/13.7/3.0	5/6.6/2.4	3/3.5/1.1
	257.9	465.6	273.9	308.7
	91.4–1143.8	137.4–2254.8	67.5–1528.9	56.2–3367.2
Duration of observation	1/1.6/0.9	9/16.7/2.1	10/13.0/3.6	8/9.2/5.8
	172.3	791.0	358.6	157.7
	2.8–4789.7	196.3–3548.1	133.0–1268.4	59.4–661.4
Bladder (ICD-9 188)				
Duration of exposure	10/12.5/12.5	7/9.6/8.0	5/5.2/5.2	1/1.0/1.5
	99.7	120.5	99.8	68.5
	36.0–504.0	31.9–697.6	28.1–617.4	1.7–1999.5
Duration of observation	0/0/2.0	4/6.5/5.4	11/14.0/9.2	8/8.4/10.6
	—	121.0	152.2	78.9
	—	17.6–1004.5	56.1–515.1	32.4–328.0

Cell contents: first line, observed/estimated/expected number of cases; second line, SMR*; third line, 95% confidence interval.

and RR = 20, respectively [Doll et al., 1994]. With these data, the relative risk of lung cancer among foundry workers which is attributable to smoking is about RR = 1.6. This is almost exactly the SMR* found in this study.

However, the explanation of increased lung cancer mortality caused by smoking seems not to be adequate, since mortality from other cancers which are known to be related to cigarette smoking (esophagus, pancreas, bladder, kidney, [IARC, 1986]) is not found to be increased.

The importance of occupational risk factors was demonstrated in the interpretation of results from a case-control study carried out in Germany in which the high and specific risk of cancers of the oral cavity, pharynx, and larynx were found associated with dusty trades such as construction work and exposures to metal dust and volatile organic compounds [Maier and Sennwald, 1994]. The authors emphasized the importance of the occupational factors because of their strong and persistent associations after adjustment for cigarette smoking, alcohol abuse, and socio-economic risk factors such as education and asbestos-exposure in concurrent jobs.

Contrary to previous studies among foundry workers, we found an increased mortality from liver cancer. Foundry specific exposures possibly related to an increased risk for primary liver cancer are nitrosamines, PAH, solvents, and metals. Substances can either be inhaled directly or indirectly as particles to which these substances are adsorbed and then swallowed after ciliary clearance from the bronchial tree.

Nitrosamines are generated under reductive conditions with secondary and tertiary amines during core making, molding, and casting operations [Wolf et al., 1984; Ducos et al., 1988]. Some of these are hepato-carcinogens in animal experiments [Berger et al., 1991].

PAHs generated by incomplete combustion of organic material (thermal cracking, pyrolysis, and partial pyrosynthesis) such as coal, tar, oils, styrole, synthetic resin binders, and additives used in the foundries are associated with increased aromatic PAH-adduct levels in white blood cells [Hemminki et al., 1988] and increased HPRT mutations in lymphocytes [Perera et al., 1993]. PAH exposures have been associated in other occupational studies with increased risk for liver cancer [Austin et al., 1987; Gustavsson et al., 1987]. Recent studies suggest that high PAH-adduct levels may play a role in human hepatocarcinogenesis and are associated with increased risk of liver cancer in conjunction with hepatitis carrier status, GST-M1 and -P1 genotypes and exposure to 4-aminobiphenyl and aflatoxin B1 [Chen et al., 2002].

Aromatic and halogenated organic solvents such as benzene, 1,2,4-trimethylbenzene, ethylbenzene, xylene, toluene, 1,1,1-trichloroethane, and trichlorofluoromethane are released into the foundry environment especially during core making, molding, and casting. There is some evidence that occupational exposure to trichlorethylene (resin solvent), methylene chloride, toluene, and xylene might be associated with an increased risk for liver cancer [Lynge, 1994; Wartenberg et al., 2000; Porru et al., 2001]. A meta-analysis among workers exposed to organic solvents revealed a small risk increase for liver cancer (SMR 144, CI = 118–175) [Chen and Seaton, 1998].

Excess risk for liver cancer was reported for workers in the primary metal industry [Houten and Sonnesso, 1980] and with exposures to welding fumes [Kauppinen et al., 1992; Puntoni et al., 2001], but epidemiological data examining the role of metal fumes in foundries [Tossavainen, 1976] are lacking.

