3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Intratracheal instillation

Hamster: Groups of 35 male Syrian golden hamsters, six weeks of age, received weekly intratracheal instillations of either (i) 2.0 mg of the particulate fraction of MIG/SS fume (containing 0.4% chromium and 2.4% nickel) in 0.2 ml saline; (ii) 0.5 mg or 2 mg of MMA/SS fume (containing 5% chromium and 0.4% nickel) in 0.2 ml saline; (iii) 0.2 ml saline alone; or (iv) 0.1 mg calcium chromate in 0.2 ml saline (see also the monograph on chromium, p. 123). The group receiving 2.0 mg MMA/SS fume had an acute toxic reaction to treatment, and, from week 26 onwards, the dose was given monthly. Following the 56 weeks of treatment, all animals were maintained for a further 44 weeks, at which time the study was terminated [survival figures were not given]. At 12 months, a single anaplastic tumour of the lung, probably a carcinoma, according to the authors, was found in the group that received 0.5 mg MMA/SS; and, at termination of the study, a single mixed epidermoid/adenocarcinoma of the lung was found in the group given 2 mg MMA/SS fume. No lung tumour was reported in the saline control, MIG/SS fume or calcium chromate-treated groups (Reuzel *et al.*, 1986).

(b) Intrabronchial implantation

Rat: Groups of 51 male and 49 female Sprague-Dawley rats, weighing 140-330 g (males) and 115-195 g (females), received surgical implants of five 1-mm stainless-steel mesh pellets into the left bronchus. The pellets were loaded with either (i) 7.0 mg of the particulate fraction of shielded metal arc welding fume (comparable to MMA/SS fume) containing 3.6% total chromium, of which 0.7% was of low solubility, with a particle size of 0.3-0.6 μm as mass median aerodynamic diameter and suspended in cholesterol (50:50 by weight); (ii) 6.7 mg of a thermal spray fume (a mixture of chromic oxide[III] and [VI], containing a total of 56% chromium, of which 40% was of low solubility, produced by blowing an air-jet containing chromic oxide through a flame) suspended in cholesterol (50:50 by weight); or (iii) cholesterol alone (about 5.0 mg). A further three rats received intrabronchial pellets loaded

with 40% benzo[a]pyrene (4.9-5.65 mg) in cholesterol as a positive control group. The experiment was terminated at 34 months; about 50% of animals were still alive at two years. No lung tumour was seen in the cholesterol control group, while all three benzo[a]pyrene-treated treated rats developed squamous-cell carcinomas or carcinomas *in situ* around the site of pellet implantation. A single, microscopic, subpleural squamous-cell carcinoma was found in the right lung of a rat given shielded metal arc welding fume, but the authors considered this to be unrelated to treatment (Berg *et al.*, 1987)

3.2 Other relevant data in experimental systems

(a) Absorption, distribution, excretion and metabolism

(i) Mild-steel welding

Male Wistar rats were exposed by inhalation to 43 mg/m³ (particle size, 0.12 μm mass median average diameter) MMA/MS welding fumes for 1 h per work day for up to four weeks; a saturation level of 550 μg/g dry lung of the welding fumes was observed. Clearance of the welding fume particles from the lung followed a two-phase exponential equation; most of the accumulated particles were excreted within a half-time of six days and the remainder with a half-time of 35 days. The two major components of the mild steel — iron and manganese — had similar pattern of saturable lung retention, but manganese was cleared much faster initially (the first half-time was 0.5 day). Some of the inhaled manganese was apparently soluble and was quickly absorbed from the lung, whereas the absorption of exogenous iron was slower and was obscured by a simultaneous occurrence of endogenous iron in lung tissue. Under the same exposure conditions, alveolar retention of the mild-steel welding fumes was much lower and its clearance much faster than the corresponding parameters for stainless-steel (Kalliomäki *et al.*, 1983a,b).

Male Sprague-Dawley rats were exposed for 46 min by inhalation to MMA/MS welding fumes (1178 mg/m³; particles, 0.13 μm mass median average diameter) containing < 0.1% chromium and cobalt. The immediate retention of the fume particles totalled 1.5 mg/lung, and the elemental composition of the fumes retained was slightly different from that of the original airborne fumes, indicating some selective retention/clearance. Iron was cleared from the lungs substantially more slowly than chromium or cobalt, and pulmonary retention of iron was represented as a three-phase exponential curve with half-times of 0.2 (50% of the deposit), 1.6 (32%) and 34 (18%) days (Lam *et al.*, 1979).

(ii) Stainless-steel welding

Dunkin-Hartley guinea-pigs were exposed by inhalation for 256 min to MIG/ SS welding fumes (990 mg/m³; particle size, 0.064 μm median diameter as deter-

mined by electron microscopy). The initial fractional deposit of the fume was 17%; the proportions of iron, cobalt, nickel and chromium retained in the lung were different from those in airborne fumes. During 80 days after exposure, the metals were cleared from the lungs at different rates: chromium > nickel > cobalt > iron, according to individual three-phase kinetic curves, with half-times ranging from 0.4-0.6 days for the first phase to 72-151 days for the third phase, depending on the metal. Iron, chromium and cobalt were eliminated mostly with faeces (maximal at days 2-3 after exposure) (Lam et al., 1979).

Wistar rats were exposed to MMA/SS welding fumes (43 mg/m³; 0.3 μm mass median diameter determined by electron microscopy) for 2 h per day for up to five days. The concentrations of chromium, nickel and exogenous iron in the lungs correlated well with the cumulative exposure time. No saturation trend was found for any of the metals. The average pulmonary concentration of chromium after the maximal exposure of 10 h was 39 ppm (mg/kg), that of nickel was 5.7 ppm (mg/kg) and that of exogenous iron, 132 ppm (mg/kg). The level of chromium was also elevated in the blood, kidneys, liver and spleen, while those of nickel and iron did not increase significantly in these tissues (Kalliomäki et al., 1982a).

Male Wistar rats were exposed to 43 mg/m³ MMA/SS welding fumes for 1 h per work day for up to four weeks. Median particle size of the fume was 0.3-0.6 μm mass median average diameter as determined by electron microscopy. A linear relationship was observed between the duration of exposure and the concentration of exogenous iron, chromium and nickel in the lung. A simplified single exponential lung clearance model gave the following half-times: exogenous iron, 50 days; chromium, 40 days; and nickel, 20 days. The concentration of chromium in the blood was significantly elevated only during exposure, and it decreased rapidly after termination of exposure; concentrations of exogenous iron and nickel were near the detection limits (Kalliomäki et al., 1983c). Use of the MIG/SS welding technique instead of the MMA/SS technique under comparable exposure conditions did not substantially change the pulmonary retention patterns of the welding fumes, but it markedly changed the clearance patterns, especially for chromium. After exposure to MMA welding fume, chromium, manganese and nickel were cleared at half-times of 40, 40 and 30 days, respectively; with the MIG fumes, the half-time for chromium was 240 days, while the clearance of manganese and nickel obeyed the double-exponential model with half-times of two and 125 days for manganese and three and 85 days for nickel (Kalliomäki et al., 1983d, 1984).

Welding fumes collected from the MMA/SS and MIG/SS assemblies were suspended in normal saline (1% suspension) and instilled intratracheally into male Wistar rats at a dose of 0.2 ml/rat, and the fate of the metals contained in the fumes was followed for up to 106 days. After exposure to the MMA/SS fumes, iron, chromium and nickel were cleared with half-times of 73, 53 and 49 days, respectively; but

with MIG/SS fume, practically none of the metal was cleared within two months. The disposition of chromium in the MMA/SS fume closely resembled that of intra-tracheally instilled soluble chromates, whereas the very slow lung clearance of chromium from the MIG/SS fumes was still slower than that of water-insoluble chromates or Cr[III] salts. Thus, the clearance of chromium strongly depends on the physicochemical form of chromium in the welding fume (Kalliomäki et al., 1986).

The dissolution of MMA/SS and MIG/SS welding fumes was studied in the lungs of male Wistar rats following one to four weeks' exposure by inhalation to 50 mg/m³ for 1 h per day. Two particle populations with different behaviours were found in the lungs of rats exposed to the MMA/SS fumes. The particles of the principal population (0.1-0.25 μm mass median average diameter as determined by electron microscopy) dissolved in both alveolar macrophages and type-1 epithelial cells in about two months; quickly and slowly dissolving forms of chromium, manganese and iron were detected in these particles. The particles of the minor population (0.005-0.1 μm determined as above) showed no signs of dissolution during the three-month observation period; they were found to contain very stable mixed spinels. Inhalation of the MIG/SS fumes resulted in lung deposition of only one particle population, which was very similar to the minor population in the MMA/SS fumes; no dissolution of these particles was observed within three months (Anttila, 1986).

(b) Toxic effects

(i) Mild-steel welding

Deposition of MMA/MS welding fumes in the lungs of male CFE rats following single exposures by inhalation or by intratracheal injection resulted in the development of reticulin fibres in the particle-laden macrophage aggregates, with only sparse collagen fibre formation, which did not increase markedly up to 450 days (Hicks et al., 1983). The particles caused alveolar epithelial thickening with proliferation of granular pneumocytes and exudation of lamellar material. Foam cells appeared in alveoli. Formation of nodular aggregates of particle-laden macrophages and giant cells was observed as a delayed effect 80-300 days after exposure (Hicks et al., 1984). Similar nonspecific pulmonary changes were seen in the lungs of Sprague-Dawley rats exposed to MMA/MS welding fumes (mass median diameter, 0.62 μm) as a single exposure to 1000 mg/m³ for 1 h or to 400 mg/m³ for 30 min per day on six days per week during two weeks (Uemitsu et al., 1984).

