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Investigations on the quantitative determination of nickel and chromium in human lung tissue

Industrial medical, toxicological, and occupational medical expertise aspects

H.J. Raithel[1], K.H. Schaller[1], A. Reith[2], K.B. Svenes[3], and H. Valentin[1]

[1]Institute of Occupational and Social Medicine and the Policlinic for Occupational Diseases, University of Erlangen-Nürnberg, Federal Republic of Germany
[2]Radium Hospital, Department of Histopathology and Electronmicroscopy, Oslo, Norway
[3]Department of Pathology, Central Hospital Vest Agder, Kristiansand, Norway

Summary. Nickel (Ni) and some of its relatively insoluble compounds as well as chromates may be able to induce cancer in the region of the lungs, as well as in the nose and paranasal sinuses after occupational exposure. Latency periods may amount to 20 years and more. The results of recent investigations have shown that these metals cumulate in the lung tissue after inhalation of relatively insoluble chromium and nickel compounds. The quantitative detection of these heavy metals in samples of pulmonary tissue hence permits the amount of past exposure to be estimated. To establish the normal values, samples of pulmonary tissue from 30 normal subjects were investigated for chromium and nickel content. The samples were taken from different segments and lobes of the lungs, taking topographical anatomical criteria into consideration. In addition, 15 persons who had formerly been exposed to nickel and/or chromium (11 nickel refinery workers, of whom 10 had died of lung cancer, 2 stainless steel welders, 1 foundry worker, 1 electrical technician) were also investigated. From the results of 495 tissue samples from the normal group, median chromium concentrations between 130 and 280 ng/g were calculated, with median nickel concentrations of 20–40 ng/g (wet weight). If these values are related to the nickel concentrations measured in refinery workers, values 112–5,860 times higher were found. The concentrations were about 500 times higher than normal for nickel, and about 60 times higher than normal for chromium in the stainless steel welders. For the foundry workers who died of lung cancer, chromium and nickel concentrations in the normal range were calculated, with the exception of the nickel concentrations in the upper and lower lobes of the right lung. The very high nickel concentrations found in the samples of lung tissue from former nickel refinery workers should be regarded as a guideline with regard to the appraisal of the causal relationship between lung cancer and occupational exposure to relatively insoluble nickel compounds. This result is also supported by epidemiological investigations on this subgroup and must thus be considered etiologically conclusive. For the welders, chromium and nickel concentrations were found that were markedly above normal, but as yet there is no epidemiologically reliable verification for the increased occurrence of malignancies in this occupational group. On the basis of present scientific knowledge, no indications were found of relevant chromium and/or nickel exposure of the lung tissue that might be able to induce lung cancer in either foundry workers or for electric technicians.

Key words: Nickel – Chromium – Lung tissue – Norm values – Occupational exposure

Dedicated to Professor V. Becker on his 65th birthday

Offprint requests to: H.J. Raithel, Institut für Arbeits- und Sozialmedizin und Poliklinik für Berufskrankheiten der Universität Erlangen-Nürnberg, Schillerstraße 25/29, D-8520 Erlangen, Federal Republic of Germany

Introduction

Chromium (Cr) and nickel (Ni) and their compounds play an important role in many fields of modern industry. Substitutes will not be available even in the future or only to a very limited extent. On a worldwide basis, the annual production of chromium is specified as just under three million tons, and for nickel as about 750,000 tons (Wedepohl 1984). It is

thus to be assumed that there are many possibilities for occupational exposure. Specific industrial medical monitoring measures have become necessary since it has been shown that both chromium and nickel and their compounds can *damage health acutely and after chronic exposure* (Leonard et al. 1981; Raithel and Schaller 1981; Langard 1982; Rigaut 1983; Sunderman jr. 1981, 1984; Raithel 1987). The following pathophysiological reactions and disease manifestations should be considered:

1. *Toxic or chemical irritative actions*, especially from nickel tetracarbonyl and hexavalent chromates
2. *Allergic diseases* in the region of the skin (contact eczema) and the respiratory tract (bronchial asthma), in particular from water-soluble nickel compounds and chromates
3. *Malignancies* of the nose and the paranasal sinuses, as well as the lungs and bronchial system

Whereas an increase in the occurrence of lung cancer has been observed both in the chromate-manufacturing and chromate-processing industry, a rise in the prevalence of lung tumors and malignancies of the nose and paranasal sinuses has been observed epidemiologically in nickel workers only in the field of nickel refining (Doll 1984). The quantitative analysis of foreign substances in biological material as a means of occupational health surveillance has increasingly been felt to be important for workers exposed to both nickel and chromate (Schaller et al. 1982; Franchini et al. 1984; Wiegand et al. 1985; Sunderman jr. et al. 1986). Today, *biological monitoring* must be regarded as an important instrument for preventive measures at the workplace. Analysis of urine and blood has attained priority for reasons of practicability. However, it should be noted that only the current exposure or concentration of the bioavailable proportion of potential noxae can be appraised by quantitative determination of foreign substances in the body fluids. Important factors influencing these parameters are the nature of absorption, the solubility behavior of the individual compounds in blood and urine, and metabolism and kinetics of elimination. Direct inferences are not possible based on the results of such analyses with regard to cumulative effects in organs. These factors play a major role, especially in an occupational medical appraisal of the causal connection between occupational exposure and late lesions, e.g., cancer. In individual cases, the crucial problem mostly consists of answering the question as to whether demonstration of a specific dust component can be causally related to a disease of provisionally unclear etiology that affects the lungs or the bronchial system, the nose, and its paranasal sinuses. Exposure to dust consisting of a single element or compound is rare. Mixed dusts of differing pathogenicity and toxicity mostly characterize the occupational situation with regard to external exposure. Examples are work in the smeltery, foundry, and welding with highly divergent working techniques and consequently different patterns of exposure.

Analyses in samples of lung tissue are appropriate for the appraisal of long-term inhalative exposure to chromium and nickel compounds difficult to dissolve. They may be suitable for providing major pointers concerning the extent of an inhalative exposure that has occurred. The information provided by such investigations has been limited so far, on the one hand, by lack of reliable normal values (especially topographical anatomical distribution patterns) and on the other by limited chromium and nickel determinations in the lung tissue of persons specific exposed to substances.

The objective of our investigation should thus be to provide information from nickel and chromium determinations in samples of lung tissue, which would facilitate appraisal of the causal connection between occupational exposure to chromium and/or nickel and malignant diseases of the lungs or bronchial system.

