Effects of Welding on Health, XII

American Welding Society

Effects of Welding

on Health, XII

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Abstract

This literature review, with 216 citations, was prepared under contract to the American Welding Society for its Safety and Health Committee. The review deals with studies of the fumes, gases, radiation, and noise generated during various welding processes. Section 1 summarizes recent studies of occupational exposures, Section 2 contains information related to the human health effects, and Section 3 discusses the effects of welding on animals and cell cultures.

American Welding Society

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Foreword

(This Foreword is not a part of *Effects of Welding on Health, XII*, but is included for informational purposes only.)

This literature review was prepared for the Safety and Health Committee of the American Welding Society to provide an assessment of current information concerning the effects of welding on health, as well as to aid in the formulation and design of research projects in this area, as part of an on going program sponsored by the Committee. Previous work consists of the reports Effects of Welding on Health I through XI each covering approximately 18 months to two years. Conclusions based on this review and recommendations for further research are presented in the introductory portions of the report. Referenced materials are available from:

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Glossary*

ACGIH	American Conference of Governmental Industrial Hygienists
BALF	Bronchoalveolar lavage fluid
CI	Confidence Interval
Cr(III)	Trivalent chromium
Cr(VI)	Hexavalent chromium
ELF	Extremely low frequency
EMF	Electromagnetic field
FCAW	Flux cored arc welding
GMAW	Gas metal arc welding
GTAW	Gas tungsten arc welding
IgA	ImmunoglobulinA
IgM	ImmunoglobulinM
IL-1	Interleukin-1
IL-4	Interleukin-4
Leukocyte	White blood cell
MRI	Magnetic resonance imaging
n	number
nm	nanometer
NIOSH	National Institute for Occupational Safety and Health
OR	Odds ratio
OSHA	Occupational Safety and Health Administration
PAH	Polycyclic aromatic hydrocarbons
PEL	Permissible Exposure Limit
PET	Positron emission tomography
PMN	Polymorphonuclear leukocyte
PMR*	Proportional mortality ratio
RR*	Relative risk
SIR*	Standardized incidence ratio
SCE	Sister chromatid exchange
SMAW	Shielded metal arc welding
SMR*	Standardized mortality ratio
TLV	Threshold Limit Value
TNF	Tumor necrosis factor
TWA	Time-weighted average
μm	micrometer
μg	microgram
μmol	micromole per liter
μT	microTesla
UV	Ultraviolet
ZnO	Zinc oxide

*Abbreviations for commonly used pulmonary function tests and for epidemiological terminology used in this document are found in Annex A and B, respectively. The appendices describe the derivation of these terms and how they are used.

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Introduction

The health of workers in the welding environment is a major concern of the American Welding Society. To stay abreast of this subject, the health literature is periodically reviewed and published in the report *Effects of Welding on Health*. Eleven volumes have been published to date; the first covered data published before 1978, while the remainder covered 2- to 3-year periods between 1978 and December, 1996. The current report includes information published between January 1997 and December, 1999. It should be read in conjunction with the previous volumes for a comprehensive treatment of the literature on the *Effects of Welding on Health*. Included in Section 1 of this volume are studies of the characteristics of welding emissions that may have an impact on the control technologies necessary to protect the welder. In keeping with previous volumes, health reports and epidemiological studies of humans are discussed in Section 2 and organized according to the affected organ system. Research studies in animals and cell cultures are discussed in Section 3.

Many of the studies on the effects of welding on health published during the current report period focused on matters that have been explored in the older literature. The question of whether or not welding causes a decrease in the function of the lungs or causes an increased incidence of pulmonary diseases such as bronchitis continues to be explored. Investigations of the association of asthma with welding increase in number as the prevalence of both occupational and non-occupational asthma increases in industrialized countries worldwide. As in the past, attention is focused on the incidence of lung cancer in welders and the contribution of the potential carcinogens nickel and chromium encountered in stainless steel welding to the incidence of the disease. Current studies do not indicate that stainless steel welders are at a greater risk for developing lung cancer than are mild steel welders, although they may be at a greater risk for experiencing changes in lung function than are mild steel welders. In addition, animal studies indicate that stainless steel welding fumes may elicit a stronger inflammatory response in the lungs than do mild steel fumes. The neurological effects of manganese received considerable attention during this report period and point to the strong need for the use of protective measures by workers exposed to this metal.

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Executive Summary

Workplace Exposures

Fume Sampling Procedures. In 1996, the European Committee for Standardization proposed a new European/International Standard for sampling airborne particles and gases generated during welding and allied processes. The requirements of this standard were evaluated by Chung et al. (Refs. 38, 39, 44) who conducted tests which showed that the choices of samplers and sampling procedures allowed by the standard could lead to an over- or underestimation of fume exposures. In these tests, samplers were placed on a life-size mannequin positioned over an automated welding test rig in a manner that represented a right-handed welder at work. No differences were seen in the exposures measured by five different sampling devices for inhalable dust. Placement of the sampler on the right or left side of the mannequin's face or under the chin yielded variable results leading the investigators to recommend that the sampler be placed on the side of the face where fume concentrations were visibly highest. Because the quantities of fumes collected when the sampler was placed on the lapel did not agree with those collected in the breathing zone, measurement of welding fume exposures by lapel sampling was not recommended. Finally, the draft standard allowed concentrations of fume constituents provided by the manufacturer's Material Safety Data Sheet to be used in lieu of analyzing individual components of collected fume samples. Chung et al. found that the fume composition determined by actual analyses of fumes generated in their laboratory did not agree completely with the analyses of fume components provided by the manufacturer. In particular, differences in the chromium content were observed among the fume compositions generated by FCAW and GMAW of stainless steel (Ref. 38) and reliance on the data sheets for fume composition would have led to underestimation of exposure to chromium.

Electromagnetic Radiation. Tenkate and Collins (Refs. 184, 186) used polysulfone film dosimeters to estimate the daily doses of ultraviolet (UV) radiation received by the eyes and skin of welders and nearby workers in a metal fabrication workshop. All doses measured by body, ocular, and environmental badges were above the ACGIH maximum permissible exposure (MPE) limit. The ocular exposures measured for the welders and boilermakers were four and five times the MPE, respectively. Tenkate and Collins (Ref. 185) investigated the elements of helmet design and the angles of incident radiation that allow UV radiation to enter the helmet and reflect into the eyes. None of four helmet designs tested completely protected the eyes from exposure to UV radiation. When the UV beam was in a horizontal orientation, some UV radiation entered through the opening between the edge of the shield and the side of the face. UV radiation infiltrating through this area could be reflected off a corner section of the filter plate into the eye. When the UV beam was in a vertical position above the head, UV radiation could enter from behind the head through the gap between the back of the top edge of the shield and the top of the head. Because of its greater reflective surface area, a narrow helmet with a larger-than-standard filter plate permitted the greatest intensity of light to reach the eye.

Local Exhaust Ventilation. In their investigation of short-term effects of welding exposures on pulmonary function, Fishwick et al. (Refs. 69, 70) found that the use of local exhaust ventilation substantially reduced acute changes in lung function. They recommended that local exhaust ventilation, which they considered the most practical exposure reduction measure, be used wherever welding was done. In a survey of particulate exposures during welding and cutting of mild steel, aluminum, or stainless steel, Vernez et al. (Ref. 207) found that concentrations of particulate at work stations provided with local exhaust ventilation were about half those in stations without it.

The effectiveness of local exhaust ventilation may be influenced by workplace parameters and by working habits of the welders. Ludwig et al. (Ref. 125) measured breathing zone concentrations of radioactive thorium during GTAW with thoriated electrodes. They found that although the use of local exhaust ventilation reduced the total exposure received by individual welders, the position

of the welder's head in relation to the emission source was considered to be the main determinant of the welder's exposure. This finding is in agreement with earlier studies of the effects of the welder's position on exposure (Refs. 204, 20). Jankovic et al. (Ref. 94) measured breathing zone concentrations of thorium outside and within the welding helmet, with or without local exhaust ventilation, while welders were performing GTAW. When local exhaust ventilation was used, the concentration of radioactive aerosol outside the welding helmet was reduced forty-fold, but the concentration inside the helmet was reduced only twofold and was greater than the outside concentration. The authors observed that incoming air from local exhaust ventilation passed around the welder's body, creating eddy currents that could have caused portions of the fume to enter beneath the helmet.

Rappaport et al. (Ref. 155) found that local exhaust ventilation was much more effective during intermittent welding than during continuous welding. Local exhaust ventilation reduced exposure to total particulate by as much as 41% during intermittent welding but it only reduced exposure by about 6% during continuous welding. In accord with the findings of Rappaport et al., Bellido-Milla et al. (Ref. 21) observed that the use of local exhaust ventilation during continuous welding did not substantially reduce exposure to welding fumes. They noted that welders properly positioned the fume extractors when they began welding, but as they worked they moved without relocating them, which substantially reduced the benefits that may have been achieved by using local exhaust.

Effects on the Respiratory Tract

Pulmonary Function. Pulmonary function tests (spirometry) were used in several studies to measure changes in lung function that occurred during a welding shift or over years of exposure to welding fumes. Declines in pulmonary function tests or decrements relative to results in healthy individuals may be indicators of sensitivity to components of welding fumes or may be evidence of progress towards chronic lung disease. Two groups of investigators evaluated acute and chronic pulmonary responses to welding fumes. In a cross-shift study conducted in New Zealand, Fishwick et al. (Refs. 69, 70) found a small but statistically significant decline in lung function among welders compared with non-welders after completion of a work shift. Welders who did not use local exhaust ventilation were 22 times more likely to experience a measurable decline in lung function after 15 minutes of welding compared with those who did use ventilation. When the same population of workers was examined two years later (Ref. 64), the welders and non-welders had similar annual declines in the pulmonary function variables measured. The annual decline in lung function over the two years was significantly associated with the acute change in lung function that had been observed in the cross-shift study. Decline in FEV_1 across a shift was a predictor of annual decline in FEV_1, which suggests the possibility that recurrent acute obstructive changes can lead to chronic airways obstruction.

The second set of studies, conducted in France by Sobaszek et al., was specifically designed to investigate the effects of fumes from stainless steel (SS) welding on lung function. The study of chronic effects compared pulmonary function measurements taken at the start of the workshift in stainless steel welders and in non-welders (Ref. 173). There were no significant differences in the results of lung function tests between the two groups; but, among the welders, increasing duration of the welding experience was significantly related to declining expiratory flow rates. In the cross-shift study, Sobaszek et al. (Ref. 172) found that significant declines in lung function at the end of a welding shift were associated with welding of stainless steel compared with mild steel, and with the use of SMAW compared with GMAW or GTAW.

Using magnetopneumography and spirometry, Nakadate et al. (Ref. 135) measured lung function and iron deposits in the lungs of welders before and after a 5-year period during which engineering changes in the plant where they worked reduced welding fume exposures. At the start of the study, decrements in lung function tests were significantly associated with the quantity of fume particles in the lungs. Five years later, improved air quality in the factory resulted in decreased quantities of welding particles in the lungs, but this did not result in improvements in pulmonary function.

Asthma and Chronic Bronchitis. In two large Swedish studies conducted by Toren et al. (Refs. 193, 194), a statistically significant increased risk for occupational asthma was associated with exposure to welding fumes. Exposure to welding fumes was also associated with an increased risk for occupational asthma in a hospital-based study in Italy (Ref. 126). Asthma-like symptoms seen in six Canadian welders examined by Contreras and Chan-Yeung (Ref. 48) were attributed to non-specific irritation rather than to sensitization to the components of welding fumes. In the group of New Zealand welders who were tested for pulmonary function before and after a work shift (Refs. 69, 70), the incidence of chronic bronchitis was significantly greater in welders with more than ten years experience than in those with less than four years experience (Refs. 32, 33).

Cancer

Lung Cancer. Nine studies found an excess risk for lung cancer among welders, but in only two of these studies was this risk statistically significant when the contributions of cigarette smoking and exposure to asbestos were factored into the risk calculation (Refs. 4, 99). In these two studies, a statistically significant elevated risks for newly-diagnosed lung cancer was found after the data were adjusted for smoking and asbestos exposure, among men who had ever had the job title of welder (Refs. 4, 99). An exposure-response relationship could not be established in either study.

In a study by Becker (Ref. 18) in which the risk for death from lung cancer was non-significantly greater in welders than in the general population, there were as many excess deaths from mesothelioma, a disease associated with asbestos exposure, as there were from lung cancer. Based on the assumption of a 1:1 ratio between asbestos-related pleural and lung cancers, Becker calculated that the excess lung cancer risk among welders was associated with asbestos exposure. Van Loon et al. (Ref. 201) found that an excess incidence of lung cancer cases among welders disappeared after the data were adjusted for exposure to asbestos, paint dust, and polycyclic aromatic hydrocarbons (PAH). In a study of lung cancer in Argentina, in which data were adjusted for smoking but not for asbestos exposure, Pezzotto and Poletto found that welders had a significantly elevated risk for squamous cell cancer of the lung. The relative risk for all lung cancers among welders was only slightly increased and was not statistically significant (Ref. 149). Another study of Argentinian men showed an elevated risk for lung cancer among welders, but it was based on five cases, and was non-significant (Ref. 128). Milatou-Smith (Ref. 132) compared lung cancer in stainless steel welders and railroad repair welders. There were non-significant increases in lung cancer in the combined group of welders compared with the general population and in the stainless steel welders compared with the railroad repair welders. Stern et al. (Ref. 176) found a non-significant excess risk for death from lung cancer among welders who worked in the construction industry compared with the rate in the general population. Danielsen et al. (Ref. 52) found steadily increasing rates of lung cancer with increasing years since first exposure as a welder, but, even after 40 years, the excess was not statistically significant. This study showed that siderosis is not a risk factor for lung cancer.

Cancer in Organs Other Than the Lung. In a multi-national cohort study that linked the incidence of cancer with occupation in three Scandinavian countries, Andersen et al. (Ref. 6) found a significant increase in cancers of the lung, pleura, kidney, and urinary bladder in weld-ers. While the incidence of cancer of the gall bladder was significantly elevated, the investigators noted that the increased incidence of gall bladder cancer in welders was based on only twelve excess cases and may have been due to chance. In contrast to this study, Teschke et al. (Ref. 189) found no increased risk for urinary bladder cancer among welders in a case-control study conducted in British Columbia.

Gustavsson et al. (Ref. 76) conducted a community-based case-control study of the incidence of cancer of the upper digestive and respiratory tract in two densely populated regions of southern Sweden. Statistically significant risks of cancers of the throat and larynx were associated with more than 8 years of exposure to welding fumes. Laryngeal cancer was also associated with exposure to asbestos. Exposure to welding fumes was not significantly associated with a risk for cancer of the oral cavity in this study or in a case-control study in northern Sweden conducted by Schildt et al. (Ref 162). In an ongoing study of cancer mortality among welders in Germany, Becker (Ref. 18) found that welders who used SMAW but not other processes had a significantly higher mortality from brain cancer, compared with the general population. A significant excess risk for pancreatic cancer was found in the occupational group of plumbers and welders in a study by Ji et al. (Ref. 97).

Four studies examined the risk of welders for non-Hodgkin's lymphoma (NHL) (Refs. 6, 49, 50, 65, 66, 87). A positive association was found only in a case-control study conducted by Fabbro-Peray and colleagues in a region of France with a high incidence of NHL (Refs. 65, 66). Welders were found to have an increased risk for multiple myeloma in a large case-control study conducted by Costantini et al. (Refs. 49, 50) but not in the multi-national cohort study conducted by Andersen et al. (Ref. 6). Neither of the latter two studies found an association between welding and leukemia.

Metal Fume Fever/Pulmonary Inflammation

Past work by Blanc et al. (Ref. 25) has suggested that metal fume fever is mediated by cytokines released from macrophages and other leukocytes during phagocytosis (engulfment of foreign particles) of metal oxide particles. Tumor necrosis factor (TNF), interleukin-1 (IL-1), and IL-8 become elevated in the lungs following inhalation of zinc oxide (ZnO). These cytokines may be involved in recruitment of other inflammatory cells (e.g., neutrophils, lymphocytes, and macrophages) after exposure to some dusts, which would account for the elevation of neutrophils in the lungs that occurs during

metal fume fever. In addition, the synthesis of IL-8 is stimulated by IL-1 and TNF, which is in accord with findings that IL-8 appears later in bronchoalveolar lavage fluid (BALF) than TNF following exposure to ZnO (Ref. 25). Finally, some cytokines (e.g., TNF, IL-1) are pyrogens and can cause an elevation in body temperature.

Kuschner et al. (Ref. 115) found that the concentrations of the cytokines IL-1, IL-6, IL-8, and TNF were significantly elevated in bronchoalveolar lavage fluid (BALF) collected from healthy volunteers 3 hours after inhalation exposure to ZnO fumes. The numbers of white blood cells (macrophages, neutrophils, lymphocytes) were not elevated at this time. An earlier study by these investigators had shown that TNF, but not the other cytokines, had declined significantly by 20 hours, and neutrophils were significantly higher at 20 hours than at 3 hours after exposure (Ref. 114).

In a parallel study, Kuschner et al. (Ref. 116) exposed human volunteers to magnesium oxide instead of ZnO. None of the subjects experienced any of the symptoms of metal fume fever and there were no significant changes in the concentrations of any of the four cytokines studied or in the numbers of white blood cells in BALF. Thus, the metal fume fever response to inhaled particles may be specific to certain metals.

In vitro studies by these investigators (Ref. 113) demonstrated that cultured monocytes (immature macrophages) released dose-dependent concentrations of TNF into the culture medium 3, 8, and 24 hours and IL-8 at 8 and 24 hours after treatment with ZnO. The sequential appearance of TNF and IL-8 mimicked that seen in BALF from ZnO-exposed human volunteers (Ref. 25). The investigators concluded that mononuclear inflammatory cells (macrophages) are probably the primary source of IL-8 and TNF in the lungs of humans exposed to ZnO fumes.

Lindahl et al. (Ref. 120) examined the possible role of another aspect of leukocyte activity, the respiratory burst, in the mediation of metal fume fever. When macrophages engulf foreign bodies such as bacteria or welding fume particles, they produce a variety of highly reactive oxygen species (ROS), including superoxide, hydroxyl radicals, and hydrogen peroxide. The ROS are important for bactericidal activity. They can act by altering the permeability of cell membranes and by reacting with the pathogen's macromolecules. Reactive oxygen species can also react with the host's macromolecules, causing deleterious effects such as strand breaks in DNA. Lindahl et al. demonstrated that exposure to ZnO and $ZnCl_2$ stimulates the release of ROS from cultured human neutrophils. The concentration of ROS increased to a maximum about 35 minutes following exposure to ZnO and at about 80 minutes following exposure to $ZnCl_2$. Corresponding concentrations of other metals (Cd^{2+}, Cr^{2+}, Cr^{3+}, Fe^{2+}, Fe^{3+}, Ni^{2+}, Co^{2+}) did not have this effect. The authors concluded that ROS might play a role in the pathogenesis of metal fume fever.

Pulmonary Inflammation. The inflammatory process, now believed to be involved in the progression of metal fume fever, is also responsible for the development of more serious chronic conditions such as pulmonary fibrosis and interstitial lung disease. Studies by Antonini et al. (Refs. 10, 11) showed that fumes generated by SMAW of stainless steel (SMAW-SS) produce a greater inflammatory response, as measured by concentrations of neutrophils, TNF, and IL-1 in BALF, than do fumes from GMAW of mild steel (GMAW-MS). In vitro studies conducted with macrophages isolated from untreated rat lungs by bronchoalveolar lavage showed that SMAW-SS fumes were more toxic and produced greater quantities of ROS than did GMAW-SS fumes. GMAW-MS fumes were the least toxic to isolated macrophages. A third study by these investigators showed that intratracheal instillation of freshly formed GMAW-SS fumes caused a greater inflammatory response in rat lungs than did fumes aged for 1 to 35 days before administration (Ref. 9), apparently due to the presence of ROS on the surfaces of newly formed fume particles. These results would suggest that studies of the health effects of welding fumes, whether conducted in animals or in vitro with cultured cells, would yield the most meaningful results if freshly-generated fumes are used.

Effects of Manganese

Excessive exposure to manganese can result in neurological damage, causing an array of symptoms, referred to as manganism, that resembles those of idiopathic Parkinson's disease.

Manganism and Parkinson's disease are both caused by degeneration of cells in the area of the brain called the basal ganglia which is responsible for producing smooth, coordinated movements. Characteristic high intensity signals confined to parts of the basal ganglia can be observed by magnetic resonance imaging (MRI) of persons with excessive manganese exposure. These manganese-related changes in MRI scans disappear within months after exposure to manganese has ceased, regardless of whether or not permanent neurological damage has occurred (Refs. 3, 13). A study conducted by Kim et al. of 34 asymptomatic manganese-exposed welders showed that the increased signal intensities in MRI scans reflects recent exposure to manganese, but does not necessarily indicate the presence of disease processes (Ref. 107).

In Parkinson's disease, there is a deficiency in the production of dopamine, a neurotransmitter vital to normal

nerve function. Treatment of Parkinson's disease patients with L-dopa, a metabolic precursor of dopamine, provides limited symptomatic relief. Wolters et al. (Refs. 163, 210) found a reduced uptake of 6-[^{18}F]fluorodopa (^{18}F-dopa) by the striatum of the basal ganglia in positron emission tomography (PET) scans of patients with Parkinson's disease but not in those with manganism. This phenomenon has been used to differentiate between the two syndromes. In a case described by Kim et al. (Ref. 105), a cranial MRI of a 48-year-old welder with signs of parkinsonism showed the high signal intensities that are characteristic of manganese poisoning. Concentrations of manganese in his blood were elevated, a shirt that he had worn for 2 days at work was found to be contaminated with manganese, and air sampling in the factory where he had last been employed indicated that he had probably been exposed to excessive levels of manganese. Despite the strong evidence that the welder had experienced excessive manganese exposures, based on PET scans which showed a reduced uptake of ^{18}F-dopa, it was concluded that he had idiopathic Parkinson's disease rather than manganism.

Ahn and Lee (Ref. 3) evaluated cognitive function in five welders who had histories of chronic manganese exposure and had MRI patterns indicative of manganese exposure. All five welders were experiencing fatigue, forgetfulness, and irritability but had none of the cardinal signs of parkinsonism. Neuropsychological tests indicated impairments of working memory, executive function, and attention span. Four of the welders also exhibited personality changes. Lucchini et al. (Ref. 124) also showed that early signs of manganese-related neurotoxicity can be detected in manganese-exposed workers in the absence of clinical signs of manganism. Neurobehavioral tests administered to 61 ferroalloy workers who had had long-term exposures to low levels of manganese showed impairments in short-term memory, in some basic tremor parameters, and in motor functions requiring alternating and rapid movements. No signs of neuropsychological disorders were detected.

Racette et al. (Ref. 152) compared the symptoms and disease course in fifteen welders with parkinsonism with that of two sets of controls with idiopathic Parkinson's disease. The severity of the disorder was similar in welders and controls. They exhibited no significant differences in the frequency of the cardinal signs of Parkinson's disease or in the frequency of clinical depression, dementia, and psychosis. In addition, the family history of Parkinson's disease and the response to treatment with L-dopa were similar in welders and controls. Cranial MRI scans performed on eight of the welders showed no signs of the high intensity signals typical of manganese-exposed workers. ^{18}F-dopa PET scans of two welders and thirteen controls were typical of

idiopathic Parkinson's disease. The age of onset of parkinsonism was the only clinical difference observed between the welders and controls. The investigators speculated that an agent in welding exposures may accelerate the development of Parkinson's disease in persons who might otherwise have developed it later in life or who are genetically predisposed to early onset Parkinson's disease. They concluded that parkinsonism in welders differs from idiopathic Parkinson's disease only in age of onset and that "welding may be a risk factor for" Parkinson's disease.

A potential weakness in this conclusion is that the PET scans provide the strongest evidence for excluding manganese as the basis for parkinsonism in the welders studied, yet they were performed on only two of the fifteen welders. A stronger conclusion might have been reached had PET scans been performed on a larger number of the welders in the study. In addition, occupational histories were not provided for the welders so it is not known whether they had been exposed to excess levels of manganese earlier in their careers. It is essential that manganese exposure, a known cause of parkinsonism that is faced by welders using some processes, be ruled out before the postulate can be accepted that welding is a risk factor for Parkinson's disease.

In their letter to the editor, Sadek and Schulz (Ref. 160) suggested that differences in MRI and PET scans were not seen by Racette et al. because, by chance, welders with manganism were not included in the study. They presented the alternative argument that, at an early stage, manganism may differ from idiopathic Parkinson's disease in several ways, including cognitive disturbances, emotional lability, and some physical signs that may not appear until later in the course of idiopathic Parkinson's disease. At a later stage, manganism "may be very indistinguishable from" and can easily be classified as early-onset idiopathic Parkinson's disease. Because the MRI scans will appear normal within months after exposure to manganese has ceased in persons who had been previously exposed to manganese, and because the effects of manganese may be cumulative (Ref. 124), MRI scans cannot be used to rule out past manganese exposures. Sadak and Schulz further pointed out that manganism is a progressive disease, and symptoms may continue to worsen long after exposure to manganese has ceased, which would increase the difficulties of distinguishing between manganism and Parkinson's disease. Thus, they concluded that some or all of the cases that Racette et al. classified as idiopathic Parkinson's disease in the welders may have actually been manganism.

Genetics and Manganism. In a case-control study of welders and ferromanganese workers who had been occupationally exposed to manganese, Zheng et al. (Refs. 212, 213) found that a variant of a gene that

reduces susceptibility to Parkinson's disease also reduces susceptibility to manganism. Individuals who had only the variant form of this gene had a 90% decreased risk of developing chronic manganism compared with persons in whom both copies of the gene were th**e** wild-type (the form of a gene that occurs most frequently within a population). In addition, they found that persons who carry this genetic variant tend to develop manganism 10 years later than other persons with similar exposures to manganese. Thus, it may not be possible to distinguish between manganism and Parkinson's disease on the basis of a familial history of the disorder.

Effects on Reproduction

Three studies were conducted which used the time-to-pregnancy approach (TTP, the time from which the use of contraception is stopped until the time conception occurs) as a measure of fertility in welders and other workers (Refs. 85, 175, 191). None of these studies found statistically significant differences in the pregnancy rates among welders and controls. Hjollund et al. conducted a comprehensive fertility study of welders in Denmark that examined semen quality, rates of fertility, and rates of spontaneous abortion in a cohort of 406 couples in which 130 of the male partners were welders (Refs. 83–85). The effects of extremely low frequency (ELF) magnetic fields on fertility were also examined in a subgroup of the study population (Ref. 86).

Paternal stainless steel welding, but not mild steel welding, was associated with a significantly increased risk for spontaneous abortion, but this was the only positive effect observed in this study. Differences in pregnancy rates between welders and non-welders were not statistically significant, and neither the welding method used nor the metal welded affected rates of conception. In addition, no significant differences between welders and controls were observed in any of the measures of semen quality studied or in levels of sex hormones, and exposure to ELF magnetic fields did not affect fertility. The investigators noted that welders had relatively low exposures to welding fumes and cautioned that the negative findings obtained in their study may not apply to populations with high-level exposure to welding fume or to welders exposed to other putative hazards to fertility such as heat.

Spinelli et al. examined the effects of occupation on the fertility of 662 couples selected from the general population in Italy (Ref. 175). A non-significant difference was observed in the TTP between fathers who were exposed to welding fumes and those who were not. This difference was not statistically significant. Thonneau et al. (Ref. 191) examined the relationship between fertility and male occupational heat exposure. Pregnancy was achieved within 3 to 6 months by a smaller percentage of the welders' partners than by the controls, but this difference was not statistically significant.

Two studies of semen quality found a greater incidence of abnormalities in welders than in controls. Both studies were conducted with men who had provided semen samples to fertility clinics. In the first study, the incidence of defects in any of the measured semen parameters was 25% among patients who were white collar workers, 47.7% among fitter-welders, 68.8% among machinery operators, and 85.7% among workers in the chemical and petroleum industries (Ref. 78). The second study used two different statistical approaches to examine the relationship between occupational exposures and semen quality (Ref. 23). Significant changes in 2 of 13 parameters of semen quality were observed by the analysis of continuous variables, while none were observed by the more traditional case-control approach in the semen from the 14 men in the study group who were currently or recently employed as welders or flame cutters.

Effects on the Immune System

Three studies examined the effects of welding on the immune system using assays including the concentrations of immunoglobulins in serum, number and function of lymphocytes (B and T cells) in blood, and activity of leukocytes isolated from blood. Results from two of these studies (Refs. 77, 195) suggest that the effects of welding on the immune system are minimal when fume exposures are lower than permissible values. The first study was conducted by Tuschl et al. with welders who used primarily GTAW and GMAW to weld stainless or mild steel (Ref. 195). Personal air monitoring indicated that the welders were exposed to average fume concentrations of 5.3 mg/m^3. The only significant effect seen was a reduction of the function of natural killer (NK) cells, a form of lymphocyte that destroys a variety of foreign cells and tumor cells. In the second study, the immune status of welders who conducted SMAW of stainless steel was evaluated by Hanovcova et al. before and after ventilation was improved in the plant (Ref. 77). Air sampling conducted early in the study showed concentrations of chromium, nickel and manganese that were well in excess of maximum allowable concentrations. At this time, the number of T lymphocytes and the concentrations of lysozyme were elevated, and the activity of phagocytic cells was depressed in the welders. After improvements were made in the workplace, only one welding station had levels of chromium in excess of

the allowable standard and the immune system parameters approached control values for all the welders. In the third study, Borska et al. examined parameters of the immune system of welders who performed SMAW of stainless steel (Refs. 29, 30). Levels of chromium, nickel, manganese, and PAH measured in workplace area samples were below maximum allowable concentrations. Concentrations of IL1, lysozyme (a bactericidal enzyme released from activated macrophages), and the immunoglobulin IgA were elevated, and concentrations of IgM and the number of cells capable of phagocytosis were decreased in the blood from welders.

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Technical Summary

The Exposure

Analytical Methods

Inductively-Coupled Plasma Mass Spectroscopy. Because it can detect very low concentrations of metals and can measure a number of metals simultaneously with high precision, Apostoli et al. (Ref. 12) used inductively-coupled plasma mass spectroscopy (ICP-MS) to measure the concentrations of metals in fumes produced by eight welding procedures. The number of metals detected ranged from five in fumes from GMAW of aluminum, to sixteen in fumes from SMAW of stainless steel, and 23 in fumes from SMAW of mild steel. Guidotti (Ref. 75) described the use of ICP-MS for obtaining trace element profiles in blood, serum, and urine of workers from different occupational settings. He pointed out that ICP-MS is especially useful for measurement of metals that are present in very low quantities in biological fluids.

Aluminum. Valkonen and Aitio (Ref. 197) described a method for determination of aluminum in urine and serum using platform atomization in pyrolytically coated graphite tubes after fourfold dilution with nitric acid. Using this method, the mean concentration of aluminum in a healthy, non-exposed population was found to be 0.06 µmol/L in serum, and 0.33 µmol/L in urine. The average concentration of aluminum in urine samples collected from 3312 Finnish workers, who were occupationally exposed to aluminum and were primarily aluminum welders, was 1.4 µmol/L.

Chromium. The Standards, Measurements and Testing Programme of the European Commission conducted an interlaboratory study to develop reference materials for the purpose of providing laboratories with a means to check and improve analytical procedures for measuring chromium species in welding fumes (Refs. 43, 151). Ten European laboratories participated in the certification of the reference materials using various spectrophotometric methods, including electrothermal atomic absorption spectrometry, flame atomic absorption spectrometry, inductively coupled plasma atomic emission spectrometry, and isotope dilution mass spectrometry (IDMS). The results obtained by the different laboratories were in good agreement.

Fume Composition

Using IDMS, Nusko and Heumann (Ref. 143) measured the concentrations of trivalent [Cr(III)], hexavalent [Cr(VI)] and elemental chromium in samples of fumes generated by SMAW, GMAW, and GTAW of stainless steel. The highest concentrations of Cr(VI) were generated by SMAW and GTAW of stainless steel (29.1 µg/mg and 9.3 µg/mg, respectively). Dennis et al. (Ref. 57) described the effects of flow rate and welding voltage on the relationship between Cr(VI), ozone, and ultraviolet (UV) radiation during GMAW.

Workplace Exposures

Particle Size. Sioutas (Ref. 166) compared the atmospheric concentrations of fine particles in the areas of four different processes (heat-treating and brazing, welding, machining, and grinding) in an automotive plant. The concentration of fine particles was highest in the aluminum machining area followed by that in the welding area. Okamota et al. (Ref. 145) examined the ratio of the quantity of respirable to inhalable particulate in workplaces where grinding, powder handling, metal casting, welding, and miscellaneous activities such as wood or metal cutting and production of metal leaf were performed**.** The ratio was highest in shops where welding took place and lowest in foundries.

Sampling Procedures. Chung et al. (Refs. 44, 38, 39) evaluated the new European/International Standard for sampling of airborne particles and gases generated during welding and allied processes proposed by the European Committee for Standardization and found that the allowable choices of samplers and sampling procedures could lead to an over- or underestimation of fume

exposures. Their findings indicated that lapel samplers were unreliable for measuring exposures to welding fumes and that reliance on data sheets for fume composition could lead to underestimation of exposure to fumes from some welding processes.

Iron Oxide. Using data obtained from records of OSHA inspections (IMIS) conducted from1979 to1989, Gomez et al. (Ref. 74) examined the effects of plant size, passage of time, and other variables on levels of personal exposures of welders working in metal fabrication to iron oxide. The mean exposures to iron oxide were below the OSHA Permissible Exposure Limit (PEL) and were found to be unchanged during the 10 year period examined and to be unaffected by the presence or absence of union representation or the size of the companies in which the welders worked.

Lead. In a survey of lead levels in personal air sampling data entered by OSHA compliance officers into the IMIS database for workers in the construction industry during the years 1984 through 1988, Jacobs (Ref. 93) found that lead levels in over 60% of the samples collected from workers in bridge, tunnel, and elevated highway construction and from workers in wrecking and demolition were greater than the OSHA PEL. In 1995, Nelson and Kaufman (Ref. 138) surveyed selected non-construction businesses in Washington State to determine the number of workers with potential lead exposure. Awareness of and compliance with the standard increased with the size of the plant and with the presence of labor unions representing the workforce.

Dioxins. Menzel et al. (Ref. 131) showed that dioxins can be generated during thermal oxygen cutting of contaminated materials. They found that dioxin exposures are not associated with welding of clean steel and are probably not associated with thermal oxygen cutting of virgin steel.

Ventilation. Rappaport et al. (Ref. 155) assessed personal exposures to total fume, manganese, nickel, and chromium among boilermakers, ironworkers, pipefitters, and welder-fitters at nine construction sites in the USA. They found that use of local exhaust reduced exposure, and exposure was increased when welding was continuous rather than intermittent. Using the statistical method of analysis of variance, Bellido-Milla et al. (Ref. 21) demonstrated that welding in an enclosed space, welding in a sitting position, and using automatic welding machines increased fume concentrations in the breathing zone. In accord with the findings of Rappaport et al. (Ref. 155), the use of local exhaust ventilation during continuous welding did not substantially reduce exposure to welding fumes or their constituent metals. Vernez et al. (Ref. 207) surveyed particulate exposures among a population of 142 metal workers. They found that the concentrations of particulate measured at the stations provided with local exhaust were about half those in stations without it.