In MRC hooded rats, single intratracheal instillations (0.5-5 mg/rat) of either 'basic' (18% SiO_2, 30% F, 23% Fe, 6% Mn) or 'rutile' (41% SiO_2, 2% Ti, 39% Fe, 3% Mn) MMA/MS welding particles, suspended in saline increased the ribonuclease and protease activity of lavaged cells by one week after administration (White et al., 1981).

Cultured alveolar macrophages from the lavaged lungs of male Brown-Norway rats were exposed for one day to total dust or to the water-insoluble fraction of fume particles [size unspecified] from MMA/MS and MIG/MS welding (15, 25 or 50 μg/ml). Both dusts were toxic to the cells in a concentration-related manner; MMA/MS dust was more toxic than that of the MIG/MS. The toxicity of the MMA/MS and MIG/MS particles was not related to the water-soluble components (Pasanen et al., 1986).

In rat peritoneal macrophages in vitro, none of three welding fumes derived from MS showed fibrogenic potential; pure magnetite dust was also inactive (Stern & Pigott, 1983; Stern et al., 1983).

When alveolar macrophages from bovine lungs were exposed in vitro to MMA/MS welding particles (both 'basic' and 'rutile'; up to 40 μg/ml) for 17 h, dose-related detachment of cells, morphological changes and a decrease in viability were seen. Toxicity was reduced significantly by supplementation of the cell culture with 10% calf serum, but not by bovine serum albumin. Release of lactic dehydrogenase, but not of N-acetyl-β-glucosaminidase, was also observed. The 'basic' fumes were slightly more active than the 'rutile' fumes (White et al., 1983).

(ii) Stainless-steel welding

Two days after a single exposure of male Sprague-Dawley rats to MMA/SS welding fumes (1000 mg/m³ for 1 h or 400 mg/m³ for 30 min per day, six days per week during two weeks; mass median diameter, 0.8 μm), hyperplasia of mucous cells was seen in the bronchial epithelium which tended to increase with time (maximal at day 7). No other significant pathological effect was observed (Uemitsu et al., 1984).

In the study of White et al. (1981; see above), MMA/SS welding particles (containing 16% SiO₂, 13% F, 2% Fe, 3% Mn, 2% Cu and 2.5% Cr (nearly all in a water-soluble Cr[VI] form)) suspended in saline also increased the ribonuclease and protease activity of lavaged cells from MRC hooded rats.

Male Sprague-Dawley rats received a single intratracheal instillation of the soluble or insoluble fraction of MMA/SS welding fume particles containing 3.5% chromium (nearly all soluble Cr[VI]) or potassium dichromate at doses equivalent to those found in the fume particles. One week after instillation, most of the toxicity of the welding particles could be related to the content of soluble Cr[VI], although the insoluble particles also produced some changes at the alveolar surface (White et al., 1982).

MIG/SS welding fume deposited in the lungs of male CFE rats had similar effects to those of MMA/MS fume, reported above (Hicks et al., 1983, 1984). MIG/SS particles injected intradermally or given by topical application to Dunkin-Hartley guinea-pigs had moderate sensitizing properties, which were stronger than

those of MMA/MS particles but weaker than those of chromates (Hicks *et al.*, 1979). After intramuscular injection to CFE rats and Dunkin-Hartley guinea-pigs, the MIG/SS and MMA/MS materials were much less toxic and irritant than the MMA/SS material. The differences in fibrogenic properties were less pronounced, but MMA/SS still had the greatest effect (Hicks *et al.*, 1987).

The toxic effects of MMA/SS fume in baby hamster kidney and Syrian hamster embryo cells were more pronounced than that of MIG/SS fume. The effect of MMA/SS fume corresponded to the content of soluble chromates (potassium dichromate), while that of MIG/SS fume was greater, implying phagocytosis of less soluble chromium particles. Freshly produced welding fume appeared to be more active than stored samples (Hansen & Stern, 1985).

Cultured alveolar macrophages from the lavaged lungs of male Brown-Norway rats were exposed for one day to the total dust or to the water-insoluble fraction of fume particles [size unspecified] from MMA/SS and MIG/SS (15, 25 or 50 µg/ml). Both dusts were toxic in a concentration-related manner, but the MMA/SS dust was more toxic than that of MIG/SS. MMA/SS particles, but not MIG/SS particles, were less toxic after prewashing. The effects of MMA/SS on cell viability were similar to those observed after exposure of cells to potassium chromate at equivalent concentrations (Pasanen *et al.*, 1986).

In rat peritoneal macrophages *in vitro*, MMA/SS had distinct fibrogenic potential (Stern & Pigott, 1983; Stern *et al.*, 1983).

When alveolar macrophages from bovine lungs were exposed *in vitro* to MMA/SS welding particles, chromium[III] chloride or potassium dichromate (at up to 30 nmol (1.6 µg) chromium/ml) for 17 h, dose-related detachment of cells, morphological changes and a decrease in viability were seen. Within the concentration range tested, the MMA/SS fume particles were more toxic than potassium dichromate, while Cr[III] had no effect on cell viability. Toxicity was reduced significantly by supplementation of the cell culture with 10% calf serum, but not by bovine serum albumin. Release of lactic dehydrogenase, but not of N-acetyl-β-glucosaminidase, was also observed (White *et al.*, 1983).

The cytotoxic effects of two MIG/SS and one MMA/SS welding fumes were tested at concentrations of 5-200 µg/ml in normal human embryonic pulmonary epithelium cells (L132) in culture. At equal concentrations, the two MIG/SS fumes had comparable cytotoxicity which was somewhat greater for the fume containing more nickel (60% *versus* 4% nickel). The MMA/SS fume was much more toxic, probably because it contained high proportions of soluble Cr[VI], fluorine and potassium; a comparable effect was obtained with an equivalent concentration of sodium chromate. The particles were phagocytized by the cells. Changes in cell morphology were also observed (Hildebrand *et al.*, 1986).

(c) *Effects on reproduction and prenatal toxicity*

No data were available to the Working Group.

(d) *Genetic and related effects*

The Working Group noted that the evaluation of genetic effects of welding fumes is complicated not only by many variations in welding techniques but also by variations in collection and storage methods prior to testing. In the studies reported, several different methods of sample collection and application were used. Particulate fractions were collected on filters and then suspended in water (Hedenstedt *et al.*, 1977; Knudsen, 1980; Hansen & Stern, 1985; Baker *et al.*, 1986), in dimethyl sulfoxide (Maxild *et al.*, 1978), in culture media (Koshi, 1979; Niebuhr *et al.*, 1980; de Raat & Bakker, 1988) or in phosphate buffer (Biggart *et al.*, 1987). In one study, particulate and volatile fractions were separated and the latter passed into a chamber containing bacteria on petri dishes (Biggart & Rinehart, 1987). Studies for genetic and related effects of welding fumes are summarized in Appendix 1 to this volume.

(i) *Mild-steel welding*

MMA and MIG welding fumes did not inhibit growth of either *Escherichia coli* W3110 *pol*A$^+$ or the repair-deficient *E. coli* P3478 *pol*A$^-$ strain (Hedenstedt *et al.*, 1977).

MS welding fumes were not mutagenic to *Salmonella typhimurium* TA97, TA98, TA100 or TA102 (Hedenstedt *et al.*, 1977; Maxild *et al.*, 1978; Etienne *et al.*, 1986). The gaseous phase from MMA/MS welding induced mutation in *S. typhimurium* TA1535 but not in TA1538, while the particulate fraction (in phosphate buffer) induced mutation in TA1538 but not in TA1535 (Biggart & Rinehart, 1987; Biggart *et al.*, 1987).

MMA/MS and MIG/MS did not increase the incidence of chromosomal aberrations in Chinese hamster ovary cells at doses up to 32 μg/ml (MMA) or 1000 μg/ml (MIG) (Etienne *et al.*, 1986) and did not induce morphological transformation of Syrian baby hamster kidney cells at doses up to 600 μg/ml (MMA) or 600 μg/ml (MIG) (Hansen & Stern, 1985). [See General Remarks for concern about this assay.] Relatively high doses of MMA/MS (50-300 μg/ml), but not of MIG/MS (250-1000 μg/ml), fumes increased the frequency of sister chromatid exchange in Chinese hamster ovary cells (Etienne *et al.*, 1986; de Raat & Bakker, 1988).

Neither MMA/MS (at 64-217 mg/m³ for 6 h per day, five days per week for two weeks) nor MIG/MS (at 144 mg/m³ for 6 h per day, five days per week for two weeks) fumes increased the frequency of sister chromatid exchange in peripheral blood lymphocytes or of chromosomal aberrations in either peripheral blood lymphocytes or bone-marrow cells of rats after exposure by inhalation (Etienne *et al.*, 1986).