Materials and methods

For *evaluation of the normal ranges*, samples of lung tissue were taken (courtesy of Dr. Schellmann) from 30 deceased persons on whom an autopsy was performed at the Institute of Forensic Medicine, Erlangen-Nuremberg University, from September 1985 to December 1986. The deceased persons comprised *29 men and 1 woman* who had died following traffic accidents or intoxications, or had committed suicide. The essential data on the autopsied persons are presented in Table 1. As far as could be established, there was no occupational expo-

Table 1. Essential parameters concerning the non-exposed subjects ($n = 30$)

Sex distribution	1 Female, 29 Males	
Age	x_m (median)	49 years
	Range:	17–83 years
Causes of death	Suicide:	6 (20%)
	Traffic and work accidents:	13 (43.3%)
	Others: (intoxication, myocardial infarction)	11 (36.7%)
Smoking habits	Smokers:	19 (63.3%)
	Nonsmokers:	5 (16.7%)
	No information:	6 (20.0%)
Pathological findings of the lung	Anthracosis:	23
	Bronchitis:	20
	Emphysema:	15

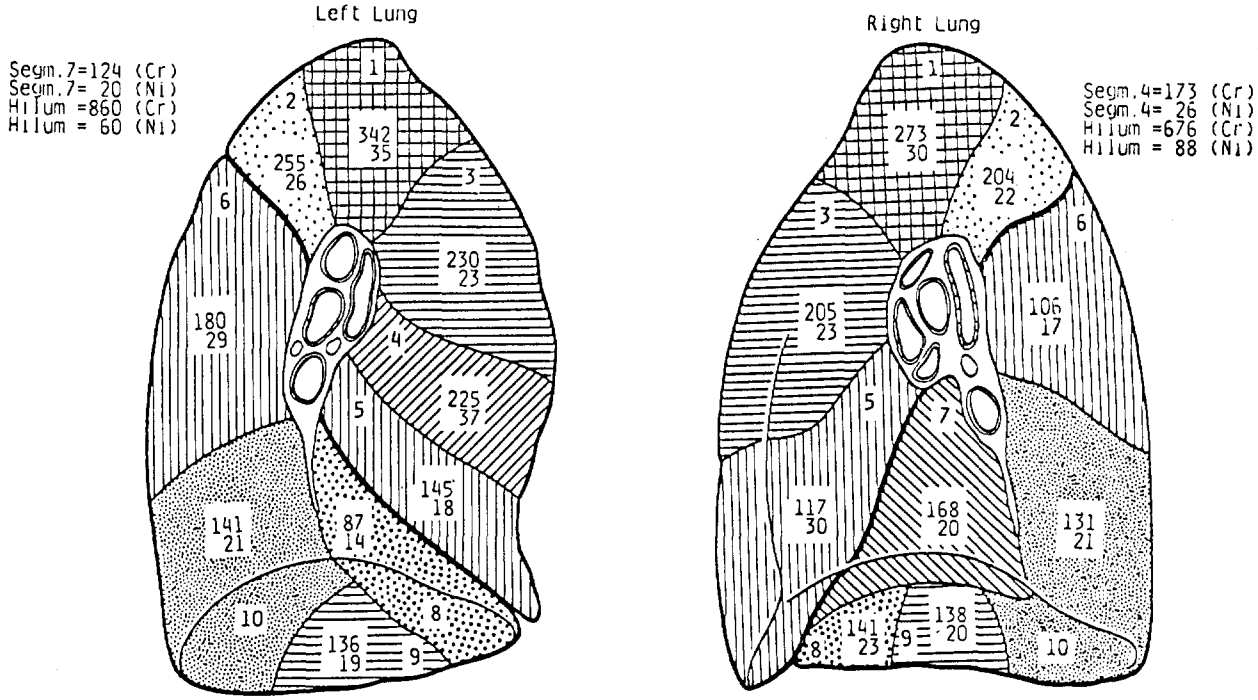

Fig. 1. Median concentrations ($N = 15$) for chromium (Cr) and nickel (Ni) measured (ng/g wet weight) in individual lung segments. The *upper number* represents the pulmonary segment; the *middle number* indicates the Cr concentration; the *lower number* indicates the Ni concentration

sure to chromium and nickel or its compounds in any of the deceased persons. In about half of the autopsied persons, there were indications of a chronic lung disease such as bronchitis, emphysema, or anthracosis. The lung samples were taken at an average of 24 h after death. In 15 of the deceased persons, a tissue sample was taken from *every segment of the lung* (cf. Fig. 1) and from the hilus region, depending upon the topographical anatomical conditions. Altogether, we analyzed ten samples from the left and ten from the right lung and, in addition, two tissue samples from the hilus lymph node.

In the other 15 deceased persons of the normal group, we investigated one sample taken peripherally and one sample taken from the center of *each lobe of the lung*, as well as a sample from the hilus region. Eleven tissue samples were available from each of the autopsy cases.

The *persons exposed to nickel and/or chromium* were:

Eleven former *nickel refinery workers* from Kristiansand in Norway

Two *stainless steel welders*, who also worked in the nickel refinery in Kristiansand in Norway

One *foundry worker* from Franconia (FRG)
One *electrical technician* from the Nuremberg-Fürth-Erlangen region (FRG)

As far as possible, the tissue samples were also taken from the subjects with the pertinent topographical anatomical criteria kept in mind. The precise locations are compiled in Table 2.

To avoid contamination, copper-beryllium-alloyed knives were used exclusively to take the samples. Quantitative analyses of the polishing dust of these knives did not reveal any detectable nickel and/or chromium content. The samples were transferred into especially cleaned plastic vessels with plastic forceps and deep-frozen up to the time of analysis. The quantitative determination of chromium and nickel was carried out by atomic absorption spectrometry with Zeeman background compensation after wet-oxidative digestion. See Raithel et al. (1987) for details regarding the analytical procedure.

