

Chapter 6

Lung Cancer and Exposure to Metals: The Epidemiological Evidence

Pascal Wild, Eve Bourgkard, and Christophe Paris

Abstract

Exposure to metallic compounds is ubiquitous, with its widespread use in industry and its presence, mostly in trace amounts, in the environment. This paper reviews the epidemiologic evidence of the relation between lung cancer and exposure to metallic compounds by building on and updating the corresponding International Agency for Research on Cancer (IARC) assessments. Given that most of the well-identified human populations with given metal exposure are in occupational settings, this review is mostly based on results in occupational epidemiology. The epidemiological evidence is shortly reviewed for accepted carcinogens: chromium, nickel, beryllium, cadmium, arsenic, and silicon, highlighting what is still unclear. We then review in more detail metals for which the evidence is less clear: lead, titanium, iron, and cobalt. There is scarce evidence for the human carcinogenicity of titanium. Exposure to titanium dioxide is associated with lung cancer excesses in one large study, but this excess may be due to confounders. The evidence for lead is contradictory. The lung cancer risk is presented as a function of a post hoc exposure ranking but no dose—response relationship is found. A weak but consistent lung cancer excess in many populations exposed to iron oxides but it is not possible to state on causality. Finally the evidence in the hard metal industry is presented, which suggests a possible carcinogenic effect of cobalt in presence of tungsten carbide. A short discussion presents the limitations of epidemiology in assessing the carcinogenicity of metals.

Key words: Carcinogens, environmental factors, lung cancer, metal carcinogens.

1. Introduction

Metals are defined in chemistry as elements that readily form positive ions and have metallic bonds. Although nonmetal elements are more commonplace on Earth than metallic elements, the latter constitute most of the periodic table of elements. Thus (including metalloids), over 80 different metallic elements exist, most of which exist with different chemical valences and in many compounds. However, many of these elements are very rare and

do not correspond to a large enough group of exposed humans to allow any epidemiological investigation of their possible effect. Nevertheless, certain rare metals are used in specific industrial applications so that there are some occupationally exposed groups, in which an epidemiological follow-up is possible.

It must be noted that the highest and most specific metal exposures occurred and still occur in occupational settings or in the immediate environment of industrial sources. The metal exposure in environmental settings is widespread but, except in immediate environment of industrial sources, much lower, much less specific and usually impossible to quantify precisely. Thus most epidemiological evidence, which can be directly related to an exposure to one or several metals, comes from cohort studies in occupational exposure groups.

We shall first screen systematically all metallic elements from the periodic table. Doing this, a first issue for each element is to identify whether there are any numerous enough human groups that are exposed to this metal or to its basic salts and compounds or whether there is any indication that such a group will exist in the future. A second issue is whether a suspicion of carcinogenicity has been raised with respect to this metal. This suspicion can be based on epidemiological studies or on other scientific evidence.

Finally we shall review the epidemiological evidence for the metals thus selected. This review will not concentrate on metals that have been officially classified as carcinogens for humans by regulatory agencies like the International Agency for Research on Cancer (IARC) or the United States National Toxicology Program (NTP) through its Reports on Carcinogens (RoC), although the rationale for each classification will be presented. For a list of possible or probable carcinogens, see the website of the American Cancer Society (http://www.cancer.org/docroot/PED/content/PED_1_3x_Known_and_Probable_Carcinogens.asp?sitearea=PED). Carcinogenicity of radioactive elements will not be discussed either, as their possible specific effect will be confounded with the effect of radioactivity. This review will concentrate on elements and their immediate compounds for which a suspicion of carcinogenicity has been published and that are typically classified as “probably or possibly carcinogenic” (2A or 2B) by IARC or “reasonably anticipated to be carcinogenic” by the NTP.

2. Metals: An Overview

Figure 6.1 shows the periodic table of elements. Starting with bottom of the table, nearly all elements with an atomic number > 86 are more or less radioactive and few human exposure groups exist. Pos-

sible exceptions with a low radioactivity and some human exposures are uranium-238 (depleted uranium) and thorium-232 dioxide. The group of lanthanides (scandium, yttrium, and the elements with atomic numbers between 57 and 71) also misnamed as rare earth elements (some lanthanides like, e.g., cerium, are quite common in the earth crust), have some industrial applications and some human exposure has been documented but no suspicion of carcinogenicity has been published to our knowledge (*see ref. (1)*). There is no suspected carcinogen within the group of alkali metals (except for an arsenic compound of lithium that has been classified as carcinogenic as an arsenic compound). Within the group of alkaline earth metals, beryllium (Be) is classified as carcinogenic to humans both by IARC and NTP. Contrary to its radioactive form, $^{90}\text{Strontium}$, suspected to be a bone carcinogen because it substitutes easily for calcium, its stable isotopes seem innocuous. The same lack of suspicion is true for the other alkali earth metals (calcium, magnesium, and barium). Most of the problematic metals are members of the group of transition metals. Thus titanium, chromium, iron, cobalt, tungsten, nickel, platinum, and cadmium have all, at some time and in some form, been suspected of, or been classified as, being carcinogenic (2). The human exposures to some others (scandium, vanadium, yttrium, zirconium, niobium, technetium, hafnium, tantalum, and rhenium) are too rare for any epidemiological investigation and these others have, to our knowledge, never been mentioned as carcinogenic. Exposure to manganese and molybdenum is less rare, and both play important biological roles as essential trace elements in enzymes. The platinum group of elements (ruthenium, osmium, rhodium, iridium, palladium, and platinum) is also composed of very rare elements but, by analogy to platinum, these elements might be suspected of being carcinogenic. Human exposure to gold (Au) and silver (Ag) is relatively widespread, but despite the toxicity of some of their compounds, there has never been any mention of carcinogenicity. Finally the possibility of mercury (Hg) being a carcinogen has been evaluated by the IARC in 1993 (3) and mercury is classified as a *possible carcinogen* but based on scant human evidence. In the last group of metals, the so-called poor metals, comprising aluminum, gallium, indium, tin, thallium, lead, and bismuth, only lead is considered as a potential carcinogen. Finally, within metalloids (boron, silicon, germanium, arsenic, antimony, tellurium, and polonium), which are not strictly metals, silicon (in the form of crystalline silica) and arsenic have been classified as human carcinogens both by IARC and NTP, but antimony has been considered as a possible carcinogen (4) based solely on animal data.

Following this brief overview of metallic elements, this chapter proceeds by shortly reviewing the epidemiological evidence of lung carcinogenicity of metals and metalloids classified as human carcinogens in one of their forms, i.e., chromium (Cr), nickel (Ni), cadmium (Cd), beryllium (Be), arsenic (As), and silicon (Si), insist-

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1 H 1.008																	2 He 4.003
3 Li 6.941	4 Be 9.012											5 B 10.811	6 C 12.011	7 N 14.007	8 O 15.999	9 F 18.998	10 Ne 20.180
11 Na 22.99	12 Mg 24.305											13 Al 26.982	14 Si 28.086	15 P 30.974	16 S 32.066	17 Cl 35.453	18 Ar 39.948
19 K 39.098	20 Ca 40.078	21 Sc 44.956	22 Ti 47.867	23 V 50.942	24 Cr 51.996	25 Mn 54.938	26 Fe 55.845	27 Co 58.933	28 Ni 58.693	29 Cu 63.546	30 Zn 65.39	31 Ga 69.723	32 Ge 72.61	33 As 74.922	34 Se 78.96	35 Br 79.904	36 Kr 83.80
37 Rb 85.468	38 Sr 87.62	39 Y 88.906	40 Zr 91.224	41 Nb 92.906	42 Mo 95.94	43 Tc (98)	44 Ru 101.07	45 Rh 102.91	46 Pd 106.42	47 Ag 107.87	48 Cd 112.41	49 In 114.82	50 Sn 118.71	51 Sb 121.76	52 Te 127.60	53 I 126.90	54 Xe 131.29
55 Cs 132.91	56 Ba 137.33	see below	72 Hf 178.49	73 Ta 180.95	74 W 183.84	75 Re 186.21	76 Os 190.23	77 Ir 192.22	78 Pt 195.08	79 Au 196.97	80 Hg 200.59	81 Tl 204.38	82 Pb 207.2	83 Bi 208.98	84 Po (209)	85 At (210)	86 Rn (222)
87 Fr (223)	88 Ra (226)	see below	104 Rf (261)	105 Db (262)	106 Sg (263)	107 Bh (262)	108 Hs (265)	109 Mt (266)	110 *	111 *	112 *	113 +	114 +	115 +	116 +	117 +	118 +
			57 La 138.91	58 Ce 140.12	59 Pr 140.91	60 Nd 144.24	61 Pm (145)	62 Sm 150.36	63 Eu 151.96	64 Gd 157.25	65 Tb 158.93	66 Dy 162.50	67 Ho 164.93	68 Er 167.26	69 Tm 168.93	70 Yb 173.04	71 Lu 174.97
			89 Ac (227)	90 Th 232.04	91 Pa 231.04	92 U 238.03	93 Np (237)	94 Pu (244)	95 Am (243)	96 Cm (247)	97 Bk (247)	98 Cf (251)	99 Es (252)	100 Fm (257)	101 Md (258)	102 No (259)	103 Lr (262)
alkali metals (+1)			alkaline earth metals (+2)				transition metals					other metals			other nonmetals		
halogens (-1)			noble gases (0)				lanthanides					actinides					

(*) elements have been discovered but have not been named yet.

(+) elements have yet to be discovered.

Fig. 6.1. Periodic table of the elements. *Elements have been discovered but have not been named yet; +Elements have yet to be discovered.

ing on the remaining scientific uncertainties. It then summarizes the epidemiological evidence for titanium (Ti), iron (Fe), lead (Pb), cobalt (Co), and tungsten (W), for which no consensus has yet been reached. A short discussion will complete this review.

3. Metals Recognized as Carcinogens

3.1. Chromium

Hexavalent chromium [Cr (VI)] was first linked to respiratory cancer as early as in the late 19th century (5). Since then, several epidemiological studies were conducted, mostly in the chromate and chromate pigments production across the world, and consistently reported high risks of lung cancer and nasal sinus cancer. This literature was assessed by IARC in 1990 in its monograph on chromium and chromium compounds (6). It concluded that "Chromium [VI] is *carcinogenic to humans*" based on "*sufficient evidence* in humans for the carcinogenicity of chromium [VI] compounds as encoun-

tered in the chromate production, chromate pigment production and chromium plating industries.” The situation is different with trivalent chromium, Cr [III], which is naturally occurring as chromic oxide in the mineral chromite. The main exposure to trivalent chromium and to metallic chromium occurs in the production of ferrochromium. Only three epidemiological studies are available within this industry, and were carried out in Sweden (7), Norway (8), and France (9). The evidence was conflicting and the only statistically significant excess occurred in the French study, in which the exposure to chromium was more or less confounded with exposure to other carcinogens in particular benzo(a)pyrene. This was summarized in the IARC monograph (6) by “Metallic chromium and chromium [III] compounds *are not classifiable as to their carcinogenicity to humans*” because of “inadequate evidence in humans for the carcinogenicity of metallic chromium and of chromium[III] compounds.” Since this IARC assessment, a number of epidemiological studies have been published (10–23), mostly confirming the lung cancer risk with chromium [VI] exposure. The last study (23) was remarkable in that the exposure assessment was based on over 12,000 urinary chromium exposure measurements. The authors concluded that their “data suggest a possible threshold effect of occupational hexavalent chromium exposure on lung cancer.” This suggestion was however strongly disputed by Michaels et al. (24). Finally, a reanalysis (25) of the data published by Gibb et al. (18) investigated the hypothesis of a possible threshold and found limited evidence in favor of a low cumulative exposure threshold.