(ii) *Mild-steel and cast-iron welding with nickel-rich electrodes*

With MMA welding fumes from cast iron employing a nickel-rich (95% Ni) electrode, no mutagenicity was detected in four strains of *S. typhimurium* (TA97, TA98, TA100 and TA102) at up to 20 mg/plate; no *hprt* locus mutation and no induction of chromosomal aberrations, but an increased frequency of sister chromatid exchange, were observed in Chinese hamster ovary cells (Etienne *et al.*, 1986). In another study, an increased frequency of sister chromatid exchange was seen in an unspecified cell line [probably human peripheral lymphocytes] exposed to 100-500 μg/ml MIG/MS welding fume from a 95%-nickel electrode (Niebuhr *et al.*, 1980). The same type of fume caused anchorage-independent growth of baby hamster kidney fibroblasts at 100-400 μg/ml (Hansen & Stern, 1984). [See General Remarks for concerns about this assay.]

MMA welding fumes from cast iron employing a nickel-rich (95% Ni) electrode did not increase the frequency of sister chromatid exchange in peripheral blood lymphocytes or of chromosomal aberrations in either peripheral blood lymphocytes or bone–marrow cells of rats after exposure by inhalation to 57 mg/m³ for 6 h per day, five days per week for two weeks (Etienne *et al.*, 1986).

(iii) *Stainless-steel welding*

Growth of the repair-deficient *E. coli* P347S *polA⁻* mutant was selectively inhibited, as compared to *E. coli* W3110 *polA⁺*, by MMA/SS but not by MIG/SS fumes, demonstrating that MMA/SS has a greater DNA damaging potential (Hedenstedt *et al.*, 1977).

Both MMA/SS and MIG/SS fumes were mutagenic to *S. typhimurium* TA97, TA98, TA100 and TA102 (Hedenstedt *et al.*, 1977; Maxild *et al.*, 1978; Etienne *et al.*, 1986). The mutagenicity of some but not all fume samples was diminished by addition of an exogenous metabolic system from rat livers.

It was reported that MMA/SS fumes did not enhance unscheduled DNA synthesis in human cells (Reuzel *et al.*, 1986) [details not given]. MMA/SS fumes induced a significant response at the *hprt* locus (6-thioguanine resistance) at 10 μg/ml in one experiment of three in the Chinese hamster V79 cell line (Hedenstedt *et al.*, 1977). [The Working Group considered the overall effect to be negative.] Responses at the *hprt* locus varied according to the way in which fume was generated (Etienne *et al.*, 1986).

Sister chromatid exchange was induced by MMA/SS and MIG/SS fumes in Chinese hamster ovary cells (Etienne *et al.*, 1986; de Raat & Bakker, 1988) and Don hamster cells (Koshi, 1979; Baker *et al.*, 1986); these fumes also induced chromosomal aberrations in Don (Koshi, 1979) and Chinese hamster ovary (Etienne *et al.*, 1986) cell lines, and mitotic delay was found after treatment of hamster Don cells

with the water-soluble and -insoluble fractions of MMA/SS fumes (Baker *et al.*, 1986).

MMA/SS (50 µg/ml) and MIG/SS (400-800 µg/ml) welding fumes induced anchorage-independent growth of Chinese baby hamster kidney cells, and 5 µg/ml MMA/SS and 18 µg/ml MIG/SS fumes caused morphological transformation of Syrian hamster embryo cells (Hansen & Stern, 1985).

MMA/SS fumes were mutagenic *in vivo* following intraperitoneal injection of 100 mg/kg bw over days 8, 9 and 10 of gestation, as observed in the mouse fur spot test (Knudsen, 1980); however, no increase in the frequency of either sister chromatid exchange in peripheral blood lymphocytes or of chromosomal aberrations in either peripheral blood lymphocytes or bone-marrow cells of rats was found after inhalation of MMA/SS fumes (60-100 mg/m^3 for 6 h per day, five days per week for two weeks) or MIG/SS fumes (124-172 mg/m^3 for 6 h per day, five days per week for two weeks) (Etienne *et al.*, 1986).

[The greater genotoxic activity *in vitro* of MMA/SS fumes as compared with MIG/SS welding fumes generally corresponds to their higher content of Cr[VI]. In the absence of chromium, the presence of nickel is sufficient to account for the observed activity *in vitro*.]

3.3 Other relevant data in humans

(a) *Absorption, distribution, excretion and metabolism*

In human lungs on autopsy, welding-fume particles seemed to be preferentially retained in central regions, mainly behind but also in front of the hilus (Kalliomäki *et al.*, 1979). Characteristic stainless-steel particles could be identified by electron probe analysis in lung tissue from two deceased arc welders (Stettler *et al.*, 1977). Analysis by energy-dispersive X-ray technique of lung tissue from one welder revealed intracellular particles containing both iron and silicon (Guidotti *et al.*, 1978), while tissue samples from ten other welders revealed large amounts of iron in fibrotic septa, but no increase in the content of silicon (Funahashi *et al.*, 1988). Lung tissue from two SS welders contained up to 500 times more nickel and 60 times more chromium than in controls, but the high nickel levels may have been due in part to exposures at a nickel refinery (Raithel *et al.*, 1988).

Urinary chromium excretion after work in active welders using MMA/SS or MIG/SS correlated with concentrations of soluble chromium compounds in the air during the work day (Tola *et al.*, 1977; Sjögren *et al.*, 1983a; Welinder *et al.*, 1983; Mutti *et al.*, 1984; see Table 8). Concentrations of chromium in urine and plasma obtained from 103 MMA/SS and MIG/SS welders at the end of the shift were strongly correlated; chromium concentrations in erythrocytes, though much lower, correlated better with plasma levels than with urinary chromium concentrations

(Angerer *et al.*, 1987). In ten MMA/SS welders, airborne chromium exposures correlated poorly with chromium concentrations in whole blood and plasma, but correlated significantly with increases occurring in blood and plasma concentrations during the shift (Rahkonen *et al.*, 1983). In welders using exclusively gas-shielded welding techniques, chromium concentrations in urine and blood were barely increased above background levels (Angerer *et al.*, 1987).

In welders with a long exposure history, urinary chromium excretion remained high during three exposure-free weeks, possibly due to slow excretion of previously retained chromium (Mutti *et al.*, 1979). Accumulation of chromium is suggested by the observation that urine and plasma chromium concentrations may not return to background levels in MMA/SS welders over a weekend (Schaller *et al.*, 1986). Increased excretion of chromium was also seen in nine retired welders (average, four years since cessation of exposure) who had done mainly MMA/SS but also some MIG and TIG welding (Welinder *et al.*, 1983). Good correlations were found in ten MMA/SS welders between chromium levels in body fluids and the retention rate for magnetic dust, as estimated by magnetopneumography (Rahkonen *et al.*, 1983).

Increased urinary nickel excretion was seen in MMA/SS welders but not in TIG welders, perhaps due to differences in the solubility of the airborne nickel compounds (Kalliomäki *et al.*, 1981). Urinary nickel excretion of ten MMA/SS welders correlated significantly with airborne exposures (Rahkonen *et al.*, 1983). Increased nickel concentrations were also seen in plasma and urine of shipyard (Grandjean *et al.*, 1980) and other welders (Bernacki *et al.*, 1978).

Increased concentrations of aluminium (Sjögren *et al.*, 1985), barium (Dare *et al.*, 1984), fluoride (Sjögren *et al.*, 1984), lead (Grandjean & Kon, 1981) and manganese (Järvisalo *et al.*, 1983) have been measured in samples of blood and urine from some groups of welders (see section 2.3).

(b)   Toxic effects

Adverse health effects of exposures during welding have been reviewed by Zober (1981a,b), Stern *et al.* (1983) and the National Institute for Occupational Safety and Health (1988).

Sensitivity to chromate resulted in contact dermatitis in five welders exposed to chromate-containing welding fumes (Fregert & Övrum, 1963). Cutaneous exposure to sparks and radiation may cause burns and other damage to the skin (Roquet-Doffiny *et al.*, 1977), and localized cutaneous erythema and small cutaneous scars are frequent in welders. The ultra-violet radiation from welding operations can cause acute keratoconjunctivitis in the absence of eye protection, but such episodes normally cause no apparent lasting clinical abnormality or decrease in visual acuity (Emmett *et al.*, 1981).

Metal fume fever is a nonspecific, acute illness characterized by fever, muscle pain and leukocytosis; it is fairly common among welders. For example, 23/59 ship repair welders had experienced metal fume fever during the previous year, and 4/59 had suffered more than six incidents of the illness during that time (Grandjean & Kon, 1981). In another study, 31% of 530 welders aged 20-59 had experienced metal fume fever at least once (Ross, 1974). This condition may rarely be associated with angioedema and urticaria (Farrell, 1987). Several cases of asthmatic reactions due to components of welding fume have been recorded (Keskinen et al., 1980; Bjørner-em et al., 1983). Acute inhalation of metal fumes containing cadmium or ozone may result in chemical pneumonitis and pulmonary oedema (Beton et al., 1966; Anthony et al., 1978).

Welders who had used electrodes with a high chromium content for many years showed signs of erosion of the nasal septum (Jindrichova, 1978). Chronic inflammation was observed in upper airway epithelium of welders (Werner, 1977).