Thorium

The radioactive metallic element thorium is incorporated into tungsten electrodes to improve their arcing properties and their durability. Laroche et al. (Ref. 117) examined the potential for thoriated electrodes to introduce radiation hazards into the workplace when they are originally ground to produce a sharp tip, when they are re-ground, and when they are used during gas tungsten arc welding. In addition, they measured the amount of radioactive material that may be removed during handling of these electrodes. The sum of all of these exposures for welders using thoriated electrodes was estimated to be below the annual limit of 5 rem, set by the U.S. Nuclear Regulatory Commission. Ludwig et al. (Ref. 125) measured radioactivity in the breathing zones of 26 welders during welding and grinding operations with thoriated tungsten electrodes. Based on these measurements, the estimated annual inhaled dose for five of the welders exceeded the annual limit of 0.1 rem that is recommended for exposure of the general population by the International Commission on Radiological Protection, but none of the welders was found to be in danger of exceeding the occupational standard of 5 rem. Jankovic et al. (Ref. 94) also measured breathing zone concentrations of thorium during welding and grinding. Local exhaust ventilation provided the greatest reduction in breathing zone concentrations of thorium during welding, but when exhaust ventilation was not used, the welding helmet provided a substantial amount of protection. Concentrations of radioactive thorium measured during welding were well below a limit derived from the permissible annual dose of radiation. Higher concentrations of radioactivity were measured during grinding. Because these exposures were brief and infrequent, accumulated doses would not approach permissible annual limits.

Electromagnetic Radiation

Tenkate and Collins (Refs. 184, 186) used polysulfone film dosimeters to estimate the daily doses of UV radiation received by the eyes and skin of welders and nearby workers in a metal fabrication workshop. All doses measured by body, ocular, and environmental badges were above the ACGIH maximum permissible exposure (MPE) limit of 3 mJ/cm^2 for UV radiation. The ocular exposures measured for the welders and boilermakers were four and five times the MPE, respectively,

indicating that UV radiation can infiltrate the welding helmet. Tenkate and Collins (Ref. 185) investigated the elements of helmet design and the angles of incident radiation that allow UV radiation to enter the helmet and reflect into the eyes. None of the four helmet designs tested completely protected the eyes from exposure to UV radiation. The primary routes of UV infiltration were from the top and the back of the helmet. When the UV beam was in a horizontal orientation, some UV radiation entered through the opening between the edge of the shield and the side of the face.

Electromagnetic Fields

Skotte and Hjollund (Ref. 170) fitted welders and metal workers with exposure meters over periods of one to three days. The highest average workday exposure to electromagnetic fields (EMFs) (21.2 µT) was recorded among welders engaged in SMAW using alternating current. Welders using GMAW (DC) had an average daily exposure of 2.3 µT. Karlsen et al. (Ref. 100) used personal exposure meters to measure welders' exposures to EMFs during seven different welding processes. The highest maximum average exposures were found during SMAW (AC), followed in descending order by GTAW (AC or DC), SMAW (DC), GMAW (DC), FCAW (DC), and spot welding.

Hygiene and Work Practices

Accident and Sick Leave Rates. Using workers' compensation claims rates, Dement and Liscomb (Ref. 55) analyzed accident rates among workers in the residential construction industry in North Carolina. Welders and cutters had the highest number of injuries followed in descending order by insulators, roofers, mechanics and repairers, carpenters, and plumbers. Bylund and Bjornstig (Ref. 37) analyzed the incidence of non-fatal occupational injuries among the 2156 mechanics and construction metal workers who worked in Umea, Sweden, during the year 1985. Of the 470 welders in the cohort, 94 had suffered injuries on the job. The incidence of injury was highest among shop mechanics, followed by plumbers, and welders. Kosmider et al. (Ref. 110) found that welders, fitters, electrical mechanics, and platers had the largest number of work-related accidents at the Szczecin Shipyard in Poland.

Szubert and Sobala (Ref. 181) analyzed the relationship between absenteeism rates and duration of employment among workers in a Polish automobile plant. For most workers, the rate of absenteeism decreased with the duration of employment. This negative relationship was not true, however, for welders and drivers, which may be a reflection of the development of work-related disease. In a study of sick leave rates resulting from temporary disability due to musculoskeletal disorders, Burdorf et al. (Ref. 35) found that back, knee, and shoulder pain were the most frequently reported disorders by welders. There was no association between absences resulting from musculoskeletal disorders and duration of employment, but workers who took sick leave due to pain in the back, neck, shoulder, or upper or lower extremities were at higher risk of incurring sick leave from the same cause in the following year.

Electrocutions. The National Institute for Occupational Safety and Health (NIOSH) (Ref. 140) reported that electrocutions were the fifth leading cause of death in the workplace and accounted for 7% of all workplace fatalities between 1980 and 1992. Of the 244 electrocutions that occurred from 1982 through 1994, six occurred among welders.

Forensic Diagnosis of Electrocution. Using a new application of a histological stain, Imamura et al. (Ref. 92) demonstrated that electrocution was the cause of death of a 30-year-old welder who died while using an arc welder to mend drainpipes.

Explosions. The death of a welder caused by the explosion of the digester at an anaerobic biowaste treatment plant was described by Umani Ronchi and Rossi (Ref. 196). The explosion was attributed to the probable leakage of methane through a break in the pipes that carry the gas out of the digester. Maxwell et al. (Ref. 129) described an incident in which a welder suffered severe injuries when using an oxyacetylene torch to heat the bronze end plate on a large marine water pump.

Burns. The case of a 21-year-old welder who was seriously burned on the front of his body while using an oxyacetylene torch was described by Kumar and Abraham (Ref. 112). The accident occurred as sparks from the torch fell on the safety valve of a generator in which acetylene gas was produced, causing it to melt and igniting the gas that escaped through the damaged valve. Still et al. (Ref. 178) described the case of a 38-year-old man who was standing between two railroad cars while welding the coupling mechanism with an oxyacetylene torch. When the train moved unexpectedly, the coupling penetrated his abdomen causing internal injuries and severe flame burns over 35% of his body from the welding apparatus.

Training. Wallace et al. (Ref. 208) described a case study performed by NIOSH at a welding shop in a vocational school in 1996. Numerous safety and health hazards were found including inadequate personal protective equipment, an improperly functioning ventilation system, and improperly positioned exhaust hoods.

Effects of Welding on Human Health

Respiratory Tract

Pulmonary Function. Fishwick et al. (Refs. 69, 70) measured the acute effects of welding on pulmonary function by conducting spirometric tests on welders and non-welders before, during, and after a work shift. At the end of the work shift, the welders had a significantly greater decrease in FEV_1 (the amount of air that can be forcibly exhaled in one second) than non-welders. The use of local exhaust during welding led to significantly smaller losses in lung performance 15 minutes after beginning work and at the end of the shift. The same group of welders and non-welders was examined 2 years later for signs of cumulative changes in lung function (Ref. 64). Workers who used personal respiratory protective equipment, local exhaust, or a combination of the two had a significantly smaller annual decline in both FEV_1 and forced vital capacity (FVC, a measure that is reduced in restrictive lung disease) than welders who used no protective equipment. Among workers who smoked, welders had a significantly steeper annual decline in FEV_1 than non-welders. Although management and subjects had been notified of the results of the first study (Ref. 70), few improvements to reduce fume concentrations in the welding areas had been made (Ref. 171). Sobaszek et al. (Ref. 172) administered lung tests to mild and stainless steel welders and non-welding controls before and after a work shift. At the end of the workshift, lung function was decreased in most of the tests among controls and in all tests among welders. Significant decrements in post-shift lung performance were associated with welding of stainless steel compared with mild steel and with use of SMAW compared with GTAW or GMAW. Welding stainless steel for more than 20 years was associated with greater decrements in post-shift lung function tests than was mild steel welding. Chronic effects of welding on lung function were measured in stainless steel welders using SMAW, GTAW, GMAW, and plasma welding techniques, and in controls from eight factories (Ref. 173). Welders who were engaged in GTAW had small, statistically non-significant, but consistent decrements in all of the lung function tests compared with those engaged in SMAW or GMAW or with the controls. For all welders, duration of welding experience was related to declines in expiratory flow rates. In a study of journeyman plumbers and pipefitters, Hessel et al. (Ref. 81) found lung abnormalities, as measured by spirometry, in 11.5% of the pipefitters, in 16.7% of the welders, and in 57.1% of the plumbers. In another study by the same group, boilermakers had significantly lower lung flows and volumes than welders (Ref. 80).

Asthma. In recent decades, the incidence of asthma has been on the rise throughout the industrialized world. Blanc and Toren (Ref. 24) critically reviewed studies containing risk estimates for occupational asthma and concluded that about 15% of adult asthma is associated with occupational factors. In studies by Toren et al. (Refs. 193, 194) of 683 cases of adult onset asthma in two large population centers in Sweden, welding fumes were among the industrial exposures that were significantly linked to an increased risk for the disease. Mastrangelo examined 387 cases of asthma and found a significantly greater relative risk for occupational asthma among welders, compared with metal assembly workers. Contreras and Chan-Yeung (Ref. 48) examined six welders who had reported to a clinic with respiratory symptoms. Three of these welders exhibited asthma-like responses when they welded in the clinic using the metals that were associated with their problems at work (stainless steel in one case, galvanized steel in the other two). These reactions were attributed to non-specific irritation rather than to sensitization to specific substances in welding fumes. Vandenplas et al. (Ref. 203) examined a maintenance man who experienced an asthmatic attack when he welded aluminum but not when he welded mild steel, leading to the conclusion that aluminum may be a cause of occupational asthma. Kelesoglu et al. (Ref. 101) examined bronchial hyperreactivity and found no significant excess among welders, compared with other blue-collar workers.

Chronic Bronchitis. Bradshaw et al. (Refs. 32, 33) studied chronic bronchitis among welders and non welders in the same plant and found a significantly incidence of chronic bronchitis among welders with greater than 10 years' experience, compared to welders with less than 4 years' experience.

Magnetopneumography. Huvinen et al. (Ref. 90) investigated the relationship between the dusts retained in the lungs of workers in a stainless steel production facility, as measured by magnetopneumography (MPG), and concentrations of chromium in workplace air and in urine. The particulate lung burden did not correlate with duration of exposure, or with actual exposures to total or hexavalent chromium. There was a relationship between the lung burden of magnetizable particles and urinary chromium concentrations. Nakadate et al. (Ref. 135) measured lung function and iron deposits in the lungs of welders before and after a 5-year period in which engineering and industrial hygiene practices were instituted that substantially reduced exposures to welding fumes. At the start of the study, they observed a deficit in pulmonary function, indicative of obstructive changes in the lung, that correlated with accumulation of welding fumes in the lungs, measured using MPG. Five years later, after

many improvements had been made in the air quality in the plant, the lung burden of magnetizable particles had significantly decreased (Ref. 136), but this did not lead to an improvement in their pulmonary function.

Pneumoconiosis. Steurich and Feyerabend (Ref. 177) described a welder who experienced fatigue and difficulty breathing. X-rays revealed small nodular opacities scattered throughout the lungs, and lung tissue biopsy revealed iron deposits and areas of fibrosis. In an unusual case of pneumoconiosis, described by Kinoshita et al. (Ref. 108), a single, poorly defined, solitary mass, 3 cm in diameter, with large quantities of iron was found in a 60-year-old man with 25 years' welding experience. This solid mass was diagnosed as pneumoconiosis and not lung cancer. Yamada et al. (Ref. 211) described an unusual medical treatment for siderosis in a 42-year-old welder who was admitted to the hospital complaining of a dry cough. A total of 911.7 mg of fume particles were washed from his lungs by bronchopulmonary lavage with over 13 liters of saline solution.

Medico-legal investigations of two cases of pulmonary disease occurring in welders determined that they were not related to occupational exposures. In France, Charpin et al. (Ref. 41) examined the case of a man who sought medical attention in 1992 after suffering recurrent sinusitis, bronchitis and purulent pleurisy. These conditions were attributed to bronchiectasis (chronic inflammation of portions of the bronchial wall) and were judged to be unrelated to his occupational exposures as a welder. In Germany, Strohbach et al. (Ref. 180) evaluated the case of a 46-year-old welder who suffered from an acute interstitial lung disease, with symptoms of dry cough, night sweats and chills, and chest pains with breathing difficulties that worsened at work. This condition improved after treatment with corticosteroids, but he developed pain in his joints, knees and fingers and was diagnosed with CREST syndrome (a limited form of scleroderma).

Case Reports. Tojima et al. (Refs. 192, 7) described the case of a 61-year-old welder with a 32-year welding career who developed symptoms of metal fume fever within hours after welding galvanized steel. Clinical examination and chest X-rays indicated he had acute chemical pneumonitis, which the authors attributed to exposure to ZnO fumes. Barbee (Ref. 16) described the case of a 43-year-old maintenance worker who developed pneumonitis with pulmonary edema 12 hours after cutting a galvanized steel grating with an oxyacetylene torch without using a respirator. His exposure was re-created at his place of employment, and air sampling revealed that he may have been exposed to levels of cadmium twice the OSHA PEL and to levels of zinc over 20 times the PEL. Bousova-Kostelnikova (Ref. 31) described an incident in

which two welders were affected by fumes while working in a newly-built storage tank. One welder used an oxyacetylene torch and the other used SMAW. No mechanical exhaust systems were used, and neither welder was equipped with a respirator. About 10 hours after finishing work, one of the welders developed difficulty breathing and was diagnosed with pulmonary edema. The second worker was less severely affected and developed symptoms of a dry, irritating cough, general malaise, and headache. The cause of these conditions was deemed to be exposure to nitrogen dioxide with a possible contribution by ozone.

Cancer

Lung Cancer. In a study by Becker (Ref. 18), lung cancer was non-significantly elevated among welders compared with machinists. The presence of seven cases of mesothelioma in the group of welders led the author to conclude that the observed excess of cancer mortality among welders in his study was predominantly due to asbestos exposure. Van Loon et al. (Ref. 201) compared occupational exposures to asbestos, paint dust, polycyclic aromatic hydrocarbons, and welding fumes among incident cases of lung cancer and in a representative sample drawn from the same population as the lung cancer cases. Exposure to asbestos was highly correlated with increased risk for lung cancer. There was an elevated risk for lung cancer associated with welding fumes, but not after the data were adjusted for exposure asbestos, paint dust, and polycyclic aromatic hydrocarbons. The authors estimated that 11.6% of lung cancer in men is attributable to occupational exposure to asbestos. These investigators also found that men with the highest level of education had a significantly lower risk for lung cancer compared with men with the least education. Jockel et al. compared occupational exposures of German men newly diagnosed with lung cancer with those of a matched group of controls (Ref. 99). The relative risks for lung cancer were significantly increased with exposure to asbestos and with ever having held the job title of welder. There was, however, a negative exposure-response relationship for welding: exposure to welding fumes for less than 1,000 hours was associated with a higher relative risk for lung cancer than was found for exposures greater than 6,000 hours. In a pooled case-control study, Ahrens et al. (Ref. 4) found a significantly elevated relative risk for lung cancer among welders in western Germany (the former Federal Republic of Germany), but not eastern Germany (the former German Democratic Republic). Welding mild steel for more than 30 years was also associated with increased risk for lung cancer in western Germany. Teschke et al. found an elevated relative risk for

mesothelioma among welders in a case-control study conducted in British Columbia, but this result was not statistically significant (Ref. 188). Milatou-Smith et al. (Ref. 132) compared lung cancer mortality between welders of stainless steel, who were exposed to relatively high levels of Cr(VI), and railway repair workers, who had low levels of exposure to Cr(VI). The stainless steel welders had a greater, but non-significant, relative risk of death from lung cancer, and the authors concluded that their study supports the classification of hexavalent chromium as a carcinogen. A letter to the editor (Ref. 8) disputed the contribution of nickel and hexavalent chromium to lung cancer in welders, citing a large European study (Ref. 165) that showed a statistically significant increased mortality from lung cancer among welders of mild steel but not stainless steel. Matos (Ref. 128) found an elevated, but non-significant relative risk for lung cancer among welders in a case-control study in Argentina. In another study of lung cancer in Argentina, Pezzotto and Poletto found that welders had a significantly elevated risk for squamous cell cancer of the lung, but a slightly increased relative risk for all lung cancers among welders was not statistically significant (Ref. 149). A hospital-based case-control study in Belgium found that exposure to chromium for longer than 30 years was associated with a significant excess risk for lung cancer (Ref. 60). In a study of causes of death among ironworkers, Stern et al. (Ref. 176) found that welders had significantly greater risks of death from all cancers and from falls, compared with the general population, and a non-significant excess risk of death from lung cancer. Danielsen (Ref. 52) investigated lung cancer among Norwegian shipyard welders who had been examined for siderosis 17 years earlier. No relationship was found between having been diagnosed with siderosis and mortality from lung cancer.

A 68-year-old man who had worked for 4 years as a full-time welder and for 30 years as a part-time welder (Ref. 79) had chronic inflammation and severe fibrosis of the lungs. He subsequently developed epidermoid cancer in the affected area of the lungs. Liu et al. (Refs. 121, 122) found that mutations in the P53 suppressor gene isolated from lung tumor specimens from workers who had pneumoconiosis associated with exposure to silica, asbestos, or welding fumes differed from those in lung cancer specimens taken from persons in the general population. They concluded that these differences might indicate that DNA damage in lung tumors associated with exposure to silica, asbestos, or welding fumes may arise by a different mechanism than do tumors associated with other causes such as tobacco smoke.

Cancers at Other Sites. Andersen et al. (Ref. 6.) conducted a comprehensive survey of cancer incidence rates between 1970 and 1990 among all adults who had re-

sided in four Nordic countries in 1970. They found a small but significant increase in the incidence of cancers of all types among male welders, compared with the male population of Finland, Norway, and Sweden combined. Cancers of the gall bladder, lung, pleura, kidney, and urinary bladder were significantly elevated among the welders. In a continuing study of cancer mortality among welders in Germany, Becker (Ref. 18) found that welders had a significantly elevated relative risk of dying from cancer of all causes, compared with a control group of machinists. Welders who used SMAW, but not other processes, had significantly higher mortality from brain cancer, compared with the general population. In a case-control study in British Columbia, Teschke et al. (Ref. 189) found a non-significant elevation in the risk for nasal cancer and no increased risk for bladder cancer among welders. Gustavsson et al. (Ref. 76) conducted a community-based case-control study of the incidence of cancer of the oral cavity, pharynx (throat), and esophagus in two densely populated regions of southern Sweden. Statistically significant risks of pharyngeal cancer and laryngeal cancer were associated with more than 8 years of exposure to welding fumes. Exposures to welding fumes were not associated with a risk for cancer of the oral cavity or esophagus. In a case-control study in Northern Sweden, Schildt et al. (Ref. 162) observed a non-significantly increased risk for oral cancer among welders. A significant excess risk for pancreatic cancer was found in the occupational group of plumbers and welders in a study by Ji et al. (Ref. 97). Fabbro-Perray et al. found that daily exposure to welding was associated with a significantly elevated risk for non-Hodgkins lymphoma (Refs. 65, 66). Holly et al. (Ref. 87) found no association between occupational exposures and non-Hodgkins lymphoma in HIV-positive men. Among HIV-negative men, a significantly increased risk for the disease was associated with certain chemicals, but not with welding and soldering. Welders were found to have a significantly increased risk for multiple myeloma in studies by Costantini et al. (Refs. 49, 50).

A welder with recurrent dermatitis and keratosis had several squamous cell carcinomas removed from his face. This man, who had been sensitive to ultraviolet light since childhood, was advised to discontinue welding (Ref. 147). Another welder, who developed a basal cell carcinoma on an exposed area of his upper chest, also had had numerous incidences of erythema from welding and sunburn. Unlike the case described above, he had no keratoses on exposed areas of his skin (Ref. 59). Olshan et al. (Ref. 146) studied neuroblastomas in children with relation to their fathers' occupations. Although the risk for neuroblastomas was significantly correlated with paternal exposure to EMFs, there was no association between neuroblastoma risk and welding,

which is considered one of the occupations most highly exposed to EMFs.

Metal Fume Fever

Van Pee et al. (Ref. 202) described a typical case of metal fume fever in a 23-year-old man who became ill 3 hours after completing a work shift in which he had been welding galvanized steel without wearing a respirator.

Kuschner et al. (Ref. 115) found that the concentrations of the cytokines interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor (TNF), but not the numbers of leukocytes, were significantly elevated in BALF collected from 15 human volunteers 3 hours after inhalation exposure to zinc oxide (ZnO) fumes. At 3 hours after exposure. Neutrophils were significantly higher in bronchoalveolar lavage (BAL) fluid collected at 20 hours than in that collected at 3 hours. Exposure of volunteers to magnesium oxide caused no significant changes in the concentrations of any of the four cytokines studied (IL-1, IL-6, IL-8, and TNF) or in the numbers of leukocytes in BALF (Ref. 116).

Effects on the Eye

Effects on the Retina. Lesions of the retina were described in welders by four investigators (Refs. 179, 56, 2, 111). Stokkermans and Dunbar (Ref. 179) described three welders diagnosed with solar retinopathy, a condition that usually develops from gazing at the sun. All of the welders had good visual acuity, but two of them had visual field defects, such as blind spots. Denk et al. (Ref. 56) described the case of a 38-year-old man who developed arc welding maculopathy, attributed to exposure to optical radiation, while welding for 2 hours without proper eye protection. Seventeen welders with central serous chorioretinopathy (a lesion of the retinal pigment epithelium) were described by Adelberg (Ref. 2) who postulated that the lesions originated as welding arc maculopathy. Subretinal neovascularization, a condition that accounts for 10% of age-related macular degeneration, was observed in a welder by Kozielec and Smith (Ref. 111).

Eye Protection. Daxer et al. (Ref. 53) evaluated the effectiveness of an eye drop preparation, commercially available in Europe, designed for protection against both solar and artificial UV radiation. They found that a liquid layer of about 10 μm, which corresponds to the thickness of the film of tears normally coating the human eye, allowed the transmission of about 25–50% of the UV-C radiation (100–280 nm) and more than 90% of the UV-B, UV-A, and visible light (290 and 500 nm). The investiga-

tors calculated that the eye drops would provide about 35% protection against photokeratitis during unprotected exposure to the welding arc.

In a survey of the use of eye protection by welders in Lagos, Nigeria, Oduntan (Ref. 144) found that proper eye protection was worn by only 44% of 339 welders, and that the use of proper eye protection was not consistent, even among some who usually wore goggles. The inadequate safety practices among Nigerian welders was attributed in part to the lack of understanding of the ocular hazards associated with welding and in part to the lack of safety standards for welders in Nigeria.

Effects of Aluminum

In a cross-sectional study of cognitive function in asymptomatic welders with up to 23 years' experience performing GMAW of aluminum, Akila et al. (Ref. 5) found that aluminum exposure was associated with detrimental effects in certain cognitive functions but had no effect on verbal comprehension. Similarly, immediate visual memory or basic visuoperceptual processes were unimpaired, although processes that involve holding a complex design in memory and that require reproducing that design were impaired. Kilburn (Ref. 104) evaluated the published data on the effects on the brain of occupational exposure to fine aluminum particles. She noted that commercial aluminum is frequently alloyed with copper, manganese, or zinc, and it is therefore possible that aluminum welders may have significant exposures to manganese which has some effects that are similar to those that have been observed in aluminum workers in some studies.

Effects of Manganese

Sato et al. (Ref. 161) described a welder with signs of parkinsonism which was diagnosed as manganese poisoning based on high concentrations of manganese in serum and urine and on cranial magnetic resonance imaging (MRI) which showed hyperintense signals indicative of manganese deposition. The size and density of the MRI signals were reduced after 10 months. Arjona et al. (Ref. 13) described a construction worker who was experiencing mental confusion, sudden unprovoked falls, and had mild rigidity and tremor in both arms. Cranial MRI revealed images indicative of manganese deposition and his urinary manganese concentration was elevated. Ten months after stopping work, his urinary manganese concentrations were normal, his physical condition improved, and an MRI scan was normal. Kim et al. (Refs. 105, 106) described a welder with signs of parkinsonism. MRI showed the high signal intensities in the brain that

are characteristic of manganese deposition. Based on PET scans which showed a reduced uptake of ^{18}F-dopa by the striatum, and despite strong evidence that the welder had experienced excessive manganese exposures, Kim et al. concluded that he had idiopathic Parkinson's disease rather than manganism.

Kim et al. (Ref. 107) conducted a study of MRI signal intensities and neurological symptoms in 34 asymptomatic manganese-exposed welders. Neurological examinations administered to each of the subjects revealed no signs of manganism in any of the workers. Cranial MRI scans indicative of manganese deposition were found in 46.1% of the manganese-exposed workers. It was concluded that the increased signal intensities in the MRI scans in the absence of any signs of parkinsonism or manganism reflects recent exposure to manganese, but does not necessarily indicate the presence of disease processes.

Cognitive Effects. Ahn and Lee (Ref. 3) evaluated cognitive function in five welders and who had histories of chronic manganese exposure and had MRI patterns indicative of manganese deposition, but had none of the cardinal signs of parkinsonism. Neuropsychological tests indicated impairments of working memory, executive function (ability to plan, organize, and develop strategies or rules), and attention span in all five welders.

Lucchini et al. (Ref. 124) administered a battery of neuropsychological tests to a group of 61 asymptomatic male ferroalloy workers who had had long-term exposures to low levels of manganese. Mean concentrations of manganese in blood and urine were significantly higher in exposed workers than in controls. Neurobehavioral tests showed that alloy workers had more impairments in motor functions requiring alternating and rapid movements, in short-term memory functions, and in some tests of tremor parameters, but there were no signs of neuropsychological disorders or clinical signs of manganese toxicity in the exposed workers.

Heart Rate. Barrington et al. (Ref. 17) attempted to correlate manganese exposure with autonomic nervous system function and cognitive and emotional dysfunction in eight workers from a shop for gouging, welding, and grinding of high-manganese railway track, Ambulatory 24-hour electrocardiograph readings showed that seven of the eight subjects had significantly decreased variability in the heart rate compared with the controls and with a reference group of healthy individuals.

Welding and Parkinson's Disease. Racette et al. (Ref. 152) conducted a case-control study of the symptoms and disease course in fifteen welders with parkinsonism. The severity of parkinsonism was similar in welders and controls. The average age at onset of parkinsonism of the welders (46 years) was significantly lower than that of the sequentially-selected controls (63 years, p < 0.0001).

Cranial MRI scans performed on eight of the welders showed signs of manganese deposition. Two of the welders and thirteen controls were examined by ^{18}F-dopa PET scans which were typical of idiopathic Parkinson's disease. The age of onset of parkinsonism was the only clinical difference observed between the welders and controls. They concluded that parkinsonism in welders differs from idiopathic Parkinson's disease only in age of onset and that "welding may be a risk factor for" Parkinson's disease.

In a letter to the editor concerning this paper, Sadek and Schulz [Ref. 160] suggested that differences in MRI and PET scans were not seen by Racette et al. because, by chance, welders with manganism were not included in the study. They noted that at later stages, manganism "may be very indistinguishable from" idiopathic Parkinson's disease and can easily be mis-classified as early-onset idiopathic Parkinson's disease.

Genetics and Manganese Toxicity. It is well established that Parkinson's disease has a genetic component since close relatives of these patients have an increased risk of developing it themselves. Mutations in up to five genes have been reported by different investigators to be related to susceptibility to idiopathic Parkinson's disease. In a case-control study, Zheng et al. [Refs. 212, 213] found that a variant of a gene reported to be related to susceptibility to idiopathic Parkinson's disease occurs more frequently in persons with a history of significant exposures to manganese who are free of any signs of manganism. They concluded that the presence of this gene variant might decrease the susceptibility of individuals to manganese-induced neurotoxicity.

Effects on the Cardiovascular System

Cardiovascular Disease. Ranjan and Lokhandwala (Ref. 154) described a welder who reported to the hospital with difficulty breathing. Signs of marked cardiac dysfunction were seen in electrocardiograms and echocardiography. The physicians attributed this disorder to welding exposures.

Hand-Arm Vibration Syndrome. Pelmear and Wills (Ref. 148) identified spot welding as the cause of six of 185 cases of Raynaud's phenomenon reported to the Occupational Health Clinics for Ontario Workers between 1993 and 1996.

Effects on Fertility

A study of factors that might influence willingness to participate in semen quality studies conducted by Larsen, Abell, and Bonde (Ref. 118) indicated that the potential

participants' chronological age or awareness of past successes or difficulties in fathering children can influence their willingness to provide semen samples. In 1998, Hjollund et al. (Ref. 85) conducted a comprehensive fertility study of welders in Denmark using a design that would reduce this selection bias by including only men who had not previously tried to father children. This study examined semen quality, rates of fertility, and rates of spontaneous abortion in a cohort of 406 childless couples in which 130 of the males were welders, 71 were non-welding metal workers, and 205 were non-metal workers (Refs. 83–86). The effects of ELF magnetic fields on markers of fertility were also examined in a subgroup of the study population.

Differences in pregnancy rates between welders and non-welders were not statistically significant, and neither the welding method used nor the metal welded affected rates of conception. The risk for spontaneous abortion did not differ between fathers who were mild steel welders and those who were non-welders (Ref. 84). Paternal stainless steel welding was, however, associated with a significantly increased risk of spontaneous abortion. No significant differences in any of the measures of semen quality studied (sperm density, sperm count, proportions of morphologically normal sperm, and sperm motility) or in levels of sex hormones in the blood (testosterone, follicle-stimulating hormone, and luteinizing hormone) were found between welders and either of the non-welding control groups (Ref. 83). Exposure to extremely low frequency (ELF) magnetic fields on markers of human fertility was examined in 57 of the male participants (36 welders, 13 non-welding metal workers, and 8 non-metal workers) and 52 of their partners (Ref. 86). An effect of ELF magnetic fields on fertility was not observed.

Spinelli et al. examined the effects of occupation and lifestyle factors on the fertility of 662 couples selected from the general population in Italy (Ref. 175). Differences in the rates of conception between welders and controls were not statistically significant. Thonneau et al. (Ref. 191) examined the relationship between fertility and male occupational heat exposure. The percent of welders' partners who became pregnant within 3 to 6 months was lower than controls, but the differences were not significant.

Harrison surveyed the association between occupation and semen parameter defects among the male partners of 1402 couples who were treated for infertility at three reproduction clinics in Australia (Ref. 78). Three semen parameters (sperm density, sperm motility, and sperm morphology) were assessed and compared with normal population values. The incidence of defects in any of the measured parameters was 48% among the welder/fitters compared with 25% among the patients who were white-collar workers. Bigelow et al. (Ref. 23) examined the re-

lationship between occupational exposures and semen quality using two different statistical approaches: case-control and analysis of continuous variables. A relationship between defects in semen quality and employment as a welder/fitter was observed using the analysis of continuous variables, but not the case-control approach.

Effects on the Newborn. In a case-control study of the association between parental occupation and spina bifida in offspring, Blatter et al. (Ref. 26) found that a significant increase in the risk for spina bifida was associated with low exposure to welding fumes (OR = 1.6, CI = 1.0–2.6) and low exposure to UV radiation during welding (OR = 2.6, CI = 1.2–5.6). The risk for fathering children with spina bifida was not increased among professional welders or metal workers. The investigators attributed this to the much greater use of protective equipment reported by professional welders.

Farrow et al. (Ref. 67) analyzed the relationship between birth weights and occupation in full-term infants born to more than 10,000 women during a 19-month period in Southwest England. Women who had been employed during the first trimester of pregnancy as a welder, as defined by the British 1990 standard occupational classification (SOC) codes, gave birth to full-term infants of normal weight.

Effects on the Immune System

Tuschl et al. (Ref. 195) examined components of the immune system in blood from 30 long-term welders who used GTAW and GMAW to weld stainless or mild steel. A significant difference between the welders and controls was seen only in tests of the function of natural killer cells (a form of lymphocyte that destroys a variety of foreign and tumor cells). Borska et al. (Ref. 29) examined immune function in 19 long-term stainless steel welders who primarily used SMAW. Elevated concentrations of IL1, IgA, and lysozyme and a decrease in IgM and in the numbers of cells capable of phagocytosis were observed in blood from welders compared with agricultural workers. Hanovcova et al. (Ref. 77) evaluated the immune status of stainless steel welders over a 3-year period. SMAW was the major procedure used in the plant but GMAW was also used. Air sampling conducted early in the study showed concentrations of chromium, nickel and manganese that were well in excess of maximum allowable concentrations. At this time, the number of T cells and the concentrations of lysozyme were higher, and the activity of phagocytic cells was lower in blood from the welders than in that from the controls. These parameters approached control values 3 years later after ventilation was improved in the plant.

Biological Monitoring

Chromium. Edme et al. (Ref. 63) examined the relationship between the solubility and valence state of chromium in personal air samples collected during welding and the concentrations of chromium appearing in the welders' urine and blood at the end of an 8-hour work shift. The welding processes examined were SMAW, GMAW, and GTAW of stainless steel and SMAW and GMAW of mild steel. Stainless steel welders using SMAW had the highest urine and blood chromium levels, which was attributed to differences in the soluble chromium content of the fumes.

Lead. Sokas et al. (Ref. 174) determined lead concentrations in blood collected from 264 active and retired Maryland construction workers (198 iron workers and 66 laborers) recruited from four different unions. The mean blood lead concentration was 8.0 µg/dL for the construction workers compared with the geometric mean value for the U.S. population of 2.8 µg/dL. Reynolds et al. (Ref. 157) measured mean blood lead concentrations of 4.7 µg/dL in 459 construction workers identified through trade unions in Iowa and Illinois. Twelve of the 16 construction workers with blood lead concentrations greater than 20 µg/dL were laborers who were engaged in bridge renovation and performed tasks such as welding, cutting, sweeping, and rivet busting. Rodriguez and Gandarillas (Ref. 158) compared blood lead levels of 220 production workers from a shipyard in Northern Spain with those of 40 office workers from the same shipyard. The average blood lead level for the production workers was 12.4 µg/dL and that of the controls was 9.8 µg/dL. Blood lead levels were significantly higher among boilermakers (14.7 µg/dL) and welders (11.9 µg/dL) than controls (9.8 µg/dL).

Manganese. Reygagne et al. (Ref. 156) measured concentrations of manganese in the breathing zone and urine of 30 French railroad track welders who performed SMAW on cross-ties composed of steel containing 13% manganese. While breathing zone concentrations of manganese ranged from 0.3 to 5.8 times the French exposure, urinary manganese concentrations were only slightly higher than those of the general population.

Aluminum. Letzel et al. found that biological half-lives of aluminum in urine from 16 aluminum welders varied widely and ranged from 12.9 to 2,14.9 (Ref. 119). Based on data obtained for all 16 welders, the biological half-life for urinary excretion of aluminum was calculated to be 30.4 days. The half-life was not related to the age of the welders or the duration of previous exposures to aluminum.

Trace Metals. Vasconcelos and Tavares (Ref. 205) monitored the concentrations of six metals in the hair and whole blood of eight male apprentices, mean age 16 years, at a technical-professional school. Mean concentrations of the metals in blood from apprentices and age-matched controls fell within published ranges for reference populations. The mean metal concentrations in the hair of controls and apprentices were similar.

Genotoxicity

Using the micronucleus assay, which detects breaks in chromosomes or loss of whole chromosomes, Burgaz et al. (Ref. 36) determined the frequency of cells with micronuclei in peripheral lymphocytes and in exfoliative cells obtained by swabs of the buccal and nasal cavities of 32 welders. A statistically significant increase in the frequency of micronucleated cells was seen in the lymphocytes and in cells from the nasal cavity, but not from the buccal cavity of welders.

Myslak and Kosmider (Ref. 133) found that sister chromatid exchanges (SCE) occurred more frequently in lymphocytes from 39 stainless steel-welders than in those from controls. A related study by Myslak and Kosmider (Ref. 134) showed that the rates of cell division in cultured peripheral blood lymphocytes from 20 stainless steel welders did not differ significantly from that in controls.

Werfel et al. (Ref. 209) compared the rate of SCE, DNA-protein cross-links, and single strand DNA breakages in lymphocytes collected from 39 chromium- and nickel-exposed welders and from an equal number of aged-matched controls who had no known occupational exposures to carcinogens. Significant increases in the frequencies of DNA single-strand breakages and SCE exchanges, but not DNA protein cross-links, were seen in lymphocytes from welders compared with controls.