3.2. Nickel

The earliest evidence with respect to a carcinogenic effect of nickel [Ni] was published in 1958 (26). In the following 30 years, several epidemiological studies were conducted in all sectors exposing workers to nickel compounds, i.e., mostly nickel extraction, refining, smelting, and use in stainless steel production. The main studies were conducted in Ontario (Canada), USA, Wales (UK), and Norway. In 1990, the International Committee on Nickel Carcinogenesis in Man (ICNCM), chaired by Sir Richard Doll, reported on the results of all the available studies, some of which had never been available in published form, in a comprehensive document (27). It concluded that “more than one form of nickel gives rise to lung and nasal cancer” and “The evidence from this study suggests that respiratory cancer risks are primarily related to soluble nickel at concentrations in excess of 1 mg Ni/m³ and to exposures to less soluble forms at concentrations > 10 mg Ni/m³.”

The IARC assessment (6) of the same year considered that “Nickel compounds are *carcinogenic to humans*” and “Metallic nickel is *possibly carcinogenic to humans*.” The first statement was based on “*sufficient evidence* in humans for the carcinogenicity of nickel sulfate, and of the combinations of nickel sulfides and oxides encountered in the nickel refining industry,” whereas the second

statement was based on experimental animal studies. Since 1990, the published evidence with respect to carcinogenicity of nickel has been conflicting. Two studies conducted in New Caledonia (28, 29) did not find any increased risk of respiratory cancer among nickel workers despite a reasonable power. The lung cancer mortality among nickel platers (30) was not found to be in excess. Similarly Sorahan and Williams (31) confirmed only partially in a recent survey the initial lung cancer excess in the Clydach (Wales) refinery described in ref. (27). On the other hand, Andersen et al. (32), Anttila et al. (33), as well as Grimsrud (34, 35), confirmed high level risks of lung cancer with consistent dose-response relationships. Although the issue remains controversial, this risk seems to be restricted to water-soluble nickel compounds (36).

3.3. Cadmium

Human exposure to cadmium [Cd] occurs predominantly through consumption of food and tobacco because cadmium bio-accumulates in plants via the contamination of topsoil by industrial activities. Cadmium and its compounds are used in a variety of industrial applications (batteries, pigments, alloys, electroplating and coating, plastics). Nowadays its predominant use is the production of nickel/cadmium batteries. In its 1993 monograph (3), IARC stated that “Cadmium and cadmium compounds are *carcinogenic to humans*” based on “*sufficient evidence*” both in humans and experimental animals. This was reinforced by the sentence “In making the overall evaluation, the Working Group took into consideration the evidence that ionic cadmium causes genotoxic effects in a variety of types of eukaryotic cells, including human cells.” The assessment of the human evidence was mostly based on several papers analyzing a US cohort of cadmium recovery workers, see, e.g., ref. (37), showing a dose-response relationship between lung cancer and cumulative cadmium exposure and a series of papers in a cohort of 17 UK cadmium processing plants, see e.g. ref. (38), in which there were suggested trends with duration and intensity of exposure to cadmium. The IARC reviewed also a series of smaller cohort for which results are contradictory. The new data with respect to cadmium and cancer have been reviewed recently (39). The US cohort was reanalyzed by Sorahan and Lancashire (40) using detailed job histories previously not taken into account. This paper confirmed the dose-response relationships between lung cancer and cumulative cadmium exposure. However, when stratifying on arsenic exposure, cadmium is only significantly related to lung cancer for subjects concomitantly exposed to arsenic. Three further cohorts have been updated since the IARC report (41–43), which did not show any increased lung cancer risk (in the absence of arsenic co-exposure). The authors of the last paper claim that these results “might indicate that the IARC evaluation is perhaps suitable for re-examination” and “that the claims that carcinogenic effects have been shown in humans ought to be treated with some skepticism.” The 2005 11th NTP Report on Carcinogens reevaluated cadmium but confirmed cadmium as “*known to be a human carcinogen*.” Finally, a

recent prospective population-based study in the vicinity of industrial sites generating a cadmium exposure (44) showed an increased lung cancer risk in relation to previously measured urinary cadmium.

3.4. Beryllium

The uses of beryllium are relatively widespread: specialty ceramics for electric and electronic appliances, nuclear and aircraft industries, aluminum and magnesium production, but jewelry and dental prosthetic industry also use beryllium alloys or pure beryllium. High long-term human exposures are probably (or hopefully were) restricted to the beryllium production industry. Its acute and chronic respiratory toxicity has long been recognized (45), even among relatively low-exposed workers. The lung carcinogenicity of beryllium is more controversial, despite the classification of beryllium by IARC (3) as a “*carcinogenic to humans*” based on “*sufficient evidence*” both in humans and experimental animals. The human evidence relied on a moderate but consistent lung cancer excess in a cohort of the seven US beryllium production facilities (*see ref. (46)* for the last paper describing this population considered by the IARC review) and a high lung cancer risk in a beryllium case registry, which included cases of beryllium-induced pneumonitis (47). The follow-up of the largest facility included in the US cohort was extended and a nested case-control study was conducted (48), which enabled a quantitative assessment of the exposure. This study could dismiss confounding by smoking and showed an increasing trend when the exposure was lagged by 10 years but a decreased risk in the upper quartile. Modeling this trend with log-transformed exposure metrics yielded a significant coefficient, but trends with nontransformed exposure metrics were not statistically significant (49). This and alleged methodological weaknesses led the authors of the latter paper (49) to challenge the conclusions concerning beryllium-lung cancer associations.

3.5. Arsenic

The relation between arsenic and lung cancers is one of the best-documented ones. While in its first assessment (50), IARC stated that “the causative role (of arsenic) is uncertain,” in its 1980 assessment (51), IARC concluded that there was “sufficient evidence that inorganic arsenic compounds are skin and lung carcinogens in humans,” while its 1987 (52) assessment was “Arsenic and arsenic compounds are *carcinogenic to humans*” but “This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group.” This classification was based on consistent lung cancer excesses and observed dose-response relationships with arsenic exposure among copper smelter workers (e.g., *ref. (53)*), which was confirmed in later studies all over the world (e.g., *refs. (54–58)*), including some environmental risks around smelters (e.g., *refs. (59, 60)*). Increased lung cancer risks were also found in arsenic-exposed copper, gold, and tin miners (61–63), and among workers involved in the manufacture of arsenical pesticides (64, 65). A more complete list of references is

available in ref. (66). Finally, high lung cancer risks in relation to drinking water arsenic have been published in Taiwan (67), Chile (68), and Bangladesh (69).

3.6. Silicon

Measured by mass, silicon makes up 25.7% of the Earth's crust. Pure silicon crystals are however only occasionally found in nature, so that there is no human exposure to speak of, except possibly in the semiconductor industry. Naturally occurring silicon is usually found in the form of silicon dioxide (also known as silica), and silicates. There are many silicates, which are complex compounds involving silicon, oxygen, and other metallic and nonmetallic elements, and considering silicates as silicon compounds is stretching this concept. Silica on the other hand, is the simplest and most common silicon compound. Moreover, human exposure is widespread and its health consequences have been studied in many studies. In its 1997 monograph (70), IARC stated that "Crystalline silica inhaled in the form of quartz or cristobalite from occupational sources is carcinogenic to humans" based on "*sufficient evidence in humans* for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources," whereas "Amorphous silica is *not classifiable as to its carcinogenicity to humans*." This classification, which was since confirmed by the NTP (71), gave rise to heated discussions (*see, e.g., ref. (72)*), notably based on the fact that studies of coal miners, who are exposed to crystalline silica, have not generally demonstrated an increased lung cancer risk. This was certainly a reason why the IARC working group added the following cautionary remark "Carcinogenicity may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs." Recent studies seem both to confirm the fact that overall, crystalline silica is carcinogenic (73, 74), and that it is not always so (75, 76). The most important problem seems now to be to understand what causes these inconsistent findings on silica and lung cancer (77).

4. Titanium

Titanium [Ti] is a light strong, corrosion-resistant metal with a white-silvery metallic color. Although it is quite common in the Earth's crust (its proportion in soils is approximately 0.5 to 1.5% (78)), it is always bonded to other elements in nature and it is very expensive to extract the metal from its ores. It can be alloyed with other elements, such as iron, aluminum, vanadium, molybdenum, and others, to produce strong lightweight alloys for aerospace (the Boeing 777 contains about 10% titanium),

military, automotive, medical (prostheses), sporting goods (golf clubs), and other applications. However 95% of titanium ore extracted is destined for refinement into titanium dioxide (TiO_2), mostly used as a pigment. Thus human exposure to titanium and titanium compounds is mainly in the production and use of TiO_2 , although some human exposure is likely to exist to titanium metal in its metallurgical industry. In 1983, NIOSH estimated that 2.7 million workers were potentially exposed to TiO_2 . There have been some animal studies (79, 80) showing increases in malignant bronchiolar/alveolar and squamous cell tumors of the lung in rats exposed to high levels of TiO_2 . Searching the scientific literature, we identified four cohort studies among TiO_2 production workers (81–84), one of which (82) was a nested case–control study in a cohort presented in ref. (81) focused on titanium tetrachloride (TiCl_4) exposure. We also identified a reanalysis (85) targeted toward exposure to TiO_2 of an earlier population-based case–control study (86). Finally, in the 2001 unpublished final report of the worldwide multicentric IARC study in the pulp and paper industry, the lung cancer mortality of subjects ever exposed to TiO_2 (212 cases versus 225.9 expected) or ever highly exposed to TiO_2 (82 cases versus 84.2 expected) was not in excess. No epidemiological results are available for titanium-exposed humans in other contexts. **Table 6.1** presents the main results of these papers. Overall, there is only one significant excess of lung cancer mortality, based on a fixed effect summary of the European study. However, the detailed exposure assessment in this cohort enabled the authors to show that this (23%) excess was not related to the TiO_2 exposure and was most likely due to other factors (smoking and other occupational exposures) and possibly to inadequate reference rates.

The recent 2006 IARC assessment, of which presently only the summary evaluation is available, concluded, based on the same studies (except the results of the pulp and paper cohort, and one US study, most likely the study focusing on TiCl_4), that “Titanium dioxide is *possibly carcinogenic* to humans” based on “*inadequate evidence* in humans” and “*sufficient evidence* in experimental animals.”

5. Iron

Iron [Fe] is the 26th element of the periodic table. It is a ductile and malleable metal, unique with his magnetic properties. It is a very reactive element and oxidizes (rusts) very easily.