Results

Normal group

For a reliable appraisal of potential occupational chromium and/or nickel exposure of the lung tissue, reliable normal values must be determined and the topographical anatomical criteria kept in mind. Only very limited data are available in the literature, and the results reported are mostly very divergent (Baumgardt et al. 1986; Iyengar 1985). This can be attributed to the analytical procedures used (in some cases highly divergent) as well as to the increasing sensitivity of atomic absorption spectrometry in recent years. The results of nickel and chromium analyses in lung tissue are presented according to the following criteria:

1. Intraindividually or taking the topographical anatomical features into consideration

Table 2. Medians (x_m), central 68th percentile ($x_1 - x_2$) and ranges of chromium and nickel concentrations measured in the individual lung segments, as well as in the hilus tissue (segment 11)

Segment		Right lung				Left lung			
		Chromium (ng/g)		Nickel (ng/g)		Chromium (ng/g)		Nickel (ng/g)	
		Wet weight	Dry weight	Wet weight	Dry weight	Wet weight	Dry weight	Wet weight	Dry weight
1	x_m	273.3	1218.1	30.0	161.8	342.2	1815.0	34.6	161.8
	$x_1 - x_2$	51– 393	254– 2068	14– 60	70– 277	90– 581	437– 3308	19– 51	102– 231
	$x_u - x_o$	34–1443	172– 6617	12–420	70–1927	68–2303	348–10565	19–605	102–2775
2	x_m	203.6	941.2	22.2	119.7	255.0	1351.9	25.7	119.7
	$x_1 - x_2$	39– 323	188– 1797	7– 39	17– 205	80– 447	394– 2054	14– 84	68– 411
	$x_u - x_o$	22–1090	113– 5001	4–300	17–1501	24–1713	122– 7858	11–537	58–2461
3	x_m	205.1	1099.0	23.0	105.8	229.9	1140.4	23.0	105.8
	$x_1 - x_2$	66– 464	333– 1844	11– 54	44– 209	69– 766	354– 3603	4– 73	23– 333
	$x_u - x_o$	16–2072	78– 9503	5–791	26–3630	34–1211	170– 5812	4–382	23–1754
4	x_m	172.7	923.5	25.9	144.4	224.8	1201.7	36.7	181.7
	$x_1 - x_2$	75– 241	349– 1293	6– 43	30– 243	67– 502	248– 2467	12– 66	56– 347
	$x_u - x_o$	48– 821	243– 3764	1–234	5–1073	33– 666	167– 3055	7–141	36– 645
5	x_m	117.0	576.0	30.1	170.4	145.3	719.9	17.9	102.2
	$x_1 - x_2$	39– 406	199– 2184	13– 58	54– 294	37– 310	189– 1617	7– 38	35– 189
	$x_u - x_o$	22– 728	110– 3716	8–137	40– 630	11– 968	55– 4439	5–248	25–1339
6	x_m	105.9	632.5	17.4	78.0	180.4	995.1	29.1	142.0
	$x_1 - x_2$	48– 281	233– 1582	9– 72	51– 387	60– 313	291– 1491	8– 48	41– 243
	$x_u - x_o$	17– 535	84– 2452	3–171	14– 785	4– 412	18– 2047	7– 84	37– 381
7	x_m	167.8	993.3	20.0	90.1	124.0	747.0	20.0	90.1
	$x_1 - x_2$	43– 357	186– 1855	8– 34	22– 159	51– 287	254– 1445	7– 30	31– 159
	$x_u - x_o$	36– 776	181– 3863	2–127	8– 582	5–1369	23– 6281	7–109	31– 500
8	x_m	140.7	654.3	23.1	99.3	86.6	429.6	13.9	86.1
	$x_1 - x_2$	32– 207	165– 1090	6– 29	27– 165	40– 205	205– 1071	5– 32	27– 159
	$x_u - x_o$	23– 315	117– 1483	4– 49	20– 262	24– 663	120– 3040	5–238	22–1092
9	x_m	138.5	640.8	19.7	107.9	136.2	818.5	18.6	96.8
	$x_1 - x_2$	47– 258	213– 1335	4– 38	14– 175	16–213	130– 1118	5– 35	25– 175
	$x_u - x_o$	39– 468	199– 2208	3– 81	14– 383	8– 556	41– 3550	2–117	8– 537
10	x_m	130.8	784.7	21.0	107.4	141.1	928.3	21.0	97.1
	$x_1 - x_2$	39– 339	184– 1647	3– 51	15– 277	30– 303	159– 1364	10– 27	51– 169
	$x_u - x_o$	33– 515	170– 2496	3– 68	15– 370	15– 356	76– 1801	6–119	29– 562
11	x_m	676.5	3298.9	87.8	438.1	869.1	4069.2	60.3	328.1
	$x_1 - x_2$	184–1095	906– 5500	47–225	191–1126	60–1449	273– 7893	19–143	81– 906
	$x_u - x_o$	122–2756	621–14898	37–458	189–2473	22–2515	112–16656	10–397	53–1806

2. Interindividually, in which stratification features such as age and smoking habits must be considered.

In Fig. 1 (in relation to wet weight) and Table 2 (right and left lung), the median, central 68th percentile, and the ranges of chromium and nickel concentrations measured in the individual lung segments as well as in the hilus tissue are shown in 15 "normal subjects."

A compilation of parameters analogous to those in Table 2 is presented for the individual lung lobes in Table 3, based on 30 subjects. The chromium concentrations are 5.7–7.9 times higher compared to the nickel values in the upper and lower lobes, 4.2 times higher in the middle lobe of the right lung, and 7.2–11.9 times higher in the hilus region. The mean values, standard deviations, and coefficients of variation of chromium and nickel concentrations in the lungs of 30 subjects are shown in Table 4.

With regard to the topographical anatomical criteria, 1.3 to 1.8 times higher concentrations are detected both for chromium and nickel in the upper areas of the lungs compared to the lower areas. By

Table 3. Medians (x_m), 68th and 95th percentiles of chromium and nickel concentrations measured in the individual lung lobes and hilus tissue ($n = 30$)