Investigations in Animals and Cell Cultures

Metal Fume Fever

Kuschner et al. (Ref. 113) demonstrated that a monocyte cell line released dose-dependent concentrations of TNF into the culture medium 3, 8 and 24 hours after exposure to ZnO and IL-8 at 8 and 24 hours after exposure. The sequential appearance of TNF and IL-8 mimics that observed in human volunteers exposed by inhalation to ZnO (Ref. 25). Based on their findings that $ZnCl_2$ and ZnO caused a dose-related increase in the release of reactive oxygen species (ROS) from cultured human neutrophils, Lindahl et al. (Ref. 120) concluded that both $ZnCl_2$

and ZnO stimulate ROS production by human neutrophils and suggested that this might play a role in the pathogenesis of metal fume fever.

Pulmonary Inflammation

In a battery of assays that examined mechanisms by which welding fumes may produce pulmonary inflammation and injury, Antonini et al. (Refs. 10, 11) showed that intratracheally instilled fumes from SMAW of stainless steel (SMAW-SS) induced a greater influx of neutrophils and significantly more TNF and IL-1 into the lungs than did fumes from GMAW of mild steel (GMAW-MS). In vitro studies conducted with macrophages isolated from untreated rat lungs by bronchoalveolar lavage showed that SMAW-SS fumes were more toxic and produced greater quantities of ROS than did GMAW-SS fumes. GMAW-MS fumes were the least toxic to isolated macrophages. Intracheal instillation of freshly formed GMAW-SS fumes caused a greater inflammatory response in rat lungs than did fumes aged for 1 to 35 days before administration (Ref. 9). Freshly formed welding fume particles were found to have higher concentrations of ROS on their surface than do aged fumes which may be responsible for the differences in their inflammatory properties.

Hexavalent Chromium

Cohen et al. (Ref. 46) found that the retention and distribution of chromium in the lungs is dependent on its solubility and that the amount of chromium retained in the lungs may be altered by concomitant exposure to ozone. Tests with alveolar macrophages isolated from treated rats showed that solubility is important in determining the immunomodulatory effects of inhaled Cr(VI) compounds on pulmonary macrophages and that co-inhalation of ozone does not modify these effects (Ref. 47).

Lipid Peroxidation and Dopamine Oxidation

Hudson et al. (Refs. 88, 89) tested the potential of welding fume components to oxidize dopamine or lipids in cell-free extracts of brain tissue. All the fume extracts inhibited lipid peroxidation and enhanced dopamine oxidation. Rates of dopamine oxidation were higher with extracts of fumes generated with flux-cored electrodes compared with solid electrodes and with fumes generated using a carbon dioxide shielding gas compared with an argon shielding gas. The authors stated that the ability of welding fume solutes to oxidize dopamine to melanin is consistent with neurotoxic activity.

Distribution of Inhaled Iron

Noda et al. exposed rats to freshly formed welding fumes 3 days a week, for 3 months (Ref. 141). Sixteen weeks after the start of exposures, regenerative changes, accompanied by iron deposits, were seen in some cells in the kidneys.

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Effects of Welding on Health, XII

Section One
The Exposure

1. Analytical Methods

1.1 Inductively-Coupled Plasma Mass Spectroscopy (ICP-MS). Apostoli et al. (Ref. 12) measured the concentrations of metals in fumes produced by eight welding processes (SMAW of stainless steel, mild steel, or nickel; GMAW of mild steel or aluminum, submerged arc welding, laser welding, and brazing). Inductively-coupled plasma mass spectroscopy (ICP-MS) was used for these analyses because it can detect very low concentrations of metals and can measure a number of metals simultaneously with high precision. The concentrations of the various metals in the fumes were verified with standard analytic procedures. The number of metals detected ranged from five in fumes from GMAW of aluminum to 23 in fumes from SMAW of mild steel. Sixteen metals were detected in fumes from SMAW of stainless steel. In one experiment, metal concentrations were measured in samples collected close to the weld and also at a point 2 meters from the weld. The relative concentrations of individual metals varied in fumes collected at these two distances, leading the authors to conclude that the hazards associated with indirect exposures may differ from those of direct exposures to welding fumes.

Trace metals in biological fluids can also be accurately and sensitively measured using ICP-MS. Guidotti (Ref. 75) described the use of this method for obtaining trace element profiles on selected workers at the Trace Elements/Environmental Toxicology Laboratory at the University of Alberta Hospitals. The aim of that work is to build up a database of trace metal concentrations found in blood, serum, and urine of workers from different occupational settings and to explore the potential clinical role of such analyses. Guidotti pointed out that ICP-MS is especially useful for measurement of metals that are present in very low quantities in biological fluids and that elements such as iron, calcium, and magnesium, which are found in greater abundance in blood and urine, would best be determined by traditional analytical methods.

1.2 Aluminum. The most widely used technique for determination of aluminum in urine and serum is graphite furnace atomic absorption spectrometry, but this technique suffers from problems with contamination, matrix effects, and standardization methods. Valkonen and Aitio (Ref. 197) described a method to address these problems using platform atomization in pyrolytically coated graphite tubes. Contamination of the urine samples was avoided by collecting samples outside the work area after showering and using sampling vials that had been exhaustively cleaned.

The method was applied to serum samples collected from 12 women and 9 men and to urine samples from 28 women and 16 men who had no occupational exposures to aluminum. The detection limits for aluminum were 0.02 micromole per liter (µmol/L) for serum and 0.07 µmol/L for urine. The mean concentration of aluminum in a healthy, non-exposed population was 0.06 µmol/L (S.D. = 0.03, range 0.02–0.13) in serum, and 0.33 µmol/L (S.D. = 0.18, range 0.07–0.82) in urine. This method was used over a 3-year period to determine aluminum concentrations in urine samples collected during routine occupational health examinations from 3312 Finnish workers, who were occupationally exposed to aluminum and were primarily aluminum welders. Urine samples were collected on Monday mornings. The average concentration of aluminum in urine samples collected for biological monitoring was 1.4 µmol/L.

1.3 Chromium. Fumes generated by welding stainless steel contain trivalent chromium [Cr(III)] and hexavalent chromium [Cr(VI)]. Since they differ markedly in their toxicity, Cr(VI) is a known human carcinogen], it is important to accurately quantify the concentrations of both species of chromium in welding fume samples. Great care must be taken during extraction and analysis of chromium from welding fumes because Cr(VI) can be reduced by conditions of low pH to the less toxic Cr(III) and at high pH, in the presence of oxygen, Cr(III) can be converted to Cr(VI). The Standards, Measurements and Testing Programme of

the European Commission conducted an interlaboratory study to develop reference materials for the purpose of providing laboratories with a means to check and improve analytical procedures (Refs. 43, 151).

In 1994, Dyg et al. (Ref. 62) developed a method to produce filters uniformly loaded with welding fumes typical of those normally collected by personal monitoring of stainless steel welders. This method was used to prepare a batch of filters loaded with fumes generated by SMAW of stainless steel, each containing approximately 100 µg Cr(VI), for use in the interlaboratory comparison. Ten European laboratories participated in the certification of the reference materials. Each laboratory analyzed the chromium content of at least five filters on a minimum of two separate days. Participating laboratories used various spectrophotometric methods including electrothermal atomic absorption spectrometry, flame atomic absorption spectrometry, inductively coupled plasma atomic emission spectrometry, and isotope dilution mass spectrometry (IDMS). The results obtained by the different laboratories were in good agreement, and the certified values for total chromium and Cr(VI) in the filters loaded with welding fumes were established by taking the average of the mean concentrations obtained at each laboratory.

2. Fume Composition

The thermal ionization IDMS method used in the European Commission's interlaboratory chromium study was developed by Nusko and Heumann (Ref. 143). In an independent study, these investigators used IDMS to determine the concentrations of trivalent, hexavalent, and elemental chromium in samples of fumes generated by SMAW, GMAW, and GTAW of stainless steel (Figure 1).
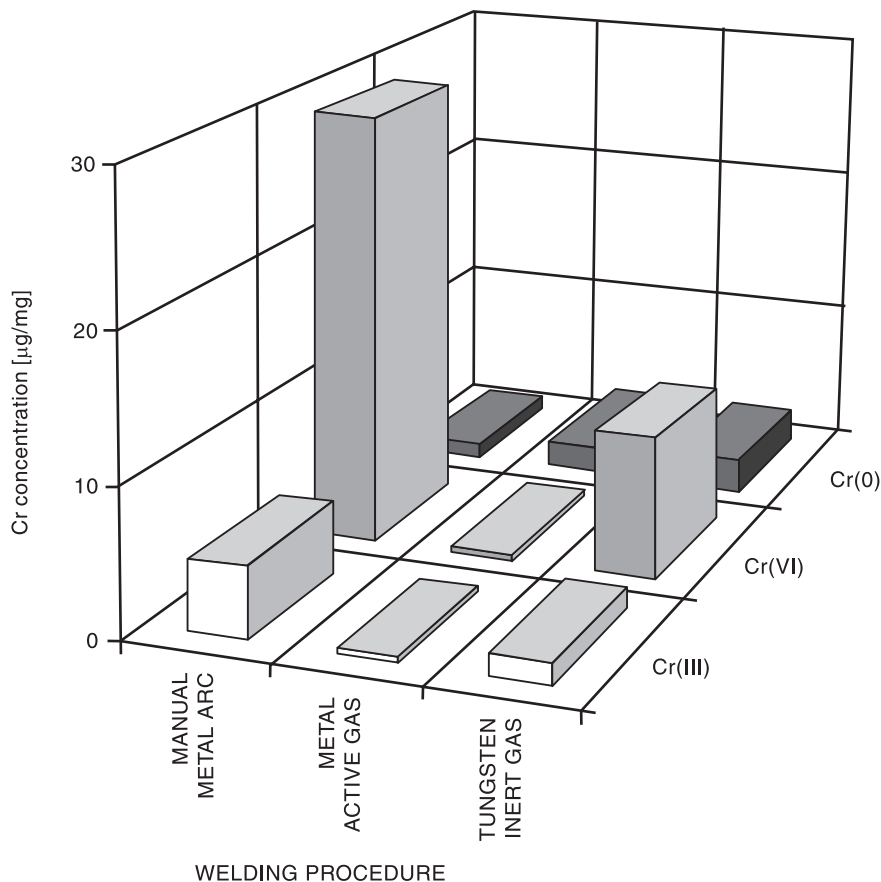
From Nusko and Heumann, Ref. 143.

**Figure 1—Cr(III)/Cr(VI) Speciation in Fumes
Generated by SMAW, GMAW, and GTAW of Stainless Steel**

The highest concentrations of Cr(VI) were generated by SMAW and GTAW of stainless steel (29.1 µg/mg and 9.3 µg/mg, respectively). Elemental chromium was present in fumes generated by all three processes and its concentration was highest (1.9 µg/mg) in fumes generated by GMAW.

Dennis et al. (Ref. 57) investigated the effects of flow rate and welding voltage on the production of Cr(VI), ozone, and ultraviolet (UV) radiation during GMAW. Without a shielding gas, there was no detectable ozone, and relatively little UV radiation was produced. When the shielding gas was introduced, ozone, UV, and Cr(VI) levels increased as the gas flow rate increased. The increase in all three components (UV, Cr(VI), and ozone) was inversely related to the fume formation rate (FFR), which declined rapidly and then more slowly as the flow of the shielding gas increased (Figure 2). The increase in ozone with declining FFR was attributed to increased levels of UV light, which activates ozone generation, and decreased levels of metal oxide fumes, which catalyze the reduction of ozone. The UV intensity varied as the voltage was increased from 15 V to 35 V and appeared to reflect changes in the mode of metal transfer from the arc. The UV levels were maximal at higher voltages where the spray mode is dominant, whereas ozone concentrations were highest at lower voltages (17 V) where the dip mode predominates. Cr(VI) concentrations were highest in the voltage range 20–25 V where the globular mode predominates.

3. Workplace Exposures

3.1 Particle Size. Particle size, chemical composition, and concentration are the primary determinants of health effects associated with aerosols. The size and shape of the particle determine the location in the respiratory tract where it may be deposited. Inhalable particles have an aerodynamic diameter equal to or less than 100 microns (µm) and can enter the respiratory tract through the mouth or nose. Thoracic particles are less than 25 µm in diameter; particles between 10–25 µm are deposited primarily in the nasopharyngeal region. Respirable particles are less than 10 µm in diameter and can be deposited in
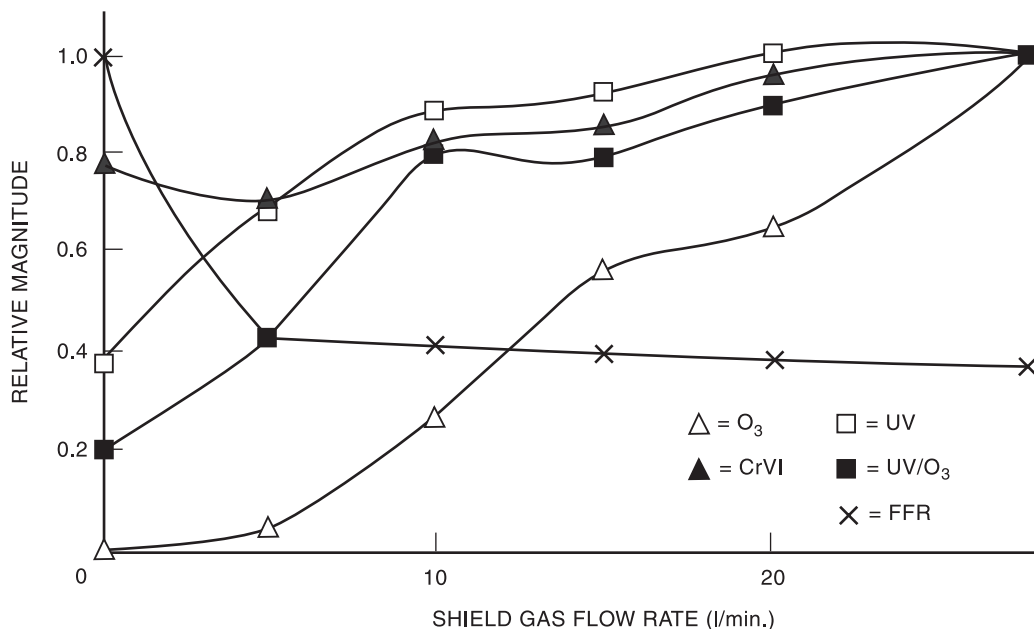
O_3 = Ozone
FFR = Fume formation rate
UV radiation was measured by two different procedures, symbolized as UV and UV/O_3. Welding was done with an automatic welder using a shielding gas containing 93% argon and 5% CO_2.

From Dennis et al., Ref. 57.

Figure 2—The Effect of Shielding Gas Flow Rate on the Relative Magnitude of UV, Ozone, Cr(VI), and Fume Formation Rate under Standard Welding Conditions

the trachea and bronchi. Fine particles smaller than 3 μm in diameter are among the most hazardous because they can be deposited in the gas exchange areas of the lungs (the alveoli). Particles in this size range can be the most difficult to remove from the workplace environment by conventional filtration or scrubbing and may tend to accumulate to high levels in factories where they are generated (Ref. 166).

Using a Micro-Orifice Uniform Deposit Impactor (MOUDI), Sioutas (Ref. 166) compared the atmospheric concentrations of fine particles in the areas of four different processes (heat treating and brazing, welding, machining, and grinding) in an automotive plant. As expected, they found that grinding produced the coarsest particles. The concentration of fine particles was highest in the aluminum machining area (mean ± SD: 210.9 ± 4.2 μg/m^3) followed by that in the welding area (167.8 ± 14.0 μg/m^3). The size distribution of the welding parti-

cles was found to be bimodal, with peaks at approximately 0.2 μm and 0.8 μm (Figure 3). The median diameter of the welding particles was 0.5–0.6 μm.

Okamota et al. (Ref. 145) examined the ratio of the mass of respirable to inhalable particulate (R/I, expressed as a percent) in area samples collected at 1644 workplaces in Japan where grinding, powder handling, metal casting, welding, and miscellaneous activities such as wood or metal cutting and production of metal leaf were performed. Inhalable particles were collected with a stationary sampler to which an elutriator was attached to collect respirable particles equal to or less than 7 μm in diameter. A substantial variation in the R/I ratio was found among the different types of workplaces examined. The ratio was highest in shops where welding took place (53 ± 19%) and lowest in foundries (23 ± 16%). The high ratio for the welding workplace reflects the large proportion of fine particles less than 1 μm in diame-
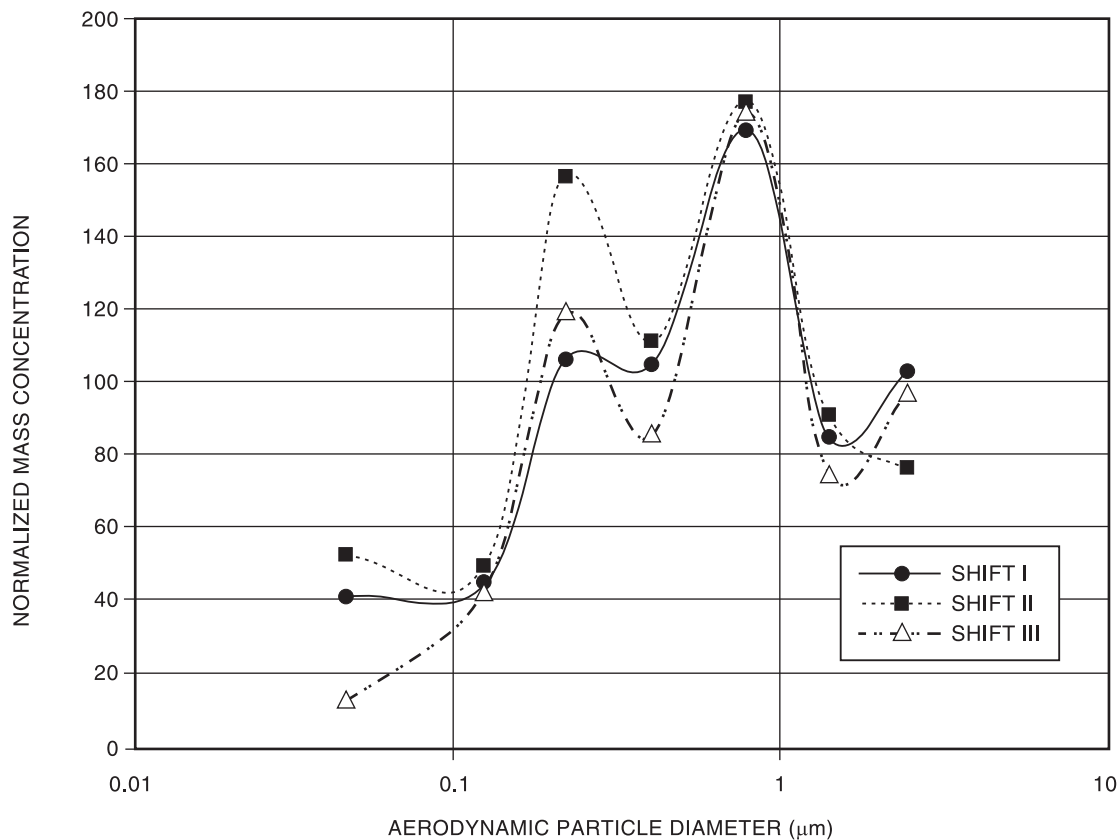
Analyses were conducted on samples collected during three work shifts throughout a 24-hour period.
Data from Sioutas, Ref. 166.

**Figure 3—Particle Size Distribution of Airborne Particles
Collected in the Welding Area of an Automotive Plant**

ter in welding fumes. Because of the high concentration of fine particles generated during welding, the authors concluded that it is essential to measure the concentration of respirable particles, not just inhalable particles, in order to demonstrate compliance with certain workplace standards.

3.2 Sampling Procedures. A new European/International Standard (ISOprEN 10882-1) for sampling of airborne particles and gases generated during welding and allied processes was proposed by the European Committee for Standardization in 1996. Although the draft standard specified a method for the gravimetric determination of welding fume and required that samplers collect the inhalable fraction of the fume, it did not specify the type of sampler to be used. Chung et al. (Refs. 38, 39, 44) evaluated the standard and found that the allowable choices of samplers and sampling procedures could lead to an over- or underestimation of fume exposures. They compared the results obtained with different sampling procedures allowed by the proposed standard and evaluated the influence of these variables on potential exposure to welding fumes generated by GMAW and FCAW of stainless steel and mild steel and by GMAW of aluminum. The parameters examined were the effects of (1) using different samplers, (2) positioning the sampler on different sides of the face or on the lapel, (3) sampling welding fumes in an environment containing grinding dusts, and (4) the use of fume analysis data provided by the manufacturer rather than direct determination of the fume composition. For these studies, welding was performed with a test rig that permitted lengthy periods of fume generation. The samplers were placed on a life-size mannequin with realistic facial features. The mannequin was positioned over the weld in a manner representing a right handed welder at work; breathing through the mouth was simulated with a pump.

Five different sampling devices for inhalable dust were tested by placing them in the breathing zone of the mannequin. The devices included four that are in general use in Europe; the fifth was a newly designed sampler (Ref. 45) that used a porous foam plug to partition the respirable and non-respirable fractions of the sampled air. It was found that all the samplers collected approximately equal amounts of fume and that the exposures measured by the five samplers were not significantly different from each other. The quantity of fumes collected by the samplers was about 25% higher than that collected through the mouth of the mannequin.

Placement of the sampler on the right or left side of the mannequin's face or under the chin yielded variable results depending, in part, on the presence and strength of drafts. The investigators recommended that the sampler be placed on the side of the face where fume concentrations were visibly highest. The quantities of fumes collected when the sampler was placed on the lapel were not in agreement with those collected in the breathing zone. Higher or lower values were obtained with the lapel sampler, depending on its orientation to the fume source and the presence or absence of drafts. Based on these observations, the use of lapel sampling for welding fumes was not recommended.

Finally, the draft standard allowed concentrations of fume constituents provided by the manufacturer's Material Safety Data Sheet to be used in lieu of analyzing individual components of collected fume samples. Finally, the draft standard allowed the concentrations of fume constituents provided by the manufacturer's Material Safety Data Sheet to be used in lieu of analyzing individual components of collected fume samples. Chung et al. evaluated this aspect of the standard by comparing the fume composition provided by the manufacturer with that determined by analysis of metals in fumes collected in a fume box and with the composition of fumes collected by samplers placed on the mannequin during GMAW of stainless or mild steel and FCAW of stainless steel. Chung et al. evaluated this aspect of the standard by comparing the fume compositions provided by the manufacturer with their own analyses of fumes collected during GMAW of stainless or mild steel and FCAW of stainless steel. Discrepancies were found for the concentrations of one or more of the metals in each of the three data sets. It was concluded that reliance on data sheets for fume composition could lead to underestimation of exposure to fumes from some welding processes.

For GMAW of mild steel, the composition determined by analysis of fume collected on samplers and the composition provided on the manufacturer's data sheet were similar (Ref. 45). For FCAW and GMAW of stainless steel, however, differences in the chromium content were observed among the fume composition provided on the data sheet, the analyses of bulk fume samples collected in the fume box, and the analyses of fumes collected with the samplers (Ref. 38). Reliance on the data sheets for fume composition would have led to underestimation of exposure to chromium.

3.3 Iron Oxide. Records of inspections conducted by the Occupational Safety and Health Administration (OSHA) are maintained in its computerized Internal Management Information System (IMIS) database. Using data obtained from IMIS records of OSHA inspections conducted from 1979 to 1989, Gomez examined the effects of plant size, passage of time, and other variables on levels of personal exposures of battery manufacturing workers to lead, dry cleaners to perchloroethylene, and welders to iron oxide (Ref. 74).

Exposures exceeding permissible limits were most often recorded among the battery workers, many of whom had mean lead exposures up to three times higher

than the OSHA industry lead standard of 0.05 mg/m^3. For dry cleaners, there were 147 observations of exposures to perchloroethylene, with a geometric mean well below the OSHA Permissible Exposure Limit (PEL) and the American Conference of Governmental Industrial Hygienists' (ACGIH) Threshold Limit Value (TLV). The welders included in the analysis used SMAW exclusively and worked in the manufacture of construction machinery or fabricated plate work, boilers, and truck and bus bodies. A total of 1452 exposure measurements were present in IMIS for welders who met these criteria. The mean 8-hour time weighted average (TWA) exposure to iron oxide for all the welders was less than 2.5 mg/m^3, compared with the OSHA standard of 10 mg/m^3 and the TLV of 5 mg/m^3.

Over the 10-year study period, exposures to lead in the battery manufacturing industry and to perchloroethylene in the dry cleaning industry declined, but levels of exposure of welders to iron oxide remained unchanged. The size of the company, as measured by the number of employees, was a clear indicator of lead exposures in the battery plants; the intensity of the lead exposures was inversely related to the size of the plant. The opposite effect was seen for dry cleaners, for whom there were nonsignificant indications that the smaller companies had lower exposures than the larger ones. No relationship between the size of the plant and the intensity of exposures was found for welders. The presence or absence of union representation at the plant was not associated with exposure levels of workers in any of the three industrial groups.

3.4 Lead. High exposures to lead can occur during demolition work where cutting, heating, or otherwise disturbing surfaces coated with lead-based paints can release lead as particles or vapors. Jacobs (Ref. 93) surveyed lead levels in personal air sampling data entered by OSHA compliance officers into the IMIS database for workers in the construction industry during the years 1984 through 1988. He found that lead levels in 66% of the 38 personal samples collected from workers in bridge, tunnel, and elevated highway construction and 67% of the 178 samples collected from workers in wrecking and demolition were greater than 200 μg/m^3, which was the OSHA PEL in effect for the construction industry at the time the samples were collected.

Nelson and Kaufman (Ref. 138) surveyed selected non-construction businesses in Washington State to determine the number of workers with potential lead exposure. Of the 1340 employers who responded to mailed questionnaires, 789 indicated that lead was used in their businesses. Many plants engaged in more than one type of activity with lead exposure. The most commonly reported activities with lead exposure (and the percent of employers of plants with lead exposures reporting these

activities) were soldering (46%), auto body repair (30%), scrap metal handling (20%), sanding, and cutting or welding surfaces coated with leaded materials (20%). Forty-five percent of the 789 employers with lead exposures in their plants reported being familiar with the provisions of the Washington State lead standard. Awareness of and compliance with the standard increased with the size of the plant and with the presence of labor unions representing the workforce.

3.5 Dioxins. The term dioxin refers to a class of highly toxic chemicals that share a similar chemical structure and a common mechanism of toxicity. This class includes polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). Dioxins are persistent and accumulate in the body fat. Their health effects include changes in hormone systems, the skin disease chloracne, and cancer. Dioxins form during combustion in the presence of chlorinated organic compounds. Based on the possibility that conditions for their formation may occur during thermal processes such as cutting or welding of contaminated metals, Menzel et al. (Ref. 131) measured exposures to dioxins during thermal oxygen cutting of clean and contaminated metals at three demolition sites, ten scrap metal reclamation sites, and three steel production plants.

Dioxin levels in six of seven personal samples collected during thermal oxygen cutting at the demolition sites exceeded the German workplace threshold limit value (the TRK-Wert) of 50 picograms/m^3 (pg/m^3) for the PCDDs and the PCDFs. Most of the pieces processed (e.g., steel constructions, high-pressure pipes, boilers) were painted but were free of grease and oil. The materials processed at the scrap metal reclamation sites included large containers and heavy duty machines that were usually painted and were often greasy and oily. Dioxin levels in 7 of the 14 personal samples collected exceeded the TRK-Wert, even though the work was done in the open air. The dioxin concentrations in area samples collected in the vicinity of open air thermal oxygen cutting were much lower than in the personal samples and were all below the TRK-WERT, but were still much higher than ambient open air values. Dioxin levels in the six personal air samples taken during thermal oxygen cutting in production plants where clean steel was handled were substantially lower than the TRK-Wert. Dioxin levels were also low in samples collected during GMAW of clean steel during mass production of bridge components.

Bioaccumulation of dioxins was evaluated by measuring dioxin levels in blood from men who had been working as welders or cutters for at least one year. Welders (n = 10)[1] and thermal oxygen cutters (n = 7) of clean

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1. n = Number of subjects.

stainless steel had levels approximately 40% higher than those of controls (white collar workers) and the general German population, but the differences were not significant. Blood dioxin levels, however, were 2.5 times higher than controls in men who worked as thermal oxygen cutters (n = 17) at scrap metal and demolition sites; this difference was statistically significant (p < 0.05). For thermal oxygen cutters, there was a direct relationship between years of experience and blood dioxin levels (r = 0.79 at p < 0.001)[2], which provides further evidence for a meaningful association between the body burden of dioxin and occupational exposure. Menzel et al. concluded that dioxin exposures are not associated with welding of virgin steel and are probably not associated with thermal oxygen cutting of virgin steel, but dioxins can be generated during thermal oxygen cutting of contaminated materials. The investigators did not examine dioxin levels during welding of contaminated metals and they stated that this needs to be tested.

3.6 Ventilation. Rappaport et al. (Ref. 155) assessed personal exposures to total fume, manganese, nickel, and chromium among boilermakers, ironworkers, pipefitters and welder-fitters at nine construction sites in the U.S.A. Workers were selected for monitoring when they were scheduled to be working with "hot processes" for at least 60 consecutive minutes. Boilermakers and ironworkers were exposed to much higher levels of total particulate and manganese than pipefitters, and welder-fitters. Limited data indicated that welder-fitters experienced exposures to higher concentrations of nickel and chromium than pipefitters. Other workers had minimal or no exposure to these metals. Use of local exhaust ventilation reduced exposure, and exposure was increased when welding was continuous rather than intermittent. For welder-fitters, exposure to total particulate during intermittent welding was 1.7 mg/m^3 when ventilation was used and 2.9 mg/m^3 when it was not. During continuous welding, the reduction in total particulate resulting from use of local exhaust ventilation was very slight: 3.1 mg/m^3 without ventilation and 2.9 mg/m^3 with ventilation.

Bellido-Milla et al. (Ref. 21) determined the concentrations of total fumes and six metals (Fe, Mn, Zn, Cu, Cr, Ni, and Cd) in breathing zone samples collected from 140 welders in a shipyard in Puerto Real, Spain. Using the statistical method of analysis of variance, the authors were able to demonstrate that welding in an enclosed space, welding in a sitting position, and using automatic

welding machines significantly increased breathing zone concentrations of the metals and total fume. In accord with the findings of Rappaport et al., the use of local exhaust ventilation during continuous welding did not substantially reduce exposure to welding fumes or their constituent metals. Bellido-Milla et al. observed that the welders properly positioned the fume extractors when they began welding, but as they worked they moved without relocating them, which substantially reduced the benefits that may have been achieved by using local exhaust.

Vernez et al. (Ref. 207) surveyed particulate exposures among a population of 142 metal workers employed by eleven companies in the canton of Vaud in Switzerland. Grinding, welding, or cutting was performed by 70% of the workers on a daily basis. The remainder occasionally performed these tasks. About 70% of the workers who participated in the study had more than 10 years' experience welding. Aerosols were collected during work with mild steel, aluminum, and stainless steel. During welding and cutting, the 8-hour TWA exposure standard (Valeur moyenne d'exposition or VME) for inert dusts of 6 mg/m^3 was frequently exceeded. About a third of the workstations at which measurements were taken were equipped with local exhaust. The concentrations of particulate measured at the stations provided with local exhaust were about half those in stations without it. No details were provided about the type of welding conducted or whether welding was intermittent or continuous.

4. Thorium

Incorporation of small amounts of thorium into tungsten electrodes facilitates starting the arc, improves arc stability and, by preventing the electrode tip from melting, decreases the rate of electrode degradation and reduces the risk of weld contamination (Ref. 94). Because all of its isotopes are radioactive and all thorium products emit alpha, beta, and gamma radiation, aerosols formed during welding or grinding of thoriated electrodes represent a potential health hazard to welders who use these techniques. Laroche et al. (Ref. 117) measured the levels of radioactivity in electrodes containing about 2% thorium, supplied by two French companies. They found that the purified thorium used in electrodes has a different mixture of thorium isotopes and daughter products than is present in the naturally-occurring mined product. For use in assessing the health risks associated with the use of thoriated electrodes, the total alpha, beta, and gamma radioactivity of the thoriated electrodes were measured using various techniques. Gamma spectrometry, photographic dosimetry, and thermoluminescence

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2. r = Correlation coefficient, a number between –1 and 1 that measures the degree to which two variables are linearly related. The closer that r is to 1, the more nearly perfect is the linear relationship between the two. A negative r indicates an inverse relationship. A value of r close to 0 indicates that there is no linear relationship between the variables.

dosimetry were performed directly on the intact electrode; alpha spectrometry was performed on samples of the electrode; and swabs of the electrodes were taken to provide a measure of the removable radioactivity on the surface of the electrodes. From these measurements, LaRoche et al. calculated that the annual radiation dose received by a worker who spends 2,000 hours per year grinding and welding with thoriated electrodes of the largest diameter studied (4.8 mm, 3/16 inch) would be 1.3 rem, equivalent to 13 millisievert (mSv)[3]. This was compared with an estimated annual dose of 0.9 rem reported to be received on the hands of thorium miners. The authors noted that their annual dose estimates were higher than others in the literature because previously reported estimations did not take into consideration the removable radioactivity on the surface of the electrodes. The annual limit for exposure of radiation workers set by the U.S. Nuclear Regulatory Commission (NRC) is 5 rem for whole body exposure (Ref. 142). The doses calculated by LaRoche et al. were well below this limit.

Ludwig et al. (Ref. 125) measured levels of radioactivity in breathing zone samples collected during welding and grinding of thoriated electrodes in several German workplaces where GTAW was used. Alpha radiation in the grinding samples was measured directly, using a proportional counter that was able to discriminate among the three radioisotopes of thorium (^{232}Th, ^{230}Th, and ^{228}Th). Gamma spectrometry following neutron activation was used for the determination of radioactivity in samples of welding aerosol. Data were obtained on the exposures of 26 welders during both welding and grinding, and were used to derive an estimate of the total annual thorium exposure of each welder. Based on measurements of ^{232}Th activity in the breathing zone, which the authors related to total thorium intake, five of the welders in this study were estimated to have annual exposures in excess of the annual limit (greater than ten times the limit in one case) of 0.1 rem (1 mSv) for inhaled thorium recommended by the International Commission on Radiological Protection (ICRP) for the general population. However, the welders' exposures were well below the ICRP occupational standard of 5 rem in any one year or 2 rem (20 mSv) per year over a 5-year period. The investigators found that the use of local exhaust ventilation reduced the total exposure received by individual welders; but the position of the welder's head in relation to the emission source was considered to be the main determinant of the welder's exposure. This finding is in agreement with other studies of the effects of the welder's position upon exposure (Refs.

20, 204). Ludwig et al. made several recommendations for reducing the radiation hazard from thoriated electrodes, including elimination of thorium from the electrodes, use of local exhaust ventilation, routine personal monitoring, regular dust removal from the workplace, and instructing the welder to keep his head out of the welding fumes.

Jankovic et al. (Ref. 94) measured breathing zone concentrations of thorium outside and within the welding helmet while welders were performing GTAW or were grinding thoriated electrodes. Thorium aerosols were generated at a much greater rate during grinding with thoriated electrodes than during welding with them. Initial sharpening of the electrode produced about 20 times more radioactive aerosol than did subsequent re-sharpening. Sharpening the electrode to a more acute angle increased the total aerosol generated per sharpening episode, and sharpening with a belt also led to greater aerosol production than did sharpening with a wheel. This latter finding contradicts reports by other investigators (Ref. 51) that thorium exposures from wheel grinding exceed those from belt grinding. The respirable fractions represented 60% and 45% of the aerosols generated during sharpening and welding, respectively.