Table 6.1
Epidemiological studies on lung cancer in relation to titanium compounds

Author [reference]	Year	Study type and location	Study population and follow-up	Lung cancer cases	RR estimate	95% CI
Cohort studies: TiO ₂ production and use						
Chen et al. [81]	1988	Mortality study in 2 US plants	n = 2,477 (1,576 exposed to TiO ₂) 1935–1983	9	SMR = 0.52	0.27–0.99
Fayerweather et al. [82]	1992	Nested case–control in the largest plant	1935–1983	24	OR (TiCl ₄) = 1.1	0.4–3.2
Fryzek et al. [83]	2003	Mortality study in 4 US plants	3,892 men, 409 women 1960–2000	61	SMR (all) = 1.0	0.8–1.3
				11	SMR (high TiO ₂) = 1.0	0.5–1.7
Boffetta [84]	2004	Mortality study in 11 European plants	14,331 men, 686 women 1927 to 1969–1995–2001	306.5	SMR = 1.23	1.10–1.38
					RR (random effect) = 1.19	0.96–1.48
IARC	2001	Worldwide mortality cohort in pulp and paper industry	Ever exposed to TiO ₂	212	SMR = 0.94	0.82–1.07
			Ever highly exposed to TiO ₂	82	SMR = 0.97	0.77–1.21
Population-based case–control studies						
Boffetta [85]	2001	Montreal (Canada) 857 cases	Ever exposed to TiO ₂	33	OR = 0.9	0.5–1.5
			Substantial exposure to TiO ₂	8	OR = 1.0	0.3–2.7

It is widespread in the Earth's crust (about 5%). The main ores of iron are hematite or ferric oxide (Fe_2O_3), magnetite or ferrous oxide (Fe_3O_4), and limonite (HFeO_2). In the experimental literature, the carcinogenic effect of iron oxides on lung has long been debated. Studies on animals show no conclusive effect of iron oxides if alone. A carcinogenic effect has however been suggested in association with benzo[a]pyrene (B[a]P), ferrous oxide particles being considered as cofactors (87–89).

Several epidemiological studies have been carried out on the risks of cancer in industries generating exposure to iron oxides: iron ore mining, iron and steel manufacturing, foundry processes, and welding processes, although few of the studies focused on iron oxides. In what follows, we shall consider each of these industries or processes. The respective findings will be discussed considering that few if any of the occupations present “pure” exposures to Fe oxides, most presenting decidedly mixed exposures.

5.1. Iron Ore Mines

Several epidemiological studies conducted among underground hematite miners showed an increased risk of lung cancer. Some of these studies, reviewed in the 1987 IARC monograph (90), attributed this risk to radon daughters because they observed a higher incidence of lung cancer among miners exposed to radon daughters than among surface miners. In a retrospective study conducted in Minnesota (91), no excess of lung cancer was found among either underground or aboveground miners compared with US white men. These results were attributed to low levels of exposure to both radon daughters and silica dust, a strict smoking prohibition underground, and the absence of underground diesel fuel use. Two French studies were carried out in iron ore miners in the Lorraine basin, where the exposure levels to radon daughters are low. A proportional mortality study (92) of 1,075 miners deceased between 1960 and 1976 showed a significant excess of lung cancer mortality 2.2 times higher than expected in reference to French male mortality, increasing with the duration of work underground (Proportional mortality rate [PMR] = 4.24 for subjects who worked underground for more than 30 years). This excess risk may have been partly due to smoking but it led to the classification of lung cancer as a recognized occupational disease in France as a complication of siderosis. In a prospective study conducted in the same area, Chau et al. (93) confirmed the excess of lung cancer among underground workers (standardized mortality ratio [SMR] = 3.89; $p < 0.001$). The authors showed that the lung cancer risk increased with the duration of work underground and that this increase became more important with increasing smoking. They concluded that the lung cancer risk in Lorraine iron ore miners was possibly related to cumulative levels of dust (consisting mostly of iron oxides) and diesel exhausts, although the role of a low exposure to radon daughters could not

be totally excluded. In a retrospective study conducted among workers of two hematite mines in China, Chen et al. (94) found an excess risk of lung cancer among underground miners exposed to radon and radon daughters that increased with levels of dust exposure among smokers but also among subjects with silicosis and silicotuberculosis, indicating a significant quartz content of this dust. A cohort study published in 2006 carried out among iron ore miners in China showed an increased risk for lung cancer among dust-exposed workers (95).

In summary, most studies conducted among iron ore miners reported an excess lung cancer risk. However, this excess is difficult to attribute to iron oxide exposure, given the numerous confounders among which radon and radon daughters, diesel fumes, and smoking are the most important. Based on these findings, IARC (90) classified “underground haematite mining with exposure to radon” as being “*carcinogenic to humans*” while for haematite and iron oxide, the evidence for carcinogenicity in humans was considered “*inadequate*.”

5.2. Iron and Steel Foundries

Iron and steel founding is an industrial process that has been considered by IARC as “*carcinogenic to humans*” (96, 97). This IARC assessment remarked that “Despite the absence of information to specify definitely the carcinogenic substances in the work environment (e.g., polycyclic aromatic hydrocarbons [PAHs], silica, metal fumes, and formaldehyde), the consistency of the excess in studies from around the world shows that certain exposures in iron and steel founding can cause lung cancer in humans.” We can note that exposure to iron oxides was not even considered as a potential carcinogen. Since this evaluation, we are aware of seven new studies considering lung cancer in iron foundries (98–104). A Polish nested case–control study (98) reported a consistent gradient of lung cancer risk, adjusted on smoking, with increasing duration of employment in a foundry: odds ratio (OR) = 1.28 (1–20 years), 1.58 (20–30 years), and 2.66 (>30 years). Adzresen et al. (104) reported an increased lung cancer risk (SMR = 164; 95% confidence interval [CI], 124–223). Sorahan et al. (101) showed an increased lung cancer mortality in 10 UK foundries (SMR = 146; 95% CI, 134–158; 551 cases) with no clear trend with exposure estimates. On the other hand, Rotimi et al. (99) and Andjekovich et al. (101) did not find any lung cancer excess in the mortality follow-up of two American steel foundries, neither did Hansen (102) in a population-based cohort of foundry workers, despite a large excess in death from pneumoconiosis. Finally, in a Spanish nested case–control study (103) carried out in a steel-producing industrial complex, a twofold lung cancer risk (not significant, adjusted on smoking) was observed among workers having worked predominantly in the foundry.

Again lung cancer is often in excess in this industrial sector and again it is not clear whether this excess is attributable to iron oxides.

5.3. Welders

Welding fumes contain a wide variety of mostly metallic compounds depending on the metals welded and the welding technique. For example, exposure to hexavalent chromium and nickel is likely during welding of stainless steel. However, except for very specialized welding, these fumes always contain iron compounds. Moreover, relatively high asbestos exposure is likely to have occurred in shipyards and a lower asbestos exposure may have occurred because of the use of asbestos welding blankets.

In the late 1980s, a large multicentric European cohort of welders (105) was set up. Exposures to chromium, nickel, and others were assessed using an ad hoc job-exposure matrix. Overall lung cancer was in significant excess but no clear difference was observed between mild steel and stainless steel welders. Moreover, no dose-response relationship could be shown between lung cancer and exposure to hexavalent chromium or nickel. A recent meta-analysis of all epidemiological studies among welders published between 1954 and 2004 (106) confirmed both the overall lung cancer excess (combined relative risk [CRR] = 1.26; 95% CI, 1.20–1.32) and the absence of difference between mild steel welders (CRR = 1.32; 95% CI, 1.10–1.59) and stainless steel welders (CRR = 1.31; 95% CI, 1.06–1.61). The authors considered this risk as unlikely to be attributable to confounding by smoking. A possible confounder is asbestos exposure, but the shipyard welders (CRR = 1.32; 95% CI, 1.16–1.51), in which this exposure was considered to be much higher, showed a similar risk as other welders. This was also the point of view expressed in the 1990 IARC monograph (6), which classified welding fumes (and not welding processes) as “*possibly carcinogenic to humans*.” These nonspecific lung cancer risks could, at least partly, be due to iron oxide exposure, but this is only one hypothesis among others.

5.4. Steel Industry

Steel production gives rise to exposure to total dust containing varying concentrations of iron between the different processes. The authors of a French study in a steel-producing factory (107) reported percentages of iron (including oxides) in total dust varying from 30% in the blast furnace plant or in the steel making plant to more than 75% in the sinter plant or in the hot rolling mill. This study was specifically aimed at assessing the possible association between iron oxide exposures and lung cancer mortality while taking into account the main possible occupational and non-occupational confounders. A factory specific job-exposure matrix assessed occupational exposures. High iron oxide exposures occurred at the floor level of the steel making plant or of the blast furnace before the installation of a ventilation system, close to the sinter strand, during hot scarfing at the heavy plate mill. No lung cancer excess was observed among workers exposed to iron oxides (relative risk [RR] adjusted on asbestos, silica, and PAHs, 0.80; 95% CI, 0.55–1.17) and no dose-response relationship was observed with intensity, duration of exposure, and cumulative exposure indices. A further,

nested case-control study in a cohort of stainless and alloyed steel-producing workers (108), targeted at assessing lung cancer risk in relation to metals and iron exposures, did not detect any effect of iron oxide exposure either: the iron-oxide OR adjusted for potential confounding factors, i.e., PAHs, silica, and smoking, was lower than 0.50. In contrast to the two preceding studies, the majority of studies carried out in iron and steel plants analyzed lung cancer mortality according to workshops or job categories, but not in terms of exposures to iron oxides and cofactors. In order to detect a possible role of iron oxide exposure, we concentrate on those workshops or plants in which such an exposure is most likely, although still possibly associated with other carcinogens. These consist of blast furnace, smelting, hot-rolling, scarfing, but, e.g., not coke oven plants. **Table 6.2** summarizes the lung cancer risks in studies in which this detail was available. In all four processes, it appears that the lung cancer risk is increased quite consistently.

5.5. Summary

The carcinogenic effect of iron oxides on lung has been suggested in the literature because excess risks of lung cancer were observed in many occupational activities involving exposure to iron oxides. A potential lung cancer risk was reported in many studies carried out in iron ore mines, in iron and steel foundries, among mild steel and stainless steel welders, and in the steel industry. However only three studies, one study (121) considering “pure” and considerable exposure to iron oxides in relation to the production of Fe_2O_3 from pyrite, and two mortality cohort studies carried out in steel-producing factories, addressed specifically the effect of iron oxides on lung cancer. In none of these three studies, when taking into account possible confounders, was such an effect observed. Finally some studies showed excesses of a non-malignant respiratory disease, usually considered as benign, called siderosis. This disease is specifically related to the exposure to iron oxides and it has been suggested that lung cancer may occur as a complication of siderosis (88). However, the single study investigating this possible relation did not find any excess, but its power was very low (122). In summary, lung cancer risks are observed in population exposed to iron oxides but effects of iron oxides were not confirmed when they were specifically studied.