Several groups of welders, in particular nonsmokers, experienced more frequent chronic rhinitis, cough, phlegm, dyspnoea, wheezing and chronic bronchitis than expected (Barhad et al., 1975; Antti-Poika et al., 1977; Akbarkhanzadeh, 1980; Kalliomäki et al., 1982b; Keimig et al., 1983; Schneider, 1983; Mur et al., 1985; Cotes et al., 1989). Indicators of pulmonary function, such as vital capacity and forced expired volume in 1 s, showed decrements related to welding exposures (Peters et al., 1973; Barhad et al., 1975; Akbarkhanzadeh, 1980; Kalliomäki et al., 1982b; Cotes et al., 1989). Small airway disease may be the first sign of pulmonary abnormalities in shipyard welders, as reflected by increased closing volume and closing capacity (Oxhoj et al., 1979) and decreased terminal flow volumes (Kilburn et al., 1985; Cotes et al., 1989). One study showed a significant correlation in welders between respiratory symptoms and thoracic magnetic dust content (Näslund & Högstedt, 1982), while no such relationship was detected in another study (Stern et al., 1988). (The methods used to detect magnetic dust have been reviewed (Lippmann, 1986), and there is evidence that magnetic properties are unstable in lung over long periods (Stern et al., 1987).) Further, some studies indicated a minimal or no difference in prevalence rates of respiratory symptoms and pulmonary function in welders compared to control groups (Fogh et al., 1969; Hayden et al., 1984; McMillan & Pethybridge, 1984). Forced ventilatory capacity was decreased to similar degrees in shipyard welders, pipe-coverers and pipe-fitters, suggesting that past asbestos exposure in some groups of welders may affect pulmonary function (Peters et al., 1973). [The Working Group noted that possible selection bias among long-term welders, interaction with smoking, questionable validity of control groups and poor characterization of the exposures decreased the value of some studies.]

Early reports suggested that inhalation of welding fumes may cause siderosis, a benign pneumoconiosis (Doig & McLaughlin, 1936; Enzer & Sander, 1938); small,

rounded opacities (Attfield & Ross, 1978) and nonspecific reticulomicronodulation (Mur et al., 1989) were seen on X-ray examination. Some authors have reported no fibrosis or related pulmonary function changes (Harding et al., 1958; Morgan & Kerr, 1963) and it has been shown that the radiographic changes may be reversible (Doig & McLaughlin, 1948; Garnuszewski & Dobrzynski, 1967; Kujawska & Marek, 1979). In other cases, analysis of histology and of pulmonary function abnormalities have indicated pulmonary fibrosis of varying degrees in welders (Charr, 1953, 1956; Angervall et al., 1960; Stanescu et al., 1967; Slepicka et al., 1970; Brun et al., 1972; Irmscher et al., 1975; Patel et al., 1977). Although considerable accumulation of iron oxide dust was documented in these studies, the demonstration of asbestosis in shipyard welders (Selikoff et al., 1980; McMillan, 1983; Kilburn et al., 1985) would suggest that factors other than iron oxide, such as silica (Friede & Rachow, 1961; Meyer et al., 1967; Fabre et al., 1976), could contribute to the pathogenesis of pulmonary fibrosis.

The number of days lost due to sickness attributed to respiratory disease was 2.3 times higher in welders at a petrochemical plant than among other workers not exposed to welding fumes (Fawer et al., 1982). In one study, absence of welders due to sickness appeared to be related primarily to smoking (McMillan, 1981).

A slight increase in serum creatinine level was seen in SS welders, which was unrelated to urinary chromium excretion; no sign of tubular damage was detected (Verschoor et al., 1988), in agreement with the results of a previous study (Littorin et al., 1984). No increased risk for chronic kidney disease was seen in welders (Hagberg et al., 1986).

(c) Effects on reproduction and prenatal toxicity

At a fertility clinic, poor sperm quality was seen more often among male SS and other metal welders than expected, and women employed as SS welders had delayed conception (Rachootin & Olsen, 1983). Among patients examined for sperm quality at other fertility clinics, welders had a significantly increased risk of reduced sperm quality (Haneke, 1973; Mortensen, 1988).

In a study using census data over a four-year period, female welders showed a slightly greater spontaneous abortion rate than other industrial workers and other employed women, but the increase was not statistically significant; no increase was seen for the wives of welders (Hemminki & Lindbohm, 1986).

(d) Genetic and related effects

The studies described below are summarized in Appendix 1 to this volume.

Husgafvel-Pursiainen et al. (1982) studied the frequency of sister chromatid exchange and chromosomal aberrations in a group of 23 male MMA/SS welders and in 22 males from the office of a printing company. The groups were healthy and

were controlled for smoking and previous exposure to clastogenic agents; none of the subjects had had a recent viral infection, vaccination or diagnostic radiation. The age difference between the welders (mean, 45 years) and the controls (mean, 37 years) was considered not to be relevant. All of the welders worked in poorly ventilated areas, had been exposed for at least four years, with a mean of 21 ± 10 (SD) years, and had had little or no exposure to other agents in their occupational history. Sampling of six workers was repeated 1.5 years later. Exposure was mainly to alkaline chromates (calcium chromate and potassium dichromate), with airborne Cr[VI] levels of 0.03-4 mg/m³, and to nickel (as poorly water-soluble alloy in iron oxide fume particles), estimated to be four to eight times lower than to chromium. Urinary levels in exposed workers were 0.2-1.55 μmol/l (10-80 μg/l) chromium and 0.05-0.15 μmol/l (3-9 μg/l) nickel. No effect of exposure was observed over control values for sister chromatid exchange (9.7 ± 0.3 cell) or chromatid and chromosome-type aberrations (1.8%); no change was observed during the 1.5-year observation period. [The Working Group noted the high frequency of sister chromatid exchange in controls.] An increased frequency of sister chromatid exchange ($p <$ 0.01) was observed in smokers in both exposed and unexposed groups.

No increase in the frequency of cytogenetic damage was observed in a well controlled, pair-matched (for sex, age, smoking habits, socioeconomic class, living area, drug and alcohol consumption) study of 24 MMA/SS workers from six industries (Littorin et al., 1983). None of the controls had had any exposure to SS fumes or to known mutagenic or carcinogenic agents. Workers had been exposed for seven to 41 years (mean, 19 years) to Cr[VI] and to lesser amounts of nickel and molybdenum. Exposures to chromium, calculated as time-weighted average exposures for one work day from personal air samplers, were 4-415 μg/m³ total chromium (mean, 81 μg) and 5-321 μg/m³ Cr[VI] (mean, 55 μg). Urinary chromium levels were 5-155 μmol/mol creatinine (mean, 47 μmol/mol creatinine) for exposed workers versus < 0.4-7.0 μmol/mol creatinine (mean, 1.5 μmol/mol creatinine) for controls. No increase was observed in the total number of structural chromosomal aberrations (4.1% in welders, 4.4% in controls) nor in sister chromatid exchange frequency (11/cell in welders, 12/cell in controls) nor in the incidence of micronuclei (0.78% in welders, 0.79% in controls). No effect of smoking was observed, except for some types of chromosomal aberration (structural rearrangements). [The Working Group noted the high background frequencies of sister chromatid exchange and aberrations and that samples were shipped with 16-h lags to the analysing laboratory.]

In a larger study, Koshi et al. (1984) observed increased frequencies of both sister chromatid exchange and chromosomal aberrations in workers engaged in both MMA/SS and MIG/SS welding, with exposures to chromium, nickel, manga-

nese and iron. Sampling was done three times over three years, with 17 workers sampled in the first survey and 44 in each of the subsequent surveys. Workers were exposed for five to 20 years (mean, 12.1 years). Air sampling using personal dust samplers showed a large variation (4-174 mg dust/m³) in individual exposure. Urinary chromium levels were 3-59 μg/l (mean, 9.8 ± 9.2) for exposed workers and 3-6 μg/l (mean, 4.1 ± 1.2) for controls, who were six and seven office workers for the first and second surveys, respectively, and 20 workers in a nonchemical research station for the third. The groups were controlled for smoking, alcohol and coffee intake, and previous exposure to diagnostic radiation or clastogenic drug intake. The three surveys, which gave significantly uniform results, showed an increase in sister chromatid exchange frequency ($p < 0.01$) from 8.11 ± 1.08 in controls (n = 33) to 8.80 ± 1.61 in exposed workers (n = 105). Smoking enhanced the frequency of sister chromatid exchange in the exposed workers ($p < 0.01$) and in controls; however, the difference was not statistically significant. The frequency of aberrant metaphases increased from 3.2 in controls to 4.7 ($p < 0.01$) in exposed workers. Increased frequencies of chromatid gaps (from 2.1% to 3.5%), chromosome gaps (from 0.23% to 0.3%) and chromatid breaks (from 0.2% to 0.3%) were observed ($p < 0.01$ or $p < 0.05$).

3.4 Case reports and epidemiological studies of carcinogenicity to humans

(a) Case reports and descriptive epidemiology

(i) Case reports

The most frequent cancer reported in welders has been of the respiratory system (Gobbato et al., 1980; Sheers & Coles, 1980; Bergmann, 1982), but skin cancer has also been reported (Roquet-Doffiny et al., 1977).

(ii) Mortality and morbidity statistics

Guralnick (1963), using vital statistics, reported on mortality among welders and flame cutters in the USA aged 20-64 in 1950. The standardized mortality ratio (SMR) for all neoplasms was 91 (182 deaths [95% confidence interval (CI), 78-105]), and that for lung, trachea and bronchial cancer was 92 (34 deaths [95% CI, 64-129]). No excess mortality was reported for cancers at other sites.

Logan (1982) analysed cancer mortality by occupation using the statistics of the UK Office of Population Censuses and Surveys. For welders, the SMR for all neoplasms was 57 in 1931 and 126 in 1971; the SMR for lung cancer was 118 in 1951 and 151 in 1971. The Registrar General (Office of Population Censuses and Surveys, 1986) reported mortality by occupation for 1979-80 and 1982-83 in the UK; the SMR for lung cancer was 146 for welders (men aged 20-64).