Welding was performed in a welding booth. Sampling was performed inside and outside of the helmet, at a distance of about 12 inches from the weld, in accordance with American Welding Society guidelines (Ref. 14). The sampling results are shown in Table 1. When only dilution ventilation (approximately two air changes per hour) was used, there was about a sevenfold reduction in the concentration of radioactive aerosol inside the helmet, compared with samples collected outside the helmet. When local exhaust ventilation was used, the radioactive aerosol concentration outside the helmet was reduced fortyfold. The authors observed that incoming air passed around the welder's body, creating eddy currents which could have caused portions of the fume to enter beneath the helmet. This could explain their finding that, when local ventilation was used, the average concentration of radioactivity from thorium inside the helmet was greater than the average concentration outside the helmet (though it was still lower than the average concentration measured inside the helmet when local ventilation was not used). A derived air concentration[4] (DAC) for ^{232}Th of 1 picocurie (pCi)/m^3 was determined by applying the NRC annual limit to a 2,000-hour work year at a breathing rate of 1.2 m^3/hour. The breathing zone concentrations of thorium during welding were well

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3. Radiation dose equivalent is usually expressed in terms of rem in the U.S. LaRoche et al. reported their data in terms of millisievert (mSv), which is the International System (SI) unit. One rem is equal to 10 mSv.

4. The Derived air concentration (DAC) is an NRC definition referring to that concentration of a radionuclide which, if breathed for 2,000 hours, would result in inhalation of one annual limit on intake (ALI).

Table 1
Breathing Zone Radioactivity from Sharpening and Welding with Thoriated Electrodes

Activity	No. of Samples	Ventilation[1]	Sampler Location[2]	^{232}Th Activity (pCi/m^3)	
				Mean	Std. Dev.
Belt sharpening	4	Dilution	(No mask worn)	2.2	2.1
GTAW	4	Dilution	Outside	0.04	0.06
GTAW	2	Dilution	Inside	0.006	0.004
GTAW	4	Local exh.	Outside	0.001	0.00008
GTAW	5	Local exh.	Inside	0.003	0.001

Notes:
(1) Dilution ventilation was approximately two air changes per hour. Local exhaust (Local exh.) ventilation was about 75 feet/minute at the site of the weld.
(2) Samplers were located inside or outside the helmet.

Data from Jankovic et al., Ref. 94.

below the calculated DAC. The excursions above the DAC that were observed during grinding of the electrodes would not be expected to result in annual exposures above the NRC limit because the workers spent only two to four brief periods a day in this activity. Thus, three groups of investigators, Laroche et al. (Ref. 117), Ludwig et al. (Ref. 125), and Jankovic et al. (Ref. 94), estimated welders' annual exposures to thorium to be well below the limits for occupational exposure set by both the NRC and the ICRP.

5. Electromagnetic Radiation

Tenkate and Collins (Refs. 184, 186) used polysulfone film dosimeters to estimate the daily doses of UV radiation received by the eyes and skin of welders and nearby workers in a metal fabrication workshop. Ten welders, four boilermakers, and six non-welders who worked in the vicinity of the welders participated in the study. The boilermakers' tasks included making tack welds, grinding, cutting, and minor fabrication of precut pieces. The welders primarily used GMAW and the boilermakers used SMAW. The welders wore helmets, the boilermakers wore helmets when welding and safety glasses at other times; all others wore safety glasses.

Potential eye and skin exposures of welders and nearby workers were measured by placing polysulfone film badges on clothing in the chest area, on the inside and outside of the welding helmet, and on the bridge and sideshields of safety glasses. The UV dose received by the eyes was measured with badges attached to the headband of each helmet, directly above the eyes and nose. All doses measured by body, ocular, and environmental badges were above the ACGIH maximum permissible exposure (MPE) limit of 3 mJ/cm^2 for UV radiation. The ocular exposures measured for the welders and boilermakers were four and five times the MPE, respectively. Exposures on the outer surface of safety glasses of non-welders were many times higher than the MPE (26–68 mJ/cm^2). Badges placed on the clothing indicated that unprotected areas of the body would receive doses well in excess of the MPE.

The investigators noted that while ocular exposures were substantially higher than the MPE, there were no obvious signs of UV-related injury to the eyes. This they attributed to the safety factors built into the MPE. The MPE was developed to protect against photokeratitis (welder's flash or arc eye) which can be caused by doses of 4 to 14 mJ/cm^2, and erythema (reddening of the skin) which can be caused by UV doses of 6 to 30 mJ/cm^2, depending on individual sensitivity. Thus, the MPE has a built-in margin of safety of up to five- and tenfold for photokeratitis and erythema, respectively, which the authors state is sufficient to protect all but those individuals most sensitive to the effects of UV light. In a similar study published in 1996, Knuschke and Barth (Ref. 109) found that ocular exposures measured by polysulfone badges at the headband of the helmet ranged from 7.5 to 70 times the MPE. Some of the workers in that shop had complained of eye problems which may have been related to exposures that exceeded the margin of safety of the MPE.

The ocular exposures of the welders measured in these studies indicate that UV radiation can infiltrate the welding helmet. Tenkate and Collins (Ref. 185) investigated the elements of helmet design and the angles of incident radiation that allow UV radiation to enter the helmet and reflect into the eyes. Helmets of four different designs were studied: standard helmet with front lift cover, standard helmet with longer-than-normal fiber

glass shield, narrow rectangular helmet with larger-than-standard filter plate, and narrow, rectangular helmet with a photochromic filter. A plaster model of a head with realistic facial features was fitted with a helmet and exposed to a collimated beam of UV radiation from a xenon-arc lamp. The UV source was held in a fixed horizontal or vertical position and the angle of incidence was varied by rotating the head form. The UV dose reaching the eye was recorded by an ultraviolet detector that was fitted into the eye socket of the head form.

None of the helmets completely protected the eyes from exposure to UV radiation. The primary routes of UV infiltration were from the top and the back of the helmet. No radiation entered the eye when the UV beam was in a vertical position beneath the bottom front of the shield. When the UV beam was in a horizontal orientation, some UV radiation entered through the opening between the edge of the shield and the side of the face. UV radiation infiltrating through this area could be reflected off a corner section of the filter plate into the eye. The angles of entry and the intensity of radiation entering the eye were the same for all four helmets tested with the horizontal orientation.

When the UV beam was in a vertical position above the head, UV radiation could enter from behind the head through the gap between the back of the top edge of the shield and the top of the head form. Of the four helmets tested, this gap was largest with the standard helmet, allowing radiation to enter through the greatest range of incident angles. The narrow helmet with the larger-than-standard filter plate permitted the greatest intensity of light to reach the eye because of its greater reflective surface area.

The interior surface of the filter plate was the only surface in any of the helmets from which substantial levels of infiltrating UV could reflect into the eyes. The authors suggested that low reflectance coatings on the inner surface of the filter plate could reduce reflection of UV into the eye. The intensity of UV reaching the eye was greater when the UV source was overhead than when it was behind the head. Such exposures could arise from welding in an enclosed, highly reflective environment, such as inside a metal tank, or from direct or reflected exposure from surfaces of nearby welding operations. These exposures could be reduced by changes in the design of the helmet, provision of curtains around welding operations, and use of surfaces with low reflectance in the work area.

6. Electromagnetic Fields

Exposure to extremely low frequency (ELF) electromagnetic fields (EMF) is measured in terms of magnetic flux density, which refers to the strength of the magnetic field over the area of exposure. The international standard unit of magnetic flux density is the tesla (T), and most occupational exposures are in the range of microtesla (μT). In a study of electrical workers in California, average workday exposures to magnetic fields ranged from 0.17 μT for electrical engineers to 2.36 μT for electric power line workers (Ref. 123). Welders are generally considered to be among the workers most highly exposed to ELF magnetic fields. The welder must often position welding cables, which carry hundreds of amperes of current, very close to his body. This current generates ELF magnetic fields that have been calculated to be on the order of millitesla a few centimeters from the welding cable (Ref. 170). Studies that used personal exposure monitors to measure instantaneous and cumulative magnetic field strength throughout a work shift have indicated that welders' average workday exposures are much lower than those calculations suggest (Ref. 206). Exposures generally range from 0.5 to 2 μT, but values in the range of 20 μT have been recorded (Ref. 170).

In a study designed to relate the welding process and the time spent in active welding to the intensity of exposure, Skotte and Hjollund (Ref. 170) fitted 50 metal workers from the Danish Metalworker Union and 15 full-time arc welders in a Danish shipyard with exposure meters that measured EMF intensities from 0.01 to 7,000 TμT. The metal workers were selected at random without regard to welding duties; the shipyard welders were purposefully selected to represent the full variety of arc welding processes used in the shipyard. The shipyard measurements were taken during 8 consecutive work hours. Measurements of the metalworkers' exposures were taken for 3 full workdays. Each participant kept records of the time spent using different welding processes and the type and magnitude of the electric current employed. Participants also recorded the time spent using other sources of ELF magnetic fields, such as electrical tools, resistance welding equipment, and induction heaters.

The metalworkers reported welding an average of 5.8% of the time, and half of them did not weld at all during the 3-day monitoring period. All of the shipyard welders performed welding activities during their monitoring period and, on average, 56% of the 8-hour measurement period was spent in welding and associated activities. The respective mean and median of the 8-hour workday exposure intensities were 0.50 and 0.18 μT for the metalworkers and 7.22 and 4.70 μT for the shipyard welders. These average exposure intensities were somewhat higher than those found in previous reports of welders' exposures surveyed by Skotte and Hjollund (Ref. 170). Instantaneous maximum exposures were on the order of 100 μT for SMAW using alternating current

(AC) and 10 µT for GMAW using direct current (DC). Active periods of welding ranged from a few seconds to several minutes. One metalworker, who recorded 5 hours of SMAW (AC) on the first day, 5 hours of GMAW (DC) on the second day, and 3 hours of GMAW (DC) on the last day, had an average exposure over the first workday of 21.6 µT, and 9.73 µT over the 3 workdays. This exposure was 20 times the mean exposure in the metal workers and was the highest average exposure measured. The average workday magnetic field intensity was 21.2 µT for the SMAW (AC) welders and 2.3 µT for the GMAW (DC) welders. The average time of welding, estimated from the time that exposure exceeded 1 µT, was one-third of the workday for the shipyard arc welders. Thus, average exposure intensities during active welding were 3 times the average workday exposure, or about 65 µT for the SMAW welders and 7 µT for the GMAW welders. The authors concluded that welding time and type of welding must both be considered when assessing welders' exposure to ELF magnetic fields.

Karlsen et al. (Ref. 100) used personal exposure monitors mounted on welders' chests to measure exposures to ELF magnetic fields during the use of seven different welding processes. Monitoring of six of the processes was carried out at a welding school. The seventh process, spot welding, was monitored at an automobile repair shop. The magnetic field monitor measured exposure in the range of 0.05 to 100 µT. The highest maximum intensity and the highest mean intensity during active welding ("arcing intensity") were found during SMAW (AC),

followed in descending order by GTAW (AC or DC), SMAW (DC), GMAW (DC), FCAW (DC), and spot welding. These results are summarized in Table 2. The arcing intensity values measured by Karlsen et al. and the corresponding "average exposures during welding" reported by Skotte and Hjollund (Ref. 170) are in close agreement for both SMAW (AC) and GMAW (DC). The authors noted that arcing intensity values for spot welding, which were by far the lowest, could have been underestimated because each spot weld lasted an average of 4 seconds (mean peak time in Table 2) and the monitors read EMF intensity every second; monitors capable of reading signals every hundredth of a second might have shown greater intensities during arcing. They suggested that the calculation of magnetic field intensity during arc time might be useful to epidemiologists as a method of estimating a welder's exposure over short periods or throughout a career.

7. Hygiene and Work Practices

7.1 Accident and Sick Leave Rates. Dement and Liscomb (Ref. 55) used workers' compensation claims to analyze accident rates among workers in the residential construction industry in North Carolina. Information about 31,133 claims registered between 1986 and 1994 was obtained for construction workers who were employed by the 7400 members of the North Carolina Homebuilders Association. The data were expressed as

Table 2
Mean Values of Electromagnetic Field Intensity During Various Types of Welding

Welding Method	Location	No. of Welders/ No. of Samples	Material Welded	Mean Intensity (µT)	Arcing Intensity[2] (µT)	% Time Welding[3]	Mean Peak Time[4] (seconds)
SMAW (AC)	School	5/21	Mild steel	36	58	61	65
GTAW (AC)	School	2/25	Aluminum	18	37	46	31
GTAW (DC)	School	2/19	Mild steel	23	37	65	59
SMAW (DC)	School	1/14	Mild steel	10	19	52	48
GMAW (DC)	School	3/13	MS/ Al[1]	7.3	13	56	32
FCAW (DC)	School	4/16	Mild steel	5.1	9.0	55	50
Spot welding[5]	Auto Body Shop	3/12	Mild steel	4.0	7.4	52	4.1

Notes:
(1) Mild steel and aluminum were welded
(2) Arcing intensity is the magnetic field intensity during active welding (mean intensity divided by % time welding).
(3) % Time welding is the percentage of time during the 7-minute sampling period spent in active welding.
(4) Mean peak time is the average number of seconds at which the magnetic field intensity was at the maximum during each time during the sampling period that the arc was on.
(5) Spot welding was done with GMAW (AC), using CO_2 as the shielding gas.

Data from Karlsen et al., Ref. 100.

average annual incidence density rates (number of cases per 200,000 work hours). The average annual rate for all claims filed was 16.40 cases per 200,000 work hours and the rate for claims involving medical costs or paid lost time from work was 10.8. The workers' compensation claim rates varied substantially among the residential construction trades: welders and cutters had the highest number (53.2) of injuries and illnesses per 200,000 work hours followed by insulators (40.9), roofers (29.5), mechanics and repairers (23.9), carpenters (22.9), and plumbers (21.6). Incidence rates for more serious injuries involving medical costs greater than $2,000 or any lost work time were also highest for welders and cutters (28.1), followed by insulators (24.3), roofers (19.4), and carpenters (15.3). Of the mechanisms of injury, being struck by an object caused the most injuries among all workers and was highest for welders and cutters (16.54), followed by carpenters (4.75) and insulators (4.47). The authors noted that chronic occupational diseases are not well captured in the workers' compensation claims among homebuilders.

Bylund and Bjornstig (Ref. 37) analyzed the incidence of non-fatal occupational injuries among the 2156 mechanics and construction metal workers who worked in Umea, Sweden, during the year 1985. Data were obtained from the University Hospital at Umea and from two National databases (the Swedish Information System on Occupational Accidents and the Swedish Work-Related No-Fault Liability Insurance System). Of the 470 welders in the cohort, 94 had suffered injuries on the job. The incidence of injury was highest among shop mechanics (38%), followed by plumbers (23%) and welders (20%), as compared with the injury incidence of 18% among all workers in the cohort. Welders had the highest

proportion of eye injuries, but none of these injuries resulted in prolonged impairment or loss of vision. The average number of sick leave days taken by injured persons was highest for sheet metal workers (61% of the 46 injured took an average of 49 sick leave days), three of whom had serious injuries that kept them from working for over a year, and lowest for welders (57% of the 94 injured took an average of 11 sick leave days).

Kosmider et al. (Ref. 110) conducted a 5-year follow-up study of accident rates among male workers employed at the Szczecin Shipyard in Poland. They found that of 1317 work-related accidents, the largest number of accidents occurred among welders, fitters, electrical mechanics, and platers.

Szubert and Sobala (Ref. 181) analyzed the relationship between absenteeism rates and duration of employment among workers in a Polish automobile plant. The rate of absenteeism was calculated for employees who had worked at the plant for less than 10 years, for 11 to 20 years, and for more than 20 years (Table 3). For most of the workers, the rate of absenteeism decreased with the duration of employment. This negative relationship was not true, however, for welders and drivers. Among drivers, the absenteeism rate increased from the shortest duration (less than 10 years) through to the longest (more than 20 years). Among welders, those who had worked at the plant between 11 and 20 years had the highest sick leave rate. The authors attributed the increased absenteeism with increased duration of employment at the plant to adverse effects of work conditions on health in these two occupational groups. Diseases of the respiratory tract and circulatory system were among the most prevalent causes of sick leave taken by welders. Since the incidence of circulatory disease did not increase with dura-

Table 3
Rates of Absenteeism[1] for Selected Causes of Sick Leave with Duration of Employment

Causes of Absence: Affected Organ System	Duration of Employment as a Welder (Years)		
	10 or less	11–20	21 or more
Circulatory system	2.25	2.09	1.91
Respiratory tract	2.09	3.1	2.09
Digestive system	0.47	0.72	0.69
Urogenital tract	0.19	0.41	0.72
Musculoskeletal system	0.32	0.78	0.89
Nervous system and sensory organs	0.86	0.91	1.04

Note:

(1) The rate of absenteeism was calculated from the formula:

(Number of sick leave days)/(Number of workers) × (days in study period)] × 100

Data from Szubert and Sobala, Ref. 181.

tion of employment, the change in rate was not viewed as an indication of effects of occupational exposure. Diseases of the respiratory tract increased by about 50% among welders employed for 11–20 years compared with those employed for 10 years or less. The most marked changes that occurred in welders with duration of employment over the entire study period were a fourfold increase in diseases of the urogenital tract and a threefold increase in diseases of the musculoskeletal system. The authors concluded that analysis of the disabilities leading to absenteeism can provide an overview of the health effects related to the hazards to which selected high risk occupational groups are exposed.

Burdorf et al. (Ref. 35) examined sick leave rates resulting from temporary disability due to musculoskeletal disorders. The all-male study population comprised 97 welders and 125 metal workers with job titles of caulker-burners, fitters, turners, sheet metal workers, plumbers, and grinders. The subjects had worked for at least 1 year at two companies in the Netherlands involved in fabrication of bridges, oil rigs, and other large construction projects. The welders worked primarily with mild steel but also did some work with stainless steel. They were involved with welding exclusively throughout the work shift and did some of their work in welding booths and some of it at the construction site. At the start of the study, the subjects were asked if they had experienced musculoskeletal pain that persisted for at least a few hours at any time during the past year and, if so, to define the part of the body in which the pain was located. During the next 2 years, data concerning frequency and duration of absence, and symptoms and diagnosis of the condition that caused the absence were collected from medical records and from information provided by the subjects.

During the 12 months preceding the study, welders and metalworkers reported similar incidences of musculoskeletal disorders (Table 4). Back, knee, and shoulder pain were the most frequently reported disorders by both groups. Welders reported neck or shoulder pain more frequently than did metal workers, but the difference was not significant. During the 2-year follow-up, 51% of the workers attributed at least one period of absence to musculoskeletal disorders, which accounted for 44% of all lost work days: 23% of the workers took at least one period of sick leave from work as a result of back pain, 17% for neck or shoulder pain, 18% for pain in the upper extremities, and 23% for pain in the lower extremities. Accidents accounted for 6% of cases of back pain, 10% of neck or shoulder complaints, and about 20% of the disorders of the upper or lower extremities. There was no association between absences resulting from musculoskeletal disorders and duration of employment, but workers who took sick leave due to musculoskeletal pain were at

Table 4
Prevalence of Musculoskeletal Complaints in the 12 Months Before the Start of the Study

Location of Pain	Welders (n = 97)		Metal Workers (n = 125)	
	n	%	n	%
Back	38	39	51	41
Neck	24	25	25	20
Shoulder	26	27	27	22
Elbow	11	12	17	14
Wrist	14	15	11	9
Knee	31	33	41	33
Ankle or foot	14	15	18	14

From Burdorf et al., Ref. 35.

higher risk of incurring sick leave from the same cause in the following year. Welders returned to work significantly more quickly than did metalworkers after absences due to neck or shoulder pain.

7.2 Electrocutions. Electrocution is one of the greatest risks facing welders (Ref. 34). The National Institute for Occupational Safety and Health (NIOSH) reported that electrocutions were the fifth leading cause of death in the workplace and accounted for 7% of all workplace fatalities between 1980 and 1992 (Ref. 140). NIOSH investigated 244 electrocutions that occurred from 1982 through 1994. The highest number of fatalities occurred among electrical utility line workers (n = 47) followed by laborers (n = 45) and electricians (n = 26). The six incidents that involved welders are described below.

The first incident involved a maintenance worker who was electrocuted while turning off a welding machine that was in a poor state of repair. The cables had numerous cuts and abrasions, and areas of the conductor cables were exposed. Large pieces of insulation were missing from the electrode holder, and there was no ground connection on the electrical receptacle box to which the welding machine was connected. In addition, there was water on the floor in the area where the victim was working. He had a severe electrical burn on his right index finger, suggesting that he came in contact with the welding machine's frame when trying to turn it off.

In the second incident, a welder was electrocuted while inserting the plug from a portable welding machine into an extension cord. The extension cord had apparently been dropped just before the incident, resulting in the loss of the cover plate on the plug and cracking its melamine casing. This damage allowed the extension cord plug to be misaligned in the receptacle. The

normally grounded metal cover on the welder plug became energized when the victim inserted it into the extension cord and he was electrocuted.

The other four welders died from electrocution while performing tasks that were not directly related to the job of welding. In one case, a welder cut into an energized wire with uninsulated metal wire cutters while helping an electrician change light fixtures. In the second incident, a welder came in contact with an energized conductor on an overhead crane while adding reinforcing steel to the bridge of a second overhead crane. In the final incident, two welders were electrocuted when the crane holding a metal shed that they were helping to move contacted an energized overhead power line.

7.3 Forensic Diagnosis of Electrocution. When a person has been electrocuted, there may be skin lesions or "electric marks" at the entry and exit points of the electric current. The size and severity of these skin lesions will vary with the dampness of the skin, the voltage, and the duration of contact with the energized source. Due to the high heat produced in the skin at the site of the lesions, electrical injury causes unique microscopic changes in the cellular structure of the skin. These changes can be seen under the microscope, and histopathologic examination of these electric marks may be useful in determination or confirmation of the cause of death. The changes include microblisters in the outermost layer of the skin through which steam escaped following the injury. The nuclei in the epidermal cells at the site of the electrical burn become stretched and elongated to produce a palisade-like appearance referred to as "streaming of the nuclei" (Ref. 68).

The microblisters and distortions of the nuclei can be viewed after staining thin slices of the skin lesion with standard histopathologic stains. Imamura et al. (Ref. 92) described a new application of a histopathologic stain (elastica-van Geison) which permits observation of the disarrangement of elastic fibers within the connective tissues of the dermis. It also improves visualization of the characteristic microscopic changes in the electric marks described above. This stain was used in an investigation of the cause of death of a 30-year-old Japanese welder who died while using an arc welder to mend drainpipes. There were no witnesses to the accident. Using the elastica-van Geison stain, histopathologic examination of the two "electric marks" found on his body confirmed that the cause of death was electrocution.

7.4 Explosions. Umani Ronchi and Rossi (Ref. 196) described a fatal accident caused by the explosion of the digester at an anaerobic biowaste treatment plant in Italy. In this type of plant, refuse is biodegraded by bacteria in an oxygen-depleted environment in a digester. Methane gas produced as a result of the bacterial digestion of the bio-

waste is collected under a dome at the top of the digester and is ultimately piped out to be used to produce energy for other processes. The explosion occurred while a worker was welding with an oxyacetylene torch on the summit of the dome of the digester. After he began welding, an explosion ensued which was attributed to the probable leakage of methane through a break in the pipes that carry the gas out of the digester. The dome was blown off the building and the body of the worker was later recovered from the biowaste mixture in the digester tank.

An accident in which a welder was using an oxyacetylene torch to heat the bronze end plate on a large marine water pump was described by Maxwell et al. (Ref. 129). When the fitting reached a temperature estimated to be 1800°F, it exploded and a large fragment of hot bronze became embedded in his thigh.

7.5 Burns. Kumar and Abraham (Ref. 112) reported the case of a 21-year-old welder in India who was seriously burned on the front of his body while using an oxyacetylene torch. The welding equipment consisted of a compressed oxygen cylinder and a generator in which acetylene gas was produced by reaction between water and calcium carbide. When the accident occurred, the welder was near the acetylene generator and the safety valve was near the area of his groin. Sparks from the torch fell on the safety valve, causing it to melt and igniting the gas that escaped through the damaged valve. The man sustained serious burns over 35% of his body.

Still et al. (Ref. 178) described the case of a 38-year-old man who was standing between two railroad cars while welding the coupling mechanism with an oxyacetylene torch. When the train moved unexpectedly, the coupling penetrated his abdomen causing internal injuries and he sustained severe burns over 35% of his body from the welding apparatus.

7.6 Exposure Estimation. Retrospective occupational epidemiology studies often lack reliable measurements of the exposure of the study population to workplace hazards and must rely on estimates of exposure drawn from personnel records and from questionnaires administered to the subjects or their next of kin. Such sources can be subject to honest error or bias. Panels of experts in industrial hygiene have been assembled in some studies in efforts to eliminate subjective factors in the estimation of past exposures to workplace hazards. Benke et al. (Ref. 22) evaluated the validity of this approach to exposure assessment during a community-based case-control study of brain tumors in Australia. A team consisting of three industrial hygienists and two occupational physicians, all experienced in chemical exposure assessment, approximated exposures to 21 chemicals on the basis of descriptions of 199 jobs. The panel was generally more accurate in assessing whether exposure had occurred

than in quantifying the level of exposure, which it consistently underestimated. Welding fumes, cutting oils, and lubricating oils and greases were the only substances among the 21 workplace chemicals assessed for which the estimates of exposure among the panelists were in "fair to good" agreement.

A device used by epidemiologists to estimate cumulative exposures of study subjects is the job-exposure matrix in which specific activities are related to actual exposures that have been measured in typical workplaces. A job-exposure matrix for exposure to chromium and nickel in welding fumes was developed by Diebold et al. (Ref. 58) on the basis of measurements made with welders engaged in SMAW, GMAW, and GTAW of mild and stainless steel in eight factories in France. Breathing zone samples were collected for a full work shift at each workstation and analyzed for total fumes, total chromium, Cr(VI), and water-soluble and insoluble nickel. The welding procedure, the metal welded, the actual time spent welding, and the personal protection methods used were recorded at each workstation. It was found that GMAW of stainless steel generated fumes with up to five times as much nickel as did SMAW and GTAW. Insoluble nickel represented a very high proportion of the total nickel in the fumes generated by all three welding procedures. Insoluble chromium compounds were generated by the three stainless steel welding procedures, whereas only SMAW generated substantial concentrations of soluble Cr(VI). For SMAW of stainless steel, the soluble chromium reached close to 70% of the total chromium, and Cr(VI) represented 60% of the soluble chromium. The concentrations for total and soluble chromium are in good agreement with those found by Edme et al. (Ref. 63, see 17.1). Values for total fume, total chromium, and

water soluble nickel and Cr(VI) were included in the job exposure matrix (Table 5).

7.7 Training. Recent NIOSH initiatives have involved hazard assessments in vocational schools with the objectives of increasing safety awareness among school administrators and students and of producing informed students who will be able to recognize, control, and remediate safety and health hazards in their future workplaces. Wallace et al. (Ref. 208) described a case study performed under this NIOSH initiative at a welding shop in a vocational school in the midwestern U.S. in 1996. Two 2-hour classes were held each day. The classroom had 17 welding bays, with two students working together in each bay. During the NIOSH study, most of the students performed SMAW of mild steel, and one student performed GMAW of mild steel using an argon-based shielding gas. None of the students wore steel-toed shoes or hearing protection. Shortly after the class started, there was a visible haze throughout the welding shop. The ventilation system was found to be functioning improperly, and inspection of fan motor units on the roof of the building showed that two of the three fans servicing the room were non-operational. In addition, the exhaust hoods in the room were improperly positioned. The student was placed between the hood and the work piece, which meant that the fumes could pass through the student's breathing zone before being exhausted. Welding fume concentrations ranged from 3.1 to 10.8 mg/m^3 in breathing zone samples collected from five students during the morning and afternoon class sessions. Concentrations of lead, chromium, nickel, cadmium, manganese, and zinc were lower than the OSHA PELs. In six samples, however, the manganese levels exceeded the ACGIH TLV of 200 µg/m^3 as a TWA. The authors concluded

Table 5
Job-Exposure Matrix for Stainless Steel and Mild Steel Welding Fumes

Procedure—Metal	Estimation of exposure (µg/m^3)			
	Total Fumes	Total Cr	Soluble Cr(VI)	Soluble Ni
SMAW—mild steel	9,000 (E)	10 (L)	0 (L)	10 (L)
SMAW—stainless steel	6,000 (E)	200 (E)	90 (E)	50 (L)
GMAW—mild steel	5,000 (E)	10 (L)	0 (L)	10 (L)
GMAW—stainless steel	4,000 (E)	200 (E)	5 (L)	150 (E)
GTAW—stainless steel	1,000 (L)	50 (L)	5 (L)	30 (L)

E = elevated exposure; L = low exposure.

Data from Diebold et al., Ref. 58.

that students in vocational schools face safety and health hazards that need to be addressed by school administrators.

Section Two
Effects of Welding on Human Health

8. Respiratory Tract

8.1. Pulmonary Function. Decrements in lung function that may be associated with inhalation of workplace pollutants can be measured in workers using spirometric tests which measure the lung volume, the maximum amount of air that can be inhaled, and the flow rates the worker can achieve after a maximal inhalation. Some of the parameters measured by pulmonary function tests are: forced vital capacity (FVC), the maximum volume of air that can be inhaled and exhaled (reduced in restrictive lung disease, e.g., fibrosis, interstitial lung disease, and to a lesser extent in obstructive disease, e.g., bronchitis, asthma); forced expiratory volume (FEV_1), the volume that can be exhaled in one second; and FEV_1/FVC, the ratio of the previous two, which is reduced in obstructive disease, but not in restrictive disease. These and other pulmonary function measurements frequently used in epidemiological studies of workers are described in greater detail in Appendix A.

In their studies of a population of welders in New Zealand, Fishwick and coworkers examined the effects of both short- and long-term welding exposures on pulmonary function. In 1996, they (Refs. 69, 70) investigated the acute effects of exposure to welding on pulmonary function, using a study population of current welders and non-welders at eight plants in New Zealand. Most of the welding performed at these sites was GMAW or GTAW of mild steel. All of the subjects responded to a questionnaire to document demographic data, smoking habits, and current or recent pulmonary symptoms. The welders also described the details of their current and past welding experience, and indicated whether they were currently using local exhaust ventilation. Spirometric tests were conducted with each of the subjects before the work shift and then again at 15 minutes and at 7 hours after the start of the shift. The 62 subjects who welded on the day of the study were designated as "current welders". The 75 subjects who did not weld on that day were designated as "non-welders." Only ten of the current welders used local exhaust ventilation. The current welders complained significantly more often than the non-welders of work-related cough (OR = 4.1, CI = 1.5–11.5) and at least one other work-related symptom

(i.e., wheeze, chest tightness, or shortness of breath, which were initiated or exacerbated during work) (OR = 2.3, CI = 1.0–5.2). A 5% decrease in FEV_1 was seen in 21 current welders after 15 minutes of welding and in 12 of the non-welders 15 minutes after starting work. No relationship was found between this change in lung function and the prevalence of respiratory symptoms among the welders. The maximum decrease in FEV_1 at the end of the workday (6.5% among current welders and 3.0% among non-welders) was the only pulmonary function measurement for which a significant difference was found between the two groups. The absence of local exhaust ventilation adjacent to the work site was the overwhelming factor related to the decrease in lung function observed after 15 minutes of welding. When local exhaust was not used, the risk for a 5% drop in FEV_1 was 22 times higher than when it was used.

These findings were reported back to management and to the study participants at each site at the completion of the study (Ref. 171). Two years later, the investigators re-visited the sites to assess whether changes in work practice had been made as result of their recommendations. Two of the eight sites surveyed had local exhaust ventilation in 1996 which remained unchanged in 1998. Local exhaust ventilation had been installed in part of one site which had had none in 1996, and, at another site, welding had been relocated to larger, presumably better ventilated premises. In the other four sites, nothing had been done to reduce the concentration of fumes in the welding areas.

In 1998, Erkinjuntti-Pekkanen (Ref. 64) conducted lung function tests with the same group of workers studied 2 years earlier by Fishwick et al. (Refs. 69, 70). In the follow-up study, workers were classified as welders if they had welded at least 5% of the average working day at the time of the original study and had continued in that job between the two surveys. Those who were former welders at the time of the first survey and workers who welded less than 5% of the time were classified as non-welders. Of the 137 workers studied in 1996, 54 male welders and 38 male non-welders were available for the follow-up examination. (The 4 females in the original study were all non-welders, and they were excluded from the follow-up analysis.) Spirometry was performed according to the same protocol as in the 1996 study: measurements (FEV_1, FVC, and FEF_{25-75}) were made before the start of welding work and then at 15 minutes and at 7 hours after the start of the work shift. Responses to questionnaires administered at the time of the initial and follow-up studies indicated that the age, height, duration of work experience, smoking habits, and ethnicity did not differ significantly between welders and non-welders. At the time of the follow-up study, eight non-welders and one welder reported having asthma. Chronic

bronchitis was more common among welders (24%) than among non-welders (5%), and 4 of the 20 welders who had never smoked had chronic bronchitis, compared with none of the 15 non-welders who had never smoked. The welders and non-welders had similar annual declines in the pulmonary functions measured. Among those who smoked, there was a significantly greater decline in FEV_1 in the welders than in the non-welders. Among non-smokers, non-welders had a steeper annual decline in FEV_1 than did welders. Workers who used personal respiratory protective equipment, local exhaust ventilation, or a combination of the two had a significantly smaller annual decline in both FEV_1 and FVC than welders who used no protective equipment. There was a significant association between the acute and chronic effects of exposure to welding fumes. Decline in FEV_1 across a shift was a predictor of annual decline in FEV_1, which suggests the possibility that recurrent acute obstructive changes can lead to chronic airways obstruction. The investigators repeated their earlier recommendation (Ref. 70) that local exhaust ventilation, which they considered the most practical exposure reduction measure, be used wherever welding is done.

Hessel et al. (Ref. 81) examined lung health, as measured by respiratory symptoms, spirometry, and chest X-rays, in a population of 99 journeyman plumbers and pipefitters and in a control population of 100 telephone workers in Alberta, Canada. All of the workers were still active in their occupations and had been so, as evidenced by the continuity of their union membership, for at least 20 years. Among the plumbers and pipefitters, there were 24 men whose longest work experience had been in welding. No significant differences were found in the lung function measurements among the plumbers and pipefitters and the controls. Chest X-rays showed a significantly greater incidence of lung abnormalities (21%) among the plumbers and pipefitters than in the telephone workers (2.1%). When the workers were divided according to whether their longest work experience was as a pipefitter, a plumber, or a welder, lung abnormalities, as measured by spirometry, were found in 11.5% of the pipefitters, in 16.7% of the welders, and in 57.1% of the plumbers. Self-reported symptoms of cough and phlegm were not significantly different among the three sub-groups. Significantly increased odds ratios (ORs) for frequent cough and frequent phlegm were found in plumbers and pipefitters, but not in welders, compared with telephone workers.

The same group of investigators (Ref. 80) performed a similar study among 52 welders and 50 boilermakers who had been members of a construction boilermakers union in Edmonton for 20 years or more and were still active in their trade. The 100 telephone workers in the previous study also served as controls in this one. Boiler-

makers had significantly increased incidences of several respiratory symptoms (frequent cough, wheeze, chest tightness, and pneumonia) compared with the controls. Welders reported chronic phlegm significantly more often than did telephone workers. There were no significant differences in lung function values between the study group and the controls, but the boilermakers had significantly lower lung flows and volumes (FEV_1, FEV_1/FVC, FEF_{25-75}, FEF_{50}) than the welders. Chest X-rays revealed significantly greater numbers of lung abnormalities in general and more circumscribed or diffuse thickening in the lungs of members of the boilermakers union than in the telephone workers.

Sobaszek et al. conducted studies of the respiratory effects of short-term (Ref. 172) and longer-term (Ref. 173) exposure to stainless steel welding fumes on welders with at least 5 years welding experience. Welders and controls worked in the same French companies (primarily shipyards or tank manufacturers). The controls were manual workers (machinists, warehousemen, and packers) without any previous or current welding exposure. Lung function tests (FVC, FEV_1, FEV_1/FVC, FEF_{25-75}, MEF, MEF_{50}, MEF_{25}) were performed on all of the participants, and questionnaires were used to obtain work exposure histories and respiratory symptoms for welders and controls, none of whom had had any known exposure to silica, asbestos, or organic solvents.