6. Lead

Lead is a toxic metal. Its neurotoxic, nephrotoxic, and hematologic effects have long been recognized (123). Nevertheless, the human exposure is quite widespread: citing the summary

Table 6.2**Lung cancer risks in blast furnace, smelting, hot-rolling, and scarfing plants**

Author [reference]	Year	Study type and location	Lung cancer cases	RR estimate	95% CI
Blast furnace					
Hurley [109]	1990	Cohort study, UK	18	SMR = 1.69	1.00–2.67 ^a
Moulin [110]	1995	Cohort study, France	26	SMR = 1.36	0.89–1.99
Finkelstein [111]	1994	Case-control study, Canada	11	OR = 1.38	0.61–3.06
Smelting					
Redmond [112]	1975	Cohort study, USA	112	SMR = 0.89 ^c	0.73–1.07 ^a
Finkelstein [113]	1990	Cohort study, Canada	7	SMR = 3.61 ^b	1.48–7.59 ^a
Hurley [109]	1990	Cohort study, UK	13	SMR = 0.90	0.48–1.54 ^a
Finkelstein [114]	1991	Cohort study, Canada	15	SMR = 1.45 ^b	0.81–2.39 ^a
Moulin [115]	1993	Cohort study, France	7	SMR = 1.04 ^b	0.42–2.15
Cao [116]	1995	Cohort study, Chine	118	SMR = 1.09	0.91–1.31 ^a
Moulin [110]	1995	Cohort study, France	17	SMR = 1.25 ^c	0.73–2.01
Moulin [110]	1995	Cohort study, France	5	SMR = 1.04 ^b	0.34–2.43
Moulin [110]	1995	Cohort study, France	14	SMR = 1.75	0.96–2.94
Blot [117]	1983	Case-control study, USA	20	OR = 2.60 ^c	1.20–5.80
Finkelstein [113]	1994	Case-control study, Canada	17	OR = 0.92	0.50–1.70
Xu [118]	1996	Case-control study, China	166	OR = 1.60	1.20–2.10
Hot rolling					
Mazumdar [119]	1975	Cohort study, USA	21	SMR = 1.14	0.71–1.74 ^a
Hurley [109]	1990	Cohort study, UK	19	SMR = 0.86	0.53–1.37 ^a
Moulin [115]	1993	Cohort study, France	17	SMR = 1.51	0.88–2.42
Moulin [110]	1995	Cohort study, France	41	SMR = 1.29	0.93–1.75
Moulin [110]	1995	Cohort study, France	28	SMR = 1.16	0.77–1.68
Scarfing					
Mazumdar [119]	1975	Cohort study, USA	2	SMR = 0.80	0.10–2.89 ^a
Beaumont [120]	1987	Cohort study, USA	35	SMR = 1.64	1.14–2.28
Moulin [110]	1995	Cohort study, France	7	SMR = 1.62	0.65–3.33

^aNot available in the original publication, computed from available data. ^bElectric furnace. ^cOpen hearth furnace.

report of the 2004 IARC assessment of the carcinogenicity of lead (124), “The widespread occurrence of lead in the environment is largely the result of anthropogenic activity, which has occurred since prehistoric times. Lead usage increased progressively with industrialization and rose dramatically with the use of lead-acid batteries and leaded fuel for automobiles in the twentieth century. The predominant use of lead is now in batteries and, to a lesser extent, in construction materials and lead-based chemicals. The use of lead in pipes, paints and gasoline has been or is being phased out in many countries. The important routes of human exposure from lead-contaminated air, dust, soil, water and food are through inhalation and ingestion. Recent human exposure has arisen predominantly from the widespread use of leaded gasoline. Also, areas near lead mines and smelters have high environmental concentrations of lead. Occupations in which the highest potential exposure to lead exists include mining, primary and secondary smelting, production of lead-acid batteries, pigment production, construction and demolition. In spite of the persistence of lead in the environment, exposures have decreased substantially in countries where lead control measures have been implemented over the past 10–30 years.”

The possible carcinogenic effect of lead has received a lot of attention recently. In 1999 a conference was dedicated to “Lead Exposure, Reproductive Toxicity and Carcinogenicity,” whose proceedings have been published in a special issue of the American Journal of Industrial Medicine (Vol 38, no. 3; 2000). Shortly afterward, the aforementioned IARC assessment reviewed the evidence and a group of French experts also reviewed the evidence (125). IARC considered that there was “*limited evidence* for the carcinogenicity to humans of exposure to inorganic lead compounds. The available epidemiological data on occupational exposure to organic lead compounds were considered to provide *inadequate evidence* for carcinogenicity to humans.” **Table 6.3** presents the results of a series of published epidemiological studies analyzed in an unpublished meta-analysis by Dr. Moulin and coworkers (126) presented at the 16th International Symposium on Epidemiology in Occupational Health, in which subgroups of study populations were ranked by increasing lead exposure level, based on the available published information. Although overall there appears to be an increased lung cancer risk, no increasing trend with lead exposure emerges from this table. The increased lung cancer risk seems therefore to be, at least partly, due to confounding exposures.

Since this meta-analysis, three studies were published. Lundström et al. (144) conducted a nested case-control study in the Swedish smelter cohort (141) and concluded that “cumulative

Table 6.3**Lung cancer risks by coded lead exposure in subpopulation of studies published before 2002**

Author [reference]	Year	Study type and location	Lung cancer cases	RR estimate	95% CI
Lowest lead exposure level		All combined		CRR = 1.36	0.71–2.57
Cordioli [127]	1987	Glass industry, Italy	13	SMR = 2.09	1.11–3.57
Sankila [128]	1990	Glass industry, mechanical workshop Finland	4	SIR = 1.60	0.44–4.10
Michaels [129]	1991	Printers, US	37	SMR = 0.89	0.62–1.22
Low-medium exposure levels		All combined		CRR = 1.07	0.81–1.41
Sankila [128]	1990	Glass industry, glass blowers, Finland	1	SIR = 0.29	0.01–1.64
Sankila [128]	1990	Glass industry, others, Finland	37	SIR = 1.33	0.93–1.83
Wingren [130]	1987	Glass industry, others, Sweden	11	OR = 1.90	0.97–3.72
Bertazzi [131]	1980	Printing industry, Italy	1	SMR = 0.50	0.02–2.79
Greene [132]	1979	Printing industry, US, whites	61	SMR = 0.83	0.64–1.07
Greene [132]	1979	Printing industry, US, non whites	23	SMR = 1.06	0.67–1.59
Anttila [133]	1995	Population based, Finland, men	25	SMR = 0.70	0.02–2.79
Anttila [133]	1995	Population based, Finland, women	1	SMR = 0.70	0.01–4.00
Wingren [134]	1990	Glass industry, Sweden	6	SMR = 2.36	0.86–5.14
Medium exposure levels		All combined		CRR = 1.45	1.15–1.84
Gerhardsson [135]	1986	Smelter workers, Sweden	3	SMR = 1.43	0.29–4.17
Wingren [130]	1987	Glass industry, Sweden	4	OR = 2.30	0.83–6.35
Gerhardsson [136]	1995	Smelter workers, Sweden	6	SMR = 1.32	0.49–2.88
Steenland [137]	1992	Smelter workers, US	23	SMR = 1.36	0.86–2.05

(continued)

Table 6.3
(continued)

Author [reference]	Year	Study type and location	Lung cancer cases	RR estimate	95% CI
Anttila [133]	1995	Population based, Finland, men	35	SIR = 1.40	1.00–1.90
Anttila [133]	1995	Population based, Finland, women	2	SIR = 4.50	0.50–16.00
High exposure levels		All combined		CRR = 1.29	1.09–1.54
Wong [138]	2000	Battery workers, US	210	SMR = 1.14	0.99–1.30
Wong [138]	2000	Smelter workers, US	107	SMR = 1.22	1.00–1.47
Gerhardsson [135]	1986	Smelter workers, Sweden	5	SMR = 1.72	0.56–4.02
Steenland [137]	1992	Smelter workers, US	49	SMR = 1.11	0.82–1.47
Ades [139]	1988	Smelter, UK	182	OR = 1.25	1.07–1.44
Cocco [140]	1997	Smelter workers, Italy	31	SMR = 0.82	0.56–1.16
Lundstrom [141]	1997	Smelter workers, Sweden	42	SMR = 2.90	2.10–4.00
Anttila [133]	1995	Population based, Finland, men	11	SIR = 1.10	0.60–2.00
Sheffert [142]	1982	Pigment industry, US	10	SIR = 1.33	0.67–2.37
Davies [143]	1984	Pigment industry, UK	4	SIR = 1.45	0.39–3.71

SIR, standardized incidence ratio

arsenic and smoking were identified as risk factors, ... lead exposure however was not." Wingren (145) updated the cohort published in 1990 (134). The slight lung cancer excess of the earlier study was not confirmed in this update. On the other hand, lung cancer mortality increased significantly with increasing categories of lead exposure in a recent Italian study in a lead and zinc foundry (146).

In summary, there is some evidence of a carcinogenic effect of (inorganic) lead compounds, but it is not compelling, at least with respect to lung cancer.

7. Cobalt and Tungsten

Cobalt is a relatively widespread element. It occurs naturally in the form of sulfides, oxides, and arsenides, but not in its metallic form. It is rarely mined alone and tends to be produced as a by-product of nickel and copper mining activities. Cobalt in small amounts is essential to many living organisms, including humans. It is a central component of the vitamin B-12. Its uses are in making wear-resistant alloys, notably for aircraft engines, in high-strength steels, and other alloys. One of its most important applications is in the hard metal industry in which it is added to metallic carbides, especially tungsten carbide, to produce metal-working tools. Occupational exposure to cobalt occurs predominantly during refining, in the alloy production, and in the hard-metal industry.