An excess risk for lung cancer among welders and flame cutters was reported by Milham (1983) in a proportionate mortality analysis for Washington State, USA, for 1950-79, which confirmed his previous results for 1950-71 (Milham, 1976). In 1950-71, increased mortality was found for all neoplasms (257 deaths; proportionate mortality ratio [PMR], 104 [95% CI, 92-118]), for bronchus and lung cancer (67 deaths; PMR, 137 [95% CI, 106-174]) and for urinary bladder cancer (12 deaths; PMR, 162 [95% CI, 89-300]).

Petersen and Milham (1980), using the same method, analysed mortality in the state of California, USA, for 1959-61; no excess of lung cancer was seen among welders and flame cutters.

Menck and Henderson (1976) reviewed all deaths from cancer of the trachea, bronchus and lung occurring in 1968-70 among white males aged 20-64 and all newly diagnosed lung cancer cases registered by the Los Angeles County Cancer Surveillance Program, USA, for 1972-73, in relation to the occupation and industries reported on death certificates or in hospital records. For welders, they found a SMR of 137 based on 21 deaths and 27 newly diagnosed cases [95% CI, 101-182].

Decouflé et al. (1977) analysed the information on occupation contained in hospital files of cancer patients at the Roswell Park Memorial Institute in New York, USA, and compared it to that of noncancer patients. Based on 11 cases, the relative risk (RR) for lung cancer associated with occupation as a welder and flame cutter was 0.85 (0.67 when adjusted for smoking). From the same study, Houten et al. (1977) reported a nonsignificant RR of 2.5 for stomach cancer for welders and flame cutters, based on three cases.

Gottlieb (1980) analysed the lung cancer deaths occurring in Louisiana, USA, ih 1960-75 among employees in the petroleum industry. Using a case-control approach, lung cancer deaths were compared to an equal number of deaths from non-neoplastic diseases. Eight of the cases and two of the controls had been welders [odds ratio, 3.5; nonsignificant].

Morton and Treyve (1982) determined all cases of lung and pleural neoplasms admitted to all 20 hospitals in three Oregon counties during 1968-72. Comparisons were made with information on occupation according to the 1970 US census. The incidence among the occupational category of 'welders, burners, etc.', was 125.8 per 10^5 as compared with 70.8 per 10^5 in the male population (comparative incidence, 178).

Death certificates for lung cancer cases from Alameda County, CA, USA, between 1958 and 1962 were analysed in relation to usual occupation by Milne et al. (1983), using a case-control approach. Lung cancer deaths were compared to all other cancer deaths occurring in persons over 18 years of age. The odds ratio for welders was 1.2 (nonsignificant), based on five cases and 16 controls.

Mortality among metal workers in British Columbia, Canada, during the period 1950-78 was analysed by Gallagher and Threlfall (1983) from death certificates using a proportionate mortality approach. The PMR for lung cancer (74 deaths; PMR, 145; 95% CI, 115-183) and for Hodgkin's disease (nine deaths; PMR, 242; 95% CI, 110-460) was significantly increased in welders. The PMR for all neoplasms in this group was 114 (207 deaths; 95% CI, 99-132).

Information on occupation contained in death certificates from the state of Massachusetts, USA, between 1971 and 1973 was analysed by Dubrow and Wegman (1984). A statistically significant association was reported between welding and prostatic cancer (standardized mortality odds ratio, 256; 14 deaths).

(b) Cohort studies

Dunn et al. (1960) and Dunn and Weir (1965, 1968) assembled a group of workers employed in 14 occupations in California, USA, and followed them up for mortality. Information was collected from union files and from a self-administered questionnaire reporting a full occupational history and smoking habits for members of the cohort in 1954-57; expected figures were based on age- and smoking-specific rates for the whole cohort. In the latest extension of the follow-up, until 1962, the SMR for lung cancer among 10 234 welders and burners was 105 (49 cases [95% CI, 78-139]). [The Working Group noted that three of the 14 groups used to calculate expected numbers had been exposed to asbestos, and the follow-up of cases was incomplete.]

An industrial population from facilities in Midland, MI, USA, was followed up for mortality by Ott et al. (1976). The cohort was constituted of all 8171 male employees between the ages of 18 and 64 on the 1954 employees census list and was followed up through 1973. There were 1214 deaths; 861 employees (10.5%) who remained untraced were assumed to be alive. Expected figures were computed on the basis of the US white male population mortality rates. The overall SMR for welders and lead burners was 98, based on 37 deaths [95% CI, 69-135], and the SMR for all malignant neoplasms was 162, based on 12 deaths [95% CI, 84-283]. No excess was found for cancer at any particular site.

Puntoni et al. (1979) followed up subjects who were shipyard workers in Genoa, Italy, employed or retired in 1960, 1970 and 1975 or dismissed or retired during 1960-75. Expected numbers were computed on the basis of mortality among the male population of Genoa. Among oxyacetylene (autogenous) welders, 66 deaths were observed, giving a significantly increased overall mortality (158); four deaths from lung cancer were reported, giving a RR estimate of 125 [95% CI, 34-320]. Overall mortality among electric arc welders was not increased; three deaths from lung cancer were observed, giving a RR estimate of 160 [95% CI, 33-466]. The authors noted that the group was potentially exposed to asbestos.

All white male welders employed in 1943-73 at the Oak Ridge, TN, USA, nuclear facilities were included in a study conducted by Polednak (1981). A total of 1059 subjects were followed up until 1974 and were subdivided in two subgroups: the first (536) was constituted of welders at a facility where nickel-alloy pipes were welded; the second (523) included welders working with mild steel, aluminium and stainless-steel. Data on smoking habits were available from about 1955. US national mortality rates were used for computing expected figures. Mortality from all causes and from all cancers was slightly lower than expected in both subgroups. There was an excess of deaths from lung cancer (17 cases; SMR, 150; 95% CI, 87-240), and the excess was slightly higher in the group of other welders (ten deaths; SMR, 175; 95% CI, 84-322) than in the nickel-alloy welders (seven deaths; SMR, 124; 95% CI, 50-255).

Beaumont and Weiss (1980, 1981) followed up for mortality a cohort of 3247 welders from local 104 of the International Brotherhood of Boilermakers, Iron Ship Builders, Blacksmiths, Forgers and Helpers in Seattle, WA, USA. Subjects were included if they had had at least three years of union membership and at least one of these years between January 1950 and December 1973. Vital status was ascertained as of 1 January 1977. Fifty deaths from lung cancer were observed *versus* 37.95 expected on the basis of US national mortality rates (SMR, 132 [95% CI, 98-174]). For deaths that occurred 20 years or more after first employment, the SMR was 174 (39 cases [95% CI, 124-238]). A re-analysis of the same data by Steenland *et al.* (1986), using an internal comparison group of members of the local union who were not welders and applying two types of regression analyses, yielded similar results.

McMillan and Pethybridge (1983) investigated the mortality of a cohort of welders, boilermakers, shipwrights, painters, electrical fitters and joiners employed for at least six months between 1955 and 1974 at HM Dockyard Devonport, UK, with follow up through 1975. The proportionate mortality of welders was compared to that of the other occupational groups. The PMR for lung cancer was 104 [95% CI, 34-243] based on five deaths. Three deaths from mesothelioma were also reported among the welders. [The Working Group noted that painters were included in the cohort and that there was potential exposure to asbestos.]

Lung cancer mortality in a cohort of foundry workers was investigated by Fletcher and Ades (1984). The cohort consisted of all men hired between 1946 and 1965 in nine steel foundries in the UK and employed for at least one year. The 10 250 members of the cohort were followed up until the end of 1978 and assigned to 25 occupational categories according to information from personnel officers. Lung cancer mortality for the subcohort of welders in the fettling shop was higher than expected on the basis of mortality rates for England and Wales (eight cases; SMR, 146; 95% CI, 62-288); however, for nonwelders in the fettling shop, the SMR was [177] (58 cases).

The mortality of welders and other craftsmen employed at a shipyard in Newcastle, UK, was investigated by Newhouse *et al.* (1985). All employees hired between 1940 and 1968 were included in the study, making a total of 3489 workers, of whom 1027 were welders; these were followed up until the end of 1982. The SMRs for welders compared with the general population of England and Wales were 147 for all causes and 191 for lung cancer. However, when the Newcastle conurbation was taken as a reference, the overall SMR was 114 (195 cases; 90% CI, 100-127), and the SMR for lung cancer was 113 (26 cases; 90% CI, 80-157). In addition, one death from mesothelioma was reported for welders, indicating possible exposure to asbestos.

Becker *et al.* (1985) followed up a cohort of 1221 stainless-steel welders first exposed before 1970 who had undergone the compulsory technical examination for welders in the Federal Republic of Germany. A population of 1694 turners was followed up as a comparison cohort. Smoking histories, as reported by workplace foremen, were similar for the two groups. The overall mortality of the cohort of welders was significantly lower than that of the general population (SMR, 66; based on 77 deaths [95% CI, 52-82]). The SMR for cancer of the trachea, bronchus and lung was 95 (six cases [95% CI, 35-207]) in comparison with the general population. In comparison with turners and assuming a ten-year latency, the welders had an age-adjusted rate ratio for all cancers of 2.4 (95% CI, 1.1-5.1) and a ratio for trachea, bronchus and lung cancer of 1.7 (95% CI, 0.7-4.0). In addition, two deaths from pleural mesothelioma were reported. [The Working Group could not exclude selection bias in the assembly of the cohort; the two deaths from mesothelioma among welders suggest that they were exposed to asbestos.]