The participants in the chronic study (Ref. 173) were 134 welders and 252 controls from eight factories. The welders were engaged in SMAW (n = 77), GMAW (n = 34), GTAW (n = 17), and plasma welding (n = 6) of stainless steel. Each welder used only one of these processes at the time of the study. Smoking habits, demographic data, and time in the current occupation did not differ significantly between welders and controls, but controls had significantly more years in the workplace than the welders. Spirometric lung function tests were performed at the beginning of the shift for all of the welders and controls. Significantly greater respiratory symptoms reported by the welders were morning and night cough, phlegm in the morning, dyspnea (shortness of breath), and chest tightness. These effects were also significant after the data were adjusted for smoking habits. The frequency of other symptoms, including chronic bronchitis and asthma, and the results of the lung function tests did not differ significantly between welders and controls. When the data were analyzed according to tobacco habits, there was still no significant effect of welding on respiratory symptoms, but a tobacco effect was significant in all of the lung function measurements except MEF. For all welders, duration of welding exposure was related to declines in the maximal expiratory flow (MEF_{25} and FEF_{25-75}). This effect was especially prominent during the first 5 years of welding and after 25 years

of welding. Sobaszek et al. noted that their findings of significantly increased clinical symptoms and non-significant differences in lung function tests in welders compared with controls from the same factories were in accord with those of other studies (Refs. 72, 130, 159) carried out in Europe and in the United States, as was the decline in lung function associated with many years of welding exposure (Ref. 215).

In the acute study, changes in lung function across a work shift were measured in welders who had worked exclusively on the day of the tests with either stainless steel (n = 91) or mild steel (n = 53) (Ref. 172). Morning cough, morning phlegm, and dyspnea were reported significantly more often by welders than by controls, and dyspnea was reported significantly more often by mild steel welders than by stainless steel welders. Initial lung function values for all groups were uniformly normal. Declines in lung function were greatest among stainless steel welders, who showed significantly lower post-shift values for FVC than were found in controls or mild steel welders. Significantly greater post-shift decrements in FVC and MEF were associated with SMAW compared with GTAW and GMAW. Among welders with more than 20 year experience, those welding stainless steel had lower post-shift values in several of the spirometric tests (FVC, FEV_1, FEF_{25-75}, MEF) than those welding mild steel. The authors noted that decrements in mid-expiratory flows (FEF_{25-75}) could be early signs of small airways impairment that might lead to chronic obstructive pulmonary disease which, according to Kennedy and Demers (Ref. 102), is not reversible and is not associated with immunologic triggers.

8.2 Asthma. The incidence of asthma has risen markedly in developed countries during the last century, and work-related asthma is one of the most commonly reported occupational diseases throughout the world. To estimate the proportion of adult asthma attributable to workplace exposures, Blanc and Toren (Ref. 24) critically reviewed studies containing risk estimates for occupational asthma published in the occupational health literature between 1966 and 1999. The studies were assigned numerical grades according to the number of patients, the source of diagnosis, documentation of exposure, sampling strategy, statistical adjustment for smoking and age, and whether or not the publication was peer-reviewed. Analysis of the 43 studies from which the authors could derive reliable estimates indicated that 9% of adult asthma is associated with occupational factors. When the numerical grades of study quality were used to weight the individual studies, the attributable risk was about 15%. The etiology of occupational asthma may be straightforward, as when work-related exposures induce new-onset asthma, or more complicated, as when workplace exposure may re-activate asthma which has been asymptomatic, or may

aggravate preexisting disease, necessitating increased medication or other medical care. All of these scenarios emphasize the importance of identifying asthma triggers in the workplace.

Jarvis and Burney (Ref. 95) reviewed the literature on the epidemiology of allergic diseases, including asthma. All allergic diseases are associated with atopy (defined as the production of a specific immunoglobulin (IgE) in response to exposure to common environmental allergens), but not everyone with atopy develops clinical disease. The authors found that newly-diagnosed asthma in children has increased about 5% per year in the United Kingdom, and similar increases have been observed among children and young adults throughout the industrialized world. Although genetic susceptibility to allergic disease is important, the authors stated that it is unlikely to explain geographical variations in disease prevalence or the increase in allergic disease over the past few decades. Spray painters, chemical processors, bakers, laboratory workers, and workers in the combined group, welding, soldering and electronic assembly were, in descending order, described as being in "high risk occupational groups" in a survey cited by Jarvis and Burney. The first three groups all had significantly greater incidences of occupational asthma than the group that included welders. Furthermore, since fumes from soldering and electronic assembly contain many components that are not common to welding fumes, it is not possible to assign any effects to welding fumes when these exposures are grouped together.

Toren et al. (Ref. 194) examined the risk for adult-onset asthma in a population of 15,813 persons who had responded to a short respiratory questionnaire sent to 20,000 randomly-selected persons, age 20 to 50, in a highly-industrialized county in Sweden. One year later, the 522 respondents who had reported asthma-like symptoms or physician-diagnosed asthma, and 2400 referents randomly drawn from the remainder of the respondents, were asked to complete a comprehensive questionnaire providing data concerning occupational exposures, respiratory symptoms, smoking, and atopy. The study population consisted of the 362 cases and the 2044 referents who responded to the second questionnaire. Exposure to welding fumes was reported by 39 of the cases of whom seven were welders. The most consistent finding in this study was an association between risk for adult-onset asthma and occupational exposure to flour dust and to isocyanate paint hardeners. Odds ratios for occupational asthma were also significantly elevated among those exposed to welding fumes (OR = 1.6, CI = 1.1–2.6) or to "rapid glues" containing acrylate, methacrylate, or cyanoacrylate monomers. The authors concluded that occupational exposure to acrylate-based paints and welding

fumes is associated with an increased risk for occupational asthma.

In a similar study in Goteborg, Sweden, Toren et al. (Ref. 193) investigated the exposure histories of 321 asthma cases (126 male, 195 female) and 1459 controls (721 male, 738 female) who had participated in an earlier study of asthma (Ref. 15) and responded to a new questionnaire on self-assessed occupational exposures. After adjustments were made for sex, smoking, and age, 11% of the asthma cases were attributed to occupational exposures. Welding fume exposure was significantly associated with asthma (OR = 2.0, CI = 1.2–3.2). Of the 25 cases who reported exposure to welding fumes in the year before being diagnosed with asthma, only one had the occupational title of welder. In this analysis, exposures to man-made mineral fibers and solvents from either painting or mechanical work were also associated with significantly increased risks for asthma. The authors concluded that there is evidence for a causal relationship between exposure to either welding fumes or textile dust and the risk for asthma.

Chatkin et al. (Ref. 42) examined 469 asthma claims accepted by the Ontario (Canada) Workers' Compensation Board, of which 89 had symptoms related to accidental exposure to high concentrations of irritants in the workplace. Of these 89 cases, 68 were among persons with preexisting asthma; one case was associated with exposure to welding fumes.

Mastrangelo et al. (Ref. 126) conducted an epidemiological study of occupational asthma in an industrial region of northeast Italy. The participants were 387 patients newly diagnosed with asthma between 1989 and 1993 at a university occupational health clinic. Of these patients, 203 were diagnosed as having occupational asthma on the basis of an association between symptoms and workplace activities and a positive response to either bronchial provocation or skin prick tests with substances encountered at work. Because none of the cases of asthma among the metal assembly workers met the criteria for "occupational asthma," these workers were used as the reference group for calculating the relative risk for asthma in all the other occupational groups. (RR is more commonly calculated by comparing odds ratios in each occupation with the odds ratios in the rest of the occupations combined.) Twelve of the 17 remaining categories of workers were found to have significantly greater risks for asthma than the metal assembly workers. Painters exposed to isocyanates and workers in the polyurethane foam industry had the greatest risk. There were ten cases of occupational asthma among welders (RR = 2.7, CI = 1.0–7.0).

Contreras and Chan-Yeung (Ref. 48) studied airways responses to welding fumes in six full-time arc welders who had reported with respiratory symptoms to a clinic in Vancouver, Canada, between November, 1992, and July, 1993. During the first of three visits, the subjects were interviewed and skin prick tests for a battery of 25 common allergens were administered. The subjects all welded mild steel during the second visit in a small, poorly ventilated room at the clinic, that had been set aside for such activities. During the third visit, welding was performed on either stainless steel or galvanized steel, whichever had been associated with the original symptoms. Spirometry was performed during and after the welding sessions. The results of the welding challenge tests and the welding fume concentrations to which

Table 6
Results of Challenge Tests During Welding of Mild, Stainless, and Galvanized Steel

Subject	Exposure duration (min)		Welding fumes* (mg/m^3)		% Fall in FEV1	
	MS	SS	MS	SS	MS	SS
1	60	60	3.37	7.75	23	18
2	60	60	3.89	2.96	7	10
3	60	60	2.24	5.19	3	9
4	60	60	—	7.80	3	6
	MS	GS	MS	GS	MS	GS
5	60	45	1.33	150.00	2	17
6	60	15	12.60	43.90	16	20

*Welding fume concentrations were measured in breathing zone samples collected during the welding challenge tests.

Notes: MS = mild steel; SS = stainless steel; GS = galvanized steel.

Data from Contreras and Chan-Yeung, Ref. 48.

the welders were exposed during these tests are shown in Table 6. Three of the welders (subjects 1, 5, and 6 in Table Contreras) had bronchial reactions to the welding fumes, evidenced by declines of 17% to 23% in FEV_1. They also had respiratory symptoms and immediate bronchial hyperresponsiveness characteristic of asthma during the welding challenge tests. The two welders who worked with galvanized steel (Subjects 5 and 6) were also subjected to provocation tests with an aerosolized zinc chloride solution, but neither showed any reaction to the highest concentration tested. Tests for reaction to common allergens were negative for these two welders, while the third man (subject 1) who reacted to welding fumes was atopic. The immediate bronchoconstriction and the absence of late reactions among these welders led the authors to conclude that the mechanism of bronchial reaction in these three welders was due to non-specific irritation rather than to sensitization to specific substances.

In a letter to the Editor, Fishwick et al. (Ref. 71) noted that the fall in FEV_1 that was found in the Contreras and Chan-Yeung study may be a predictor of "longer term sequelae." Chan-Yeung and Contreras (Ref. 40) agreed with Fishwick et al., citing results among workers in other industries showing that "acute decline in lung function during a shift is an independent predictor of longitudinal decline in lung function." The Fishwick group later reported the results of the two-year follow-up to their acute lung function study (Ref. 64), with results that were consistent with those observations (see 8.1).

Kelesoglu et al. (Ref. 101) investigated bronchial hyperreactivity in painters, welders, and general blue-collar workers (controls) in Ankara, Turkey. Using non-specific bronchial provocation with methacholine, they found significantly less bronchial hyperreactivity among the painters than among the controls. Results for welders were not significantly different from those of the controls.

Aluminum was identified as the most likely cause of occupational asthma in a maintenance man in Belgium who routinely welded mild steel using SMAW and GMAW and also welded aluminum once a month using SMAW. After 4 years of this work, he experiencedchest tightness and wheezing on the days when he welded aluminum. Vandenplas et al. (Ref. 203) examined the patient 18 months after the onset of symptoms and had him perform test welding under controlled conditions in the hospital workshop. One day after baseline spirometric measurements were taken, the patient welded aluminum for 1 hour using flux-coated electrodes, which resulted in a transient fall in FEV_1 with a maximum decrease of 17%. On the following day, he welded aluminum using the same procedure for 2 hours. This exposure provoked an asthmatic attack, with progressive reduction in FEV_1, which reached a maximum of 52%. One month later he was given additional inhalation challenges. Welding aluminum for 2 hours, using electrodes from which the flux had been removed, resulted in a 55% reduction in FEV_1. One month after that procedure, the patient returned to the clinic and welded mild steel using SMAW with rutile electrodes for 2 hours and developed no bronchial reaction and no change in FEV_1. Inhalation challenges had shown no non-specific irritant effects, and two control asthmatic subjects did not show bronchial responses to aluminum welding. These findings led the authors to conclude that aluminum should be considered a possible cause of occupational asthma.

8.3 Chronic Bronchitis. Bradshaw et al. (Refs. 32, 33) reported on the incidence of chronic bronchitis and work-related respiratory symptoms in the population of 62 welders and 75 non-welders in New Zealand that was studied for acute effects on lung function by Fishwick et al. (Refs. 69, 70). All subjects who had performed a weld on the day of the study were classified as welders; there were 35 ex-welders among the non-welders. Chronic bronchitis was defined as regular phlegm production for at least 3 months of the year and for at least 2 years. There were no significant differences in the incidence of bronchitis between GMAW and GTAW welders. Compared with workers with less than four years total welding exposure, welders with greater than ten years' experience had a significantly greater incidence of chronic bronchitis (16.7% incidence, OR = 9.5, CI = 1.3–71.9) after the results were adjusted for smoking. The authors noted that, among workers with chronic bronchitis, those whose symptoms were of longer duration also had associated airways obstruction.

8.4 Magnetopneumography. Magnetopneumography (MPG) is a non-invasive technique that allows the measurement of the quantities of dusts containing a magnetizable component that have accumulated in the lungs. MPG can provide information about the spatial distribution of the retained dust and internal movements of alveolar macrophages (a type of leukocyte or white blood cell). It can be used to monitor the uptake of occupational contaminants by the lungs of individual workers and to perform epidemiologic studies of the long-term retention in, and clearance rates of dusts from the lungs. For welders, magnetite (Fe_3O_4) serves as the tracer element that is measured during MPG. After a short magnetization pulse, MPG measures the remanent magnetic field (RMF) of the magnetite in pulmonary dust particles which is then related to the quantity and distribution of magnetite and other retained metals in the lung. Certain problems such as the distribution of dusts in the lungs, uncertainty related to the exact position of the subject during the scanning of the chest for measurement of the

RMF, and anatomic variations between subjects can influence the precision of the measurement of the mass of the retained dusts. Methods for overcoming some of these problems were addressed in a recent study by Forsman and Hogstedt (Ref. 73).

Huvinen et al. (Ref. 90) investigated the relationship between the dusts retained in the lungs of workers in a stainless steel production facility, as measured by MPG, and concentrations of chromium in workplace air and in urine. The study group comprised 128 workers from different sections of the ferrochrome and stainless steel plants. Eleven of the subjects were from the welding/repair shop; an additional five persons from the office staff served as controls. Urine and breathing zone air samples were collected for all workers except for the welders and controls. Mean total dust concentrations in breathing zone samples collected one year before the study were less than 4 mg/m^3. Workers in the welding/repair shop had the highest RMF, followed by workers in the ferrochrome and steel smelting shops. All other workers had RMF values similar to those of the controls. There was no correlation between the RMF and duration of exposure for any of the workers, or between the RMF and actual exposures to total or hexavalent chromium in workers for whom breathing zone samples had been collected; but there was a relationship between the RMF and urinary chromium concentrations. The investigators noted that the accumulation of dusts in the lungs was low in this group of workers, which they attributed to the low levels of exposure in the plant. They concluded that MPG cannot be recommended for routine monitoring of worker exposure in a plant where dust exposure levels are low.

Nakadate et al. (Refs. 135, 136) used MPG to examine whether decrements in pulmonary function are related to the quantity of welding fume particles accumulated in the lungs. The subjects were 143 male welders who worked in a Japanese tractor assembly plant in 1994. Their mean age was 45 years, and they had been welding for an average of 20 years. The welders were generally engaged in GMAW of mild steel and worked in a well-ventilated building with a high roof. Local exhaust units were available in the welding areas. All of the subjects responded to a questionnaire concerning respiratory symptoms, medical history, and smoking habits, and all had had periodic chest X-ray examinations. On average, the prevalence of chronic cough, chronic phlegm, and current tobacco use increased with the iron content of the lung. The pulmonary function tests administered measured FVC, FEV_1, FEV_1/FVC, and MEF_{25}. After the data were adjusted for age and smoking, decrements in FEV_1/FVC were the only lung function changes that were significantly associated with the quantity of magnetizable material in the lung. The decrement in FEV_1/FVC

and an increase in mu, a mathematical function derived by the authors from the expiratory volume curve, indicated that obstructive changes in the lung were associated with the cumulative exposure to welding fumes measured by MPG.

Five years later, Nakadate et al. (Ref. 136) repeated the spirometry and MPG study with 46 of the 143 welders. In the interim, production in the factory had decreased, automated welding by robots had been progressively introduced, and the use of respiratory protection had been strongly encouraged. In line with these improvements, the quantity of magnetic material accumulated in the lungs of these 46 subjects had declined significantly and the RMFs were lower by an average of 66% than those measured in 1994. However, the pulmonary function values were unchanged between 1994 and 1999. Lung function did not improve with the decreased lung burden of magnetizable particles. Nakadate et al. concluded that improvements in the working environment result in reducing welders' exposure to welding fumes and facilitate clearance of particles already accumulated in the lungs, but do not necessarily result in improvement in lung function, at least not over a 5-year period.

A direct correlation between the RMF and pulmonary function was observed, however, when just the measurements taken in 1999 were analyzed. Subjects in the 1999 study with RMFs greater than 4.0 nanotesla (nT) had a significantly lower FEV_1/FVC than those with RMFs less than 4.0 nT. In addition, analysis of the results obtained in 1999 showed a significant correlation between the RMF and the duration of the welding experience (Ref. 214). This relationship did not hold true for cutters. There was a significantly greater accumulation of particles in the lungs of welders than in the lungs of cutters with equal years of experience. This observation was attributed to differences in particle size produced by the two types of operations. The investigators noted that chest X-rays did not reveal fibrotic changes in the lung, and they suggested that particles that are not associated with fibrotic nodules may be more easily cleared from the lung.

8.5 Pneumoconiosis. Siderosis (arc welder's lung), a form of pneumoconiosis (dust deposits in the lung) in which iron oxide accumulates in the lungs, can result from inhalation of welding fumes. It is detectable by chest X-ray or by microscopic examination of biopsied lung tissue and is generally considered to be a benign condition with few, if any, symptoms. Some welders with siderosis have also been diagnosed with fibrosis, which can lead to interstitial lung disease, a condition in which the tissue between the alveoli loses elasticity, causing breathlessness during exercise, dry cough, and a reduction in pulmonary function. In some cases, the presence

of fibrosis may indicate that concomitant exposures to fibrotic substances such as quartz or asbestos had occurred.

Steurich and Feyerabend (Ref. 177) described a case of a welder with siderofibrosis. He had used SMAW for 30 years and had worked primarily in poorly ventilated areas, without the benefits of local exhaust ventilation. Eye protection was the only protective equipment used. After experiencing fatigue and difficulty breathing, which gradually increased in severity over a period of several months, he sought medical attention. He had no cough, and lung function tests were normal. X-rays revealed small nodular opacities scattered throughout the lungs, and lung tissue biopsy revealed iron deposits and areas of fibrosis. The patient stopped welding and returned for a follow-up examination 7 years later. Chest X-rays and lung function were unchanged during this time.

An unusual case of pneumoconiosis in a 60-year-old man with 25 years' welding experience was described by Kinoshita et al. (Ref. 108). A single, poorly defined, solitary mass, 3 cm in diameter, was observed by chest X-ray and chest computed tomography scan (CT scan). Large quantities of iron were observed in biopsies of the lesion. Further examination confirmed that this solid lesion was pneumoconiosis and not lung cancer. The authors noted that pneumoconiosis rarely takes the form of a solitary mass.

Yamada et al. (Ref. 211) described an unusual medical treatment for siderosis in a 42-year-old welder who was admitted to the hospital complaining of a dry cough. He had 20 years of welding experience and had not worn a mask while welding. Signs of siderosis, including diffuse small nodular shadows, were seen in chest X-rays and small patchy opacities were revealed in the lungs by CT scan. Arterial blood gas levels and pulmonary function were normal. Mild fibrosis was observed in biopsied lung tissue. Welding fume particles were observed in alveolar spaces and engulfed in macrophages. To reduce the progression of fibrosis, fume particles were washed from the lungs by bronchopulmonary lavage. The lungs were lavaged with over 13 liters of saline solution which was allowed to drain out of the lungs by gravitational flow. A total of 911.7 mg of particles was recovered from the lungs in the lavage fluid. Eight days later, a reduction in the small patchy lesions and nodular lesions was observed by CT scan. His dry cough was gone, and the welder returned to work with the admonition to wear a respirator.

Medico-legal investigations of two cases of pulmonary disease occurring in welders determined that they were not related to occupational exposures (Refs. 41, 180). In France, Charpin et al. (Ref. 41) examined the case of a man who sought medical attention in 1992 after suffering recurrent sinusitis, bronchitis, and purulent pleurisy. The patient had worked in a cement factory from 1961 to 1965, and then for the next 25 years he worked as a shipyard welder where he had occasional exposures to asbestos. He was diagnosed with bronchiectasis, a condition in which portions of the bronchial wall become chronically inflamed, leading to an irreversible dilation of the bronchi and increased mucous production causing symptoms of bronchitis and difficulty breathing. The most common cause of bronchiectasis is chronic or recurring infection. In addition, he had severe stenosis (a narrowing or stricture) of the main left bronchus (one of the two main branches of the trachea). Fibrosis and mineral deposits containing iron, silicon, aluminum, and titanium were found in the area of the stenosis. The bronchiectasis was deemed responsible for his pleurisy and bronchitis, and was judged to be unrelated to his occupational exposures as a welder.

In Germany, Strohbach et al. (Ref. 180) evaluated the case of a 46-year-old welder who suffered from acute interstitial lung disease. The patient became ill after 27 years of welding experience, during which time he had worked in poorly ventilated spaces without benefit of a respirator. He complained of dry cough, night sweats and chills, and chest pains with breathing difficulties that worsened at work. Chest X-rays revealed bronchial pneumonia with multiple shadows. On the basis of a lung biopsy, he was diagnosed with interstitial lung disease, which, because of his long career as a welder, was considered to be siderosis. Treatment for 6 months with corticosteroids brought about improvement in his pulmonary conditions, with relief of his breathing difficulties and cough. However, he developed pain in his joints, knees and fingers. These symptoms plus the detection of circulating antibodies against a cell nuclear protein (anti-centromere antibody) led to the diagnosis of CREST syndrome, which is a limited form of scleroderma, an uncommon disease which causes the deposition of fibrous connective tissue in the skin, lungs, and other internal organs. Because of this diagnosis, the authors did not recommend treating this case as an occupational disease.

Dufresne et al. (Ref. 61) measured lung concentrations of "angular and fibrous particles" in samples of autopsied lungs provided by the Workers Compensation Board of Quebec, Canada. While most of the lung samples were from workers in mining and metal foundries, four samples from welders were included. In addition, samples from 13 asbestos miners with mild asbestosis were included as positive controls for fibrous particles, and there were 20 background samples from the general population. The highest concentrations of metal particles were found in the lungs of welders. In terms of millions of particles greater than 0.25 μm per mg of dry lung tissue, welders' lungs had an average of 6.13, compared

with 1.1 for the next highest group, iron foundrymen, and 0.16 in the background lung samples.

8.6 Case Reports. In a case described by Tojima et al. (Refs. 7, 192), a 61-year-old welder with a 32-year welding career, developed symptoms of malaise, coughing, and difficulty breathing within hours after welding galvanized steel. His arterial blood neutrophils were elevated and his arterial blood oxygen level was subnormal. While he presented with symptoms of metal fume fever, clinical examination and chest X-ray indicated he had acute chemical pneumonitis (inflammation of the lungs) and chronic siderosis. While they noted that this is rarely reported, the authors attributed the pneumonitis to exposure to ZnO fumes.

Barbee (Ref. 16) described the case of a 43-year-old maintenance worker who developed general malaise, chills, and fever 12 hours after spending an hour cutting a galvanized steel grating with an oxyacetylene torch without using a respirator. Feeling better the next day, he returned to work and continued cutting the galvanized grate with a power saw rather than with the oxyacetylene torch. Over the next two days, his symptoms returned, he developed shortness of breath, and his condition progressively worsened. He was admitted to the hospital. His blood oxygen was low and neutrophils were elevated. During the next 24 hours, his condition continued to deteriorate. Chest X-ray and CT scans led to the diagnosis of acute respiratory distress syndrome, a condition in which fluid accumulates in the lungs (pulmonary edema) and which can develop from untreated chemical pneumonitis. The patient remained on mechanical ventilation for 10 days and was discharged from the hospital 2 days after that. His exposure was re-created at his place of employment, and air sampling revealed that he may have been exposed to levels of cadmium twice the OSHA PEL and to levels of zinc over 20 times the PEL. The chemical pneumonitis may well have resulted from exposure to cadmium.

Bousova-Kostelnikova (Ref. 31) described an incident in the Czech Republic in which two welders were affected by fumes while working in a storage tank. The tank was newly built and had not yet been used. Its volume was approximately 100 m^3 and it had an opening of approximately 60 cm in width. The first welder used an oxyacetylene torch and the second used SMAW. No mechanical exhaust systems were used, and neither welder was equipped with a respirator. Both started to cough within 15 to 30 minutes after beginning to weld but they continued working for approximately 2 hours. Their coughing increased in severity for several hours after leaving work. About 10 hours after finishing the job, the welder who had been using an oxyacetylene torch developed difficulty breathing and reported to the hospital where he was diagnosed with and treated for pulmonary edema. The cause of this condition was deemed to be exposure to nitrogen dioxide with a possible contribution by ozone. He was released from the hospital 12 days later and was able to return to work as a welder with the proviso that he use protective equipment consistently. The second worker was less severely affected. He developed a dry, irritating cough that lasted throughout the evening. That night he had general malaise and a headache. He returned to work the next day, but had symptoms such as breathlessness upon exertion. His condition resolved spontaneously within 3 days. Examination 12 days after the incident showed some changes in pulmonary function and in chest X-rays. The acute upper airways irritation experienced by this patient was also attributed to exposure to oxides of nitrogen (NO_x). The author concluded that ventilation and local exhaust, as well as a forced air breathing apparatus, are essential when working in confined spaces. The use of a device to monitor the area for the presence of NO_x while welding in a confined space was recommended.

9. Cancer

Andersen et al. (Ref. 6) conducted a multi-national cohort study that linked the incidence of cancer with occupation in the population born between 1906 and 1945 that resided in the four Nordic countries Denmark, Finland, Norway, and Sweden in 1970. This cohort of 10 million people represented half the population of these nations. Data concerning occupation, industry, and employer were obtained from the 1970 census records in each country. Based on these data, the study population was divided into 53 occupational groups. The incidence of cancer during the years 1970 to 1990 was obtained from national cancer registries and more than one million cases of cancer were identified among in the study population. Standardized incidence ratios (SIRs, see Appendix B) were used to calculate the relative cancer incidence in the various organs in which they occurred in each occupational group compared with that in the population of each country and with that in the entire study population.

For welders, the values from only Finland, Norway, and Sweden were included in the analyses because the welders were grouped with mechanics and iron and metal workers in the records from Denmark. Males and females were considered separately within occupational groups. However, because there were few female welders, they were combined with other occupational groups and were not included in the analysis of welders. Incidence rates were calculated for cancer at 31 different organ sites in a population of 44,734 male welders. In welders from all three countries combined, incidence

Table 7
Cancer Sites with Significantly Elevated or Reduced Standardized
Incidence Ratios (SIR) in the Combined Population of Welders

Site	Finland No.[1]	Finland SIR	Norway No.	Norway SIR	Sweden No.	Sweden SIR	Total No.	Total SIR	CI
Gall bladder	10	219[2]	3	63	18	182[2]	31	162[2]	110–229
Lung	188	122[2]	211	131[2]	251	118[2]	650	123[2]	114–133
Pleura	5	187	15	317[2]	12	168	32	220[2]	150–310
Kidney	21	83	56	151[2]	97	125	174	124[2]	107–144
Bladder	34	117	121	146[2]	134	98	289	117[2]	104–131
Melanoma	13	62	42	84	64	88	119	83[3]	69–99

Notes:
(1) No. = observed number of cases.
(2) SIRs are significantly elevated.
(3) SIRs are significantly reduced.

Data from Andersen et al., Ref. 6.

rates were significantly elevated in five organs: gall bladder, lung, pleura, kidney, and bladder (Table 7). Cancer of the pleura (95% of these cases are classified as mesothelioma) had the highest combined SIR, but when the countries were considered separately, it was significantly elevated only in Norway. The SIR values for cancer of the kidney and bladder were also significantly elevated only in Norway. While the incidence of cancer of the gall bladder was significantly elevated in two of the three participating countries, the investigators noted that the increased incidence of gall bladder cancer in welders was based on only twelve excess cases and may have been due to chance.

Lung cancer was significantly elevated in welders from all three participating countries and was also found to be the most frequent type of cancer among all men in all occupations in the study. In welders, the incidence of melanoma was significantly lower than the incidence in the general population of the participating countries. SIRs for all cancers combined ranged from 79 for farmers to 159 for waiters. Welders had a slightly elevated risk for all cancers combined (3678 cases, SIR = 107, CI = 103–110), which was statistically significant. A potential weakness in the study noted by the investigators was that the occupations of the participants were derived from the 1970 census data from each participating country, and it is clear that, for some persons, the occupation in 1970 was not representative of their entire working lives. The likelihood for staying within one occupation increases with the skills and training required for the type of work performed, so the welders may have been one of the more stable occupational groups.

9.1 Cancer of the Respiratory Tract. Becker (Ref. 18) updated a historical study of cancer mortality among welders in Germany, which began in 1980 (Ref. 19), to include deaths that occurred through 1995. The original study population consisted of 1,213 welders and a control group of 1,688 machinists, all of whom had worked for at least 6 months between 1950 and 1970. Smoking habits were similar for both welders and controls; no information concerning direct exposure to asbestos was collected. By the end of the 1995 follow-up, 274 of the welders and 448 of the controls had died. There was a higher mortality from all causes and from all cancers among welders who used only SMAW compared with welders who did not use SMAW or who used SMAW only part of the time. But differences in the mortality rates were not statistically significant. The brain was the only organ site for which significant differences were observed between welders who worked exclusively with SMAW and those who did not. All four deaths from brain tumors in the cohort of 1,213 German welders were found in this subgroup of welders (0.6 deaths were expected, based on the incidence rate in the general population).

Compared with the control group, the welders had a significantly elevated relative risk (RR, see definitions of epidemiological terms in Appendix B) of dying from cancer of all causes (RR = 1.35, CI = 1.02–1.81). As had been found in past surveys of this cohort, the increased relative risk for lung cancer was not statistically significant (RR = 1.3, CI = 0.8–2.12). In contrast, a highly significant increase in mesothelioma was observed among the welders. There were seven deaths from mesothelioma in the cohort of welders compared with a predicted number of less than one, based on the occurrence of mesothe-

lioma in the general population (standardized mortality ratio, SMR = 1180, CI = 473–2430). Exposure to asbestos is recognized as the primary cause of mesothelioma, and asbestos exposure is also associated with cancers of the lung, especially among smokers. Becker assumed there to be a ratio of 1:1 between asbestos-related lung cancer deaths and those from mesothelioma. According to this estimate, which Becker considered to be conservative, seven of the deaths from lung cancer among welders in the cohort could be attributed to asbestos exposure. Once the seven asbestos-related cases were taken into account, the risk of lung cancer among welders no longer differed from that of the general population. Becker concluded, "the observed occupation-related increase of cancer mortality [among welders in this study] is likely to be predominantly due to asbestos exposure."

Using data collected in a prospective study that started in 1986 in the Netherlands (Ref. 199), Van Loon et al. investigated the risk of lung cancer associated with the known or suspected occupational carcinogens asbestos, paint dust, polycyclic aromatic hydrocarbons (PAH), and welding fumes (Ref. 201). The study population consisted of 58,279 Dutch men, who had responded to a questionnaire sent to members of the general population age 55–69, in 1986. A subcohort of 1630 cancer-free men was randomly selected from the study population and was followed for data analysis. Using national and regional cancer registries, 677 incident lung cancer cases were identified in the study population between September 1986 and December 1992. Complete job histories were obtained for 524 of those cases and 1316 men in the subcohort. A cumulative estimate of exposure to each of the identified potential carcinogens was derived for each of these subjects by multiplying his estimated probability of exposure (developed from the job histories by two industrial health professionals) by his years of experience. The estimated cumulative exposures were then ranked as none, low, medium, and high. Relative risks (RR) were computed for each occupational carcinogen using the subcohort to represent the study population Men with the highest estimated cumulative exposures to asbestos had the greatest relative risk for lung cancer (RR = 3.49, CI = 1.69–7.18), and the trend for increased risk with increasing exposure to asbestos was statistically significant. Although the increased relative risks for lung cancer associated with paint dust and PAHs were not significant, the trend towards increased risk with increasing exposure was significant for both of these factors. The positive association that was found between the estimated cumulative exposure to welding fumes and the risk of lung cancer became non-significant after the data were adjusted for exposure to asbestos, paint dust, and PAHs. Furthermore, the risk for lung cancer was not elevated at the highest estimated level of exposure to welding fumes.

The authors concluded that, after adjustment for smoking and diet, 11.6% of lung cancer in men is attributable to lifetime occupational exposure to asbestos.

Using these data, Van Loon (Ref. 200) analyzed the risks for lung cancer in terms of socioeconomic status and found that higher status, as measured by the highest attained level of education, was significantly associated with a decreased relative risk for lung cancer. The relative risk at the highest level of education ("university or higher vocational") remained significantly lower than that of the lowest level (primary school) after adjustment for smoking and for occupational exposure to the risk factors (asbestos, paint dust, PAHs, and welding fumes) considered above (RR = 0.53, CI = 0.34–0.84).

Jockel et al. (Ref. 99) performed a case-control study of the association between exposure to asbestos and lung cancer. Cases were 839 German males newly diagnosed with lung cancer. An equal number of men, randomly drawn from registries of residents, and matched with the cases by age and area of residence, served as controls. All were interviewed for lifetime job histories, smoking habits, and medical history. A series of 19 questions was used for quantifying exposure to asbestos, and those participants whose work histories indicated welding experience were further interviewed to determine the type of welding performed, metals welded, experience welding coated metals, and the duration and frequency of welding. After adjustment was made for smoking, cumulative exposure to asbestos of more than 5280 working hours was associated with a significantly increased risk of lung cancer (OR = 1.47, CI = 1.04–2.07). Major occupational groups associated with at least a 50% statistically significant excess risk of lung cancer included metal production and processing, mechanics and plumbers, and engine/vehicle building; the cumulative welding experience in these groups was nearly twice that in all study subjects combined. After adjustment for smoking and asbestos exposure, there was a significantly increased odds ratio for lung cancer for subjects who had ever held the job title of welder (OR = 1.93, CI = 1.03–3.61). However, the adjusted odds ratios for lung cancer decreased with increasing cumulative welding experience. For cumulative welding exposures of less than 1,000 hours, the OR was 1.38 (CI = 0.91–2.09); for 1,000 to 6,000 hours, the OR was 1.14 (CI = 0.73–1.79); and for more than 6,000 hours, the OR for was 1.10 (CI = 0.73–1.66). Welders who had ever worked in the aircraft/aerospace industry had an increased risk for lung cancer after adjustment for smoking and asbestos exposure. In a preliminary report on this study (Ref. 98), Jockel et al. had suggested that beryllium may play a role in the higher risk of lung cancer that was seen in this industry, but the number of beryllium-exposed welders in this study was too small to test this hypothesis. They noted that welding has been

associated with a moderately increased risk of developing lung cancer in other investigations but concluded that it is not clear from their work that welding fumes and metal dusts associated with welding are responsible for the observed excess risk.