The mortality of a French cobalt production facility was studied in two successive studies (147, 148), but the initial excess of lung cancer was not confirmed in the follow-up study. The main evidence with respect to a possible carcinogenic risk of cobalt comes from four studies in the hard-metal industry (149–152). In one of the studies (152), an unadjusted twofold lung cancer risk was observed in a cobalt production workshop without exposure to tungsten carbide exposure, but the main evidence is in workers exposed simultaneously to cobalt and tungsten carbide. The first paper (149) described the mortality experience (1951 to 1982) of the workforce of three hard-metal producing plants (3,163 workers) in Sweden. Overall there was a nonsignificant excess in cancer of the lung (SMR = 1.34; 17 cases; 95% CI, 0.77–2.13), which was higher when restricted to subjects exposed for longer than 20 years since first exposure (SMR = 2.30; 4 cases; 95% CI, 0.62–5.9). This excess became statistically significant when considering subjects exposed for longer than 10 years and whose first exposure was longer than 20 years ago (SMR = 2.78; 7 cases; 95% CI, 1.11–5.72). Another mortality cohort study (1956–1990) of a hard-metal producing plant located in France was published by Lasfargues et al. (150). This small study included 709 male subjects. In this study, there was a significant excess for lung cancer (SMR = 2.13; 10 cases; 95% CI, 1.02–3.93), mainly due to a large excess in the highest exposure group (SMR = 5.03; 6 cases; 95% CI, 1.85–10.9). However, mortality did not increase with duration of employment and time since employment. Potential confounding was treated in some detail for smoking and is unlikely to explain the observed results. Other potential occupational carcinogens (asbestos, nickel, etc.) were not discussed. The third study was published by Moulin et al. (151) and describes the mortality experience (1968–1991) of the workforce of ten French hard-metal producing plant with a total of 5,777 male

subjects showing a borderline significant excess for lung cancer (SMR = 1.30; 63 cases; 95% CI, 1.00–1.66). A nested case–control study was included using an industry-specific job-exposure matrix ranking exposures to sintered and unsintered hard metal dust, and identifying exposure to other carcinogens. Smoking habits were obtained for 82% of the cases and 79% of the controls. The OR for simultaneous exposure to cobalt and tungsten carbide rated as >2 (on a scale from 0 to 9) was equal to 1.93 (95% CI, 1.03–3.62) adjusted for all other cobalt exposures (alone or simultaneous with other agents). The OR increased significantly with duration of exposure and cumulative exposure reaching OR = 4.13 (95% CI, 1.49–11.5) in the highest exposure quartile. Adjusting on smoking did not change the ORs to any extent. The last study (152) described the mortality experience (1968–1992) of the workforce of the largest facility (2,860 subjects) included in the preceding study. Overall there was a statistically significant lung cancer excess (SMR = 1.70; 46 cases; 95% CI, 1.24–2.26) mostly in subjects having worked in hard metal production steps before sintering (SMR = 2.42; 9 cases; 95% CI, 1.10–8.63), while in the workshops after sintering, only a relatively small excess is observed (SMR = 1.28; 5 cases; 95% CI, 0.41–5.9). According to the job-exposure matrix, the SMR of all hard-metal exposure rated as higher than 2 was in statistically significant excess (SMR = 2.02; 26 cases; 95% CI, 1.32–2.96) and increased with duration and cumulative exposure. In an internal regression adjusted on smoking and IARC carcinogens, the RR increased significantly with duration of exposure to unsintered hard metal dust at a level rated as >2.

In summary, although the possibility of some residual confounding cannot be excluded, it seems unlikely that the increased lung cancer risks in hard-metal workers were due to smoking or other carcinogens. However, the epidemiological evidence is limited in that it is mostly restricted to the population of French workers. These epidemiological findings agree however with experimental data. Injection of cobalt salts in different animal species produced sarcomas at the injection points (153). Recent studies have confirmed the genotoxic potential of these compounds both *in vitro* (154, 155) and *in vivo* (156). Interestingly, these experiments showed that the association of cobalt salts and tungsten carbide presented higher mutagenic effects than cobalt salts alone when measured by the comet (155) or micronuclei assays (156). Recently, IARC reviewed the evidence of the carcinogenicity of cobalt particle with or without tungsten carbide (157). Cobalt metal with tungsten carbide was evaluated as *probably carcinogenic* to humans on the basis of *limited evidence in humans* for increased risk of lung cancer and *sufficient evidence* in experimental animals for the carcinogenicity of cobalt metal powder and cobalt sulfate. On the other hand, the evidence for the carcinogenicity of cobalt metal without tungsten carbide was considered *inadequate*. It was noted that “a number of the IARC working

group members supported an evaluation in Group 1 (i.e. *carcinogenic to humans*) because: (1) they judged the epidemiological evidence to be sufficient ... and/or (2) they judged the mechanistic evidence to be strong enough to justify upgrading the default evaluation from 2A to 1."

Finally, no epidemiological data are available with respect to exposure to tungsten alone, except in the paper by Wild et al. (152), in which a relatively small group of workers employed solely in the tungsten carbide production workshop did not show any excess of lung cancer mortality.

8. Discussion

The epidemiological evidence with respect to the carcinogenic effect of metals has been reviewed several times in the past (66, 158, 159). To a certain extent, our review is an update of the earlier review by Hayes (66). On the other hand, our focus is different, as our aim was neither to review the overall carcinogenicity, as we concentrated on epidemiological studies of lung cancer, nor to review the toxicological evidence. Moreover, we presented in more detail the epidemiological studies for metals for which the evidence is either recent (TiO₂, cobalt/tungsten), is still uncertain (lead), or for which exposure is very widespread and there remains a doubt (iron).

Does this review allow statements to be made about the metals themselves? To ask the question is to answer it. The human exposure to the metallic elements in their metallic form is usually not the predominant exposure. For example, the three most common elements discussed here, silicon, titanium, and even iron, barely exist, as a human exposure, in their metallic form. The epidemiologic evidence is thus not for exposure to metals but to their basic compounds, in the case of these three elements, to their oxides. For titanium and silicon, their dioxide is the virtually unique compound for which large human exposure groups exist. But even for iron, it can be difficult to identify exposure to only one of its two most common oxides, corresponding respectively to its bivalent and trivalent form. For chromium, the epidemiological evidence seems clear, in that only its hexavalent chromium is carcinogenic. This result is based on studies among workers, most of whom are exposed to a series of chromium compounds, which may well vary in the carcinogenic potential. The fact that the carcinogenicity may depend on the specific compounds is, for instance, specifically recognized in the already cited IARC assessment of nickel (6), which states that human data are only available for certain compounds, and that the overall assessment for nickel compounds is based on animal data. Another issue is the physical structure of the compounds. The fact that some compounds are water soluble, others not, seem to make a difference (Ni, As). The

crystalline structure may also make a difference. For instance, quartz is a recognized carcinogen, whereas noncrystalline silica seems to be innocuous. One must therefore be very cautious about the potential carcinogenic effect of nano-structured compounds, whose industrial use is becoming more common. This caution was recently underlined in a draft NIOSH report on TiO_2 , whose nano-structured habit is already used in some marketed sunscreens (<http://www.cdc.gov/niosh/review/public/TIO2/default.html>).

Last but not least, the carcinogenicity depends on the co-exposures, which are not necessarily carcinogenic by themselves. This seems to be the case for cobalt, as neither cobalt nor tungsten seem to be carcinogenic alone, but as discussed above, their joint exposure as hard-metal dusts is strongly suspected to be carcinogenic based both on human and animal data. At least, in this industry, the co-exposures are relatively well identified, whereas in other industrial settings, e.g., in the different metallurgical industries, often many known or suspected carcinogens coexist, to say nothing about personal exposures (smoking, drugs).

Another relevant consideration is to acknowledge that some potentially carcinogenic metals are necessary trace elements in life (*see ref. (159)* for a review) or can even be used in anticancer drugs (*160*), which would tend to show that the carcinogenic effect of metals and metal compounds depends on the dose. To cite Duffus (*142*), "Metal ions are needed by the human body as essential nutrients. It is likely that there are homeostatic mechanisms which must be overcome before any adverse effect such as cancer can occur. This implies the existence of thresholds for metal carcinogenicity." The same review cautions against overinterpreting epidemiological study results on exposure to metals for the reasons stated before and for lack of adequately measured occupational exposures. It is therefore clear that epidemiological results alone can only exceptionally provide a final proof of metal carcinogenicity and that a plausible mechanism supported by experimental data is necessary for a reliable assessment. Thus, the carcinogenicity of beryllium, cadmium, and the combination of cobalt and tungsten carbide relies only on limited epidemiological data but is supported by findings of cancer occurrence in experimental studies.

Another case is for lead, which has been shown to be weakly mutagenic, and genotoxic in humans, but the epidemiological evidence is contradictory. Conversely, the quite consistent, although relatively weak, lung cancer excesses in populations exposed to iron oxides cannot be interpreted causally for lack of such experimental confirmation. Finally, there are few doubts about the carcinogenicity of hexavalent chromium, nickel and arsenic compounds or crystalline silica, but nevertheless some issues remain which have been discussed in what precedes. Only further epidemiological studies in populations with precisely estimated exposure to specific compounds and co-exposures can resolve the remaining uncertainties.

References

- Hirano, S. and Suuki, K. T. (1996) Exposure, metabolism, and toxicity of rare earths and related compounds. *Env. Health Persp.* **104**, 85–95.
- Kazantzis, G. (1981) Role of cobalt, iron, lead, manganese, mercury, platinum, selenium, and titanium in carcinogenesis. *Env. Health Persp.* **40**, 143–161.
- International Agency for Research on Cancer (IARC). (1993) Beryllium, cadmium, mercury and exposures in the glass manufacturing industry. IARC Monogr Eval Carcinog Risks Hum, Vol 58. Lyon, France: IARC.
- De Boeck, M., Kirsch-Volders, M., and Lison, D. (2003) Cobalt and antimony: genotoxicity and carcinogenicity. *Mutat. Res.* **533**, 135–152.
- Langard, S. (1990) One hundred years of chromium and cancer: a review of epidemiological evidence and selected case reports. *Am. J. Ind. Med.* **17**, 189–215.
- International Agency for Research on Cancer (IARC). (1990) Chromium, nickel and welding fumes. IARC Monogr Eval Carcinog Risks Hum, Vol 49. Lyon, France: IARC.
- Axelsson, G., Rylander, R., and Schmidt, A. (1980) Mortality and incidence of tumours among ferrochromium workers. *Br. J. Ind. Med.* **37**, 121–127.
- Langard, S., Andersen, A., and Ravnstad, J. (1990) Incidence of cancer among ferrochromium and ferrosilicon workers: an extended observation period. *Br. J. Ind. Med.* **47**, 14–19.
- Moulin, J. J., Portefaix, P., Wild, P., Mur, J. M., Smagghe, G., and Mantout, B. (1990) Mortality study among workers producing ferroalloys and stainless steel in France. *Br. J. Ind. Med.* **47**, 537–543.
- Horiguchi, S., Morinaga, K., and Endo, G. (1990) Epidemiological study of mortality from cancer among chromium platers. *Asia-Pacific J. Publ. Health* **4**, 169–174.
- Davies, J., Easton, D., and Bidstrup, P. (1991) Mortality from respiratory cancer and other causes in United Kingdom chromate production workers. *Br. J. Ind. Med.* **48**:299–313.
- Korallus, U. and Ulm, K. (1993) Steinmann-Steiner-Haldenstaett W. Bronchial carcinoma mortty in the German chromate-producing industry: the effects of process modification. *Int. Arch. Occup. Environ. Health* **65**, 171–178.
- Kano, K., Horikawa, M., Utsunomiwa, T., Tati, M., Satoh, K., and Yamaguchi, S. (1993) Lung cancer mortality among a cohort of male chromate pigment workers in Japan. *Int. J. Epidemiol.* **22**, 16–22.
- Pastides, H., Austin, R., Lemeshow, S., et al. (1994) A retrospective-cohort study of occupational exposure to hexavalent chromium. *Am. J. Ind. Med.* **25**, 663–675.
- Deschamps, F., Moulin, J. J., Wild, P. et al. (1995) Mortality study among workers producing chromate pigments in France. *Int. Arch. Occup. Environ. Health* **67**, 147–152.
- Sorahan, T., Burges, D., Hamilton, L., and Harrington, J. (1998) Lung cancer mortality in nickel/chromium platers, 1946–95. *Occup. Environ. Med.* **55**, 236–242.
- Sorahan, T. and Harrington, J. (2000) Lung cancer in Yorkshire chrome platers, 1972–97. *Occup. Environ. Med.* **57**, 385–389.
- Gibb, H., Lees, P., Pinsky, P., et al. (2000) Lung cancer among workers in chromium chemical production. *Am. J. Ind. Med.* **38**, 115–126.
- Fryzek, J., Mumma, M., McLaughlin, J., Henderson, B., and Blot, W. (2001) Cancer mortality in relation to environmental chromium exposure. *J. Occup. Environ. Med.* **43**, 635–640.
- Luippold, R. S., Mundt, K. A., Austin, R. P., et al. (2003) Lung cancer mortality among chromate production workers. *Occup. Environ. Med.* **60**, 451–457.
- Stern, F. (2003) Mortality among chrome leather tannery workers: an update. *Am. J. Ind. Med.* **44**, 197–206.
- Luippold, R., Mundt, K., Dell, L., and Birk, T. (2005) Low-level hexavalent chromium exposure and rate of mortality among US chromate production employees. *Occup. Environ. Med.* **47**, 381–385.
- Birk, T., Mundt, K. A., Dell, L. D., Luippold, R. S., Miksche, L., Steinmann-Steiner-Haldenstaett, W., and Mundt, D. J. (2006) Lung cancer mortality in the German chromate industry, 1958 to 1998. *J. Occup. Environ. Med.* **48**, 426–433.
- Michaels, D., Lurie, P., and Monforton, C. (2006) Comment on “Lung cancer mortality in the German chromate industry, 1958 to 1998.” *J. Occup. Environ. Med.* **48**, 995–997.