Alcohol-related cancers in this study did not show a uniform pattern of increased mortality, which might indicate an excess alcohol consumption or suggest alcohol abuse as an explanation for the excess mortality from liver cancer. Mortality from cirrhosis in this cohort was increased only by 6% in comparison to the general population. Thus, occupational factors must be taken into consideration.

The elevated mortality for liver cancer in this study is a new finding. The present study differs from those that do not observe an increased risk since it includes more recent foundry technologies up to the year 1985. In the light of epidemiological and experimental data it cannot be excluded that the increased mortality for liver cancer found in this study—possibly together with co-factors [Chen et al., 2002]—is related to exposures in foundries. A detailed investigation by a case-control approach would be desirable in order to identify factors, which might be responsible for the observed excess risk for liver cancer.

Though employees could only be classified according to company-internal cost accounting positions per department or activity, additional analyses of cancer mortality can be done and are in progress by work area and different technologies, which prevailed in the plants under consideration. Results will be presented in a subsequent article. The significant mortality pattern of those employees having terminated work before retirement deserves particular attention from a scientific as well as from a public health point of view.

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REFERENCES

Andjelkovich DA, Mathew RM, Richardson RB, Levine RJ. 1990. Mortality of iron foundry workers: I. Overall findings. J Occup Med 32:529–540.

Austin H, Delzell E, Grufferman S, Levine R, Morrison AS, Stolley PD, Cole P. 1987. Case-control study of hepatocellular carcinoma, occupation, and chemical exposures. J Occup Med 29(8):665–669.

Axelson O, Steenland K. 1988. Indirect methods of assessing the effects of tobacco use in occupational studies. Am J Ind Med 13:105–118.

Becker N, Wahrendorf J. 1997. Atlas of cancer mortality in the Federal Republic of Germany (1981–1990). 3rd edition. Berlin, Heidelberg, New York, Tokyo: Springer.

Berger MR, Schmahl D, Edler L. 1991. Relationship between dose and risk reduction: Statistical evaluation of a combination experiment with three hepatocarcinogenic *N*-nitrosamines in rats. IARC Sci Publ 105:311–317.

Borgers D, Menzel R. 1984. Who smokes most? Münch Med Wschr 126(38):1092–1096. (In German).

Chen R, Seaton A. 1998. A meta-analysis of painting exposure and cancer mortality. Cancer Detect Prev 22(6):533–539.

Chen SY, Wang LY, Lunn RM, Tsai WY, Lee PH, Lee CS, Ahsan H, Zhang YJ, Chen CJ, Santella RM. 2002. Polycyclic aromatic hydrocarbon–DNA adducts in liver tissues of hepatocellular carcinoma patients and controls. Int J Cancer 99(1):14–21.

Chow WH, Malker HS, Hising AW, McLaughlin JK, Weiner JA, Stone BJ, Ericsson JL, Blot WJ. 1994. Occupational risks for colon cancer in Sweden. J Occup Med 36:647–651.

Delzell E, Monson RR. 1981. Mortality among rubber workers. IV. General mortality patterns. J Occup Med 23:850–856.

Doll R, Peto R, Wheatley K, Gray R, Sutherland I. 1994. Mortality in relation to smoking: 40 years' observations on male British doctors. BMJ 309:901–911.

Dubrow R, Wegman DH. 1984. Cancer and occupation in Massachusetts: A death certificate study. Am J Ind Med 6:207–230.

Ducos P, Gaudin R, Maire C, Mavelle T, Bouchikhi B, Derby G. 1988. Occupational exposure to volatile nitrosamines in foundries using the "Ashland" core-making process. Environ Res 47(1):72–78.

Fletcher AC. 1986. The mortality of foundry workers in the United Kingdom. In: Goldsmith DF, Winn DM, Shy CM, editors. Silica, silicosis and cancer—controversy in occupational medicine. New York, Philadelphia, Eastbourne, Toronto, Hong Kong, Tokyo, Sydney: Praeger. p 385–401.

Gilbert EE. 1982. Some confounding factors in the study of mortality and occupational exposures. Am J Epidemiol 116:117–188.

Gustavsson P, Gustavsson A, Hogstedt C. 1987. Excess mortality among Swedish chimney sweeps. Br J Ind Med 44(11):738–743.

Hansen ES. 1991. Cancer mortality among Danish molders. Am J Ind Med 20:401–409.