Ahrens et al. (Ref. 4) combined data from two large case-control studies of lung cancer conducted in different parts of western and eastern Germany (the former Federal Republic of Germany and German Democratic Republic, respectively) The pooled studies comprised 3541 male cases and 3498 population-based controls. After adjustment for smoking and asbestos exposure, employment as a welder or burner resulted in a statistically significant increased risk for lung cancer among the combined population (OR = 1.5, CI = 1.08–2.09). No correlation was found between the duration of the welding experience and the development of lung cancer. In western Germany, 25% of the lung cancer cases, compared with 19% of the controls, described welding as part of their jobs (OR = 1.21, CI = 1.02–1.43), but an association between welding and lung cancer was not observed in eastern Germany. Welding of mild steel for more than 30 years was associated with a significantly increased risk for lung cancer (OR = 1.71, CI = 1.20–2.44) in western Germany, but the risk was smaller among eastern German mild steel welders and was non-significant (OR = 1.08, CI = 0.59–1.98). According to the authors, these results clearly demonstrate the confounding effects of smoking and asbestos, but adjusting for those exposures did not account for all of the excess risk for lung cancer among mild steel welders in western Germany. The differences between eastern and western Germany could not be explained.

Teschke et al. (Ref. 188) conducted a case-control study of occupation and mesothelioma in British Columbia to determine whether there were previously unrecognized sources of asbestos exposure in that area. The occupations and exposures of 51 (92% male) mesothelioma patients were compared with those of 154 (82% male) sex- and age-matched controls randomly selected from the provincial voters list. The risk for mesothelioma was significantly elevated for sheet metal workers, plumbers and pipefitters, shipbuilding workers, and painters. The risk for welders was elevated, but it was not statistically significant (OR = 3.9, CI = 0.8–22).

Hilt (Ref. 82) examined the records of the Department of Labour Inspection in Norway and noted that 161 (4.6%) of the 3,510 lung cancer cases in Norwegian men diagnosed between 1991 and 1993 had been reported by their physicians as being work-related. Multiple exposures were reported for many of the cases. The primary exposures to which the 161 cancer cases were most frequently attributed were asbestos (148 cases), nickel (21 cases), crystalline silica (18 cases), PAH (11 cases), and welding fumes (7 cases). While seven of the men had reported exposures to welding fumes, only one was a career welder.

De Silva et al. (Ref. 54) conducted a retrospective study to evaluate mortality rates from cancers of the lungs and pleura in a cohort of 199 welders who had worked at a U.S. military depot where tanks had been disassembled, refitted and repaired since the 1940s. Stainless steel welding fumes, cadmium in weather resistant paints, and asbestos were among the known and suspected carcinogens to which welders had been exposed. All welders who were employed at the depot at any time between 1966 and 1980, the period of greatest exposure to potential carcinogens, were included in the study. Causes of death were obtained from death records. The estimated risks of death from all malignant cancers and from cancer of the lungs and pleura among these welders did not differ significantly from those of the general population.

Milatou-Smith et al. (Ref. 132) updated a study that was designed to compare the mortality rates from lung cancer in welders who had been exposed to fumes containing high and low levels of hexavalent chromium. Analyses of mortality through 1984 had been published previously (Refs. 167, 169). The high-exposure group consisted of 233 men who had been exposed to fumes from SMAW of stainless steel for at least 5 years between 1950 and 1965. A cohort of 208 welders employed for at least 5 years during the same period by the national railway system, formed the low-exposure group. The railway track welders used thermite[5] welding, which does not involve chromium, and GMAW, which generates substantially less soluble Cr(VI) than SMAW. The two cohorts were followed until the end of 1992. The total number of deaths from all causes and the number of deaths from all malignant tumors among the stainless steel workers were both lower than expected based on Swedish national rates. The total number of deaths from lung cancer in this group was higher than expected, but the increase was not statistically significant (SMR = 164, CI = 60–358). Compared with the railway track welders, the stainless steel welders had a greater, but non-significant relative risk of death from lung cancer (RR = 3.98, CI = 0.84–18.8). Despite the lack of statistical significance, and because the stainless steel welders were exposed to higher levels of chromium than the railway track welders, Milatou-Smith et al. concluded that their study supports the overall evaluation by the International Agency for Research on Cancer (#IARC) that Cr(VI) is carcinogenic to humans (Ref. 91).

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5. Thermite is a mixture of finely-divided metallic aluminum and ferric oxide that when ignited produces extremely high temperatures as the result of the union of the aluminum with the oxygen of the oxide.

Table 8
Standardized Mortality Rates (SMR) in the
European Cohort of Welders in Relation to Lung Cancer

Years Employed as a Welder	All Welders Combined		Stainless Steel Ever Welders		Predominantly Stainless Steel Welders		Mild Steel Welders		Shipyard Welders	
	SMR	No. Cases[1]	SMR	No. Cases	SMR	No. Cases	SMR	No. Cases	SMR	No. Cases
>20	—	—	152	22	174	13	198[2]	25	107	25
0–10	—	—	157	13	176	11	173	15	96	10
All	134	116	128	39	123	20	179[2]	40	136	36

Notes:
(1) No. Cases = Number of lung cancer cases
(2) Statistically significant (P<0.05).

Data from Simonato, Ref. 165.

On the other hand, a letter to the editor (Ref. 8) disputed the contribution to lung cancer of nickel and Cr(VI) from welding of stainless steel. It cited a large European study of lung cancer in welders published in 1991 (Ref. 165) that showed a statistically significant excess mortality from lung cancer only among welders of mild steel (see Table 8).

Matos (Ref. 128) analyzed the risks for lung cancer associated with occupational exposures in Argentinean men. All male lung cancer cases who were residents of Buenos Aires or who were admitted to four hospitals in that city during a 2-year period ending in March, 1996, were eligible for the study. Of these men, 200 were able to complete interviews with the investigators, as were 397 hospital-based controls, who had been admitted for conditions unrelated to tobacco use and were matched to the cases by age and hospital. Among the industries studied, increased odds ratios for lung cancer were found in workers in the alcoholic beverages, chemicals/plastics, pottery/glass/minerals, and sawmills/woodmills industries. Among occupations, only salesmen had significantly elevated odds ratios for lung cancer. A non-significant 50% increase in risk for lung cancer was found among welders (OR = 1.5, CI = 0.4–4.3).

Rosario City, the second-largest urban area in Argentina, has a greater-than-average incidence of lung cancer. Pezzotto and Poletto (Ref. 149) conducted a case-control study of occupational risks for lung cancer, interviewing all 367 males newly diagnosed with primary lung cancer and admitted to any of three hospitals in Rosario City. The 586 age-matched controls were selected from patients admitted to the same three hospitals for diseases unrelated to smoking. All cases and controls responded to a questionnaire on job history and smoking habits.

Cases and controls who had never worked in occupations involving exposure to any of the agents classified by IARC as known or possible human carcinogens were categorized as unexposed administrative workers. Odds ratios for lung cancer were computed and adjusted for age and smoking history. Significantly elevated risks for all lung cancers (OR = 1.6, CI = 1.1–2.3) and for squamous cell cancer of the lung (OR = 2.0, CI = 1.2–3.6) were found for the population of exposed workers. A significant excess risk for squamous cell cancer of the lung was found for welders (OR = 2.9, CI = 1.0–10.1), but the slightly increased risk among welders for all lung cancers combined was not significant (OR = 1.1, CI = 0.4–3.1).

Droste et al. (Ref. 60) conducted a case-control study to investigate the relationship between lung cancer and occupational exposure to carcinogens. The 478 cases with lung cancer were recruited from ten hospitals in the Antwerp region of Belgium between 1995 and 1998. The 536 controls were male patients in the same hospitals who did not have any type of cancer or respiratory tract ailment. All subjects were men who had lived or worked in the region since 1969. All participants provided historical information about tobacco use, jobs held for at least 6 months, and specific occupational exposures to known carcinogens. The carcinogens addressed in the study included nickel and chromium. Welding fume exposure was not specifically identified. After adjustment was made for age, smoking, and socioeconomic status, workers in the metal goods manufacturing category in which welders were included had significantly increased odds ratios for lung cancer (OR = 1.6, CI = 1.0–2.5). Exposure to chromium for longer than 30 years was associated with a significant excess risk for lung cancer (OR = 1.7,

CI = 1.0–2.8). No other exposures to chromium or nickel were significantly associated with an excess risk for the disease.

Stern et al. (Ref. 176) analyzed causes of death and employment history for 13,301 members of the International Union of Bridge, Structural, and Ornamental Ironworkers who had died between 1984 and 1991. Mortality from all malignancies (n = 3,682, SMR = 109, CI = 106–113) and from lung cancer (n = 1,523, SMR = 128, CI = 121–135) was significantly increased among the deceased workers compared with the general population. Compared with the entire group of ironworkers, welders had significantly greater than expected mortality from all cancers (n = 237, SMR = 115, p < 0.05) and from falls (n = 13, SMR = 374, p < 0.01), but the observed increase in mortality from lung cancer was not statistically significant (n = 92, SMR = 123, p > 0.05).

Danielsen et al. (Ref. 52) investigated the incidence of lung cancer among 428 Norwegian shipyard welders. The welders had been examined for siderosis in 1975, and they were followed until 1992. The death rate from all causes was lower in this group of welders than in the general population, which was attributed by the authors to the healthy worker effect. An excess number of lung cancers (SIR = 155, CI = 74–284), was observed among the welders compared with the general population, but this was not statistically significant. The relative incidence of cancer increased with increasing years since first exposure as a welder but this relationship did not become significant even after more than 40 years. There was no relationship between having been diagnosed with siderosis in 1975 and mortality from lung cancer in the following 17 years.

Haskovcova et al. (Ref. 79) described the case of a 68-year-old man diagnosed with siderosis complicated by severe chronic inflammation and extensive fibrosis. He subsequently developed epidermoid cancer in the affected area of the lungs. During the 34 years prior to the diagnosis, he had been employed as a full-time welder for 4 years and performed welding operations occasionally after that.

Concern about the high incidence of pneumoconiosis (dust deposits in the lung) and lung cancer among industrial workers in China led Liu et al. (Refs. 121, 122) to investigate whether lung tumors associated with pneumoconiosis may originate via a genetic mechanism distinct from those which are non-occupational in origin. While their work has focused on mutations in suppressor genes isolated from lung tumors from workers with silicosis, Liu et al. also examined tumors from workers exposed to asbestos or welding fumes. Suppressor genes regulate the cell cycle and protect the cell from damage to its genome. They normally limit the growth of tumors, but, when they are mutated, suppressor genes may fail to

keep a tumor from growing. Mutations of the p53 suppressor gene are the most common genetic lesions found in human cancers. Mutations associated with cancer can occur in different sections of the gene called exons that carry the code for the gene's protein product. In different individuals, cancers of a particular organ may be associated with mutations in different exons.

Liu et al. used molecular biology techniques to compare mutations of the p53 gene in lung tumor specimens from 36 workers who had been exposed to silica, 10 who had been exposed to asbestos, and 6 who had been exposed to welding fumes. All of these workers had been diagnosed with pneumoconiosis as well as lung cancer. Examination for mutations was confined to the four exons of the p53 gene (exons 58) where most mutations are known to occur. They found that most of the mutations were clustered in exon 8 (50% of those in cells from asbestos-exposed workers, 44% in those exposed to silica, and 75% in those exposed to welding fumes). Liu et al. compared their data with those of other investigators who have reported that the mutation frequency of exon 8 in lung cancer specimens taken from persons in the general population range from 17.5% to 23.5%. They concluded that differences between their data and those of other investigators may indicate that DNA damage in lung tumors associated with exposure to silica, asbestos, or welding fumes may arise by a different mechanism than do tumors associated with other causes such as tobacco smoke.

9.2 Nasal and Bladder Cancer. A case-control study of bladder and nasal cancer in workers conducted by Teschke et al. (Ref. 189) was part of the study that included mesothelioma discussed in 9.1 (Ref. 188). All cases at least 19 years old and registered with the British Columbia Cancer Agency between 1990 and 1992 were eligible for the study. Controls were randomly selected from the provincial voter list. Since bladder cancer tends to occur at a younger age in persons with industrial backgrounds than in non-industrial workers, cases with bladder cancer were restricted to those born after 1915 in order to increase the proportion of industrial workers among the cases with this disease. The 48 cases of nasal cancer and the 105 cases of bladder cancer were compared with 159 and 139 age- and sex-matched controls, respectively. The difference in the number of controls used for the two cancer sites was related to the age cut-off in the bladder cancer group. All subjects were interviewed in person or by telephone to obtain occupational, residential, smoking, and medical histories and information about exposures to materials considered to be known or probable carcinogens by the International Agency for Research on Cancer (IARC#). Textile workers had the highest risk for nasal cancer (6 cases, OR = 7.6, CI = 1.4–56.6). An increased risk for bladder cancer was found for miners,

drillers, and blasters (19 cases, OR = 4.5, CI = 1.6–14.7). The data for welders showed a non-significant elevation in the risk for nasal cancer (2 cases, OR = 3.5, CI = 0.2–53.7). Welders did not have an increased risk for bladder cancer (4 cases, OR = 0.9. CI = 0.2–5.6). As stated by the investigators, the main limitation of this study was its small size, which could have resulted in imprecise odds ratios.

In contrast to this study, bladder cancer was found to be significantly elevated in welders in the Scandinavian cohort study of Andersen et al. (Ref. 6) described in 9.1. However, the excess risk in the combined countries was only 17%, and when the bladder cancer rate was analyzed in each country separately, it was significantly elevated only in Norway.

9.3 Cancer of the Mouth and Throat. The incidence of cancer of the oral cavity, pharynx (throat), and esophagus has been increasing and that of cancer of the larynx has decreased over the last 20 years in Sweden. To investigate life style and occupational exposures that might contribute to the development of squamous cell carcinoma in these organs, Gustavsson et al. (Ref. 76) conducted a community-based case-control study. The 545 cases were all men aged 40–79 who lived in two densely populated regions of southern Sweden and were diagnosed with one of these types of cancer between1988 and 1990. They were identified through regional hospital records and cancer registries. The 641 age-matched controls were randomly selected from computerized population registers of persons residing in the same geographical region as the cases. Information concerning relevant life style factors, occupational histories, and work tasks was obtained by interview. An industrial hygienist assessed the intensity of the exposure to 17 specific occupational factors, including asbestos, metal dusts, welding fumes, chromium, and nickel. Relative risks for cancer were adjusted for geographical region, age, and alcohol and tobacco consumption.

The analyses of individual factors showed a significantly increased risk of laryngeal cancer with exposure to asbestos. This observation was supported by a positive dose-response relationship as high exposures to asbestos led to greater relative risks for the disease than did low exposures. Exposure to PAH was associated with cancer of the esophagus but the dose-response relationship was negative. Statistically significant risks of pharyngeal cancer (RR = 2.3, CI = 1.1–4.7) and laryngeal cancer (RR# = 2.0, CI = 1.0–3.7) were associated with more than 8 years of exposure to welding fumes. Exposures to welding fumes were not associated with a risk for cancer of the oral cavity or esophagus.

The risk for oral cancer in Swedish workers was also examined by Schildt et al. (Ref. 162) who conducted a case-control study of the association between occupa-

tions and the incidence of squamous cell oral cancer. Included in the study were 410 cases (134 women, 276 men) of cancer of the mouth that were diagnosed and reported to the Cancer Registry in four counties in northern Sweden between 1980 and 1989. The 410 age- and sex-matched controls resided in the same counties as the cases. Occupational histories were obtained by mailed questionnaires. Pulp industry workers (18 cases, OR = 4.0, CI = 1.2–12) and wood or wood product workers (12 cases, OR = 5.5, CI = 1.2–25) were found to have a significantly increased risk for cancer of the mouth. A non-significantly increased risk was observed for welders (7 cases, OR = 2.3, CI = 0.6–9.1).

9.4 Pancreatic Cancer. Ji et al. (Ref. 97) conducted a population-based case-control study of 451 cases of pancreatic cancer, diagnosed between 1990 and 1993, and identified through the cancer registry in Shanghai, China. The cases, aged 30 to 74, were matched by age and sex with 1552 controls randomly selected from Shanghai residents. Information concerning life style factors, occupational history, and medical history was obtained by person-to-person interviews. Of the occupations considered, employment as an electrician was associated with the greatest risk for pancreatic cancer (11 cases, OR = 7.5, CI = 2.6–21.8), suggesting a possible role for EMFs. Using a job exposure matrix, the authors estimated the risk for pancreatic cancer to be elevated threefold for men who were most likely to have been exposed to EMFs. Among men, elevated risks were also found for metal workers (12 cases, OR = 2.1, CI = 1.0–4.8), toolmakers (16 cases, OR = 3.2, CI = 1.4–7.1), glass manufacturers, potters and construction workers (10 cases, OR = 2.6, CI = 1.1–6.3), and plumbers/welders (10 cases, OR = 3.0, CI = 1.2–7.5). Females classified as plumber/welders were not at an excess risk for pancreatic cancer (4 cases, OR = 1.8, CI = 0.5–6.4). Based on the work of other investigators (Ref. 127), the authors suggested that the elevated risk seen for male plumbers and welders may be related to exposure to PAHs or aromatic amines.

9.5 Non-Hodgkin's Lymphoma, Leukemia, and Multiple Myeloma. In recent years, non-Hodgkin's lymphoma (NHL) has been among the most rapidly increasing malignancies in developed countries. While immunodeficiency is an established risk factor, it does not account for the entire increase in the incidence of this disease (Ref. 66). Fabbro-Peray et al. (Refs. 65, 66) conducted a case-control study to investigate if occupational and environmental exposures to ionizing radiation, electromagnetic fields, and chemical products (e.g., benzene, coal-tar, rubber, pesticides) may be risk factors for NHL. The study was performed in Languedoc-Roussillon, a county in southern France with one of that country's highest rates of NHL. The 445 cases were diagnosed

with NHL between 1992 and1995. All cases were at least 18 years of age and were HIV negative. The 1025 controls were from the same geographical area and were randomly selected from voter lists. Subjects were interviewed to obtain data about medical histories, immune system disorders, professional histories, occupational exposures, and smoking habits. Persons with a history of hives had an increased risk of NHL (OR = 1.7, CI = 1.2–2.2), providing support for the role of immunologic disorders in NHL. Benzene exposure was the greatest risk factor for NHL (OR = 4.6, CI = 1.1–19.2). Radio operators also had an excess risk (OR = 3.1, CI = 1.4–6.6), suggesting a possible role for EMFs. A significantly elevated risk for NHL was associated with daily exposure to welding (23 cases, OR = 2.5, CI = 1.2–5.0). A small, non-significant excess risk was observed for cases who welded at least once weekly but less frequently than 5 days per week (17 cases, OR = 1.4, CI = 0.7–2.9). The authors attributed the excess NHL observed among welders to EMF exposures but it is not possible in this type of study to separate EMF exposures from other types of exposures unprotected welders could have encountered in the workplace.

Prompted by reports that HIV infection is associated with an increased risk for NHL, Holly et al. (Ref. 87) conducted a case-control study of occupational and environmental exposures among HIVpositive and HIVnegative homosexual men in the San Francisco Bay Area. Cases were 312 homosexual men with NHL and controls were 420 homosexual men who were free of this disease. No associations between NHL risk and occupational exposures were found for HIV-positive men. The authors concluded that in these men, the increase in NHL can be attributed to their failing immune systems rather than to occupational or environmental factors. Among HIV-negative subjects, a significant increase in the odds ratio for NHL was associated with exposures to tar, soot, pitch, or ash (OR = 2.3, CI = 0.96–5.6), and non-significant increased risks for NHL were observed among HIV-negative cases who had exposure to herbicides (OR = 2.0, CI = 0.89–4.7) or radioactivity (OR = 4.7, CI = 1.7–13). Men in the combined group of welders and solderers did not have an elevated risk for NHL.

Costantini et al. (Refs. 49, 50) conducted a population-based case-control study of occupational exposures and the hematolymphatic malignancies NHL, leukemia, and multiple myeloma. The study was conducted in twelve different areas of Italy with a combined population of 7 million residents. The 2,737 cases were identified through hospital records and included all men, 20 to 74 years of age, who were diagnosed with hematolymphatic malignancies between 1991 and 1993. The 1,779 controls were randomly selected men who resided in the same area as the cases. Information on tobacco smoking,

Table 9
Standardized Incidence Ratios (SIR) for NHL, Leukemia, and Multiple Myeloma in the Combined Population of Welders in the Multinational Nordic Study

Site	No. Cases	SIR	CI
Hodgkin's disease	30	102	69–145
NHL	113	99	83–120
Multiple myeloma	51	90	67–119
Acute leukemia	36	96	67–132
Other leukemia	64	116	90–149

Data from Andersen et al., Ref. 6.

occupational history, extra-occupational exposure to solvents and pesticides, and medical history was obtained by person-to-person interviews. In this study, welders were found to have a significant, threefold increased risk for multiple myeloma (7 cases, OR = 3.3, CI = 1.3–8.5). The risks for NHL (19 cases, OR = 1.2, CI = 0.6–2.3) and leukemia (6 cases, OR = 0.9, CI = 0.3–2.3) were not elevated in welders.

In their multinational study of occupations and malignancies in the Nordic nations described in Section 9, Andersen et al. (Ref. 6) found no association between welding and–Hodgkin's disease, NHL, multiple myeloma, or leukemia. The data for these diseases is shown in Table 9. Only the data for the three nations (Finland, Norway, and Sweden) combined are shown since none of the SIRs for any of these malignancies were statistically significant in any individual country.

In summary, four studies examined the risk of welders for NHL. A positive association was found only in the study conducted in France by Fabbro-Peray et al. (Refs. 65, 66). Welders were found to have an increased risk for multiple myeloma in the large case-control study conducted by Costantini et al. (Refs. 49, 50) but not in the cohort study conducted by Andersen et al. (Ref. 6). Neither of the latter two studies found an association between welding and leukemia.

9.6 Skin Cancer. Prolonged exposure to solar or UV radiation is a well-established risk factor for skin cancer. Actinic keratosis, a common non-malignant lesion of the outermost layer of the skin (epidermis), is also caused by long-term exposure to UV light. Actinic keratosis may transform into squamous cell carcinoma, a cancer that originates in the middle layer of the epidermis. Basal cell carcinoma, another form of skin cancer that has been associated with exposure to UV radiation, originates in the lowest layer of the epidermis.

Pambor (Ref. 147) described the case of a 57-year-old welder with recurrent dermatitis and keratoses on the sides of his face. Several squamous cell carcinomas were removed from his face. During his 30-year welding career, he had had repeated episodes of erythema (sunburn-like redness of the skin) on the side of his face and occasionally suffered from photokeratitis. He apparently had a heightened sensitivity to UV light since, as a child, he had had recurring sunburns and he had to take precautions to avoid exposure to the sun throughout his life. Because of the possible relationship between his occupational exposure to UV light and the development of skin cancer, his physician recommended that the patient discontinue welding in order to avoid the recurrence of skin cancer.

Donoghue and Sinclair (Ref. 59) described the case of a 45-year-old boilermaker with a basal cell carcinoma on the sternal angle (an area on the central upper chest) which was frequently exposed by the opening in his v-neck shirt during welding. Throughout his 28-year career, the patient had experienced numerous incidences of erythema with subsequent peeling of the skin on this area of his chest following welding. He had welded mostly mild steel, using SMAW during the first 4 years and using primarily GMAW thereafter. He also occasionally welded aluminum, cast iron, and stainless steel. He indicated that he did not tan readily and had experienced frequent sunburn. Unlike the welder in the case reported by Pambor, no solar keratoses were found on his face or other areas of exposed skin.

9.7. Cancer in Children of Welders: Neuroblastoma. Neuroblastoma, a tumor of the nervous system, is the most common tumor found in infants, and about 75 % of cases are found in children under 5 years of age. Olshan et al. conducted a case-control study to evaluate parental occupation and the risk of neuroblastoma (Ref. 146). The 504 cases were under 19 years of age and were newly diagnosed with neuroblastoma during the period 1992 to 1996 in 139 participating hospitals in the U.S.A. and Canada. Controls were obtained by telephone random digit dialing. Each case was matched with one control on the basis of age. Interviews were conducted to determine occupational activities of both parents during the 3 months before conception, during each of the trimesters of pregnancy, and after birth until the time of diagnosis. Parental occupations were classified into 73 paternal and 57 maternal occupational groups. Offspring of fathers employed as broadcast, telephone and dispatch operators, electrical power installers and power plant operators, landscapers and groundskeepers, and painters had an increased risk of neuroblastoma, but the results were not always statistically significant. A non-significantly decreased risk for neuroblastoma was found in children of welders and cutters (OR = 0.5, CI = 0.1–1.6). The inves-

tigators noted that while the size of the study was large, the small numbers of parents in many occupational groups limited the power of the study to discern significant effects. Their results suggested a potential association between neuroblastoma and parental exposure to metals, pesticides, solvents, and EMFs. This finding of an association between neuroblastoma and high exposures to EMFs but not welding and cutting is consistent with other studies of diseases that have been associated with exposure to EMFs (Ref. 190). Although welders are thought to be among the workers with the highest exposure to EMFs (see Section 6), they are not often found to have a significant risk for the EMF-linked diseases under study.

10. Metal Fume Fever

Metal fume fever is a short-lived illness, caused by excessive inhalation of zinc oxide (ZnO) and some other metal fumes. Its flu-like symptoms (e.g., fatigue, muscle ache, weakness, coughing) develop within several hours of exposure and resolve within 24 hours of onset. It is characterized by an increased number of neutrophils (a type of leukocyte) in bronchoalveolar lavage fluid (BALF). Van Pee et al. (Ref. 202) described a typical case of metal fume fever. A 23-year-old man who became ill 3 hours after completing a work shift in which he had been welding galvanized steel without wearing a respirator. He reported to the emergency room with fever, shortness of breath, cough, chest pain, headache, muscle aches, and nausea. Examination showed elevated fever and an increased number of neutrophils in the blood. He recovered completely about 12 hours after the onset of illness.

Studies by Blanc et al. (Ref. 25) have suggested that metal fume fever is mediated by cytokines that are released from leukocytes during phagocytosis (a process by which macrophages and other leukocytes engulf foreign particles) of metal oxide particles. Cytokines are mediators that can elicit reactions in distant cells or tissues. Some cytokines (e.g., TNF, IL-1) are pyrogens and can cause an elevation in body temperature. IL-8 is a chemo-attractant, and can elicit the migration of neutrophils into an area of inflammation.

In a continuation of studies of the pulmonary inflammatory response that characterizes metal fume fever, Kuschner et al. (Ref. 115) measured cytokine concentrations in BALF collected from 15 healthy volunteers 3 hours after inhalation exposure to zinc oxide (ZnO) fumes. The volunteers were exposed via face mask to ultrafine ZnO particles of various concentrations (median 33 mg/m^3) for 10 to 30 minutes. The subjects served as

their own controls and the results of these tests were compared with cytokine concentrations in BALF collected 4 weeks later following sham exposure to clean air.

At 3 hours after exposure, the concentrations of all of the cytokines measured, interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor (TNF), were significantly higher than those found in BALF following the sham exposure. The numbers of white blood cells (macrophages, neutrophils, lymphocytes) were not elevated at this time. The concentrations of all the cytokines, except IL-1, were positively related to the ZnO dose. Comparison with data obtained in an earlier study (Ref. 114) showed that TNF, but not the other cytokines declined significantly by 20 hours after exposure. On the other hand, neutrophils were significantly higher in BALF collected at 20 hours than in that collected at 3 hours. These data support earlier reports by these investigators that cytokine levels become elevated soon after exposure to ZnO (Ref. 25), suggesting that they play a role in mediating metal fume fever. The investigators iterated their hypothesis that TNF plays an important role in mediating metal fume fever as early as 3 hours after exposure to ZnO fumes. The elevation of IL-8, a known chemo-attractant for neutrophils, precedes the appearance of elevated white blood cell numbers in BALF.

In a parallel experiment, Kuschner et al. (Ref. 116) used magnesium oxide (MgO) instead of ZnO to determine if the cytokine response was a general response to inhalation of any type of fine metallic particles or if it was specific to ZnO. Six volunteers were exposed to 6 to 230 mg/m³ MgO particles less than 1.8 μm in diameter for different periods of time. The subjects served as their own controls as in the experiment with ZnO described above. No changes in pulmonary function were observed during the 20 hours following exposure, and none of the subjects experienced any of the symptoms of metal fume fever. Analyses of BALF showed no significant changes in the concentrations of any of the four cytokines studied (IL-1, IL-6, IL-8, and TNF) or in the numbers of white blood cells (neutrophils, macrophages, and lymphocytes) in BALF. The investigators concluded that chemical composition as well as particle size determine the respiratory effects of inhaled fine particles.

11. Effects on the Eye and Vision

11.1 Retina. Visible light (400–780 nm) and near infrared (780–1,400 nm) are only minimally absorbed by the lens and cornea and pass unobstructed to the retina (Ref. 183). Short exposures to intense radiation in these wavelengths can injure the retina. Short exposures to intense

The resulting disorder is known as solar retinopathy when it is caused by gazing at the sun or as arc welding retinopathy when it is caused by viewing the welding arc. Since this condition affects the macula (a small oval area on the inner surface of the retina near the optic nerve), it is also referred to as arc welding maculopathy. The macula may appear normal immediately after exposure, but a well-defined lesion develops in the fovea (an area in the center of the macula that is essential for vision) over the next few weeks. Visual acuity is usually reduced within a few days after exposure. In many cases, it returns to normal within a year, although a lesion may remain on the macula (Ref. 179). In some patients, the quality of vision is permanently affected by a blind spot or distortions.

Stokkermans and Dunbar (Ref. 179) reviewed the records of patients diagnosed with solar retinopathy during routine eye examinations conducted over a 26-month period in 1995–1997 at the primary care eye clinic of the Bascom Palmer Eye Institute in Florida. Of the 14,500 patients examined at the clinic during this period, 20 patients were found to have macular lesions indicative of solar retinopathy. Twelve of the patients reported having gazed into the sun and three reported having looked at the welding arc without eye protection. None of the welders had experienced ocular discomfort after viewing the arc. All of the patients had good visual acuity (20/25 in one of the welders and 20/20 in two) but two of the welders had visual field defects, such as blind spots. One of the welders also reported having looked at the sun during a solar eclipse, so that his condition could have been attributed to either or both of these sources.

Denk et al. (Ref. 56) described the case of a 38-year-old man who developed a reduction in vision in both eyes and had acute ocular pain after having used arc welding equipment for 2 hours without proper eye protection. Examination by his local ophthalmologist revealed a lesion in the fovea of both eyes but, based on his symptoms, his condition was diagnosed as photokeratitis. Further examinations 9 months later at the University eye clinic in Tubingen, Germany, revealed visual field defects in both eyes and a macular lesion in one eye. Denk et al. concluded that, as a result of exposure to optical radiation while welding, the patient had developed arc welding maculopathy which had been masked by photokeratitis during the first days after exposure.

Central serous chorioretinopathy (CSCR) is a retinal disorder in which fluid accumulates under the macula. The buildup of fluid appears to be due to one or more small breaks in the retinal pigment epithelium (a single cell layer that lines the back of the retina). Usually the fluid buildup disappears after a few weeks to a few months with little long term damage. Some patients will have residual symptoms such as decreased color and contrast sensitivity, distorted or blurry vision, and blind

spots. CSCR primarily affects men between the ages of 20 and 45. About half the persons with this disorder experience one or more recurrences. The cause is unknown and CSCR has not previously been associated with welding.

Adelberg (Ref. 2) obtained occupational histories for 17 patients that came to his ophthalmologic practice with signs of CSCR. All of the patients had been welders for 5 to 30 years before the onset of symptoms. Eleven had experienced photokeratitis from exposure to the welding arc. Adelberg concluded that the CSCR observed in these patients was associated with their welding exposures. He postulated that retinal pigment epithelial lesions caused by welding arc maculopathy may change years after exposure to become manifest as CSCR.

Another type of lesion in the retinal epithelium, subretinal neovascularization, was observed in a welder by Kozielec and Smith (Ref. 111). This condition accounts for 10% of age-related macular degeneration, which is a major cause of partial or complete loss of vision in the elderly. Subretinal neovascularization is characterized by an abnormal proliferation of blood vessels in the choroid, a vascular tissue located behind the retina. These vessels can leak fluid and cause an elevation or detachment of the macula, potentially leading to a loss of central or detailed vision.

When the welder examined by Kozielec and Smith (Ref. 111) sought medical attention, he was experiencing blurred vision in his left eye. This condition was attributed to his use of SMAW without wearing eye protection on four occasions over a 5-year period. On each of these occasions, he developed photokeratitis. His vision became blurred 1 week after the fourth incident, and he was seen by an ophthalmologist 2 weeks later. Examination revealed a blind spot in the vision of his left eye and macular lesions in both eyes. Subretinal neovascularization was found in the left eye and was successfully treated by laser surgery. The authors concluded that welding arc injury should be considered a risk factor for subretinal neovascularization.

11.2 Eye Protection. An eye drop preparation containing 8-hydroxy-1-methylchinolinium methylsulphate, designed for protection against both solar and artificial UV radiation, is commercially available in parts of Europe. In a study designed to measure the degree of protection that these drops could provide against exposure to UV radiation, Daxer et al. (Ref. 53) examined the absorption of spectral transmissions in the wavelength range 250 to 500 nm by commercial preparations of the eye drops. Using a 1,000-watt halogen lamp as the light source, the investigators measured the transmission of radiation in the visible/UV spectrum through films of varying thickness made by allowing the eye drop to spread on a UV-transparent quartz plate.

A thick droplet layer, equal to or greater than 500 μm, was very effective in blocking transmission of radiation in the entire wavelength range tested. However, a liquid layer of about 10 μm, which corresponds to the thickness of the film of tears normally coating the human eye, allowed the transmission of about 25–50% of the UV-C radiation (100–280 nm) and more than 90% of optical radiation with wavelengths between 290 and 500 nm (UV-B, UV-A, and visible light). Because UV-C is absorbed from sunlight by the ozone layer, the solar UV radiation between 290 and 400 nm is of greatest concern. Film thicknesses that could be sustained in the eye proved to be ineffective in preventing transmission of these wavelengths. Based on the threshold UV dose known to produce solar photokeratitis, it was calculated that the eye drops would provide less than 7% protection, and it was concluded that this pharmaceutical preparation would not provide sufficient protection against solar radiation. The eye drop preparation was more effective, however, in absorbing UV-C, which is a major component of the radiation produced by arc welding. The investigators calculated that the eye drops would provide about 35% protection against photokeratitis during unprotected exposure to the welding arc. They caution that this is insufficient to protect the eyes from injury due to optical radiation.

Oduntan (Ref. 144) surveyed the use of eye protection by 339 welders in Lagos, Nigeria. Information about welding experience and data concerning the number of hours welded, use of eye protection, type of welding performed, and ocular discomfort experienced in the week preceding the survey was obtained by questionnaire. The mean age of the welders was 32 years and their mean welding experience was 12 years. Arc welding equipment was used by 84% of the welders, and the others performed oxyacetylene welding. Welding goggles were worn by 44% of the welders, 46% wore sunglasses, and 10% used no eye protection. The use of eye protection was not consistent, even among some who usually wore goggles, as 63% of the respondents reported wearing no eye protection for periods ranging from a few minutes to 8 hours during the week before the survey. During the week prior to the survey, 81% of the respondents had experienced exposure to nearby welding arcs for periods of 5 minutes to 10 hours during the previous week. Foreign body injury to the eye was experienced by 28% of the welders during the week before the survey. Oduntan compared these data with the results of a similar survey conducted in Australia by TenKate and Collins in 1990 (Ref. 187). In the Australian study, only 11% of the welders reported experiencing foreign bodies in their eyes during the week preceding that survey. This difference was presumably due to the more extensive use of eye protection in Australia. Oduntan attributed the

inadequate safety practices among Nigerian welders in part to the lack of understanding of the ocular hazards associated with welding and in part to the lack of safety standards for welders in Nigeria.