	Localization		Chromium (ng/g)		Nickel (ng/g)	
			Wet weight	Dry weight	Wet weight	Dry weight
Left lung	LL	x_m	150.8	790.8	24.9	126.8
		$x_{16/84}$	67.7– 300.0	329.7– 1448.3	10.3– 82.1	57.2– 405.4
		$x_{5/95}$	20.5– 671.9	107.7– 3232.8	7.9–156.3	38.8– 793.9
	UL	x_m	277.5	1374.8	40.0	195.4
		$x_{16/84}$	79.1– 563.3	397.7– 3202.0	15.2–120.1	81.5– 600.0
		$x_{5/95}$	44.1–2031.4	212.0– 9240.7	12.2–319.3	61.9–1566.3
	Hilus	x_m	950.3	4611.3	76.7	387.3
		$x_{16/84}$	67.9–1905.6	345.9– 9537.1	20.5–252.6	103.4–1262.4
		$x_{5/95}$	34.5–2617.5	180.8–16334.2	9.4–367.9	50.0–1903.7
Right lung	LL	x_m	170.3	850.7	20.2	107.2
		$x_{16/84}$	57.1– 295.2	284.7– 1428.9	7.9– 71.1	42.1– 337.6
		$x_{5/95}$	21.4– 577.6	105.9– 2756.8	3.6–139.5	19.0– 639.5
	ML	x_m	133.2	742.4	35.1	175.9
		$x_{16/84}$	56.2– 423.8	288.2– 2049.1	15.4– 77.3	77.4– 381.6
		$x_{5/95}$	35.1– 711.9	198.4– 3434.2	6.0–175.4	29.7– 840.7
	UL	x_m	229.8	1078.0	36.7	189.6
		$x_{16/84}$	81.7– 380.9	402.1– 1968.0	13.8– 91.0	71.0– 449.5
		$x_{5/95}$	29.9–1404.1	141.1– 6719.0	7.5–314.4	42.2–1516.6
	Hilus	x_m	702.5	3375.3	95.6	468.3
		$x_{16/84}$	231.7–1890.6	1177.1–10495.4	53.4–294.5	260.1–1473.5
		$x_{5/95}$	81.5–3158.1	416.0–17159.2	30.0–697.0	147.3–3762.8

LL, lower lobe; ML, middle lobe; UL, upper lobe

Table 4. Individual data on chromium and nickel concentrations in lung tissue [mean ($\bar{x}$), standard deviation (SD), coefficient of variation (CV)]. Subjects 1–15: 20 lung tissue samples/subject; Subjects 16–30: 10 lung tissue samples/subject

Parameter		Subject no.														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Chromium (ng/g)	$\bar{x}$	259.2	52.1	71.4	29.0	223.1	285.4	324.2	299.1	320.9	179.6	304.1	87.0	897.9	136.2	186.6
	SD	88.2	26.9	18.9	22.9	225.2	114.1	104.7	157.4	221.2	146.9	222.4	27.2	616.9	141.0	83.8
	CV (%)	34.0	51.7	26.5	78.8	101.0	40.0	32.3	52.6	69.0	81.8	73.1	31.2	68.7	103.5	45.0
Nickel (ng/g)	$\bar{x}$	54.8	19.8	39.3	22.6	19.8	17.2	60.2	39.8	36.7	18.7	33.1	16.3	242.4	17.0	28.7
	SD	59.5	12.6	12.1	11.0	22.7	12.8	29.8	20.8	27.4	20.4	52.5	9.4	207.3	6.8	19.8
	CV (%)	108.7	64.0	30.8	48.8	114.4	74.7	49.5	52.2	74.7	109.5	158.7	57.3	85.5	40.1	66.9

Parameter		Subject no.														
		16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Chromium (ng/g)	$\bar{x}$	168.5	2049.9	124.5	213.5	570.1	197.0	253.5	285.7	266.3	120.6	98.9	1021.0	118.1	59.3	64.3
	SD	79.4	1229.3	55.5	79.2	216.9	188.5	100.1	105.9	122.0	98.8	37.3	1019.9	54.8	37.8	25.8
	CV (%)	47.1	60.0	42.9	37.1	38.0	95.7	39.5	37.1	45.8	81.9	37.7	99.9	46.4	63.7	40.1
Nickel (ng/g)	$\bar{x}$	25.4	429.9	14.7	14.2	81.0	9.9	190.8	41.6	107.8	60.9	67.6	75.2	27.2	20.3	15.7
	SD	7.7	292.5	10.7	6.2	32.4	8.8	46.2	23.3	20.4	12.9	33.7	55.8	11.4	10.8	7.9
	CV (%)	30.3	68.0	72.8	43.7	40.0	88.9	24.2	56.0	18.9	21.2	49.9	74.2	41.9	53.2	50.3

far the highest values were found in the *hilus tissue* for both metals. These were 2–6 times higher both for chromium and nickel than the concentrations in the lung tissue. The ratio of metal concentrations in the lung tissue in relation to the dry weight or wet weight, respectively, was between 4.7 and 5.6 for chromium and between 4.9 and 5.3 for nickel.

Relatively large *interindividual variations* were shown in the two halves of the lung (cf. Table 4). For chromium, we found values between 29.0 ng/g and 2,049.9 ng/g for chromium and between 9.9 ng/g and 429.9 ng/g for nickel (in relation to wet weight). The *intrapulmonary concentration differences* are characterized with coefficients of variation of 26%–104% for chromium and 19%–159% for nickel (Table 4).

For further evaluation of the results, we carried out the following statistical calculations: (1) correlative comparison of the nickel and chromium concentrations in terms of topographic anatomical criteria; (2) correlative comparison of the intrapulmonary nickel and chromium concentrations; (3) correlative comparison of the contralateral nickel and chromium concentrations.

Regarding calculation 1, the regression equations and the correlation coefficients r are shown in Table 5. There is a good to very good *correlation between nickel and chromium concentrations* throughout with regard to topographical anatomical criteria (P less than 0.05). The correlation coefficients r were between 0.65 and 0.91. This means, in concrete terms, that in the lung regions in which relatively high nickel concentrations were found, relatively high chromium concentrations could also be demonstrated. The same naturally also applies to the low concentrations.

Regarding 2, good to very good correlations were also shown in the intrapulmonary comparison, apart from the nickel and chromium concentrations in the hilus region. The coefficients were between 0.70 and 0.93 (Table 6). This means that in the same lung, for example, relatively high nickel concentrations in one *upper lobe* correspond to relatively high concentrations in the *lower lobe or middle lobe* and vice versa.

The comparatively poorer correlation in the region of the hili must be attributed essentially to the anatomical and functional peculiarity of this tissue (lymph-node material). On the basis of clinical and pathological experience, it is to be assumed that the parahilar lymph nodes are to be regarded as the essential sites of dust storage as well as the transport means of inhaled foreign bodies.

Concerning 3, correlative comparison of the contralateral nickel and chromium concentrations (Table 7) revealed a high level of significance with correlation coefficients of 0.70–0.90 on the basis of $n = 30$. In concrete terms, it is to be inferred from this that high nickel or chromium concentrations in the *left* lower and upper lobes correspond to comparably high nickel and chromium concentrations in the *right* lower and upper lobe. This also applies to the concentrations in the hilus tissue.