Englund *et al.* (1982) linked information from the Swedish Cancer Registry files for 1961-73 to the population census file of 1960. Welders were among the occupational groups for which the incidence of tumours of the nervous system was higher than in the general population, with a standardized incidence ratio (SIR) of 135 based on 50 cases [95% CI, 100-178].

Sjögren and Carstensen (1986) analysed the results of a linkage between the 1960 census file of male welders or gas cutters and the Swedish Cancer registry files between 1961 and 1979. Smoking data from a national survey were used to adjust incidence ratios, and the Swedish male national population was chosen as a reference. A 30% increase in the incidence of cancer of the trachea, bronchus and lung, based on 193 cases, was reported after adjustment for smoking; other sites at which excesses were observed were larynx (22 cases; RR, 1.3) and kidney (70 cases; 1.3). There was a nonsignificant increase in risk for mesothelioma (four cases; 1.5).

The possible associations between intracranial gliomas and occupation were examined by McLaughlin *et al.* (1987), linking information from the 1960 census and the Swedish cancer registry for 1961-79. Expected values were derived from nation-

al age- and sex-specific reference rates. An elevated SIR of 140 was found for welders and metal cutters, based on 46 cases [95% CI, 103-187].

Sjögren (1980) and Sjögren *et al.* (1987) studied and subsequently updated the mortality of a small cohort of 234 stainless-steel welders with high exposure to chromium in Sweden. Welders were included in the cohort only if representatives from the company stated that asbestos had not been used or had been used only occasionally and never such as to generate dust. In the extension of the study, a cohort of 208 railway track welders with low levels of exposure to chromium was also included in the design. Only welders with at least five years of employment between 1950 and 1965 were included in the study and followed up until the end of 1984. Expected deaths were calculated using national rates. Both groups were characterized by a low overall mortality (SMRs, 72 and 70, respectively). Mortality from cancer of the trachea, bronchus and lung was increased among welders with high chromium exposure (SMR, 249, based on five deaths; 95% CI, 80-581); the SMR was 33 (one death; 95% CI, 0-184) among welders with low exposure. According to Swedish measurements (Ulfvarson, 1979), stainless-steel welders are exposed on average to about 100 μg/m^3 Cr associated with use of coated electrodes. The level measured during railroad track (mild steel) welding was usually less than 10 μg/m^3 Cr (see Table 6).

A large cohort of shipyard and machine shop workers in Finland was followed up for cancer incidence by Tola *et al.* (1988). The cohort included a subset of 1689 welders who had welded mainly mild steel, with no exposure to hexavalent chromium. Only workers employed for at least one year between 1945 and 1960 were included in the study and followed up (99.7% complete) for cancer incidence from 1953 to 1981 through the Finnish Cancer Registry. Smoking habits were ascertained by a postal questionnaire sent to a one-third stratified sample of the members of the cohort or of the next-of-kin of decedents. The expected figures were based on the urban population in the same geographic area. The results did not indicate substantial differences with regard to smoking habits between the study population and the general population. Welders employed in shipyards had a SIR for lung cancer of 115 based on 27 deaths (95% CI, 76-167), and welders employed in machine shops had a SIR of 142 based on 14 deaths [95% CI, 77-237]. For neither of the groups was there an association with time since first exposure.

The International Agency for Research on Cancer has reported (IARC, 1989) the results of a large multicentre cohort study carried out on the working populations of welders employed in 135 companies located in eight European countries. The study included reanalyses of previous studies described above (Becker *et al.*, 1985; Sjögren *et al.*, 1987; Tola *et al.*, 1988) and newly assembled cohorts. The populations of the three previous studies constituted approximately one-third of the total cohort and contributed equally to the different subgroups of welders. A total of

11 092 welders were included in the analysis and followed through 1982-87, depending on the country. The completeness of follow-up was 97%. The SMR for deaths from all causes was 93, based on 1093 deaths (95% CI, 87-98). Mortality from all malignant neoplasms was increased (303 deaths; SMR, 113; 95% CI, 100-126), due mainly to a statistically significant excess of cancer of the trachea, bronchus and lung (116 deaths; SMR, 134; 95% CI, 110-160). Other sites for which excess deaths were seen were larynx (7 deaths; SMR, 148; 95% CI, 59-304), bladder (15 deaths; SMR, 191; 95% CI, 107-315), kidney (12 deaths; SMR, 139; 95% CI, 72-243) and lymphosarcoma (6 deaths; SMR, 171; 95% CI, 63-371). Subjects were assigned to one of three mutually exclusive groups: welding in shipyards, mild-steel welders and ever stainless-steel welders; the latter group also included those who had been predominantly stainless-steel welders. Lung cancer mortality was as follows: welders in shipyards (36 deaths; SMR, 126; 95% CI, 88-174); mild-steel welders (40 deaths, SMR, 178; 95% CI, 127-243); ever stainless-steel welders (39 deaths; SMR, 128; 95% CI, 91-175); and predominantly stainless-steel welders (20 deaths; SMR, 123; 95% CI, 75-190). Lung cancer mortality tended to increase with time since first exposure for mild-steel and stainless-steel welders; this pattern disappeared among mild-steel welders when broken down by duration of exposure and was most evident among predominantly stainless-steel welders, for whom a statistically significant trend was evident ($p < 0.05$): the distributions of observed:expected lung cancer deaths in the four groups of years since first exposure (0-9, 10-19, 20-29, >30) were 2:3.11, 5:5.67, 7:5.54 and 6:1.92, respectively. Five deaths from pleural mesothelioma were reported — one in the shipyard welders, two among mild-steel welders and two among stainless-steel welders (see Table 11). The results for cancer incidence followed the same pattern as those for cancer mortality.

Howe *et al.* (1983) examined the mortality of a cohort of 43 826 male pensioners of the Canadian National Railway company in 1965-77. During this period, 17 838 deaths occurred, and cause of death was ascertained for 94.4% by computerized record linkage to the Canadian national mortality data base. The only occupational information available was on that at the time of retirement. The 4629 individuals who had been exposed to welding fumes showed excess mortality from brain tumours (ten deaths; SMR, 318; 95% CI 153-586).

Stern (1987) pooled 1789 cases of lung cancer and 146 cases of leukaemia reported in epidemiological studies of different designs, most of which are reviewed here. Compared to the expected number of cases as derived from the reviewed publications, a risk ratio of 1.4 was found for respiratory cancer and 0.92 for leukaemia. The risk ratio for acute leukemia, based on 40 cases, was also 0.92.

The risks for lung cancer in the studies described above are summarized in Table 12.

Table 11. Risks for death from respiratory cancer[a] and from pleural mesothelioma[b] by length of employment and follow-up among subcohorts of welders[c]

Study group	0-19 years since first employment						≥20 years since first employment					
	1-9 years' employment			≥10 years' employment			1-9 years' employment			≥10 years' employment		
	Lung cancer		Meso-thelioma	Lung cancer		Meso-thelioma	Lung cancer		Meso-thelioma	Lung cancer		Meso-thelioma
	Obs	SMR	Obs	Obs	SMR	Obs	Obs	SMR	Obs	Obs	SMR	Obs
Shipyard welders	10	264		1	69		15	116	1	10	96	
Mild-steel welders	8	116	1	7	253		10	254		15	173	1
Ever stainless-steel welders	15	115		2	67		9	145		13	157	1
Predominantly stainless-steel welders[d]	5	85		2	69	1	2	161		11	176	

[a]Cancers of trachea, bronchus and lung (ICD8, 162)

[b]Additional deaths due to pleural mesothelioma (ICD8, 163), which were not included in calculation of SMR

[c]From IARC (1989)

[d]Subset of ever stainless-steel welders group who were employed in companies with at least 70% of stainless-steel activity or had at least one occupational period of stainless-steel welding only

Table 12. Lung cancer in welders (cohort studies)[a]

Reference (country)	No. of cases observed	SMR, PMR or SIR	95% CI	Comments
Dunn & Weir (1968) (USA)	49	105	78–139	
Puntoni et al. (1979) (Italy)	4	125 212	34–320 58–542	Autogenous welders; two sets of standard rates used (male population of Genoa and male staff of hospital)
	3	160 254	33–466 52–743	Electrical welders; two sets of standard rates used
Polednak (1981) (USA)	17 7	150 124	87–240 50–255	All welders Welders exposed to nickel compounds
	10	175	84–322	Other welders
Beaumont & Weiss (1981) (USA)	50	132	98–174	
McMillan & Pethybridge (1983) (UK)	5	104	34–243	PMR for respiratory cancer (three mesotheliomas)
Fletcher & Ades (1984) (UK)	8	146	62–288	
Newhouse et al. (1985) (UK)	26	113	80–157	Shipyard welders; SMR, 191 when compared with general population of England and Wales (one mesothelioma)
Becker et al. (1985) (FRG)	6	95	35–207	Stainless-steel welders; expected number based on national mortality statistics
	6	1.7	0.7–4.0	Cohort of turners used as controls (two mesotheliomas) (rate ratio)
Sjögren & Carstensen (1986) (Sweden)	193	142	123–163	Unadjusted SMR (four mesotheliomas)
Sjögren et al. (1987) (Sweden)	5	249	80–581	Stainless-steel welders
Tola et al. (1988) (Finland)	27 14	115 142	76–167 77–237	Welders in shipyards (SIR) Welders in machine shops (SIR)

[a]SMR, standardized mortality ratio; SIR, standardized incidence ratio; PMR, proportionate mortality ratio; CI, confidence interval

(c)   *Case-control studies*

Questions relating to employment as a welder or exposure to welding fumes are often included in case-control studies of cancer. In many of these studies, a long list of occupations/exposures is investigated, and any positive association found is likely to be reported; therefore, the possibility of a publication bias toward positive results must be taken into account when reviewing case-control studies.