25. Park, R. M. and Stayner, L. T. (2006) A search for thresholds and other nonlinearities in the relationship between hexavalent chromium and lung cancer. *Risk Anal.* **26**, 79–88.
26. Morgan, J. G. (1958) Some observations on the incidence of respiratory cancer in nickel workers. *Br. J. Ind. Med.* **15**, 224–234.
27. Doll, R., Andersen, A., Cooper, W. C. et al. (1990) Report of the International Committee on Nickel Carcinogenesis in Man. *Scand. J. Work. Environ. Health* **16**, 1–82.
28. Goldberg, M., Goldberg, P., Leclerc, A., Chastang, J. F., Marne, M. J., and Dubourdieu, D. (1994) A 10-year incidence survey of respiratory cancer and a case-control study within a cohort of nickel mining and refining workers in New Caledonia. *Cancer Causes Control.* **5**, 15–25.
29. Goldberg, M. and Goldberg, P. (2003) Occupational exposures and lung cancer in New Caledonia. *Occup. Environ. Med.* **60**, 584–589.
30. Pang, D., Burges, D. C., and Sorahan, T. (1996) Mortality study of nickel platers with special reference to cancers of the stomach and lung, 1945–93. *Occup. Environ. Med.* **53**, 714–717.
31. Sorahan, T. and Williams S. P. (2005) Mortality of workers at a nickel carbonyl refinery, 1958–2000. *Occup. Environ. Med.* **62**, 80–85.
32. Andersen, A., Berge, S. R., Engeland, A., and Norseth, T. (1996) Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. *Occup. Environ. Med.* **53**, 708–713.
33. Anttila, A., Pukkala, E., Aitio, A., Rantanen, T., and Karjalainen, S. (1998) Update of cancer incidence among workers at a copper/nickel smelter and nickel refinery. *Int. Arch. Occup. Environ. Health.* **71**, 245–250.
34. Grimsrud, T. K., Berge, S. R., Martinsen, J. I., and Andersen, A. (2003) Lung cancer incidence among Norwegian nickel-refinery workers 1953–2000. *J. Environ. Monit.* **5**, 190–197.
35. Grimsrud, T. K., Berge, S. R., Steinar, R., Haldorsen, T., and Andersen, A. (2005) Can lung cancer risk among nickel refinery workers be explained by occupational exposures other than nickel? *Epidemiology* **16**, 146–154.
36. Grimsrud, T. K., Berge, S. R., Haldorsen, T., and Andersen, A. (2002) Exposure to different forms of nickel and risk of lung cancer. *Am. J. Epidemiol.* **156**, 1123–1132.
37. Stayner, L., Smith, R. L., Thun, M., Schnoor, T., and Lemen, R. (1992). A dose-response analysis and quantitative assessment of lung cancer risk and occupational cadmium exposure. *Ann. Epidemiol.* **2**, 177–194.
38. Kazantzis, G., Lam, T. H., and Sullivan, K. R. (1988) Mortality of cadmium-exposed workers. A five-year update. *Scand. J. Work Environ. Health.* **14**, 220–23.
39. Verougstraete, V., Lison, D., and Hotz, P. (2003) Cadmium, lung and prostate cancer : a systematic review of recent epidemiological data. *J. Toxicol. Environ. Health Part B* **6**, 227–255.
40. Sorahan, T. and Lancashire, R. J. (1997) Lung cancer mortality in a cohort of workers employed at a cadmium recovery plant in the United States: an analysis with detailed job histories. *Occup. Environ. Med.* **54**, 194–201.
41. Jarup, L., Bellander, T., Hogstedt, C., and Spang, G. (1998) Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. *Occup. Environ. Med.* **55**, 755–759.
42. Sorahan, T., Lister, A., Gilthorpe, M. S., and Harrington, J.M. (1995) Mortality of copper-cadmium alloy workers with special reference to lung cancer and non-malignant diseases of the respiratory system, 1946–92. *Occup. Environ. Med.* **52**, 804–812.
43. Sorahan, T. and Esmen, N. A. (2004) Lung cancer mortality in UK nickel-cadmium battery workers, 1947–2000. *Occup. Environ. Med.* **61**, 108–116.
44. Nawrot, T., Plusquin, M., Hagervorst, J., Roels, H. A., Celis, H., Thijs, L., Vangronsveld, J., Van Hecke, E., and Staessen, J. A. (2006) Environmental exposure to cadmium and risk of cancer : a prospective population-based study. *Lancet. Oncol.* **7**, 119–126.
45. Mroz, M. M., Balkisson, R., and Newman, L. S. (2001). In: Bingham E., Cohnsen B., Powell C. H., eds. *Patty's Toxicology*. New York: John Wiley and sons, pp. 177–220.
46. Ward, E., Okun, A., Ruder, A., Fingerhut, M., and Steenland, K. (1992) A mortality study of workers at 7 beryllium processing plants. *Am. J. Ind. Med.* **22**, 885–904.
47. Steenland, K. and Ward, E. (1991) Lung cancer incidence among patients with beryllium disease: a cohort mortality study. *J. Natl. Cancer Inst.* **83**, 1380–1385.

48. Sanderson, W. T., Ward, E. M., Steenland, K., and Peterson, M. R. (2001) Lung cancer case—control study of beryllium workers. *Am. J. Ind. Med.* **39**, 133–144.
49. Levy, P. S., Roth, H. D., and Deubner, D. C. (2007) Exposure to beryllium and occurrence of lung cancer: a reexamination of findings from a nested case—control study. *J. Occup. Environ. Med.* **49**, 96–101.
50. International Agency for Research on Cancer (IARC). (1973) Arsenic and inorganic arsenic compounds. IARC Monogr Eval Carcinog Risks Hum, Vol 2. Lyon, France: IARC.
51. International Agency for Research on Cancer (IARC). (1980) Arsenic and arsenic compounds. IARC Monogr Eval Carcinog Risks Hum, Vol 23. Lyon, France: IARC.
52. International Agency for Research on Cancer (IARC). (1987) Arsenic and arsenic compounds. IARC Monogr Eval Carcinog Risks Hum, Supplement 7. Lyon, France: IARC.
53. Lee-Feldstein, A. (1986) Cumulative exposure to arsenic and its relationship to respiratory cancer among copper smelter employees. *J. Occup. Med.* **28**, 296–302.
54. Henderson, V. L., Callahan, C. M., and Paik, M. (1987) Some effects of cigarette smoking, arsenic, and SO₂ on mortality among US copper smelter workers. *J. Occup. Med.* **29**, 831–838.
55. Jarup, L., Pershagen, G., and Wall, S. (1989) Cumulative arsenic exposure and lung cancer in smelter workers: a dose-response study. *Am. J. Ind. Med.* **15**, 31–41.
56. Xu, Z. Y., Blot, W. J., Xiao, H. P., Wu, A., Feng, Y. P., Stone, B. J., Sun, J., Ershow, A. G., Henderson, B. E., and Fraumeni, J. F. (1989) Smoking, air pollution, and the high rates of lung cancer in Shenyang, China. *J. Natl. Cancer Inst.* **81**, 1800–1806.
57. Enterline, P. E., Day, R., and Marsh, G. M. (1995) Cancers related to exposure to arsenic at a copper smelter. *Occup. Environ. Med.* **52**, 28–32.
58. Lundstrom, N. G., Englyst, V., Gerhards-son, L., Jin, T., and Nordberg, G. (2006) Lung cancer development in primary smelter workers: a nested case-referent study. *J. Occup. Environ. Med.* **48**, 376–380.
59. Cordier, S. and Theriault, I. H. (1983) Mortality patterns in a population living near a copper smelter. *Environ. Res.* **31**, 311–322.
60. Pershagen, G. (1985) Lung cancer mortality among men living near an arsenic-emitting copper smelter. *Am. J. Epidemiol.* **122**, 311–322.
61. Chen, R., Wei, L., and Huang, H. (1993) Mortality from lung cancer among copper miners. *Br. J. Ind. Med.* **50**, 505–509.
62. Simonato, L., Moulin, J. J., Javelaud, B., Ferro, G., Wild, P., Winkelmann, R., and Saracci, R. (1994) A retrospective mortality study of workers exposed to arsenic in a gold mine and refinery in France. *Am. J. Ind. Med.* **25**, 625–633.
63. Qiao, Y. L., Taylor, P. R., Yao, S. X., Erozan, Y. S., Luo, X. C., Barrett, M. J., Yan, Q. Y., Giffen, C. A., Huag, S. Q., Maher, M. M., Forman, M. R., and Tockman, M. S. (1997) Risk factors and early detection of lung cancer in a cohort of Chinese tin miners. *Ann. Epidemiol.* **7**, 533–541.
64. Mabuchi, K., Lilienfeld, A. M., and Snell, L. M. (1985) Cancer and occupational exposure to arsenic: a study of pesticides workers. *Prev. Med.* **9**, 119–123.
65. Sobel, W., Bond, G. G., Baldwin, C. L., and Ducommun, D. J. (1988) An update of respiratory cancer and occupational exposure to arsenicals. *Am. J. Ind. Med.* **13**, 263–270.
66. Hayes, R. B. (1997) The carcinogenicity of metals in humans. *Cancer Causes Contr.* **8**, 3171–3385.
67. Chen, C. L., Hsu, L. I., Chiou, H. Y., Hsueh, Y. M., Chen, S. Y., Wu, M. M., and Chen, C. J. (2004) Ingested arsenic, cigarette smoking, and lung cancer risk: a follow-up study in arseniasis-endemic areas in Taiwan. *JAMA* **292**, 2984–2990.
68. Ferreccio, C., Gonzalez, C., Milosavlevic, V., Marshall, G., Sancha, A. M., and Smith, A. H. (2000) Lung cancer and arsenic concentrations in drinking water in Chile. *Epidemiology* **11**, 673–679. Erratum in: *Epidemiology* **12**, 283.
69. Chen, Y. and Ahsan, H. (2000) Cancer burden from arsenic in drinking water in Bangladesh. *Am. J. Public Health* **94**, 741–744.
70. International Agency for Research on Cancer (IARC). (1997) Silica and some silicates. IARC Monogr Eval Carcinog Risks Hum: Lyon, France: IARC.
71. The National Toxicology Program (NTP). (2005) Report on Carcinogens, 11th ed. U.S. Department of Health and Human Services, Public Health Service. January 31, 2005.
72. Soutar, C. A., Robertson, A., Miller, B. G., Searl, A., and Bignon, J. (2000) Epidemio-