Table 5. Correlation of Ni and Cr concentrations regarding the topographical situation (ng/g dry weight)

Correlation		No.	$y' = ax + b$	r
Ni-LL-left	vs Cr-LL-left	30	$y' = 4.09x + 149$	0.91*
Ni-UL-left	vs Cr-UL-left	30	$y' = 3.53x + 932$	0.66*
Ni-hilus-left	vs Cr-hilus-left	30	$y' = 4.27x + 2683$	0.77*
Ni-LL-right	vs Cr-LL-right	30	$y' = 2.54x + 471$	0.65*
Ni-ML-right	vs Cr-ML-right	29	$y' = 4.31x + 123$	0.88*
Ni-UL-right	vs Cr-UL-right	30	$y' = 3.42x + 547$	0.81*

LL, Lower lobe; ML, middle lobe; UL, upper lobe; * $P < 0.05$

Table 6. Correlation of the intrapulmonary Cr and Ni concentrations (ng/g dry weight); * $P < 0.05$

Correlation		No.	$y' = ax + b$	r
Ni-UL-left	vs Ni-LL-left	30	$y' = 0.77x - 33$	0.93*
Cr-UL-left	vs Cr-LL-left	30	$y' = 0.53x + 56$	0.77*
Ni-UL-right	vs Ni-LL-right	30	$y' = 0.30x + 95$	0.70*
Cr-UL-right	vs Cr-LL-right	30	$y' = 0.29x + 471$	0.73*
Ni-ML-right	vs Ni-LL-right	29	$y' = 0.49x + 72$	0.72*
Cr-ML-right	vs Cr-LL-right	30	$y' = 0.41x + 444$	0.78*
Ni-UL-right	vs Ni-ML-right	30	$y' = 0.53x + 59$	0.83*
Cr-UL-right	vs Cr-ML-right	30	$y' = 0.69x + 93$	0.93*
Ni-LL-left	vs Ni-hilus-left	30	$y' = 1.57x + 271$	0.83*
Ni-UL-left	vs Ni-hilus-left	30	$y' = 1.27x + 198$	0.80*
Cr-UL-left	vs Cr-hilus-left	30	$y' = 0.86x + 3717$	0.52*
Ni-LL-right	vs Ni-hilus-right	30	$y' = 2.36x + 498$	0.42*
Cr-LL-right	vs Cr-hilus-right	30	$y' = 3.20x + 2101$	0.52*
Ni-ML-right	vs Ni-hilus-right	29	$y' = 1.96x + 430$	0.52*
Cr-ML-right	vs Cr-hilus-right	30	$y' = 1.97x + 2666$	0.60*
Ni-UL-right	vs Ni-hilus-right	30	$y' = 1.03x + 607$	0.43*
Cr-UL-right	vs Cr-hilus-right	30	$y' = 1.40x + 2765$	0.57*

Table 7. Correlation of Ni and Cr concentrations in both lungs (left-right, ng/g dry weight); * $P < 0.05$

Correlation		No.	$y' = ax+b$	r
Ni-LL-left	vs Ni-LL-right	30	$y' = 0.33x + 108$	0.76*
Ni-UL-left	vs Ni-UL-right	30	$y' = 0.77x + 46$	0.90*
Ni-hilus-left	vs Ni-hilus-right	30	$y' = 1.09x + 189$	0.85*
Cr-LL-left	vs Cr-LL-right	30	$y' = 0.27x + 636$	0.70*
Cr-UL-left	vs Cr-UL-right	30	$y' = 0.60x + 359$	0.89*
Cr-hilus-left	vs Cr-hilus-right	30	$y' = 0.72x + 1110$	0.72*

Table 8. Median (x_m) and ranges of Cr and Ni concentrations (ng/g wet weight) in human pulmonary tissue regarding smoking habits

	Localization		Chromium (ng/g)		Nickel (ng/g)	
			Nonsmokers ($n = 5$)	Smokers ($n = 19$)	Nonsmokers ($n = 5$)	Smokers ($n = 19$)
Left lung	LL	x_m	142.0	186.80	25.4	24.6
		Range	68.1– 288.9	41.0– 629.3	17.4– 99.3	8.4–125.8
	UL	x_m	200.0	292.3	27.4	47.4
		Range	111.5– 285.4	48.6–1,372,2	13.9– 64.9	10.9–380.8
	Hilus	x_m	1,628.0	868.9	130.6	96.6
		Range	87.5–2,724.4	67.7–2,256	57.5–341.3	9.4–396.6
Right lung	LL	x_m	104.7	212.5	42.0	20.0
		Range	69.6– 308.9	10.7– 752.9	4.1– 55.6	3.4–163.5
	ML	x_m	128.0	227.3	23.0	36.0
		Range	91.6– 238.8	36.2– 664.9	3.4– 58.7	8.8–185.6
	UL	x_m	157.3	301.6	27.7	37.0
		Range	120.9– 382	36.6– 664.9	15.3– 53.7	6.5–503.7
	Hilus	x_m	730.8	730.8	151.7	90.9
		Range	345.8–3,565.8	44.6–2,756.1	75.6–667.1	23.8–728.4

With reference to *smoking habits* (Table 8), we were able to determine 1.3–2.0 times higher chromium concentrations in smokers than in nonsmokers. On the other hand, no correlation between the nickel values and smoking behavior could be detected.

With regard to *correlation with age*, the regression analyses revealed a rise in the chromium concentrations only in the upper lobes of the lungs and in the hilus region. This correlation was significant on the 5% level. On the other hand, the nickel values did not show any dependence on age.