(i)   *Lung cancer*

Breslow *et al.* (1954) conducted a case-control study of 518 histologically confirmed lung cancer patients admitted to 11 hospitals in California, USA, in 1949-52, and randomly selected matched controls who were patients of the same age, sex and race admitted to the same hospitals for a condition other than cancer or a chest disease. Interviews for occupational and smoking histories were conducted by persons who were unaware of the case or control status of the interviewee. An elevated RR was seen for welders and sheet-metal workers doing welding, based on 14 cases and two controls [odds ratio, 7.2; 95% CI, 1.9-44.3; smoking-adjusted odds ratio, 7.7].

Blot *et al.* (1978) carried out a case-control investigation among male residents of a coastal area in Georgia, USA. A total of 458 newly diagnosed cases and deaths from lung cancer were compared to 553 controls collected from hospitals or from mortality registries, and matched by vital status, sex, age, race and county of residence. Persons with bladder cancer or chronic lung disease were excluded from among the controls. The results revealed an increased risk for all employment in shipyards but not for welders and burners (RR, 0.7, based on 11 cases and 20 controls).

A similar case-control study was conducted by Blot *et al.* (1980) in coastal Virginia, USA, including 336 deaths from lung cancer and 361 controls deceased from causes other than chronic respiratory diseases in 1976. Information on smoking habits and on occupation was collected by interviewing next-of-kin. Lung cancer risk was slightly elevated among workers in the shipbuilding industry, but an analysis of 11 exposed cases and nine exposed controls showed that welders and burners were not at increased risk [RR, 0.9; 95% CI, 0.4-2.3].

A case-control study of lung cancer among residents of Florence, Italy, by Buiatti *et al.* (1985) included all 376 histologically confirmed cases of primary lung cancer admitted to the main regional hospital in 1981-83. A group of 892 hospital controls of the same sex, age, period of admission and smoking habits was identified, and the ILO classification of occupation and a list of 16 known or suspected carcinogens were used for assessing occupational history. Men who had 'ever worked' in welding had an increased risk (adjusted for smoking), based on seven cases and five controls (odds ratio, 2.8; 95% CI, 0.9-8.5).

Silverstein *et al.* (1985) identified all deaths among members of the United Automobile Workers International Union ever employed at a metal stamping plant between 1966 and 1982 in Michigan, USA. Causes of death were obtained from death certificates, and information on employment from company lists. The data were analysed in a case-control fashion, with cancer deaths as cases and noncancer deaths as controls. Employment as a maintenance welder or millwright was considered to constitute exposure to coal-tar pitch volatiles and welding fumes, and all other occupations were considered to be unexposed. The RR for lung cancer was 13.2 (95% CI, 1.1-154.9), based on three cases. [The Working Group noted that millwrights may be engaged in gas cutting and not exposed to welding fumes in the usually accepted sense.]

Kjuus *et al.* (1986) conducted a case-control study in two industrialized areas of Norway and included 136 newly diagnosed male lung cancer cases and 136 controls identified through the medical files of the main hospital during 1979-83. Forty additional cases and 40 controls were included during the last two years of the study period from another hospital. Patients with obstructive lung disease were excluded from among the controls. Potential exposure to carcinogens was specifically investigated using the Nordic Classification of Occupations, and, for the last two years of the study period, subjects were asked about past exposure to 17 chemical agents and five specific work processes. For subjects already interviewed, exposures were inferred from the available occupational history. An increased risk was found for all welders (RR, 1.9; 95% CI, 0.9-3.7; 28 cases) and for the subset of stainless-steel welders (RR, 3.3; 95% CI, 1.2-9.3; 16 cases) after adjustment for smoking. Half of the cases exposed to stainless-steel welding had also been moderately or heavily exposed to asbestos; when this was taken into consideration in a logistic regression model, risk associated with stainless-steel welding was no longer statistically significant.

Gérin *et al.* (1986) presented preliminary results of a multicancer case-control study in hospitals in the Montréal, Canada, area. Lung cancer patients were used as cases and patients with cancers at 13 other sites as controls; a group of population subjects was also included in the control group. A detailed job-exposure matrix was constructed, and each subject was categorized after direct interview and evaluation of responses by experts in industrial hygiene. Welders were at increased risk for lung cancer (RR, 2.4; 95% CI, 1.0-5.4), based on 12 cases and 20 controls. For ten welders exposed to nickel, the RR was 3.3 (95% CI, 1.2-9.2).

Schoenberg *et al.* (1987) carried out a case-control investigation of lung cancer among white males in six areas of New Jersey, USA. Cases of cancer of the lung, trachea or bronchus were histologically confirmed and ascertained through hospital pathology records, the state cancer registry and death certificates in 1980-81. Controls were matched by age, race, area of residence and (for dead cases) date of

death; subjects with respiratory disease were excluded. The study population comprised 763 cases and 900 controls. Information was obtained by personal interview either directly or from next-of-kin, and information on industry and job title was coded according to the 1970 census index system. Occupation as a welder or flame cutter was reported by 38 cases and 38 controls (smoking-adjusted RR, 1.2 [95% CI, 0.8-1.9]). Welders, burners, sheet-metal workers and boilermakers employed in shipyards had a significantly increased risk (RR, 3.5; 95% CI, 1.8-6.6); for those without reported exposure to asbestos, the RR was 2.5 (95% CI, 1.1-5.5).

A population-based case-control study was conducted by Lerchen et al. (1987) of 506 primary lung cancer cases reported to the New Mexico (USA) Tumor Registry between 1 January 1980 and 31 December 1982 and 771 controls who were interviewed about their occupational histories and smoking habits. The age-, ethnicity- and smoking-adjusted RR for welders in all industries was 3.2 (95% CI, 1.4-7.4), based on 19 cases and ten controls. When welders ever employed in shipyards were analysed separately, the RR was lower (2.2; 95% CI, 0.5-9.1), based on six cases and three controls, than for welders elsewhere than in shipyards (RR, 3.8; 95% CI, 1.4-10.7), based on 13 cases and seven controls.

Benhamou et al. (1988) conducted a case-control study in France of 1260 male lung cancer cases collected in 1976-80 and 2084 hospital controls matched by age, hospital of admission and interviewer. Cases and controls were classified as either nonsmokers or smokers. The RR for welders and flame cutters after adjusting for smoking was 1.4 (95% CI, 0.79-2.9), based on 18 exposed cases and 23 exposed controls.

A nested case-control analysis of deaths due to lung cancer among civilians employed at the Portsmouth Naval Shipyard, Maine, USA, between 1952 and 1977 was conducted by Rinsky et al. (1988); the cohort had previously been investigated by Najarian and Colton (1978) and Rinsky et al. (1981). Controls without cancer were matched on date of birth, year of first employment and duration of employment. Potential exposure to asbestos and to welding by-products was estimated from the job histories. The study population comprised 405 lung cancer deaths and 1215 controls from within the cohort of shipyard workers. The RR for subjects with probable exposure to welding by-products was 1.1 (95% CI, 0.8-1.7) based on 41 cases and 111 controls. When subjects with potential exposure were also included, the RR was 1.5 (95% CI, 1.2-1.8), based on 236 exposed cases and 597 controls.

A population-based case-control study of lung cancer was conducted by Ronco et al. (1988) in two industrialized areas of northern Italy. All 126 deaths from lung cancer occurring among male residents in the area in 1976-80 and a random sample of 384 other deaths (excluding chronic lung conditions and smoking-related cancers) occurring in the same area during the same period were included in the study. Smoking habits and occupational information were collected from next-of-kin by

interview (without knowledge of case or control status) using two lists of known and suspected occupational carcinogenic exposures. Subjects never employed in any of the occupations listed were considered to be unexposed. Logistic regression analysis adjusting for age, smoking and other occupational exposure gave a risk estimate of 2.9 (95% CI, 0.87-9.8) for welders, based on six cases.

The studies described above are summarized in Table 13.