- logical evidence on the carcinogenicity of silica: factors in scientific judgement. *Ann. Occup. Hyg.* **44**, 3–14.
73. Pelucchi, C., Pira, E., Piolatto, G., Coggiola, M., Carta, P., and La Vecchia, C. (2005) Occupational silica exposure and lung cancer risk: a review of epidemiological studies 1996–2005. *Ann. Oncol.* **17**, 1039–1050.
 74. Cassidy, A., 't Mannetje, A., van Tongeren, M., Field, J. K., Zaridze, D., Szeszenia-Dabrowska, N., Rudnai, P., Lissowska, J., Fabianova, E., Mates, D., Bencko, V., Foretova, L., Janout, V., Fevotte, J., Fletcher, T., Brennan, P., and Boffetta, P. Occupational exposure to crystalline silica and lung cancer risk: a multicenter case-control study in Europe. *Epidemiology* **18**, 36–43.
 75. Brown, T. P. and Rushton, L. (2005) Mortality in the UK industrial silica sand industry: 2. A retrospective cohort study. *Occup. Environ. Med.* **62**, 446–452.
 76. Chen, W., Bochmann, F., and Sun, Y. Effects of work related confounders on the association between silica-exposure and lung cancer: a nested case-control study among Chinese miners and pottery workers. *Int. Arch. Environ. Health* **80**, 320–326.
 77. Cocco, P., Dosemeci, M., and Rice, C. (2007) Lung cancer among silica-exposed workers: the quest for truth between chance and necessity. *Med. Lav.* **98**, 3–17.
 78. Barksdale, J. (1968). *The Encyclopedia of the Chemical Elements*. Hampel CA Ed. New-York: Reinhold Book Corporation, 732–38 “Titanium”.
 79. Lee, K. P., Trochimowicz, H. J., and Reinhardt, C. F. Pulmonary response of rats exposed to titanium dioxide (TiO₂) by inhalation for two years. *Toxicol. Appl. Pharmacol.* **79**, 179–192.
 80. Dungworth, D. L., Mohr, U., Heinrich, U., Ernst, H., and Kittel, B. (1994) Pathologic effects of inhaled particles in rat lungs: associations between inflammatory and neoplastic processes. In: Mohr U, Dungworth DL, Mauderly JL, Oberdoster G, eds. *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract*. Washington, DC: ILSI Press; pp 75–98.
 81. Chen, J. L. and Fayerweather, W. (1988) E. Epidemiologic study of workers exposed to titanium dioxide. *J. Occup. Med.* **30**, 937–942.
 82. Fayerweather, W. E., Karns, M. E., Gilby, P. G., and Chen, J. L. (1992) Epidemiologic study of lung cancer mortality in workers exposed to titanium tetrachloride. *J. Occup. Med.* **34**, 164–169.
 83. Fryzek, J.P., Chadda, B., Marano, D., White, K., McLaughlin, J. K., and Blot, W. J. (2003) A cohort mortality study among titanium dioxide manufacturing workers in the United States. *J. Occup. Environ. Med.* **45**, 400–409.
 84. Boffetta, P., Soutar, A., Cherrie, J.W., Granath, F., Andersen, A., Anttila, A., Blettner, M., Gaboricau, V., Klug, S. J., Langard, S., Luce, D., Merletti, F., Miller, B., Mirabelli, D., Pukkala, E., Adami, H. O., and Weiderpass, E. Mortality among workers employed in the titanium dioxide production industry in Europe. *Cancer Causes Control* **15**, 697–706.
 85. Boffetta, P., Gaboricau, V., Nadon, L., Parent, M. F., Weiderpass, E., and Siemiatycki, J. (2001) Exposure to titanium dioxide and risk of lung cancer in a population-based study from Montreal. *Scan. J. Work Environ. Health* **27**, 227–232.
 86. Siemiatycki, J. (1991) *Risk factors for cancer in the workplace*. Boca Raton (FL): CRC Press, 1991.
 87. Haguenoer, J. M., Shirali, P., Hannonthiaux, M. H., and Nisse-Ramond, C. (1996) Interactive effects of polycyclic aromatic hydrocarbons and iron oxides particles. Epidemiological and fundamental aspects. *Cent. Eur. J. Public Health* **4**, 41–45.
 88. Stokinger, H. E. (1984) A review of world literature finds iron oxides noncarcinogenic. *Am. J. Ind. Med.* **45**, 127–133.
 89. Garry, S., Nesslany, F., Aliouat el, M., Haguenoer, J. M., and Marzin, D. Potent genotoxic activity of benzo[a]pyrene coated onto hematite measured by unscheduled DNA synthesis in vivo in the rat. *Mutagenesis* **18**, 449–455.
 90. International Agency for Research on Cancer (IARC). (1987) Haematite and iron oxide. IARC Monogr Eval Carcinog Risks Hum, Supplement 7. Lyon, France: IARC.
 91. Lawler, A. B., Mandel, J. S., Schuman, L. M., and Lubin, J. H. (1985) A retrospective cohort mortality study of iron ore (hematite) miners in Minnesota. *J. Occup. Med.* **27**, 507–517.
 92. Mur, J. M., Meyer-Bisch, C., Pham, Q. T., Massin, N., Moulin, J. J., and Cavelier, C. (1987) Risk of lung cancer among iron ore miners: a proportional mortality study of 1,075 deceased miners in Lorraine (France). *J. Occup. Med.* **29**, 762–768.
 93. Chau, N., Benamghar, L., Pham, Q. T., Teculescu, D., Rebstock, E., and Mur, J.M. (1993) Mortality of iron miners in Lorraine (France): Relation between lung

- function and respiratory symptoms and subsequent mortality. *Br. J. Ind. Med.* **50**, 1017–1031.
94. Chen, S. Y., Hayes, R. B., Liang, S. R., Li, Q. G., Stewart, P. A., and Blair A. (1990) Mortality experience of hematite mine workers in China. *Br. J. Ind. Med.* **47**, 175–181.
 95. Su, L. P., Guan, H. Y., Zhao, L. F., Zhang, J. M., and Chen, W. H. (2006) Cohort mortality study of dust exposed miners in iron mine. *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* 2006; **4**, 360–363 (in Chinese).
 96. International Agency for Research on Cancer (IARC). (1987) Iron and steel foundry. IARC Monogr Eval Carcinog Risks Hum, Supplement 7. Lyon, France: IARC.
 97. International Agency for Research on Cancer (IARC). (1984) Polynuclear aromatic compounds. Part III: Industrial exposures in aluminium production, coal gasification, coke production and iron and steel foundry. IARC Monogr Eval Carcinog Risks Hum, Vol. 34. Lyon, France: IARC.
 98. Becher, H., Jedrychowski, W., Flak, E., Gomola, K., and Wahrendorf, J. (1989) Lung cancer, smoking, and employment in foundries. *Scand. J. Work Environ. Health* **15**, 38–42.
 99. Rotimi, C., Austin, H., Delzell, E., Day, C., Macaluso, M., and Honda, Y. (1993) Retrospective follow-up study of foundry and engine plant workers. *Am. J. Ind. Med.* **24**, 485–498.
 100. Sorahan, T., Faux, A. M., and Cooke, M. A. (1994) Mortality among a cohort of United Kingdom steel foundry workers with special reference to cancers of the stomach and lung, 1946–90. *Occup. Environ. Med.* **51**, 316–322.
 101. Andjelkovich, D. A., Janszen, D. B., Brown, M. H., Richardson, R. B., and Miller, F. J. (1995) Mortality of iron foundry workers: IV. Analysis of a subcohort exposed to formaldehyde. *J. Occup. Environ. Med.* **37**, 826–837.
 102. Hansen, E. S. (1997) A cohort mortality study of foundry workers. *Am. J. Ind. Med.* **32**, 223–233.
 103. Rodriguez, V., Tardon, A., Kogevinas, M., Prieto, C. S., Cueto, A., Garcia, M., Menezes, I. A., and Zaplana, J. (2000) Lung cancer risk in iron and steel foundry workers: A nested case-control study in Asturias, Spain. *Am. J. Ind. Med.* **38**, 644–650.
 104. Adzresen, K. H., Becker, N., Steindorf, K., and Frentzel-Beyme, R. (2003) Cancer mortality in a cohort of male German iron foundry workers. *Am. J. Ind. Med.* **43**, 295–305.
 105. Simonato, L., Fletcher, A. C., Andersen, A., Anderson, K., Becker, N., Chang-Claude, J., Ferro, G., Gérin, M., Gray, C. N., Hansen, K. S., et al. (1991). A historical prospective study of European stainless steel, mild steel and shipyard welders. *Br. J. Ind. Med.* **48**, 145–154.
 106. Ambroise, D., Wild, P., and Moulin, J. J. (2006) Update of a meta-analysis on lung cancer and welding. *Scand. J. Work. Environ. Health* **32**, 22–31.
 107. Bourgkard, E., Wild, P., Courcot, B., Diss, M., Ertlinger, J., Goutet, P., Hémon, D., Marquis, N., Mur, J. M., Rigal, C., Rohn-Janssens, M. P., and Moulin, J. J. (2007) Lung cancer mortality and iron oxide exposure in a French steel-producing factory. Accepted for publication.
 108. Moulin, J. J., Clavel, T., Roy, D., Dananché, B., Marquis, N., Févotte, J., et al. (2000) Risk of lung cancer in workers producing stainless steel and metallic alloys. *Int. Arch. Occup. Environ. Health* **73**, 171–180.
 109. Hurley, J. F., Miller, B. G., and Jacobsen, M. (1990) Mortality 1967–1977 of industrial workers and ex-workers from the British Steel Industry: further analyses. Institute of Occupational Medicine, Report N° TM/90/07, 1990 Aug.
 110. Moulin, J. J., Lafontaine, M., Mantout, B., Belanger, A., Michel, M., Wild, P. et al. (1995) Mortality due to bronchopulmonary cancers in workers of 2 foundries. *Rev. Epidemiol. Santé Publ.* **43**, 107–121 (in French).
 111. Finkelstein, M. M. (1994) Lung cancer among steelworkers in Ontario. *Am. J. Ind. Med.* **26**, 549–557.
 112. Redmond, C. K., Gustin, J., and Kamon, E. (1975) Long-term mortality experience of steelworkers: Mortality patterns of open hearth steelworkers (a preliminary report). *J. Occup. Med.* **17**, 40–43.
 113. Finkelstein, M. M. and Wilk, N. (1990) Investigation of a lung cluster in the melt shop of an Ontario steel producer. *Am. J. Ind. Med.* **17**, 483–491.
 114. Finkelstein, M. M., Boulard, M., and Wilk, N. (1991) Increased risk of lung cancer in the melting department of a second Ontario steel manufacturer. *Am. J. Ind. Med.* **19**, 183–194.
 115. Moulin, J. J., Wild, P., Mantout, B., Portefaix, P., Fournier-Betz, M., Mur, J. M., et al. (1993) Mortality from lung cancer and cardiovascular diseases among stain-