12. Effects on the Nervous System: Aluminum

Results of studies of the effects of occupational exposure to aluminum on neurobehavioral and cognitive functions have been inconsistent, in part because different methods of assessment of cognitive function have been used in different studies and in part because of variations in the magnitude of exposure of subjects to aluminum (Ref. 5). Akila et al. conducted a cross-sectional study of cognitive function in welders with up to 23 years' experience performing GMAW of aluminum (Ref. 5). Participants worked at ten companies where aluminum welding with GMAW had been used for a long time. Two of the companies also employed mild steel welders, who were used as controls. None of the participants was exposed to other neurotoxic substances in the workplace. Information concerning occupational history, past exposures to neurotoxic agents, and general heath and life style was obtained by interviews with a physician. Aluminum concentrations in urine and serum were determined for each participant using the method developed by Valkonen and Aitio (Ref. 197) described in 1.2 of this volume. Based on their urinary aluminum concentrations, the welders were grouped as reference (n = 28, <1 µmol/L urine), low exposure (n = 27, 1.1 – 4.0 µmol/L), and high exposure (n = 24, >4.1 µmol/L). The three female welders belonged to the highest exposure group, but they were excluded from the remainder of the study because there were no female referents with whom they could be compared. A test battery of 16 tasks, administered to each participant, was used to evaluate psychomotor function, simple visual reaction time, performance of attention-related tasks, verbal and visual or visuospatial abilities, and verbal and visual learning and memory.

The aluminum welders performed as well as the mild steel welders on the psychomotor function tests, the verbal memory tasks, and two of the four attention tests. Deficits in the test of memory for designs (a test for memory and learning) were significant only for the low exposure group (p = 0.029). The low exposure group also performed more poorly than the high exposure and referent groups on the more difficult block design items (a test of visuospatial abilities). Performance on the digit symbol recall task (another test of memory and learning) did not differ between the high and low exposure groups, but the performance of both groups was reduced compared with that of the referents. Finally, the performance

on the forced choice synonyms task (a test of verbal abilities) was significantly reduced in the high exposure group but not in the low exposure group. Four other tests, that examined verbal abilities, visuospatial skills, memory and learning, and attention, showed positive exposure-response relationships, strengthening the probability of an association between the impairment and the exposure to aluminum.

Akila et al. concluded that aluminum exposure was associated with detrimental effects in certain cognitive functions but had no effect on verbal comprehension in these workers. Similarly, immediate visual memory or basic visuoperceptual processes were unimpaired, although processes that involve holding a complex design in memory and that require reproducing that design, as in the difficult block design items test, were impaired. Thus, tasks requiring working memory, particularly that relating to processing of visuospatial information, may be affected in asymptomatic aluminum-exposed workers. The investigators indicated that additional studies are needed to determine whether the deficit lies in the ability to hold the complex design in memory or in the formulation and execution of a plan for reconstructing the design.

Kilburn (Ref. 104) evaluated the published data on the effects on the brain of occupational exposure to fine aluminum particles. Neurobehavioral changes associated with aluminum exposure include tremor, impaired balance, reduced recall memory, and slow speed of cognitive functions, especially those functions that involve dual task and concept juggling and attention. She noted that the recent study of Akila et al. (Ref. 5) demonstrated cognitive impairment in aluminum welders which appears to be proportional to urinary concentrations of aluminum. Their findings were not affected by factors that confounded other studies, such as exposure to neurotoxic chemicals, differences in the methods of assessment, and lack of data concerning body burden of aluminum. She concluded that while substantial evidence supports the hypothesis that aluminum is neurotoxic for human beings, many of the studies performed to date did not sufficiently rule out exposures to other neurotoxic agents. In particular, she noted that commercial aluminum is frequently alloyed with copper, manganese, or zinc, and it is therefore possible that aluminum welders may have significant exposures to manganese which has some effects that are similar to those observed in aluminum workers in some studies. The study of Akila (Ref. 5) did not address whether welding also exposed the workers to manganese. Kilburn suggested that the most sensitive markers of the toxic effects of aluminum that could be used to monitor workers at risk are balance, color-confusion index, visual-field performance, and neuropsychological function by recall memory and concept juggling.

13. Effects on the Nervous System: Manganese

Excessive manganese exposure can result in neurological damage, causing an array of symptoms, referred to as manganism, that resembles those of idiopathic (of unknown cause) Parkinson's disease. As in Parkinson's disease, manganism is a slowly progressing, degenerative disorder of the nervous system, with symptoms that include dystonia (repetitive and patterned movements), tremors when at rest, bradykinesia (sluggish initiation of movements), muscle rigidity, and postural instability (impaired balance, which may lead to a rapid, shuffling gait to prevent falling). The face may become expressionless or "masked" due to loss of control of the facial muscles. While neuropsychiatric changes can occur in both manganism and Parkinson's disease, they are thought to appear earlier in manganism.

Manganism and Parkinson's disease are both caused by degeneration of cells in the area of the brain called the basal ganglia[6], a collection of nuclei deep in the white matter of the cerebral cortex which is one of the movement control centers of the brain and is responsible for producing smooth, coordinated movements. In Parkinson's disease, brain cells in the substantia nigra produce subnormal quantities of dopamine, a neurotransmitter vital to normal nerve function. Treatment with levodopa (L-dopa), a metabolic precursor of dopamine, provides limited relief from symptoms of Parkinson's disease. While idiopathic Parkinson's disease and manganism have very similar symptoms and are very difficult to differentiate, it has been reported that manganism is more resistant to treatment with L-dopa than is Parkinson's disease. Wolters et al. (Refs. 163, 210) found a reduced uptake of 6-[18F]fluorodopa ([18F]-dopa) by the striatum[1] in positron emission tomography (PET#) scans of patients with Parkinson's disease but not with manganism, and this phenomenon has been used to differentiate between the two syndromes. A few cases have been reported in which welders and other workers with parkinsonism who were known to have had excessive exposure to manganese were found to have reduced uptake of [18F]-dopa in PET scans. In these cases, based on the PET scans the investigators attributed the disorder to idiopathic Parkinson's disease with incidental exposure to manganese (Ref. 105) or with a possible partial contribution of manganese to the disorder (Ref. 1).

13.1 Magnetic Resonance Imaging (MRI). In 1989, Newland et al. (Ref. 139) reported that characteristic

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6. Included in the basal ganglia are the accumbens, globus pallidus, substantia nigra, corpus striatum, and subthalamic nucleus. The striatum (comprised of the caudate and putamen) and the globus pallidus form the corpus striatum.

high intensity signals confined to parts of the basal ganglia (i.e., the striatum, globus pallidus, and substantia nigra) can be observed on T1-weighted magnetic resonance imaging (MRI) of the brains of monkeys experimentally treated with manganese. Then, in 1993, Nelson (Ref. 137) observed a similar cranial MRI pattern in a patient with severe manganese neurointoxication. The 44-year-old patient had worked as an arc welder for 25 years, repairing railroad tracks made of a manganese-steel alloy and welding and cutting castings that were 20% manganese. The high intensity signals were almost completely gone when MRIs were repeated 6 months after he stopped welding, but his neuropsychiatric symptoms had not improved. Thus, manganese-related changes in MRI scans tend to disappear following withdrawal from the manganese source as manganese is cleared from the tissue, even though permanent neurological damage may have occurred.

In 1997, Arjona et al. (Ref. 13) used MRI to diagnose manganese poisoning in a 54-year-old construction worker who had frequently worked near welders. He reported having mild mental confusion, followed a few weeks later by sudden unprovoked falls without loss of consciousness or other symptoms. Neurological examination revealed mild rigidity and tremor in both arms. Cranial MRI revealed high intensity signals on T1-weighted images in the corpus striatum of the basal ganglia indicating manganese deposition. His urinary manganese concentration (24 µg/L) was elevated compared with normal levels (1–8 µg/L). The patient stopped work at this time. Ten months later his urinary manganese concentrations were normal, and his mental confusion and tremors had disappeared. An MRI taken at this time showed almost complete resolution of the high-intensity signals.

Sato et al. (Ref. 161) described a 56-year-old man who, after working for 30 years as a welder, presented with signs of parkinsonism including postural instability, dystonia of the shoulders and limbs, masked face, bradykinesia, and rigidity. He was diagnosed with manganese poisoning, based primarily on high concentrations of manganese in serum and urine, and a marked elevation of urinary manganese following administration of a chelating agent. Cranial MRI showed hyperintense signals on T1-weighted images in the globus pallidus and other parts of the brain, indicative of manganese deposition. The size and density of the MRI signals were reduced after 10 months.

Kim et al. (Refs. 105, 106) described the case of a 48-year-old Korean welder who was diagnosed with idiopathic parkinsonism after having welded for 2 hours a day for 10 years, followed by 10 hours a day for 2 years. One year before he stopped welding, he developed progressive tremors in his right arm and leg. He sought

medical help when he developed symptoms of brady-kinesia, masked face, and rigidity of the right wrist and el-bow. His tremor and rigidity improved slightly when he was treated with L-dopa. An MRI showed the symmetri-cal high signal intensities in the globus pallidus and mid-brain that are characteristic of manganese poisoning. He stopped welding at this time and 6 months later the high intensity MRI signal had almost disappeared. Tests con-ducted 2 months after he stopped welding showed that concentrations of manganese in his blood (3.26 μg/dL; normal <2 μg/dL) and urine (3.57 μg/L; normal 2 μg/L) were somewhat elevated. In addition, substantial quanti-ties of manganese appeared in the urine after he was treated with the chelating agent calcium disodium ethyl-enediaminetetraacetate (EDTA). A sample of cloth from a shirt that he had worn for 2 days at work was found to be contaminated with manganese, and air sampling in the factory where he had last been employed indicated that he may well have been exposed to excessive levels of manganese. Monitors worn by five welders who worked in that factory showed mean breathing zone manganese concentrations of 630 μg/m^3, three times the ACGIH TLV of 200 μg/m^3. Based on PET scans that showed a reduced uptake of ^{18}F-dopa by the striatum, and despite the strong evidence that the welder had experienced ex-cessive manganese exposures, Kim et al. concluded that he had idiopathic Parkinson's disease rather than manga-nism. The investigators remarked that PET scans are use-ful for differentiating manganism from idiopathic Parkinson's disease in patients who had been exposed to manganese.

Kim et al. conducted a study of MRI signal intensities and neurological symptoms in asymptomatic manga-nese-exposed workers from ten factories in South Korea (Ref. 107). The 34 manganese-exposed welders in the study and nine of the non-exposed manual laborers worked at six facilities where automobile assembly, ship building and manufacture of steel structures took place; 39 exposed and 6 non-exposed manual workers were em-ployed at three manganese smelting plants, and 16 ex-posed workers and one non-exposed worker came from a welding rod manufacturing plant (Table 10). Information concerning life style, occupation, and medical history was obtained by questionnaire.

Mean breathing zone manganese concentrations ob-tained for each of the manganese-exposed workers were highest for the welders (0.53 mg/m^3), followed by the workers in welding rod manufacture (0.15 mg/m^3) and the smelters (0.14 mg/m^3). Blood manganese levels were non-significantly (p = 0.058) elevated in manganese-exposed workers compared with the two groups of non-exposed workers. Neurological examinations administered to each of the subjects revealed no signs of manganism in any of the workers. Each of the participants was sub-jected to cranial MRI examination. Increased MRI signal intensities indicative of manganese deposition were found in 46.1% of the manganese-exposed workers, in 18.8% of the non-exposed manual workers, and in none of the clerical workers. The positive findings in the non-exposed workers were attributed to bystander exposures. As is shown in Table 10, the enhancement of MRI signal intensities was greatest for the welders, followed by manganese smelters. None of the workers in welding rod manufacture had enhanced MRI signal intensities. The investigators concluded that the increased signal intensi-ties in the T1-weighted MRI in the absence of any signs

Table 10
Number of Study Participants, Breathing Zone Manganese
Concentrations, and Frequency of Enhanced MRI Signal Intensities

Facility: (Number of firms):	Welding (6)	Smelting (3)	Welding Rod Manufacture (1)
Number of participants			
Mn-exposed workers	34	39	16
Non-exposed workers	9	6	1
Clerical workers	8	5	3
Mean breathing zone Mn levels for exposed workers (range)	0.53 mg/m^3 (0.1–1.56)	0.14 mg/m^3 (0.08–1.4)	0.15 mg/m^3 (0.02–0.42)
Percent exposed workers with enhanced MRI signal intensities	73.5%	41%	0%

Adapted from Kim et al., Ref. 107.

of parkinsonism or manganism reflects recent exposure to manganese, but does not necessarily indicate the presence of disease processes.

13.2 Cognitive Effects. Ahn and Lee (Ref. 3) evaluated cognitive function in five welders who worked in a shipyard in Korea and who had histories of chronic manganese exposure. All five welders were experiencing fatigue, forgetfulness, and irritability but had none of the cardinal signs of parkinsonism. Neuropsychological tests indicated impairments of working memory, executive function (ability to plan, organize, and develop strategies or rules), and attention span in all five welders. Four of them also exhibited signs of personality changes, and three showed signs of depression. All of the welders had MRI patterns indicative of manganese exposure. The investigators noted that some areas of the frontal lobe of the brain in which manganese signals are seen in MRI are responsible for cognitive function. They concluded that since cognitive dysfunction appears earlier than do other signs of manganese toxicity, early detection of this disorder is important for "protection of workers at risk."

Lucchini et al. (Ref. 124) administered a battery of neuropsychological tests to a group of 61 male ferroalloy workers who had had long-term exposures to low levels of manganese and 87 unexposed controls. The objective of the study was to determine whether early signs of manganese-related neurotoxicity could be detected in these asymptomatic workers. The participants worked in a plant located in Brescia, Italy, that produces ferro-Mn and silico-Mn alloys for use in the steel industry. Controls worked at a hospital in Brescia and had no known exposures to neurotoxins. None of the subjects had current or past occupational exposures to lead, mercury, or organic solvents. The subjects were given questionnaires and tests that could detect neurobehavioral, motor, and psychological symptoms as well as symptoms of Parkinson's disease. The results were correlated with manganese levels in blood and urine samples collected at the time of testing. Fifteen-year exposure histories were available in all areas of the plant. The exposures to manganese had been reduced substantially with time in all areas except in the maintenance shops where the welding took place. Manganese exposures in the maintenance shops were about 170 $\mu g/m^3$ throughout this period. Based on these data and the length of employment at the plant, a cumulative exposure index (CEI) was calculated for each alloy worker and used to determine whether neurological test results were related to cumulative manganese exposures. The exposed subjects were employed at the plant an average of 15.1 years, and the average annual manganese exposure during that time was calculated to be 70.8 $\mu g/m^3$. Mean concentrations of manganese in blood and urine were significantly higher in exposed workers (9.18 $\mu g/L$ blood and 1.53 $\mu g/g$ crea-

tinine, respectively) than in controls (5.74 $\mu g/L$ blood and 0.40 $\mu g/g$ creatinine). Airborne manganese concentrations correlated positively with blood manganese (n = 55, p = 0.0068), whereas there was no relationship between the CEI and the concentration of manganese in blood or urine.

Irritability, loss of equilibrium, and rigidity were reported more frequently by alloy workers than by controls. In addition, neurobehavioral tests showed the alloy workers to have more impairments in motor functions requiring alternating and rapid movements, in short-term memory functions, and in some tests of tremor parameters. While neurobehavioral effects were evident, there were no signs of neuropsychological disorders in the exposed workers, and there were no clinical signs of manganese toxicity. A positive relationship was found between the cumulative exposure indices and some of the neurobehavioral test results, indicating that the effects of manganese may be cumulative. Based on the relationship between the CEIs and appearance of neurobehavioral deficits, the investigators calculated that it may be necessary to reduce manganese concentrations below 100 $\mu g/m^3$ to protect manganese-exposed workers over their entire working life.

13.3 Heart Rate. Barrington et al. (Ref. 17) examined the correlation between autonomic nervous system function and cognitive and emotional dysfunction in eight manganese alloy welders and machinists. All of the subjects had been referred to the author because of cognitive or autonomic symptoms. One of the subjects included in the study was a welder whose case had been previously evaluated by members of the same medical group and is discussed above (Ref. 137). All eight subjects had neurological symptoms or complaints, two had motor disorders, and none had evidence of structural or ischemic heart disease. The eight age-matched controls were likewise free of cardiac disease. Manganese levels in the track repair shop had been measured only once in the 10 years prior to the diagnosis of the first case. After that, an exhaust fan was installed in the welding area, and personal air samples were taken annually during the next 4 years. Analyses of these samples indicated that manganese exposures were frequently in excess of the ACGIH TLV of 200 $\mu g/m^3$. Because the authors deemed the sampling data inadequate for estimating manganese exposure, they ranked the subjects' cumulative exposures based on their job descriptions and years of employment. Blood and urinary manganese were measured in all the subjects and controls, but there was no correlation between the manganese content of either blood or urine and the assigned exposure rankings among the manganese-exposed subjects. Ambulatory 24-hour electrocardiograph (ECG) readings showed that seven of the eight subjects had significantly decreased variability in heart

rate compared with the controls and with a reference group of healthy individuals. There was no correlation between severity of exposure and the extent of the decrease in variability of the ECG, nor was there any correlation between cumulative exposure rankings and any of the neurological and psychological symptoms (irritability, headaches, poor memory, and impotence) exhibited by the subjects. The authors noted that the lack of apparent correlation between measures of exposure and symptoms of organic brain dysfunction is consistent with other reported studies of manganese neurotoxicity. They concluded that analysis of 24-hour ECG for variability of heart rate may be useful in the evaluation of workers exposed to manganese and other neurotoxins.

13.4 Welding and Parkinson's Disease. Racette et al. (Ref. 152) conducted a case-control study of the symptoms and disease course in welders with parkinsonism. The fifteen career welders who participated in the study were identified among 953 patients diagnosed with parkinsonism between 1996 and 2000 at the Movements and Disorders Center of the Washington University School of Medicine in St. Louis, Missouri. Based on information provided by the welders, the investigators calculated that they had spent an average of 47,144 hours welding during their careers. No information was provided concerning the type of welding they had performed or the metals with which they had worked. They were compared with two control groups with idiopathic Parkinson's disease. The first group consisted of 100 male and female Parkinson's disease patients who were sequentially selected from the records of the Movements and Disorders Center. The second group of controls comprised six Parkinson's disease patients selected from the same center who were sex- and age-matched with the welders. The disease duration was 8.5 years in the welders, 6.6 years in sequentially-selected controls, and 9.5 years in matched controls.

The severity of parkinsonism was similar in welders and controls. They exhibited no significant differences in the frequency of cardinal Parkinson's disease signs (bradykinesia, tremor, rigidity, postural instability) or in the frequency of clinical depression, dementia, and psychosis. In addition, the family history of Parkinson's disease and the response to treatment with L-dopa was similar in welders and controls. The average age at onset of parkinsonism of the welders (46 years) was significantly lower than that of the sequentially-selected controls (63 years, p < 0.0001).

Cranial MRI scans were performed on eight of the welders, and none showed signs of the high intensity signals typical of manganese-exposed workers. The investigators did not state whether any of these patients were still engaged in welding. This issue was clarified in an exchange of letters to the editor between Sadek and

Schulz (Ref. 160) and Racette et al., who replied (Ref. 153) that six of the welders in the study were still engaged in welding at the time of the diagnosis. But, even though the MRI scans were negative at the time of the study, the possibility suggested by Sadek and Schulz that the welders had been exposed to manganese earlier in their careers is not ruled out, because MRI scans generally appear normal within a few months after removal from exposure to manganese.

Two of the welders and thirteen controls were examined by ^{18}F-dopa PET scans. All of these subjects had experienced symptoms of parkinsonism for an average of 2 years and showed signs of bradykinesia and rigidity. The two welders and all but one of the controls had resting tremors. The PET scans of both the welders and the controls were typical of idiopathic Parkinson's disease, with reduced ^{18}F-dopa uptake by the striatum, particularly by the putamen.

The age of onset of parkinsonism was the only clinical difference observed between the welders and controls. The investigators stated that their findings do not prove that manganese is the active agent in welding fumes and that other components of the welding emissions could be responsible agents. They speculated that an agent in welding exposures may accelerate the development of Parkinson's disease in persons who might otherwise have developed it later in life or who are genetically predisposed to early onset Parkinson's disease. They concluded that parkinsonism in welders differs from idiopathic Parkinson's disease only in age of onset and that "welding may be a risk factor for" Parkinson's disease.

A potential weakness in this conclusion is that the PET scans provide the strongest evidence for excluding manganese as the basis for parkinsonism in the welders studied and, yet, they were only performed on two of the fifteen welders. A stronger conclusion might have been reached had PET scans been performed on a larger proportion of the welders in the study. In addition, occupational histories were not provided for the welders and it is not know whether they were exposed to excess levels of manganese earlier in their careers. It is essential that manganese exposure, a known cause of parkinsonism that is faced by welders using some processes, be ruled out before the postulate can be accepted that welding is a risk factor for Parkinson's disease.

In their letter to the editor, Sadek and Schulz (Ref. 160) suggested that differences in MRI and PET scans were not seen by Racette et al. because they because, by chance, welders with manganism were not included in the study. They argued that, at an early stage, manganism may differ from idiopathic Parkinson's disease in several ways, including cognitive disturbances, emotional lability, and some physical signs that may not appear until

later in the course of idiopathic Parkinson's disease. At a later stage, manganism "may be very indistinguishable from" idiopathic Parkinson's disease and can easily be classified as early-onset idiopathic Parkinson's disease. Because the MRI scans will appear normal within months after exposure to manganese has ceased in patients who had been previously exposed to manganese, and because the effects of manganese may be cumulative (Ref. 124), MRI scans cannot be used to rule out past manganese exposures. Thus, some or all of the cases that Racette et al. classified as idiopathic Parkinson's disease in the welders may have actually been manganism. Sadak and Schulz further pointed out that that manganism is a progressive disease, and symptoms may continue to worsen long after exposure to manganese has ceased, which would increase the difficulties of distinguishing between manganism and Parkinson's disease.

13.5 Genetic Susceptibility. It is well established that Parkinson's disease has a genetic component since close relatives of patients with the disorder have an increased risk of developing it themselves. Such a relationship has not been established for manganism. Mutations in up to five genes have been reported by different investigators to be related to susceptibility to idiopathic Parkinson's disease. Zheng et al. (Refs. 212, 213) conducted a case-control study to determine whether any of these genes also plays a role in susceptibility to manganism. The cases in this study were 49 welders and ferromanganese smelters from three metallurgical plants in China who had been occupationally exposed to manganese fume and dust during their work. The cases were identified during annual routine medical surveillance and their diagnoses confirmed by occupational disease panels. The 50 healthy controls worked at the same plants and had occupational exposures to manganese similar to the cases. Cases and controls were matched for sex, age, cigarette and alcohol use, and the duration of exposure to manganese. All participants had been exposed to manganese for at least 6 years.

A variant (CYP2D6L or the "L" mutation) of CYP2D6, the gene that codes for the enzyme debrisoquine hydroxylase, was found to occur significantly less frequently in the workers with chronic manganism (16.3%) than in the controls (29.0%). The individuals who were homozygous (L/L) for this variant (i.e., both alleles or copies of the CYP2D6 gene carried the "L" mutation) had a 90% decreased risk of developing chronic manganism compared with persons in whom both copies of the gene were the normal or wild-type[7] (Wt/Wt) (OR = 0.10, CI = 0.01–0.82). A significant as-

sociation was also found between the variant of the CYP2D6 gene and the time of onset of chronic manganese poisoning. The cases who had either homozygous (L/L) or heterozygous (L/Wt) copies of the gene developed manganism an average of 10 years later than the cases who were homozygous for the wild type (Wt/Wt). No differences in the frequencies of any of the other four gene mutations studied were observed between the cases and the controls. The investigators concluded that their results suggest that the CYP2D6L gene variant might decrease the susceptibility of individuals to manganese-induced neurotoxicity. They noted that their data should be considered preliminary because of the limited sample size.

14. Effects on the Cardiovascular System

14.1 Cardiovascular Disease. Ranjan and Lokhandwala (Ref. 154) described the case of a welder in India who reported to the hospital with difficulty breathing. Pulmonary function tests showed signs of restrictive and obstructive disorders with greatly reduced flow rates. Signs of marked cardiac dysfunction were seen in electrocardiograms and echocardiography. Mild mitral regurgitation and depressed right ventrical contractility were detected but there was no evidence of myocarditis, congenital heart disease, hypertension or any other. The patient had worked in a welding plant for 20 years and was engaged in active welding during the last 5 years. He began experiencing severe respiratory discomfort during welding which led him to return to activities involving the cutting of iron rods. The physicians attributed his respiratory difficulties to tobacco smoking and welding. They did not believe that smoking could account for his cardiomyopathy and attributed this disorder to welding exposures. They remarked that the occupational health and safety standards are inadequate and called for a thorough evaluation of the hazards of welding in India.

14.2 Hand-Arm Vibration Syndrome. The long-term use of vibrating tools can cause Hand-Arm Vibration Syndrome (HAVS) which includes neurological, muscular, and circulatory system disturbances. Raynaud's phenomenon (vibration white fingers), the most common symptom of excessive vibration exposure, is characterized by tingling, numbness, and loss of color in the fingers on exposure to cold. In industry, HAVS can be caused by use of vibratory hand tools such as grinders, chain saws, and pneumatic chipping hammers and picks. Using a database maintained by the Occupational Health Clinics for Ontario Workers, Pelmear and Wills (Ref. 148) identified 185 cases of Raynaud's phenomenon reported between 1993 and 1996. All but ten of these cases

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7. The wild-type is that form of a gene that is the most common version in a population.

were associated with the use of equipment that caused continuous hand-arm vibration exposure. In the remaining ten cases, impact vibration was the only or a significant vibration exposure. Four of these cases were women who had experienced impact vibration as punch press operators. The remaining six cases were men whose HAVS was attributed in total or in part to spot welding. Two of the men had 4 years' experience spot welding and had no other occupational source of vibration exposure. The remaining four had 3 or 4 years' experience spot welding in addition to 2 to 12 years' experience using equipment with continuous vibration exposure. The authors concluded that equipment that causes vibration with high impact should be recognized as causes of HAVS and that spot welders and press operators are at risk for developing this condition.

15. Effects on Reproduction

15.1 Effects on Fertility. Infertility problems are experienced by 10–15% of all couples. Smoking, coffee consumption, and exposure to occupational or environmental pollutants such as pesticides, solvents, and some metals are thought to affect fertility. Epidemiologists have traditionally used the success or failure of a couple to conceive within the period of one year as a measure of fertility. In recent years, the time-to-pregnancy (TTP, the time from which the use of contraception is stopped until the time conception occurs) has been used as an indicator of fertility.

Semen quality, another frequently used indicator of fertility, has been measured in a number of epidemiological studies of welders. The participation rate in semen quality studies is frequently low, which raises the concern that workers who agree to participate may not be representative of the study population from which they were derived. To examine factors which might influence willingness to participate in semen quality studies, Larsen, Abell, and Bonde (Ref. 118) analyzed data from previous studies of semen quality that they had conducted with metal workers, farmers, and engineers. They found that the potential participants' chronological age or awareness of past successes or difficulties in fathering children can influence their willingness to provide semen samples. In metal workers, interest in participation increased with age, up to a maximum of 53% at 25–29 years, and declined to 18% for men older than 45. Metal workers who had failed to father children for a period of 2 years were more likely to provide semen samples than were other subjects.

In 1998, Hjollund et al. conducted a comprehensive fertility study of welders in Denmark using a design that would reduce this selection bias by including only men who had not previously tried to father children and should, therefore, have had no known or suspected fertility problems. This study examined semen quality, rates of fertility, and rates of spontaneous abortion in a large cohort of couples in which 130 of the male partners were welders (Refs. 83–85). The effects of ELF magnetic fields on markers of fertility were also examined in a subgroup of the study population (Ref. 86).

Fecundity (defined by the investigators as the probability of conceiving during a menstrual cycle) was studied in a cohort of 406 childless couples recruited by letters sent to members of a metal workers union and three other trade unions in Denmark (Ref. 85). All couples were planning their first child and stopped using birth control when they enrolled in the study. The men in the study included 130 welders, 71 non-welding metal workers who served as internal controls, and 205 non-metal workers in various trades (office and commercial workers, nurses and day-care workers) who served as external controls. The couples were followed until pregnancy was clinically confirmed or for a maximum of six menstrual cycles following cessation of the use of birth control.

Each month, the welders provided information on their welding experience, the type of metal welded, the welding method used, their average daily welding exposure, and use of local exhaust ventilation. These data indicated that the exposures to welding fumes were relatively low. This was supported by measurements of chromium, manganese, nickel, and lead in urine samples collected from 6 stainless steel welders, 21 mild steel welders and 48 non-welders before and after a work shift. There were no differences in concentrations of the metals in pre- and post-shift urine samples, nor were there differences between welders and non-welders.

The pregnancy rates reported during the study period were highest among non-welding metal workers (67.7%), followed by welders (63.1%) and non-metal workers (56.6%). The differences in fecundity between welders and non-welders were not statistically significant, and neither the welding method used nor the metal welded affected the rate of conception. No relationship was found between fecundity and exposure to radiant heat, lead, organic solvents, lubricant, or refrigerants.

While this study did not show that welding exposures affect fertility, an interaction was found between smoking and welding. Among smokers, welders had significantly lower fecundity (p = 0.04) than internal controls (non-welding metal workers) but not external controls (non-metal workers). A significant relationship between the number of years of welding experience and changes in fertility was observed in welders who smoked. The effect on fecundity was most notable for stainless steel welders who smoked compared with smoking non-welders.

The authors concluded that while the study indicated that welding may reduce fertility among smokers, the results were debatable. They pointed out that the study had not been designed to test the hypothesis of an interaction between the effects of smoking and exposure to welding fume, and the results were due in part to the high fecundity among smoking non-welders. Also, the number of smokers in the internal control group was quite small.

To test whether welding alters the rate of spontaneous abortion, Hjollund et al. collected data on loss of fetuses from the 406 women in the Danish study cohort (Ref. 84). A spontaneous abortion was defined as the loss of a fetus that occurred at any time up to 28 weeks of gestation. Data on clinically recognized spontaneous abortions were obtained by reports from the women in the study who experienced them. Subclinical spontaneous abortions, defined as the loss of a fetus during the early days of pregnancy, are not generally noticed by women and are usually detectable only by biochemical tests. In this study, subclinical spontaneous abortion was detected by analysis of human chorionic gonadotrophic hormone (hCG) in urine samples collected for ten days following the onset of each menstrual cycle.

During the 6-month course of the study, 258 of the 406 women became pregnant. A number of the women had spontaneous abortions and became pregnant again, resulting in a total of 280 pregnancies. Of these pregnancies, 71 were terminated by clinically detectable spontaneous abortions and 35 were subclinical spontaneous abortions detected by hCG analysis. The risk for either type of spontaneous abortion did not differ between fathers who were mild steel welders and those who were non-welders. Paternal stainless steel welding was, however, associated with a significantly increased risk of
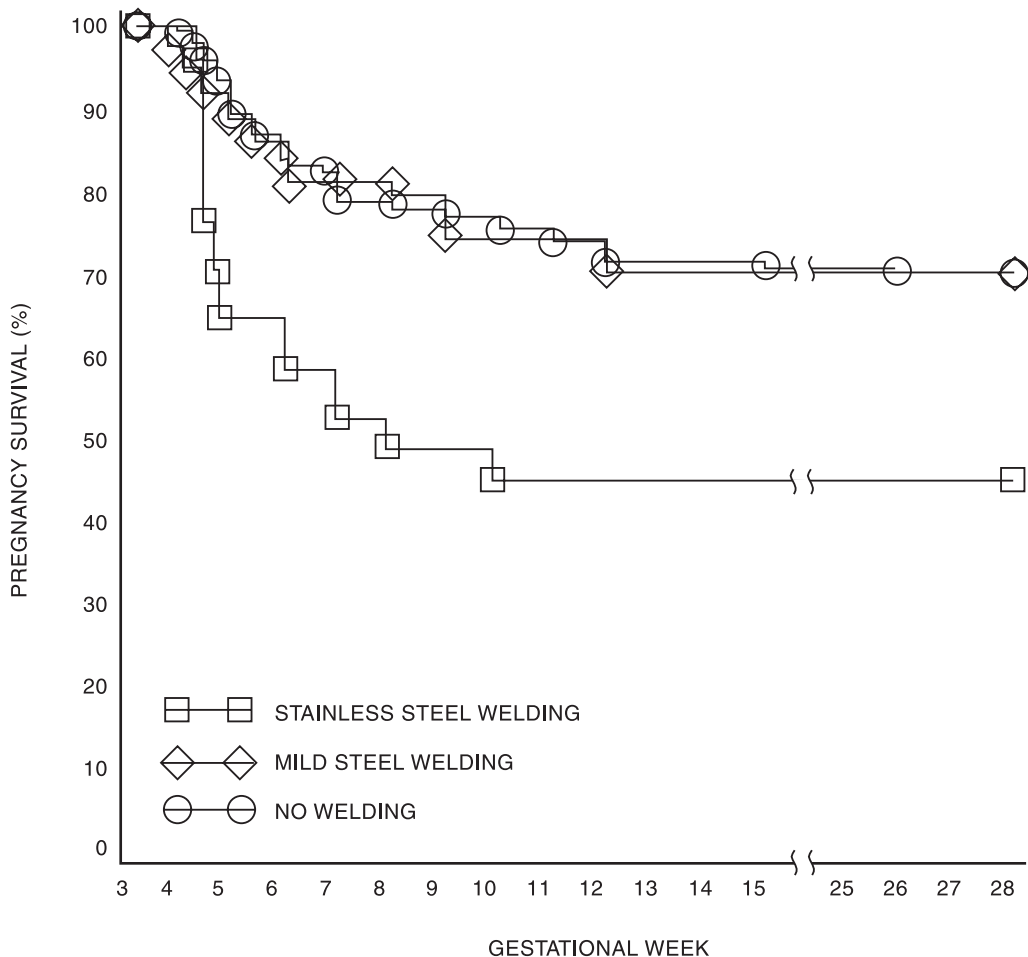
From Hjollund et al., Ref. 84.

Figure 4—Survival Curve for Pregnancies According to Paternal Welding

spontaneous abortion (relative risk = 3.5, CI = 1.3–9.1). The relationship between fetal survival and male welding is shown in Figure 4. The investigators noted that hexavalent chromium has been found to be mutagenic to germ cells in rat studies, and they suggested that the increased risk of spontaneous abortions in wives of stainless steel welders could be due to mutations in the male genome.

To study the effects of welding on markers of semen quality in this Danish cohort, semen and blood samples were collected from each of the 406 male participants at the time of enrollment in the study and once a month during the course of the study (Ref. 83). No significant differences in any of the measures of semen quality studied (sperm density, sperm count, proportions of morphologically normal sperm, and sperm motility) or in levels of sex hormones in the blood (testosterone, follicle-stimulating hormone, and luteinizing hormone) were found between welders and either of the non-welding control groups. The authors noted that some earlier studies had found an increased risk of reduced semen quality among welders, while others did not find such an association. They reiterated that welders in the current study had relatively low exposures to welding fumes and cautioned that the negative findings obtained in the current study may not apply to populations with high-level exposure to welding fume or to welders exposed to other putative hazards such as heat.

Finally, the impact of ELF magnetic fields on fertility was examined in 57 of the male participants (36 welders, 13 non-welding metal workers, and 8 non-metal workers) and 52 of their partners (Ref. 86). Exposure to ELF magnetic fields was measured for 3 workdays and 2 nights by personal exposure meters. All participants were equipped with exposure meters in the 0.01–70 μT range and additional meters in the 1–7,000 μT range were provided to the men. ELF exposures of women were not significantly related to fecundity or sexual hormone levels in blood. Some effect of ELF on fecundity was noted in a group of men who received medium and high exposures at levels greater than 1.0 μT compared with those who received low exposures at that field strength. The response, however, was not dose-dependent and the results were significant only for the men with medium exposure. The authors noted that the small number of men in the study detracted from its significance as did the lack of a dose-response effect, and they concluded that the data did not demonstrate an effect of ELF magnetic fields on fertility.