Table 9. Ni and Cr concentrations in lung tissue of 10 nickel-refinery workers (Kristiansand, Norway) who had died from bronchiogenic carcinoma (with reference to normal values)

Subject	Ni (ng/g lung tissue)		Cr (ng/g lung tissue)	
	Wet weight	Dry weight	Wet weight	dry weight
A	18,000	273,900	162.1	2,488.4
B	23,800	311,400	221.3	2,892.3
C	36,800	604,500	387.3	7,150.8
D	28,600	277,300	561.9	5,448.0
E	93,900	931,900	502.2	5,003.6
F	30,200	399,300	273.0	3,615.2
G	6,700	59,400	251.4	2,242.9
H	1,600	17,900	153.0	2,391.5
I	3,000	29,300	356.9	3,473.0
J	5,800	59,300	582.2	5,907.3
Normal values (68th percentile)	8–120	41–600	56–563	285–3,202
(x_m)	31.4	159	192.2	967.4

Subjects with occupational chromium and/or nickel exposure

The samples of lung tissue of *11 former nickel refinery workers* (Kristiansand, Norway) were analyzed. Of these subjects, ten had died of lung cancer. In addition, *two stainless steel welders*, who likewise worked at the nickel refinery mentioned above, were also investigated. The results of quantitative nickel and chromium determinations are summarized in Ta-

Table 10. Ni and Cr concentrations in lung tissue of a nickel-refinery worker with reference to the topographical situation. Cause of death: apoplexy

Localization	Cr (ng/g)		Ni (ng/g)	
	Dry weight	Wet weight	Dry weight	Wet weight
Right-UL-peripheral	5,263	333	104,000	6,600
Right-UL-central	5,401	36	91,200	6,000
Right-ML-peripheral	3,150	181	57,500	3,300
Right-ML-central	792	90	10,800	1,200
Right-LL-peripheral	1,782	111	41,800	2,600
Right-LL-central	2,440	133	32,400	1,800
Left-UL-peripheral	3,390	206	45,800	2,800
Left-UL-central	1,326	130	16,300	1,600
Left-UL-peripheral	1,343	96	29,100	2,100
Left-LL-central	3,867	364	41,500	3,900

Tabele 11. Ni and Cr concentrations of two deceased stainless steel welders with reference to special regions of the lung

Localization	Nickel (ng/g)				Chromium (ng/g)			
	Dry weight		Wet weight		Dry weight		Wet weight	
	A	B	A	B	A	B	A	B
Right upper lobe, peripheral	55,150	43,050	8,500	3,860	26,130	25,320	4,030	2,270
Right upper lobe, medial	17,580	62,400	2,590	5,440	17,190	31,450	2,530	2,740
Right upper lobe, central	16,350	49,020	2,880	5,740	31,490	28,600	5,540	3,350
Right middle lobe, peripheral	6,710	22,840	970	2,520	12,170	18,500	1,750	2,040
Right middle lobe, medial	28,120	16,560	4,590	2,000	24,070	11,900	3,930	1,440
Right middle lobe, central	6,710	1,620	1,210	200	15,380	7,240	2,770	910
Right lower lobe, peripheral	26,150	30,280	3,410	3,410	36,680	11,880	4,790	1,500
Right lower lobe, medial	4,800	20,650	630	2,290	6,000	14,020	790	1,490
Right lower lobe, central	5,210	39,170	780	4,940	9,610	29,130	1,430	3,280
Left upper lobe, peripheral	13,710	1,010	1,910	130	17,460	3,880	2,430	440
Left upper lobe, medial	25,820	31,960	3,080	3,590	19,450	12,290	2,320	1,380
Left upper lobe, central	10,070	230	1,670	43	3,250	610	540	110
Left lower lobe, peripheral	6,660	115,870	1,080	14,590	7,440	67,100	1,210	8,480
Left lower lobe, medial	4,690	119,480	780	12,550	6,810	86,790	1,140	9,130
Left lower lobe, central	5,640	70,250	890	8,040	5,380	42,750	850	4,890

Table 12. Ni concentrations in lung tissue of a foundry worker who died of bronchiogenic carcinoma (comparison to normal values)

Localization	Ni (ng/g lung tissue)	Norm values	
		Median	(90th percentiles)
Right ML	87.3	35.1	(6–175)
Right ML and tumorous tissue	183.9	—	—
Right LL	541.0	20.1	(7–314)
Right UL	450/517	36.7	(4–140)
Left UL	296.6	40.0	(12–319)
Left LL	147	24.9	(8–156)
Left lung (two samples)	11.8/37.9	24.9/40.0	(8–319)

bles 9–11. Whereas only one tissue sample was available in each case for the ten refinery workers who died of lung cancer, it was possible to make metal analyses in the other subjects, keeping the topographical anatomical conditions in mind. We compared and contrasted the values obtained with the normal ranges we found.

We measured extremely high values with regard to nickel concentrations in all *refinery workers:* these exceeded the normal ranges by the factor 112–5,860 (in relation to the dry weight). On the other hand, the chromium concentrations were in some cases in the region of normal or raised a maximum of 7.4. Values exceeding the normal range could not be detected for chromium, even to an extent approximately comparable to that for nickel.

Since the suspicion has also been expressed in occasional publications (Hill 1966) that sulfuric acid, contamined in particular by arsenic, might be crucially involved in the induction of cancer conditions, we likewise measured this element quantitatively in lung tissue in the 11 former refinery workers. However, the arsenic concentrations found were mainly within the normal range.

The nickel and chromium concentrations in lung tissue of former stainless steel welders (A and B) who had also worked in the area of nickel refining are summarized in Table 11. Rupture of an aneurysm in the brain or in myocardial infarction were detected as causes of death on autopsy. Both the chromium and nickel concentrations were markedly in excess of the normal range in most regions of the lungs. The nickel exposure was relatively higher than chromium. Up to more than 500 times the normal value was found for nickel, but the concentrations for chromium were raised by a maximum factor of 60 (wet weight).

In Table 12, the nickel concentrations in the lung tissue of a *foundry worker* who had died of lung cancer are compared with the normal ranges determined. This subject had been working in a Lower Franconian foundry for many years and had heavy smoking habits as well. The nickel values found were mainly in the region of normal or were raised by maximum factor of 27 (right lower lobe of the lungs, referring to the median value).

In Table 13, the chromium and nickel concentrations in a former *electrical technician* are shown in relation to topographical anatomical factors in lung tissue. The subject had died of severe craniocerebral

Table 13. Cr and Ni concentrations in lung tissue of a deceased electrician. (< DL = below the detection limit)

	Localization	Chromium (ng/g)		Nickel (ng/g)	
		Wet weight	Dry weight	Wet weight	Dry weight
Left lung	LL central	73.4	425.7	36.3	210.5
	UL peripheral	101.9	540.1	44.3	234.8
	UL central	37.6	199.3	< DL	< DL
	Hilus	248.9	1219.6	79.9	391.5
Right lung	LL peripheral	41.9	243.0	17.8	103.2
	LL central	59.5	345.1	169.5	983.1
	ML peripheral	104.7	565.4	61.2	330.5
	ML central	32.2	173.9	25.3	136.6
	UL peripheral	27.4	145.2	22.9	121.4
	UL central	101.0	535.3	65.9	349.3
	Hilus	101.0	494.9	32.4	158.8

trauma due to an accident. It could be established with regard to his occupational history that he had been working in a Franconian electronic company for 12 years. According to information from his working colleagues, mechanical work such as turning, milling and cutting materials containing nickel and chromium had only been undertaken occasionally. Values in the normal range were found both for chromium and nickel in the entire lungs, including the hilus (with the exception of nickel, central right lower lobe). No relevant exposure of the lung tissue to chromium or nickel can be assumed.