- less steel producing workers. *Cancer Causes Control* **4**, 75–81.
116. Cao, R., Dong, D., and Dong, G. (1995) Mortality study of cancer among Anshan iron and steel workers. *Chung. Hua. Chung. Liu. Tsa. Chih.* **17**, 49–54 (in Chinese).
 117. Blot, W. J., Morris Brown, L., Pottern, L. M., Stone, B. J., and Fraumeni, J. F. (1983) Lung cancer among long-term steel workers. *Am. J. Epidemiol.* **117**, 706–716.
 118. Xu, Z., Morris Brown, L., Pan, G. W., Liu, T. F., Gao, G. S., Stone, B. J., et al. (1996) Cancer risk among iron and steel workers in Anshan, China, Part II: Case-control studies of lung and stomach cancer. *Am. J. Ind. Med.* **30**, 7–15.
 119. Mazumdar, S., Lerer, T., and Redmond, C. K. (1975) Long-term mortality study of steelworkers: Mortality patterns among sheet and tin mill workers. *J. Occup. Med.* **17**, 551–555.
 120. Beaumont, J. J., Leveton, J., Knox, K., Bloom, T., McQuinston, T., Young, M., et al. (1987). Lung cancer mortality in workers exposed to sulfuric acid mist and other acid mists. *J. Natl. Cancer Inst.* **79**, 911–921.
 121. Axelsson, O., and Sjöberg, A. (1979) Cancer incidence and exposure to iron oxide dust. *J. Occup. Med.* **21**, 419–422.
 122. Danielsen, T. E., Langrød, S., and Andersen, A. (1998) Incidence of lung cancer among shipyard welders investigated for siderosis. *Int. J. Occup. Environ. Health* **4**, 85–88.
 123. Hernberg, S. (2000) Lead poisoning from a historical perspective. *Am. J. Ind. Med.* **38**, 244–254.
 124. International Agency for Research on Cancer (IARC). (2004) Inorganic and organic lead compounds. IARC Monogr Eval Carcinog Risks Hum, Vol 87. Lyon, France: IARC.
 125. Institut National de Recherche et de Sécurité. (2004) The carcinogenic risk of lead: Evaluation in occupational settings. B Hervé-Bazin editor, EDP Sciences, Paris, France, 2004 (in French).
 126. Moulin, J. J., Hervé-Bazin, B., Goutet, P., and Wild, P. (2002) Cancer risk and occupational lead compounds: a meta-analysis. *Med. Lav.* **93**, 388.
 127. Cordioli, G., Cuoghi, L., Solari, P. L., Berrino, F., Crosignani, P., and Riboli, E. (1987) Tumor mortality in a cohort of glass industry workers. *Epidemiol. Prev.* **9**, 16–18 (in Italian).
 128. Sankila, R., Karjalainen, S., Pukkala, E., Oksanen, H., Hakulinen, T., Teppo, L., and Hakama, M. (1990) Cancer risk among glass factory workers: an excess of lung cancer? *Br. J. Ind. Med.* **47**, 815–818.
 129. Michaels, D., Zoloth, S. R., and Stern, F. B. (1991) Does low-level lead exposure increase risk of death? A mortality study of newspaper printers. *Int. J. Epidemiol.* **20**, 978–983.
 130. Wingren, G. and Axelsson, O. Mortality in the Swedish glassworks industry. *Scand. J. Work Environ. Health.* **13**, 412–416.
 131. Bertazzi, P. A. and Zocchetti, C. (1980) A mortality study of newspaper printing workers. *Am. J. Ind. Med.* **1**, 85–97.
 132. Greene, M. H., Hoover, R. N., Eck, R. L., and Fraumeni, J. F. Jr. (1979) Cancer mortality among printing plant workers. *Environ. Res.* **20**, 66–73.
 133. Anttila, A., Heikkilä, P., Pukkala, E., Nykyri, E., Kauppinen, T., Hernberg, S., and Hemminki K. (1995) Excess Lung cancer among workers exposed to lead. *Scand. J. Work Environ. Health.* **21**, 460–469.
 134. Wingren, G. and Englander, V. (1990) Mortality and cancer morbidity in a cohort of Swedish glassworkers. *Int. Arch. Occup. Environ. Health.* **62**, 253–257.
 135. Gerhardsson, L., Lundström, N. G., Nordberg, G., and Wall, S. (1986) Mortality and lead exposure: a retrospective cohort study of Swedish smelter workers. *Br. J. Ind. Med.* **43**, 707–712.
 136. Gerhardsson, L., Hagmar, L., Rylander, L., and Skerfving, S. (1995) Mortality and cancer incidence among secondary lead smelter workers. *Occup. Environ. Med.* **52**, 667–672.
 137. Steenland, K., Selevan, S., and Landrigan, P. (1992) The mortality of lead smelter workers: an update. *Am. J. Public Health* **82**, 161–164. Erratum in: *Am. J. Public Health* (1993) **83**, 60.
 138. Wong, O. and Harris, F. (2000) Mortality among employees of lead battery plants and lead-producing plants, 1947–1995. *Am. J. Ind. Med.* **38**, 255–270.
 139. Ades, A. E. and Kazantzis, G. (1988) Lung cancer in a non-ferrous smelter: the role of cadmium. *Br. J. Ind. Med.* **45**, 435–442.
 140. Cocco, P., Hua, F., Boffetta, P., Carta, P., Flore, C., Flore, V., Onnis, A., Picchiri, G. F., and Colin, D. (1997) Mortality of Italian lead smelter workers. *Scand. J. Work Environ. Health.* **23**, 15–23.

141. Lundstrom, N. G., Nordberg, G., Englyst, V., Gerhardsson, L., Hagmar, L., Jin, T., Rylander, L., and Wall, S. (1997) Cumulative lead exposure in relation to mortality and lung cancer morbidity in a cohort of primary smelter workers. *Scand. J. Work Environ. Health* **23**, 24–30.
142. Sheff t, A., Thind, I., Miller, A. M., and Louria, D. B. (1982) Cancer mortality in a pigment plant utilizing lead and zinc chromates. *Arch. Environ. Health* **37**, 44–52.
143. Davies, J. M. (1984) Long term mortality study of chromate pigment workers who suffered lead poisoning. *Br. J. Ind. Med.* **41**, 170–178.
144. Lundstr m, N. G., Englyst, V., Gerhardsson, L., Jin, T., and Nordberg, G. (2006) Lung cancer development in primary smelter workers: a nested case-referent study. *J. Occup. Environ. Med.* **48**, 376–380.
145. Wingren, G. (2004) Mortality and cancer incidence in a Swedish art glassworks—an updated cohort study. *Int. Arch. Occup. Environ. Health* **77**, 599–603.
146. Davies, J. M. (2005) Study on mortality by specific cause among workers at a lead and zinc foundry in Sardinia. *G. Ital. Med. Lav. Ergon.* **27**, 43–45 (in Italian).
147. Mur, J. M., Moulin, J. J., Charruyer-Seinerra, M. P., and Lafitte, J. (1987) A cohort mortality study among cobalt and sodium workers in an electrochemical plant. *Am. J. Ind. Med.* **11**, 75–81.
148. Moulin, J. J., Wild, P., Mur, J. M., Fournier-Betz, M., and Mercier-Gallay, M. (1993) A mortality study of cobalt production workers: an extension of the follow-up. *Am. J. Ind. Med.* **23**, 281–288.
149. Hogstedt, C. and Alexandersson, R. (1990). Mortality among hard-metal workers. *Arbete H lsa* **21**, 3–26 (in Swedish).
150. Lasfargues, G., Wild, P., Moulin, J. J., Hammon, B., Rosmorduc, B., Rondeau du Noyer, C., Lavandier, M., and Moline, J. (1994) Lung cancer mortality in a French cohort of hard-metal workers. *Am. J. Ind. Med.* **26**, 585–595.
151. Moulin, J. J., Wild, P., Romazini, S., Lasfargues, G., Peltier, A., Bozec, C., Deguerry, P., Pellet, F., and Perdrix, A. (1998) Lung cancer risk in hard-metal workers. *Am. J. Epidemiol.* **148**, 241–248.
152. Wild, P., Perdrix, A., Romazini, S., Moulin, J. J., and Pellet, F. Lung cancer mortality in a site producing hard metals. *Occup. Environ. Med.* **57**, 568–573.
153. Leonard, A. and Lauwerys, R. (1990) Mutagenicity, carcinogenicity and teratogenicity of cobalt metal and cobalt compounds. *Mutat. Res.* **239**, 17–27.
154. Anard, D., Kirsch-Volders, M., Elhajouji, A., Belpaeme, K., and Lison, D. (1997) In vitro genotoxic effects of hard metal particles assessed by alkaline single cell gel and elution assays. *Carcinogenesis* **18**, 177–184.
155. De Boeck, M., Lison, D., and Kirsch-Volders, M. (1998) Evaluation of the in vitro direct and indirect genotoxic effects of cobalt compounds using the alkaline comet assay. Influence of interdonor and interexperimental variability. *Carcinogenesis* **19**, 2021–2029.
156. De Boeck, M., Hoet, P., Lombaert, N., et al. (2003) In vivo genotoxicity of hard metal dust: induction of micronuclei in rat type II epithelial lung cells. *Carcinogenesis* **11**, 1793–1800.
157. International Agency for Research on Cancer (IARC). (2006). Cobalt in hard metals and cobalt sulfate, gallium arsenide, indium phosphide and vanadium pentoxide. IARC, Monogr Eval Carcinog Risks Hum, Vol. 86. Lyon, France: IARC.
158. Duffus, J. H. (1996) Epidemiology and the identification of metals as human carcinogens. *Sci. Prog.* **79**, 311–326.
159. Navarro Silvera, S. A., and Rohan, T. E. Trace elements and cancer risk: a review of the epidemiologic evidence. *Cancer Causes Control* **18**, 7–27.
160. Desoize, B. (2004) Metals and metal compounds in cancer treatment. *Anticancer Res.* **24**, 1529–1544.