Table 13. Lung cancer in welders (case–control studies)[a]

Reference (country)	No. of cases exposed	RR	95% CI	Comments
Breslow et al. (1954) (USA)	14	7.2	1.9–44.3	RR, 7.7 adjusted for smoking
Blot et al. (1978) (USA)	11	0.7	–	
Blot et al. (1980) (USA)	11	0.9	0.4–2.3	
Rinsky et al. (1988) (USA)	41	1.1	0.8–1.7	Probable welding exposure
	236	1.5	1.2–1.8	Potential welding exposure
Buiatti et al. (1985) (Italy)	7	2.8	0.9–8.5	Adjusted for smoking
Silverstein et al. (1985) (USA)	3	13.2	1.1–154.9	
Kjuus et al. (1986) (Norway)	28	1.9	0.9–3.7	All welders; adjusted for smoking
	16	3.3	1.2–9.3	Stainless-steel welders; adjusted for smoking
Gérin et al. (1986) (Canada)	12	2.4	1.0–5.4	All welders
	10	3.3	1.2–9.2	Welders exposed to nickel
Schoenberg et al. (1987) (USA)	38	1.2	0.8–1.9	Welders or flame cutters; adjusted for smoking
Lerchen et al. (1987) (USA)	19	3.2	1.4–7.4	All welders
	6	2.2	0.5–9.1	Welders employed in shipyards
	13	3.8	1.4–10.7	Welders not employed in ship-yards
Benhamou et al. (1988) (France)	18	1.4	0.79–2.9	Adjusted for smoking
Ronco et al. (1988) (Italy)	6	2.9	0.87–9.8	Adjusted for smoking

(ii) *Cancers of the urinary organs*

Howe *et al.* (1980) conducted a population-based case-control study of bladder cancer occurring in Canada in 1974-76 on a total of 632 case-control pairs matched by age, sex and neighbourhood of residence. Occupational histories were collected

through direct interview, and two check lists of suspected occupations and substances carcinogenic for the bladder were used to obtain information on exposure. Exposure to welding fumes resulted in a RR of 2.8 (95% CI, 1.1-8.8) based on 17/6 discordant pairs (case ever worked, control never worked/case never worked, control ever worked as welder).

A case-control investigation of the lower urinary tract was conducted by Silverman *et al.* (1983) in the Detroit, USA, area. All histologically confirmed male cases, newly diagnosed from December 1977 to November 1978 in 60 of the 61 hospitals in the area, were included in the study. In total, 303 whites with bladder cancer and 296 population-based randomly selected white controls were included in the analysis. Information on occupation was collected by interview. The RR for the combined group of welders, flame cutters and solderers was 0.6 (95% CI, 0.3-1.0), based on 18 cases and 30 controls. Similar results were found when the analysis was limited to the same category within the motor vehicle manufacturing industry (RR, 0.6; 95% CI, 0.3-1.2; based on 12 cases and 22 controls).

Claude *et al.* (1988) carried out a hospital-based, matched case-control study of cancer of the lower urinary tract in northern Federal Republic of Germany. Cases were identified in the three main hospitals of the region between 1977 and 1985. The occupations of 531 male cases and their matched controls were ascertained. The RR for welders was 1.2 (95% CI, 0.52-2.8), based on 12/10 discordant pairs.

A population-based case-control investigation of bladder cancer was conducted in Canada between 1979 and 1982 by Risch *et al.* (1988). Of the 1251 eligible individuals, 835 (67%) cases were interviewed, with the consent of their physician, and 792 (53%) of the 1483 eligible controls agreed to be interviewed. The authors pointed out that this method might have affected the representativeness of cases and controls. When the data were analysed by the 26 occupations/industries specifically investigated through the questionnaire, employment in welding activities yielded a risk estimate of 1.1 (95% CI, 0.71-1.6).

The association of renal-cell carcinoma with various potential risk factors was studied by Asal *et al.* (1988) in a case-control study of 315 cases and 313 hospital and 336 population controls in the USA. Individuals were classified by occupation only if the period of exposure was one year or longer. The odds ratio for employment as a welder in comparison with population controls was 1.2 (95% CI, 0.7-2.2), based on 29 exposed cases. Results obtained using hospital controls were similar.

(iii) *Cancers at other sites*

A case-control study of *nasal cancer* was carried out in Denmark, Finland and Sweden by Hernberg *et al.* (1983a,b) with 287 cases identified through the national cancer registries between 1977 and 1980. A total of 167 cases (58%) were included in the study when deceased patients or nonrespondents were omitted. An equal num-

ber of controls were matched for country, sex and age at diagnosis, and both cases and controls were interviewed by telephone according to a standard protocol. The risk estimate for welding, flame-cutting and soldering was 2.8 (95% CI, 1.2-6.9) based on 17/6 discordant pairs. [See also the monographs on chromium and nickel, pp. 206 and 400-401.]

Following a report by the Danish Occupational Health Agency of a large number of cases of *laryngeal cancer* in welding workplaces, Olsen *et al.* (1984) conducted a case-control study to investigate the role of occupational exposure. All male laryngeal cancer patients newly diagnosed between 1980 and 1982 in the main five hospital departments in the country were included in the study, excluding the cases which prompted the study. For each case, four controls were selected from the same municipal person-registry in which the case was listed. The refusal rate was 4% among cases and 22% among controls, leaving 271 cases and 971 age- and sex-matched controls for the analysis. The RR related to welding, adjusted for age, alcohol and tobacco consumption, was 1.3 (95% CI, 0.9-2.0), based on 42 cases and 115 controls. The risk was highest for cancer located in the subglottic region (RR, 6.3; 95% CI, 1.8-21.6). Separate analysis for welders exposed to stainless-steel welding fumes gave a RR of 1.3 (95% CI, 0.7-2.7), based on 12 cases and 30 controls.

Stern, F.B. *et al.* (1986) carried out a case-control study of deaths due to *leukaemia* within a population of 24 545 male nuclear shipyard workers in Portsmouth, NH, USA, employed between 1952 and 1977 and who had died before 31 December 1980. Controls were selected from among other deaths, and four controls per case were matched by age, data of hire and length of employment; each control should not have died before the case. The entire occupational history of each individual was reconstructed using company files and other industrial sources. The risk estimate for ever having worked in welding was 2.3 (95% CI, 0.92-5.5) for all leukaemia and 3.8 (95% CI, 1.3-11.5) for myeloid leukaemia.

A case-control study of *chronic myeloid leukaemia* was carried out in Los Angeles County, CA, USA, by Preston-Martin and Peters (1988) between 1979 and 1985. Of the 229 eligible cases, 137 (60%) were interviewed by telephone; 130 pairs matched for age, sex and race were eventually included in the analysis. Employment as a welder yielded a crude RR of 19 [95% CI, 2.8-232.5], based on 19/1 discordant pairs.

Norell *et al.* (1986) conducted a case-control study of *pancreatic cancer* in the Stockholm-Uppsala region. Out of 120 eligible cases, 99 (83%) were included in the study. Both hospital- and population-derived controls were selected, with a response rate of 91% for the former and of 85% for the latter group. Information was collected through a self-administered questionnaire and further checked by telephone. The risk estimates for exposure to 'welding materials' were 1.7 (90% CI,

0.9-3.2), based on 13 cases and 27 hospital controls, and 2.0 (90% CI, 0.9-4.3), based on 11 population controls.

Olin *et al.* (1987) conducted a case-control study of *astrocytomas* in Sweden to investigate the possible etiological role of occupational exposures. Incident cases were identified from the two main hospitals in Stockholm and in Uppsala in 1980-81. Both hospital- and population-based controls of the same sex, age and date of diagnosis as the case were included in the study. Of the original 404 study subjects, 367 (91%) were included in the study, comprising 78 cases, 197 hospital controls and 92 population controls. Information was collected through self-administered questionnaire or filled in by the spouse. No increase in risk was reported for welding activities, with risk estimates of 0.6 (95% CI, 0.2-1.7), based on five cases and 15 hospital controls, and 0.2 (95% CI, 0.1-0.7), based on 19 population controls.

A case-control study of workers employed between 1943 and 1977 at two nuclear facilities in Oak Ridge, TN, USA, was conducted by Carpenter *et al.* (1988), in order to examine the possible association of primary *central nervous system cancers* (ICD8, 191, 192) with occupational exposure to chemicals. Job titles/departments were evaluated for potential exposure to 26 chemicals or chemical groups. Seventy-two white male and 17 white female cases were identified; four controls were selected for each case and matched on race, sex, nuclear facility where initially employed, year of birth and year of hire. The odds ratio for 33 cases ever exposed to welding fumes was 1.2 [95% CI, 0.6-2.4].

The hypothesis that childhood cases of *Wilms' tumour* might be related to parental perinatal exposures was tested by Kantor *et al.* (1979) by a case-control approach using the Connecticut (USA) Tumor Registry files for 1935-73. A total of 149 cancer-free controls were identified from health department files and matched to the 149 cases by age, sex and year of birth. Information on the occupation of the father was obtained exclusively from birth certificate files. Welder as the occupation of the father was mentioned on the birth certificates of three cases and no control (not significant).

A similar case-control study of *Wilms' tumour* was conducted by Wilkins and Sinks (1984), using the Columbus, OH, USA, Children's Hospital Tumor Registry files between 1950 and 1981. For each of 105 cases, two children were randomly selected from the Ohio birth certificate files and used as controls after matching for age, sex and race. For no case and for two controls the father's occupation at the time of birth was welder (not significant).

In a further case-control study (Bunin *et al.*, 1989), paternal occupational exposures of 88 cases of Wilms' tumour, obtained from a job-exposure matrix, were compared with those of an equal number of controls, obtained by random digital dialling and matched for date of birth. For a job cluster with exposure to aromatic and aliphatic hydrocarbons, metals and inorganic compounds, elevated crude odds ra-

tios were seen for exposure before conception (5.3, 95% CI 1.5-28.6), during pregnancy (4.3, 95% CI, 1.2-23.7) and after pregnancy (3.3, 95% CI, 0.9-18.8). Within this cluster, the occupation of the father was welder for five cases but for only one control.