Discussion

According to the present level of scientific knowledge, it can be assumed that both chromium and nickel, as well as their compounds, can induce damage to health after acute and chronic exposure (Rigaut 1983; Doll 1984; Sunderman jr. 1984; Langard 1982; Raithel and Schaller 1981; Raithel 1987). Lung cancer and cancer of the nose and paranasal sinuses are frequently observed in nickel refinery workers and in persons exposed to chromate; this is an especially acute problem in occupational medicine and social law. The results of recent investigations have shown that these metals cumulate in lung tissue, especially during occupational exposure to the relatively insoluble chromium and nickel compounds (Turhan et al. 1985; Baumgardt et al. 1986; Raithel 1987). Quantitative detection of these heavy metals in samples in lung tissue thus permits conclusions to be drawn regarding the occurrence of exposure in the distant past. Zober et al. (1984) and Kollmeier et al. (1985) have also referred to the significance of such analyses.

Since chromium and nickel and their compounds must be regarded as metals of ubiquitous occurrence today owing to progressive industrialization, the evaluation of normal values and ranges is an important precondition for the appraisal of potential occupational cumulation of chromium and nickel in the lung tissue. The results published so far for nickel and chromium content in samples of normal lung tissue are quite different (Raithel et al. 1987).

In view of the divergent results, it was necessary to establish objective distribution patterns of chromium and nickel in both halves of the lung in terms of topographical anatomical criteria and thus to evaluate reliable normal ranges. Some authors (Vanoeteren et al. 1982; Turhan et al. 1985) took tissue from different lobes of the lung, but as far as we know the segmental approach we used has not been carried out so far by other study groups.

In agreement with the results of other study groups, the values obtained in the "normal group" of 30 deceased subjects show *intraindividual differences* for both chromium and nickel. The concentrations that were higher on average in the upper areas of the lungs and in the right middle lobe must be attributed essentially to the physiologically better ventilation conditions in these regions of the lungs. This can result in an increased deposition of dusts which pass into the lungs (diameter less than 5 µm). The 2–6 times higher chromium and nickel concentrations in hilar lymph node material should be regarded as the result of lymphogenic transport of inhaled foreign substances.

There were also distinct *interindividual* concentration differences. Although in the cases we investigated occupational exposure to chromium and nickel could not be established, brief exposure in the private sector cannot be ruled out with certainty in individual cases. Besides this, environmental influences such the area of residence (large city, small town, rural area, etc.) are likely to play a role. Further important marginal conditions to be considered are age, smoking habits, pulmonary diseases, or abnormal findings in the area of the respiratory tract such as chronic bronchitis, emphysema, and anthracosis.

The regression analyses revealed a *rise in chromium concentration* in the upper lobe of the lungs as well as the hilus region with increase of *age*. This correlation was significant on the 5% level. On the other hand, the nickel values did not show any dependence on age. Because of the relatively low number of subjects ($n = 30$), these results can only be rated as a tendency with regard to this correlation and should be checked in larger numbers of subjects.

Kollmeier et al. (1985) found a rising concentration with increasing age both for nickel and chromium. These results are based on investigations carried out in only one sample of lung tissue.

The *chromium concentrations in smokers* were about 1.3–2.0 times higher than in nonsmokers. On the other hand, the nickel values did not show any dependence on smoking behavior. The chromium and nickel contents we then measured in various filter cigarettes varied from 800–1850 ng/cigarette for nickel, and from 400–1500 ng/cigarette for chromium. These results do not provide a plausible explanation for the relatively higher chromium concentrations in lung tissue. In the interpretation of these results, it must also be considered that concomitant pulmonary diseases such as chronic bronchitis, emphysema were detected ultrastructurally in all smokers. The extent to which ventilation disorders caused by this are responsible for the higher chromium concentrations compared to nonsmokers cannot be appraised on the basis of our investigations.

If the normal nickel concentrations in lung tissue determined in a total of 30 deceased persons are compared with the results communicated in the recent scientific literature, a high measure of agreement is shown with the nickel values found by Kollmeier et al. (1985); Seemann et al. (1985), and Rezuke et al. (1987). With regard to the chromium concentrations, there are agreements above all with the results of the investigations by Hyodo et al. (1980); Turhan et al. (1985); Gerhardson et al. (1985); Seemann et al. (1985), and Kim et al. (1985).

If the normal ranges we established are related to the nickel concentrations measured in the *refinery workers* (ten died of lung cancer), extreme exposure of the lung tissue was found. The normal ranges for nickel were exceeded by a factor of 51–2,990 (in relation to the wet weight) in this subgroup. On the other hand, we found concentrations of chromium that were in the normal range or only slightly exceeded it in some cases. These results become comprehensible if the massive external exposure to dust containing nickel which is difficult to dissolve (as documented in Fig. 2), is taken into consideration. Average values exceeding the TRK value of 0.5 mg/m^3 is valid today in the Federal Republic of Germany by a factor of 200, and even higher values could be observed in the 1960s. The nickel concentrations found by Morgan and Adams (1980) in Welsh nickel refinery workers also indicated for the first time that there was a considerable cumulation of this metal in lung tissue.