Hemminki K, Perera FP, Phillips DH, Randerath K, Reddy MV, Santella RM. 1988. Aromatic DNA adducts in white blood cells of foundry workers. IARC Sci Publ 89:190–195.

Houten L, Sonnesso G. 1980. Occupational exposure and cancer of the liver. Arch Environ Health 35(1):51–53.

IARC. 1984. Polynuclear aromatic compounds, part 3, industrial exposures in aluminium production, coal gasification, coke production, and iron and steel founding. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 34. Lyon: IARC.

IARC. 1986. Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 38. Tobacco smoking, International Agency for Research on Cancer. Lyon, France.

IARC. 1987. Overall evaluations of carcinogenicity: An updating of IARC monographs volumes 1–42, supplement 7. Lyon, France: International Agency for Research on Cancer. 224–225.

Kauppinen T, Riala R, Seitsamo J, Hernberg S. 1992. Primary liver cancer and occupational exposure. Scand J Work Environ Health 18:18–25.

Lynge E. 1994. Danish cancer registry as a resource for occupational research. J Occup Med 36:1169–1173.

Maier H, Sennwald E. 1994. Risk factors for squamous cell carcinoma of the head and neck. Results of the Heidelberg case-control studies. Hauptverband der gewerblichen Berufsgenossenschaften (HVBG) St. Augustin. (In German).

Palmer W, Scott WD. 1981. Lung cancer in ferrous foundry workers: A review. Am Ind Hyg Assoc J 42:329–340.

Perera FP, Tang DL, O'Neill JP, Bigbee WL, Albertini RJ, Santella R, Ottman R, Tsai WY, Dickey C, Mooney LA, Savela K, Hemminki K. 1993. HPRT and glycophorin A mutations in foundry workers: Relationship to PAH exposure and to PAH–DNA adducts. Carcinogenesis 14(5):969–973.

Porru S, Placidi D, Carta A, Gelatti U, Ribero ML, Tagger A, Boffetta P, Donato F. 2001. Primary liver cancer and occupation in men: A case-control study in a high-incidence area in Northern Italy. Int J Cancer 94(6):878–983.

Puntoni R, Merlo F, Borsa L, Reggiardo G, Garrone E, Ceppi M. 2001. A historical cohort mortality study among shipyard workers in Genoa, Italy. Am J Ind Med 40(4):363–370.

Rittgen W, Becker N. 2000. SMR-analysis of historical follow-up studies with missing death certificates. Biometrics 56:1164–1169.

Sherson D, Iversen E. 1986. Mortality among foundry workers in Denmark due to cancer and respiratory and cardiovascular diseases. In: Goldsmith DF, Winn DM, Shy CM, editors. Silica, silicosis and cancer—controversy in occupational medicine. New York, Philadelphia, Eastbourne: Praeger. p 403–414.

Sherson D, Svane O, Lynge E. 1991. Cancer incidence among foundry workers in Denmark. Arch Environ Health 46:75–81.

Sorahan T, Faux AM, Cooke MA. 1994. Mortality among a cohort of United Kingdom steel foundry workers with special reference to cancers of the stomach and lung, 1946–1990. Occup Environ Med 51:316–322.

Statistisches Bundesamt. 1978. Health System. Series S.3. Questions on health. W. Kohlhammer GmbH, Stuttgart, and Mainz. (In German).

Stewart PA, Schairer C, Blair A. 1990. Comparison of jobs, exposures, and mortality risks for short-term and long-term workers. J Occup Med 32:703–708.

Swantson C. 1950. The iron and steel industry. Lancet I:191–197.

Tola S. 1980. Epidemiology of lung cancer in foundries. J Toxicol Environ Health 6:275–280.

Tossavainen A. 1976. Metal fumes in foundries. Scand J Work Environ Health 2(Suppl 1):42–49.

Turner HM, Grace HG. 1938. An investigation into cancer mortality among males in certain Sheffield trades. J Hyg 38:90–103.

Wartenberg D, Reyner D, Scott CS. 2000. Trichloroethylene and cancer: Epidemiologic evidence. Environ Health Perspect 108(Suppl 2):161–176.

Wolf D, Blome H, Schütz A. 1984. Measurement problems and evaluation of carcinogenic materials of group I in the air of industrial work places, exemplified in the case of *N*-nitrosamines. Staub-Reinhaltung der Luft 44:33–37. (In German).