We were also able to detect a relatively high exposure to chromium and nickel in the lungs of the two *stainless steel welders*. In relation to the normal ranges, the nickel concentrations were maximally

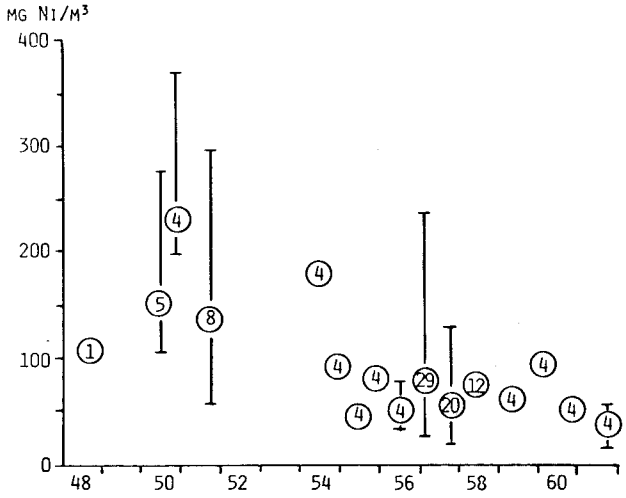

Fig. 2. Concentrations of nickel in dusty air leaving the roof monitors of the Copper Cliff Sinter Plant in the period from 1948–1961 (Warner 1985); numbers in circles indicate number of examinations per year

more than 500 times the normal values and for chromium up to 60 times (in relation to wet weight) the normal values. This shows that these subjects must have been exposed externally to nickel and chromium in terms of occupational medicine criteria. In welding techniques with basic or rutile-enveloped rod electrodes, welding smoke or aerosols containing chromate are formed. The relatively high nickel concentrations found must have occurred because the two stainless steel welders were working in the field of nickel refining, so that there was a substantial nickel exposure in addition in the neighborhood. The stainless steel welders we investigated did not die of malignancies of the respiratory tract, but from an apoplectic insult or myocardial infarction. It cannot be decided on the basis of our investigation as to what extent the markedly raised chromium and nickel concentrations in these special cases would have been suitable to induce lung cancer at a greater age. In a paper only recently published by Kishi et al. (1987), six chromate workers who had been occupationally exposed for over 10 years and all died of lung cancer, average chromate concentrations were demonstrated, which were 165 times higher than the median value in "normal persons." Kim et al. (1985) also found chromium concentrations in lung tissue raised by a factor of 90 in a chromate worker who died of bronchial carcinoma. The normal range for chromium of 70–1010 ng/g lung tissue (Kishi et al. 1987) or 170 ng/g (Kim et al. 1985) found by the two Japanese study groups mentioned are in good agreement with our results.

Compared to the occupationally exposed persons mentioned above, nickel analyses in the lung tissue of

a *foundry worker* who died of lung cancer revealed concentrations in the normal range, apart from the right lower lobe of the lungs where the normal range was exceeded by a factor of 27 in comparison to the median value. A comparable exposure to nickel and/or chromium such as we observed in refinery workers could not be objectively established.

The analysis of pulmonary tissue samples of the *electrical technician* who had died in an accident showed normal concentrations throughout for both chromium and nickel. The occasional contact with materials containing chromium or nickel documented in the occupational history had not led to any analytically detectable elevation of the two metals in the lung tissue in this subject.

It is to be observed *synoptically* that by far the highest nickel exposure was found in the former nickel refinery workers from Norway. These results must also be regarded as a guideline with regard to appraisal of the causal relationship between bronchial carcinomas and the occupational effects of relatively insoluble nickel compounds. This applies all the more since, so far, in the context of epidemiological investigations, the increased occurrence of malignant lung tumors as well as cancers of the nose and the paranasal sinuses could only be demonstrated for this specific subgroup. In view of this, there are indications for a toxicologically relevant chromium and/or nickel exposure of lung tissue, which would probably not have been adequate to induce lung cancer in either the foundry worker or in the electrical technician whom we investigated. On the contrary, the smoking habits over many years in the foundry worker must be recognized as having great causal significance according to occupational medical expertise.

In the stainless steel welders, chromium and nickel concentrations were found that were very much higher than normal. As yet there is no epidemiologically reliable verification for an increase in malignancies in this occupational group. In this connection, we must wait for the results of future studies. In the two specific single cases we investigated, the environmental exposure to nickel dust in refining must be taken into consideration when interpreting the results.

From the present results, the following conclusions can be drawn:

1. Atomic absorption spectrometry with Zeeman background compensation is an adequately sensitive analytical technique today for reliable quantification of nickel and chromium in lung tissue.

2. Because of interindividual variations, in the future only normal ranges should be specified for both chromium and nickel in lung tissue – even in persons not exposed occupationally.

3. Investigations using large numbers of subjects are necessary in order to show the extent to which special "normal ranges" should be determined, depending on smoking habits, age, conditions of residence, etc.

4. Owing to varying metal concentrations, the result of one tissue analysis is not representative in questions of occupational medicine expertise concerning the causal relationship between lung cancer and alleged occupational chromium and/or nickel exposure. On the contrary, multiple determinations are necessary and should include anatomical criteria. Preservation of the entire lung should be aimed at for post-mortem autopsies. In tissue sampling, attention must be paid to uncontaminated sampling and processing of samples.

5. The results of investigations available at present do not allow any unequivocal inferences as to the chromium and/or nickel concentrations in lung tissue from which a rise in cancer risk can be assumed. We found by far the highest nickel concentrations in former nickel refinery workers where there was massive external exposure to relatively insoluble nickel compounds as late as the 1950s and 1960s. In epidemiological terms, there is an unequivocal rise in the risk of contracting lung cancers as well as malignancies of the nose and paranasal sinuses; this has been established objectively only for this group at present. Taking into account this knowledge, the extremely high nickel concentrations in lung tissue found in refinery workers must be regarded as proof of a causal connection between the occurrence of lung cancer and past exposure to relatively insoluble nickel compounds. On the other hand, in terms of occupational medicine and toxicology, cases in which the normal nickel concentration in lung tissue is exceeded, such as that detected, for example, in a foundry worker who had died of lung cancer, should only be regarded as an indication of relatively low occupational exposure. At present, this exposure concentration cannot be regarded as a major contributory cause toward the development of lung cancer.

The former chromate workers in Japan who died of lung cancer and had chromium concentrations of 90 or 165 times higher than the normal values also indicate that substantial chromate exposure, with subsequent values markedly exceeding the normal range of chromium in lung tissue, can play a major role in causing a pulmonary tumor.

6. In the future, objective establishment and quantification of these metals in pulmonary tissue should be aimed at when occupational chromium and/or

nickel-induced lung cancer is suspected. This technique is even more important since in most cases reliable data on earlier occupational exposure, often decades in the past, can mostly not be obtained. Timely and harmonious cooperation of family doctors, occupational physicians, pathologists, and employers' liability insurance associations is necessary.

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