A time-to-pregnancy (TTP) approach was also used by Spinelli et al. to examine the effects of occupation and lifestyle factors on the fertility of 662 couples selected from the general population in Italy (Ref. 175). This study was part of a multinational study on infertility sponsored by the European Union. As in the study by Hjollund et al., all of the couples included in the study desired children and had used contraception until the time at which they wished to conceive. Unlike the subjects in the Danish study, who were enrolled prior to conception, participants were selected for the Italian study after their children were born, so statistics concerning the TTP were based on recall by the mothers. Women who gave birth to children in one of four hospitals during a 2-month period in 1993 were selected for inclusion in the Italian study. Time-to-pregnancy was determined by interviewing the mothers 1 week after having given birth. Information concerning lifestyle (e.g., smoking, consumption of alcohol and caffeinated drinks) and parental occupation was also obtained during the interviews. The average TTP for all of the couples in the study was 6.75 months; 11.25% had a TTP of more than 1 year. The most important factors affecting the TTP in women were age and parity (multiparous women had a higher rate of conception than those having their first child). The monthly rate of conception (the reciprocal of the TTP) was also affected by smoking and coffee consumption.

Neither paternal smoking nor paternal occupational exposure to solvents significantly affected the rate of conception. However, employment of the father in manual industrial work reduced the rate by 26% (CI = 11–38%, p < 0.01). Of the 326 fathers who were industrial workers, 14.4% waited longer than 12 months for conception to occur, compared with 7.8% of the fathers who were not manual workers (p < 0.001). Analysis of data from the 68 manual workers who were exposed to welding fumes in the workplace revealed that 17.6% waited more than 1 year for conception compared with 10.5% of the fathers who were not exposed to fumes, but this difference was not statistically significant.

A third time-to-pregnancy study that included welders was conducted by Thonneau et al. (Ref. 191). The objective of this work was to examine the relationship between fertility and male occupational heat exposure. Women who had delivered babies during a five-month period in seven maternity units in France were recruited for the study. Data concerning life style and occupation of the male partner were obtained from self-administered questionnaires. The cohort was divided into three groups according to occupational exposures. The first group comprised the 140 couples in which the male partner had occupational exposure to heat. The 35 men who spent at least 3 hours a day driving were considered separately because the elevated scrotal temperatures caused by extended periods in the sitting position has been associated with "deteriorated sperm characteristics." The remaining 227 couples served as non-exposed controls.

The TTPs for the heat-exposed group (median = 4.0 months; mean = 11.8) and for the drivers (median = 4.5; mean = 14.4) were significantly higher (p < 0.05) than

that for the controls (median = 2.8; mean = 7.8). Bakers and welders were analyzed separately because they were deemed to have the highest occupational heat exposure of the men in the heat-exposed group. The percent of the bakers' partners who became pregnant within 3 to 6 months after stopping contraception was significantly less than that of controls (Table 11). The percent of welders' partners who became pregnant within 3 to 6 months was also lower than controls, but the differences were not significant.

Harrison conducted a retrospective survey of the association between occupation and semen parameter defects among the male partners of 1,402 couples who were treated for infertility at three reproduction clinics in Australia (Ref. 78). At the initial, pre-treatment evaluation of the patients, three semen parameters (sperm density, sperm motility, and sperm morphology) were assessed and compared with normal population values. These data were analyzed according to occupational groups. The incidence of defects in any of the measured parameters was 25% among the patients who were white collar workers. The incidence of semen parameter defects was increased among fitter/welders (47.7%), miners (54%), machinery operators (68.8%), workers in the chemical and petroleum industries (85.7%), and workers in the building/construction industries (41.5%).

Bigelow et al. (Ref. 23) examined the relationship between occupational exposures and semen quality using two different statistical approaches: case-control and analysis of continuous variables. The subjects in the study were 845 men who provided one or more semen samples to the infertility clinic at the University of Calgary during a 19-month period in 1990 and 1991. Of these subjects, the 319 men who had no recent workplace

exposures to chemical or physical agents served as controls. Data on lifestyle factors and occupational exposures, including past and present occupations and specific occupational duties, were obtained by questionnaire.

Thirteen semen parameters were examined in the analysis of continuous variables. Significant increases in mean semen volume (p < 0.001) and in a parameter of sperm morphology (tapering heads, p < 0.01) compared with the unexposed group were seen in the 55 men who had worked in agriculture during the 3 months before their semen was analyzed. Current employment as welders or flame cutters was reported by eleven men, and three others reported having worked in welding or flame cutting during the 3 months before the analysis. Significant declines in the percent progressive sperm (p < 0.05) and significant increases in the percent coiled tail defects (p < 0.01) were observed in the semen from these men. No other occupational groups showed statistically significant changes in any of the 13 semen parameters.

With the case-control approach, semen quality was considered to be abnormal if any one of three parameters (sperm concentration, motile progressive sperm, or sperm morphology) was not within the normal range. No association between semen abnormalities and present or past employment as a farmer or as a welder or flame cutter was seen. Using the analysis of continuous variables, the investigators were able to detect subtle, but significant, occupation-related changes in semen quality that were not detected using the case-control approach.

15.2 Effects on the Newborn. Spina bifida is a defect in which an infant is born with a lesion in the spinal column through which spinal cord tissue sometimes protrudes. In 1996, Blatter et al. (Ref. 28) published the initial results of a casecontrol study of the association between parental occupation and spina bifida in offspring. The study included 353 children with spina bifida selected from nine different hospitals in the Netherlands. The 1,329 controls were randomly selected from municipal birth registries. All cases and controls were born between 1980 and 1992. Data concerning industry, occupational title, and daily occupational activities for both parents were collected using questionnaires mailed in 1992. From these data, it was determined that, among the mothers, the risk for producing a child with spina bifida was highest (OR = 5.6, CI = 1.817.8) for women working in agricultural occupations. For the fathers, an increased risk for producing a child with spina bifida was found for welders (OR = 2.1, CI = 0.67.0) but the risk was not statistically significant.

In the next phase of this work, Blatter et al. (Ref. 27) used the data provided by the parents of the study cohort in 1992 to examine the association between different forms of spina bifida and risk factors such as maternal age, parental occupation, and family history. Specifically,

Table 11
Time to Pregnancy Among Bakers, Welders, and Non-Exposed Controls

	Non-Exposed	Bakers	Welders
Number of subjects:	227	7	16
Percent of conceptions within:			
3 months	55	14[1]	37[3]
6 months	74	29[2]	62[4]

Notes:
(1) p < 0.05
(2) p < 0.02
(3) p = 0.17
(4) p = 0.40

Data from Thonneau et al., Ref. 191.

210 of the spina bifida patients were classified into groups based on whether their lesions were "open" (nervous tissue was exposed) or "closed" (the lesion in the spinal cord was covered with skin) and on the position of the lesion along the spine. The referents consisted of 671 children selected from the general population who lived in the same regions as the cases.

A strong association was found between mothers working in agriculture and open spina bifida (OR = 14.3, 95% CI: 2.9–77.7, n = 4), but no paternal occupations were associated with either open or closed lesions. The risk for producing a child with high spina bifida was significantly increased for mothers who worked in industry or transportation and for fathers who worked in construction (OR = 5.4, CI = 1.9–14.0, n = 12) or who were welders (OR = 12.1, 95% CI = 1.5–64.2, n = 2). Because this risk was based on only two welders, the results must be interpreted with caution, as was stated by the investigators.

To obtain more precise data on occupational exposures, telephone interviews were held with a subset of the fathers whose questionnaire responses indicated that they had worked at jobs with potential exposures to physical or chemical hazards for at least the last 3 months before conception (Ref. 26). Detailed information was collected about specific tasks performed, the frequency (hours per week) of exposure, the use of chemical or physical agents, use of protective equipment, and bystander exposures. Fathers whose questionnaire responses indicated that they had held jobs without potentially hazardous exposures were grouped as non-exposed workers. Fathers with questionable exposures were excluded from this phase of the study. In all, fathers of 122 children with spina bifida and fathers of 411 controls had jobs with potentially hazardous exposures and were interviewed. The non-exposed groups consisted of 100 case fathers and 353 referent fathers.

Men in the exposed group were placed into five industrial categories (transportation, construction, metal work and mechanics, agricultural work, and printers, painters, plastic and paper workers). The levels of exposure (categorized as low or medium to high exposures) to 25 specific pollutants (e.g., paints, glues, cleaning agents, metal working fluids, heavy metals, metal dust, welding fumes, welding-associated heat, and welding-associated UV radiation were assessed for men in each of the five industrial categories.

A significant increase in the risk for spina bifida was associated with low exposure to welding fumes (OR = 1.6, CI = 1.0–2.6) and low exposure to UV radiation during welding (OR = 2.6, CI = 1.2–5.6). The risk for spina bifida was non-significantly associated with exposure to cleaning agents, pesticides, and stainless steel dust. No other associations were found among the 25 chemical or physical agents examined. The small increase in risk

from exposure to welding fumes was primarily found in workers in three occupational categories: construction, agricultural work, and printers, painters, plastic and paper workers. The risk for spina bifida was not increased among professional welders or metal workers. The investigators attributed this to the much greater use of protective equipment reported by professional welders.

Based on reports that low birth weight may be a sign of exposure to occupational or environmental pollutants and may be a predictor of health problems in later life, Farrow et al. (Ref. 67) analyzed the relationship between birth weights and occupation in full-term infants born to more than 10,000 women during a 19 month period in southwest England. Data on lifestyle factors, occupational history, and jobs held during the first trimester of pregnancy were obtained by postal questionnaire. Of the women who entered the study and provided all of the required information, 9282 had been employed during the period relevant to the study, 301 were housewives, and 168 either were students or were not employed. No significant differences were seen in the birth weights of full-term infants born to the women in these three groups. Statistically significant differences in the mean birth weights became apparent when the women who had worked were grouped into nine occupational categories defined by the British 1990 standard occupational classification (SOC) codes. Welders were a subgroup in the SOC code for plant and machine operators. Full-term infants born to women in this group had the lowest birth weights. However, when the data were adjusted for infant sex, maternal height, parity, smoking, caffeine consumption, and race, none of the differences among any of the occupational groups was statistically significant.

16. Effects on the Immune System

Some metals in welding fumes (e.g., Cr, Ni, Cd) have been reported to modulate activities of the immune system, causing either suppressive or potentiating effects on specific aspects of immunity. Several investigative groups evaluated the effects of welding on the immune system by comparing indicators of cellular immunity and levels of circulating antibodies in the blood of welders with those of controls.

Tuschl et al. (Ref. 195) compared components of the immune system of 30 long-term welders who worked in a plant in Austria with those of 16 workers from the same plant who had no exposures to welding fumes. The welders had an average welding experience of 18.6 years and used primarily GTAW and GMAW to weld stainless or mild steel. SMAW had been the major welding procedure used in the plant until 1986. Personal air monitoring performed at ten workstations before initiation of the

study indicated that the welders were exposed to welding fume concentrations ranging from 0.9 to 13 mg/m³ (average exposure: 5.3 mg/m³). Workers who had acute illnesses, were taking medications, or had had X-rays taken at any time during the last 6 months before the study were excluded because of the potential effects on the immune system. Immunological assays were conducted with blood collected on Monday mornings from welders and controls.

Concentrations of immunoglobulins in serum, number and types of lymphocytes (B and T cells) present in blood, and activity of T cells and leukocytes isolated from blood were examined in a series of immunological assays. Tests of the function of natural killer (NK) cells, a form of lymphocyte that destroys a variety of foreign cells and tumor cells showed that the NK cell activity was significantly reduced in welders compared with that in controls. The investigators conjectured that the reduction in NK cells, which are an important defense against virus infection, could be related to the increased rate of respiratory infections that was reported by some of the welders in the study.

The results of all other immunological assays were the same in welders and controls. No differences were seen in the numbers and types of T lymphocytes, phagocytosis by macrophages and neutrophils, the ability of lymphocytes to react to foreign lymphocytes, or the production of immunoglobulins. Neither the serum concentrations of immunoglobulins IgA, IgM, and IgG nor the ability of cultured B cells to produce IgG differed between welders and controls. Thus, the workplace exposures encountered by the welders in this study did not appear to lead to a substantial impairment of immunity.

Two studies of the immune system of welders were conducted in the Czech Republic. One was conducted by Borska et al. (Ref. 29) with 19 stainless steel welders who worked in a plant that made stainless steel appliances for the food industry. The welders had an average of 16 years welding experience. SMAW was the primary welding procedure used. Levels of chromium, nickel, manganese, and PAH in workplace area samples were below maximum allowable concentrations. The controls were 19 agricultural workers who had no occupational welding exposures. Elevated concentrations of IL1, IgA, and lysozyme (a bactericidal enzyme released from activated macrophages) and a decrease in IgM and in the numbers of cells capable of phagocytosis were observed in blood from welders compared with agricultural workers. Similar results were observed when welders were compared with a group of 30 to 100 healthy blood donors (Ref. 30). In addition, IgE was elevated in welders compared with the blood donors.

Hanovcova et al. (Ref. 77) evaluated the immune status of stainless steel welders from another plant in the Czech Republic over the 3-year period 1987 to 1989. Tests were conducted on blood drawn annually from 22 to 53 welders and 14 to 23 controls. The control group comprised non-exposed persons (clerks, technicians, and economists) from the same plant as the welders. Data were also compared with long-term laboratory reference values (LRV) obtained from blood donors who did not work at the plant. SMAW was the major procedure used in the plant but GMAW was also used. Air sampling conducted in 1988 showed concentrations of chromium (range: 0.01 to 20.8 mg/m³), nickel (range: 0.004 to 3.4 mg/m³), and manganese (range: 0.06 to 16.3 mg/m³) that were well in excess of maximum allowable concentrations. After improvements were made in the workplace in 1989, only one welding station had levels of chromium in excess of the allowable standard. A study published separately by Tejral et al. (Ref. 182) indicated that the general health status of the welders was comparable to that of non-exposed controls.

The number of T cells and the concentrations of lysozyme were higher, and the activity of phagocytic cells was lower in blood from the welders than in that from the controls. While immunoglobulin levels did not differ between welders and controls, they were lower in welders than in the laboratory reference values. Comparisons among tests conducted annually in welders during the years 1987 through 1989 showed that T lymphocyte numbers, leukocyte phagocytic activity, and IgA concentrations approached control values after ventilation was improved in the plant.

Results from the two Czech plants were comparable and the effects on the immune system were more extensive than those seen by Tuschl (Ref. 195) in Austria. Differences between the results of studies done in Austria and the Czech Republic could have been related to differences in fume exposures. Differences could also have arisen, in part, from differences in the health status of the subjects. While Tuschl et al. deliberately excluded persons with illnesses or exposures (e.g., X-rays) that might have stimulated or otherwise affected the immune system, such exclusions were apparently not made in the studies conducted in the Czech Republic.

17. Biological Monitoring

17.1 Chromium. Edme et al. (Ref. 63) examined the relationship between the solubility and valence state of chromium in personal air samples collected during welding and the concentrations of chromium appearing in the welders' urine and blood at the end of an 8-hour work shift. The welding processes examined were SMAW, GMAW, and GTAW of stainless steel and SMAW and GMAW of mild steel. The 146 welders who participated

in the study used only one of these processes on the day that the blood, urine, and personal air samples were collected. Total chromium, water soluble chromium, and water soluble Cr(VI) were measured in the personal air samples. All participants had worked as welders in one of eight companies in France for at least 5 consecutive years. The 32 controls worked at the same companies as the welders but did not work in the vicinity of the welders or in contaminated work areas.

Concentrations of chromium in air samples taken during SMAW and GMAW of stainless steel were similar and were about four times higher than those collected during GTAW of stainless steel (Table 12). Most of the chromium in SMAW stainless steel fumes was water soluble, and an average of 60% of the soluble chromium was Cr(VI). Total chromium in GMAW and GTAW stainless steel fumes is primarily insoluble and soluble chromium represented less than 10% of the total chromium. As expected, the chromium content of mild steel fumes was very low. Nevertheless, levels of chromium were significantly higher in body fluids from mild steel workers than in those from controls. The source of the chromium in the blood and urine of mild steel welders may have been welding of stainless steel before the study was conducted or cross pollution from nearby stainless steel processes. No significant differences were seen between blood and urine concentrations of chromium from welders who smoked and from welders who did not, although the values were slightly higher for non-smokers. Stainless steel welders using SMAW had the highest urine and blood chromium levels. The investigators suggested that the differences in the concentrations of chro-

mium in the body fluids were due to differences in the soluble chromium content of the fumes.

17.2 Lead. Sokas et al. determined lead concentrations in blood collected from 264 active and retired Maryland construction workers (198 iron workers and 66 laborers) recruited from four different unions (Ref. 174). At the time of the study, none of the participants were known to be performing work in which they were exposed to lead. Information about health status, demographics, work history, and other possible sources of lead exposure was obtained by interview. Lead concentrations were determined in blood samples collected from each participant at the time of the interview. The mean blood lead concentration was 8.0 μg/dL for the construction workers compared with the geometric mean value for the U.S. population of 2.8 μg/dL. Blood lead levels were slightly higher in the 124 subjects who had ever worked in demolition than in those who had not (8.8 μ/dL vs. 7.2 μg/dL, $p = 0.004$) and in the 79 construction workers who had ever burned painted metal and had welded on outdoor structures compared with the 48 construction workers who had never engaged in these activities (8.6 μg/dL vs. 6.8 μg/dL, $p = 0.01$). The authors noted that this study population was not "heavily leaded" and that their blood lead levels were similar to levels found in the general population in the middle of the twentieth century, before lead was removed from gasoline, paint, and food cans.

A similar study was conducted in 1994 to1996 by Reynolds et al. (Ref. 157) who surveyed blood lead concentrations in 459 construction workers identified through trade unions in Iowa and Illinois. Blood was obtained from participants after completion of an inter-

Table 12
Concentrations of Chromium in Personal Air Samples and in
Blood and Urine Samples from Stainless Steel and Mild Steel Welders

Welding Procedure	Number of Welders	Cr Concentration in Air Sample			Cr Concentration in Body Fluid		
		ws* Cr(VI) (μg/m³)	ws Total Cr (μg/m³)	Total Cr (μg/m³)	Whole Blood (μg/L)	Plasma (μg/L)	Urine (μg/L)
Stainless steel							
SMAW	57	86	140	201	4.8	4.4	12.9
GMAW	37	3.7	13.2	185	3.1	3	3.7
GTAW	22	2.4	4.7	52	2.2	1.9	2.1
Mild steel							
SMAW	14	1	1.8	8.1	1.6	1.3	2.2
GMAW	16	1	1	7.3	1.9	1.4	2.6

*ws = water soluble

Data from Edme et al., Ref. 63.

viewer-administered questionnaire. The mean blood lead concentration was 4.7 µg/dL for the entire cohort of Iowa-Illinois construction workers, which was only modestly higher than the U.S. national average. Mean blood lead levels by trade group were: laborers (7.6 µg/dL), painters (5.9 µg/dL), ironworkers (5.2 µg/dL), plumbers (4.4 µg/dL), and electricians (2.4 µg/dL). Blood lead levels of laborers ranged from 0.1 to 50 µg/dL and those of ironworkers ranged from 0.9 to 23.2 µg/dL. Laborers performed more highway/bridge renovation than did other construction workers. Twelve of the 16 construction workers with blood lead concentrations greater than 20 µg/dL were laborers who were engaged in bridge renovation and performed tasks such as welding, cutting, sweeping. and rivet busting. These workers reported that neither respirators nor engineering controls were used during bridge renovation work.

Rodriguez and Gandarillas (Ref. 158) compared blood lead levels of 220 production workers from a shipyard in Northern Spain with those of 40 office workers from the same shipyard. The average blood lead level for the production workers was 12.4 µg/dL and that of the office workers was 9.8 µg/dL. Blood lead levels were significantly higher among boilermakers (14.7 µg/dL) and welders (11.9 µg/dL) than among the office workers. While none of the blood lead levels were higher than permissible standards, the authors concluded that lead exposure existed in the shipyard and that preventive measures should be implemented.

17.3 Manganese. Welders who repair railroad tracks can be exposed to high levels of manganese because railroad cross-ties are frequently constructed from a steel alloy with a high manganese content. Reygagne et al. (Ref. 156) measured concentrations of manganese in the breathing zone and urine of 30 French railroad track welders to assess whether these workers were at risk from overexposure to manganese. Grinding and welding were conducted for 2 to 3 hours per day. SMAW was carried out on cross-ties composed of steel containing 13% manganese. Breathing zone samples were collected during welding of the cross-ties, and urine samples were collected before and after the work shift.

Breathing zone levels of iron and manganese were frequently higher than the 8-hour TWA French exposure standard (the valeur moyenne d'exposition or VME #) while the levels of the other substances measured (notably chromium, nickel, and fluorides) were less than 30% of their respective VMEs. The concentrations of total particulate in breathing zone samples ranged from 4 to 39 mg/m^3. While breathing zone concentrations of manganese ranged from 0.3 to 5.8 times the VME, urinary manganese concentrations were only slightly higher than those of the general population. This observation is in line with those of other investigators (Refs. 96, 205, 216)

who have reported a poor correlation between external exposure to manganese and its concentration in the urine and blood of exposed welders. Reygagne et al. recommended that respiratory protection be used during railroad track repair because of the high atmospheric concentrations of total fumes, iron, and manganese.

17.4 Aluminum. Letzel et al. determined the biological half-life of aluminum in urine from 16 aluminum welders (Ref. 119). Spontaneous urine samples from the aluminum welders were collected before and after an exposure-free vacation period of 24 to 45 days. Urine samples were collected during the last work shift before, and at the resumption of work activities after the exposure-free period. The aluminum concentrations were analyzed using graphite furnace atomic absorption spectrometry. Large intra- and inter-individual fluctuations in the aluminum concentrations were found in urine samples, and the investigators recommended using aluminum concentrations based on creatinine values for biological monitoring of aluminum welders.

During the exposure-free interval, the median concentration of urinary aluminum decreased from 118.1 mg/g creatinine to 52.7 µg/g creatinine. Half-lives varied widely and ranged from 12.9 to 214.9 days among individual welders. Based on data obtained for all 16 welders, the biological half-life for urinary excretion of aluminum was calculated to be 30.4 days. The half-life was not related to the age of the welders, the duration of previous exposures, the length of the exposure-free interval, or the aluminum concentration in urine measured before the exposure-free interval. A wide range in half-lives for urinary excretion of aluminum was also observed among aluminum welders by Sjogren et al. (Ref. 168) who found that half-lives ranged from 9 days to more than 2 years. In contrast to the findings of Letzel et al., half-lives in the Sjogren et al. study varied with the duration of the exposure-free period, and were highly dependent on the duration of the welding experience.

17.5 Trace Metals. Vasconcelos and Tavares monitored the concentrations of six metals in the hair and whole blood of eight male apprentices, mean age 16 years, at a technical-professional school in Opporto City, Portugal (Ref. 205). The apprentices spent 14 hours per week performing SMAW of mild steel. Concentrations of Fe, Cu, Mn, Zn, Pb, and Ca were measured in blood and hair samples every 2 months throughout the 2-year training period. Concentrations of these metals in breathing zone samples collected during welding were relatively low (Table 13). The results were compared with metal concentrations in hair and blood collected at the same time from eight age-matched male students who lived in Opporto City and were not associated with the school. At the end of the 2-year apprenticeship, the students had

Table 13
Metal Levels in Fumes, City Air, and Blood Samples from Apprentices and Controls[1]

| Metal | Concentration in Air | | Concentration in Blood | |
	Fumes[2] (µg/m³)	City Air (µg/m³)	Apprentices (mg/L)	Controls (mg/L)
Ca	950	1.4	52.5 (6.1)	49.7 (5.8)
Cu	9.6	0.12	830 (98)[3]	653 (81)
Fe	1700	1.8	475 (54)[3]	536 (32)
Mn	430	0.029	8.18 (1.9)[3]	11.5 (4.8)
Pb	6.6	0.5	74 (23)	82 (73)
Zn	67	0.56	5.27 (0.89)	4.9 (.54)

Notes:
(1) The blood concentrations shown were from samples collected at the end (months 22 and 24) of the study. Values in parentheses are standard deviations.
(2) Fume samples were collected in the breathing zone.
(3) Blood concentrations in apprentices are significantly different from controls (p = 0.05).

Data from Vasconcelos and Tavares, Ref. 205.

significantly higher mean copper concentrations and significantly lower mean iron and manganese concentrations in blood than controls (in spite of iron being one of the most abundant metals, and manganese being relatively abundant in the fumes). Blood levels of the remaining metals were similar. All metal concentrations in blood from apprentices and controls fell within published ranges for reference populations. The mean metal concentrations in the hair of controls and apprentices were similar. The authors stated that the similarities between controls and apprentices were not surprising since the apprentices were exposed to low levels of welding fumes, and they concluded that "hair metal concentrations do not seem to be a good indicator for low occupational exposure."

18. Genotoxicity

Some chromium and nickel compounds are genotoxic and can cause alterations or mutations in the genetic material (DNA). Mutations of genes involved in the control of cell growth or cellular differentiation may lead to the formation of tumors. Reproductive disorders such as infertility, fetal death, or congenital defects in offspring may result from genetic alterations in germ cells (Ref. 103). A variety of techniques is available for measurement of genotoxic effects in blood cells collected from exposed workers. Sister chromatid exchanges (SCE), defined as the reciprocal interchange of DNA between chromatids, are widely used markers of genetic damage. They are relatively easy to detect and are a sensitive indicator of low levels of DNA damage. The micronucleus

assay is used to detect breaks in chromosomes or loss of whole chromosomes. If a chromosome break or loss occurs, a micronucleus forms and is visible in the cytoplasm.

Burgaz et al. (Ref. 36) determined the frequency of cells with micronuclei in peripheral lymphocytes and in exfoliative cells obtained by swabs of the buccal (inside of the cheek) and nasal cavities of 32 welders. Results from welders were compared with those from 25 controls matched for age and smoking habits. A statistically significant increase in the frequency (percent) of micronucleated cells was seen in the lymphocytes and in cells from the nasal cavity, but not from the buccal cavity of welders. Urinary concentrations of chromium and nickel did not differ between welders and controls. The investigators concluded that their data suggest that genotoxic effects can result from exposure to welding fumes.

Myslak and Kosmider (Ref. 133) determined the frequency of SCE in lymphocytes in blood samples drawn from 39 stainless steel welders and from 22 sex- and age-matched unexposed controls. Sister chromatid exchanges occurred more frequently in lymphocytes from welders than in those from controls. Tobacco smoking was significantly related to SCE frequency in the controls but not in the welders. No relationship was found between SCE frequency and age, urinary nickel concentrations, or duration of exposure. There was, however, a significant correlation between the frequency of SCE and the concentrations of chromium in urine from welders who smoked, suggesting a possible synergism between chromium exposure and smoking. A related study by these investigators (Ref. 134) compared the kinetics of cell division in cultured peripheral blood lymphocytes from 20

stainless steel welders with that in lymphocytes collected from controls. However, the number of cells present after 70 hours in the third round of cell division was lower in lymphocyte cultures from welders who smoked compared with those from smokers in the control group. The rates of cell division did not vary significantly between the welders and the controls; but in samples from welders who smoked, the number of cells present after 70 hours in the third round of cell division was lower, compared with samples from smokers in the control group.

The carcinogenicity of Cr(VI) and divalent nickel ions is thought to be related to their potential to damage DNA. Hexavalent chromium can readily pass through cell membranes where it can be converted to other chromium species that more readily interact with the genetic material. Nickel compounds may cause chromosomal damage by catalyzing the formation of oxygen radicals which can interact with the DNA. Such damage may lead to DNA strand breakage, to DNA-protein cross links between DNA strands, and to interchanges of sections of DNA strands between chromosomes (SCEs).

In 1991, Popp et al. (Ref. 150) reported finding a statistically significant increase in the frequency of DNA-protein crosslinks and a significant decrease in SCE frequency in lymphocytes collected from chromium- and nickel-exposed welders compared with non-exposed controls. No evidence of DNA strand breakages was found. These studies were later repeated by the same investigators using a different group of welders, with markedly different results (Ref. 209). In the more recent work, Werfel et al. compared the rate of SCE, DNA-protein cross-links, and single strand DNA breakages in lymphocytes collected from 39 chromium- and nickel-exposed welders and from an equal number of aged-matched controls who had no known occupational exposures to carcinogens (Ref. 209). Alkaline filter elution was used to measure DNA-protein cross links and, following the addition of proteinase (an enzyme that breaks peptide bonds in proteins), DNA strand breakage. In this study, unlike the previous one (Ref. Popp), the frequency of DNA protein cross-links did not differ significantly between welders and controls. Significant increases in the frequencies of DNA single-strand breakages and SCE exchanges, however, were seen in lymphocytes from welders as compared with controls (p = 0.0001). There were no differences in the results between smokers and non-smokers. The concentrations of chromium and nickel in blood collected during each of the two studies indicated that welders in the second study were exposed to substantially higher workplace concentrations of nickel and chromium than were welders in the initial study. From this, the investigators deduced that DNA-protein cross-links are formed mainly at lower exposures to chromium and nickel, but DNA strand breakages

would predominate with higher exposures. Exposure levels approximated from blood analyses indicated that DNA-protein cross-links may form at exposures to chromium in the range of the TLV, indicating that the TLV may not be sufficiently low to protect workers from the genotoxic effects of chromium.

Section Three
Investigations in Animals and Cell Cultures

19. Metal Fume Fever

The presence of the cytokines TNF and IL-8 in BALF from human volunteers as early as 3 and 8 hours, respectively, after inhalation exposure to ZnO fumes (Refs. 25, 115) supports the concept that cytokines play a role in the promotion of metal fume fever. Kuschner et al. (Ref. 113) conducted in vitro studies to test the hypothesis that, following stimulation by ZnO, alveolar macrophages are the source of these cytokines. Cultured monocytes (immature macrophages) were exposed in vitro to varying concentrations of ZnO, and the levels of TNF and IL-8 were measured in the culture medium in which the cells were growing at 3, 8, and 24 hours after exposure. Dose-dependent concentrations of TNF were found in the medium after each of these time intervals. The concentration of IL-8 was significantly elevated after 8 and 24 hours. The sequential appearance of TNF and IL-8 mimics the sequence observed in ZnO-exposed volunteers (Ref. 25). The investigators concluded that mononuclear inflammatory cells (macrophages) are probably the primary source of IL-8 and TNF in the lungs of humans exposed to ZnO fumes.

Lindahl et al. (Ref. 120) examined the possible role of another aspect of leukocyte activity, the respiratory burst, in the mediation of metal fume fever. When macrophages engulf foreign bodies such as bacteria or welding fume particles, they produce a variety of highly reactive oxygen species [ROS#] including superoxide, hydroxyl radicals, and hydrogen peroxide. The ROS are important for bactericidal activity and can act by altering the permeability of cell membranes and by reacting with the pathogen's macromolecules such as DNA. While ROS may play a role in promoting the inflammatory response, they can also react with the host's macromolecules, and can cause deleterious effects such as strand breaks in DNA. Lindahl et al. examined whether $ZnCl_2$ and ZnO can stimulate the release of ROS from human neutrophils isolated from blood drawn from volunteers. Reactive oxygen species were detected by luminol-amplified chemi-

luminescence. In this assay, neutrophils are placed in a vial containing a small amount of culture medium to which the chemical luminol has been added. Luminol reacts with ROS to give off a photon of light that is detected by and measured in a liquid scintillation counter.

Addition of either ZnO or $ZnCl_2$ to the culture medium caused a dose-related increase in the chemiluminescence produced by the neutrophils. Chemiluminescence increased to a maximum about 35 minutes after the addition of ZnO and at about 80 minutes following the addition of $ZnCl_2$. Corresponding concentrations of the other metals tested (Cd^{2+}, Cr^{2+}, Cr^{3+}, Fe^{2+}, Fe^{3+}, Ni^{2+}, Co^{2+}) did not have this effect. The authors concluded that both $ZnCl_2$ and ZnO stimulate production of ROS by human neutrophils, and they suggested that ROS might play a role in the pathogenesis of metal fume fever.

20. Pulmonary Inflammation

Antonini et al. (Refs. 10, 11) performed a battery of tests to examine mechanisms by which welding fumes may produce pulmonary inflammation and injury. In the first study (Ref. 10), fume samples generated by SMAW using a stainless steel consumable electrode (SMAW-SS) and by GMAW using a mild steel electrode (GMAW-MS) were suspended in saline solution and administered to rats by intratracheal instillation. Rats treated with ferric oxide and saline solution served as controls. The rats were sacrificed and their lungs were lavaged 1, 14, and 35 days after treatment. The numbers of neutrophils and macrophages and the concentrations of two inflammatory cytokines, TNF and IL1 in the lavage fluid served as indicators of inflammatory processes. The enzyme lactic dehydrogenase (LDH) was used as an indicator of general cellular injury (cytotoxicity) and beta-n-acetyl glucosaminidase (-NAG) was used to indicate phagocytic activity or cellular injury to macrophages.

One day after treatment, the numbers of cells in lavage fluid from rats treated with either fume sample were significantly greater than those in BALF from negative controls, due largely to an increase in the number of neutrophils. At later time points, both neutrophils and macrophages were elevated in BALF from rats treated with SMAW-SS fumes but not in those treated with GMAW-MS fumes. On the first day after treatment, TNF and IL-1 were significantly elevated in BALF from rats treated with either of the two fume samples as compared with the iron oxide and saline controls. Significantly more TNF and IL-1 were induced by fumes from SMAW-SS than by those from GMAW-SS. The cytokines were not measurable at later time points in the BALF from rats treated with either fume sample. On day 1, levels of albumin, LDH, and -NAG were elevated in BALF

from rats treated with either fume sample, but on day 14 they were elevated only in rats treated with SMAW-SS fumes, indicating that the SMAW-SS fumes were more toxic to the lungs than were GMAW-MS fumes.

In vitro studies were conducted to determine the effects of welding fumes and their insoluble and soluble components on the viability and function of macrophages isolated from untreated rat lungs by bronchoalveolar lavage. The effects of three fume samples were studied: SMAW-SS, GMAW-MS, and GMAW using a stainless steel electrode (GMAW-SS). Fume samples were separated into soluble and insoluble components by incubating in saline solution for 24 hours at 37°C. Macrophage viability was assayed by measuring the ability of cells to exclude trypan blue after incubation with fume samples for 24 hours. Tests of cellular function and injury were conducted after incubation of macrophages with fume samples for 1 hour. The activity of primed macrophages was measured by the release of ROS into the culture medium. Reactive oxygen species were detected by the fluorescence generated by the oxidation of dichlorofluorescin. These tests were conducted with intact fumes and with the soluble and insoluble fractions of fume particles.

Viability tests showed that SMAW-SS fumes were the most cytotoxic of the fumes tested followed by GMAW-SS fumes. The cytotoxicity of the GMAW-MS fumes did not differ significantly from that of controls (Figure 5). Intact SMAW-SS fume samples caused the release of significantly greater quantities of ROS and -NAG into the culture medium than did the other fumes tested. The soluble components of stainless steel fumes were more cytotoxic than the insoluble fractions as evidenced by the effects on viability and release of LDH and NAG into the culture medium. Macrophage activation, as measured by the release of ROS, was greater with the particulate fraction than the soluble fraction, especially for the SMAW-SS fumes (Figure 6). In summary, SMAW-SS fumes were the most toxic of the fumes tested and caused the greatest activation of macrophages, as measured by release of ROS. GMAW-MS fume, and its soluble and insoluble components, had the least effect on all of the parameters tested.

Chemical analyses of the fumes and their fractions were conducted to assess whether differences in the inflammatory response to the different fume types could be attributed to their composition (Refs. 10, 11). SMAW fumes had substantially more soluble materials than did those generated by GMAW (the soluble materials constituted 34.5%, 0.6%, and 2% of SMAW-SS, GMAW- SS and GMAW-MS fumes, respectively). The relative concentrations of seven metals (Fe, Cr, Ni, Cu, Ti, V, and Mn) were determined in the intact welding fume samples and in their soluble and insoluble components using in-
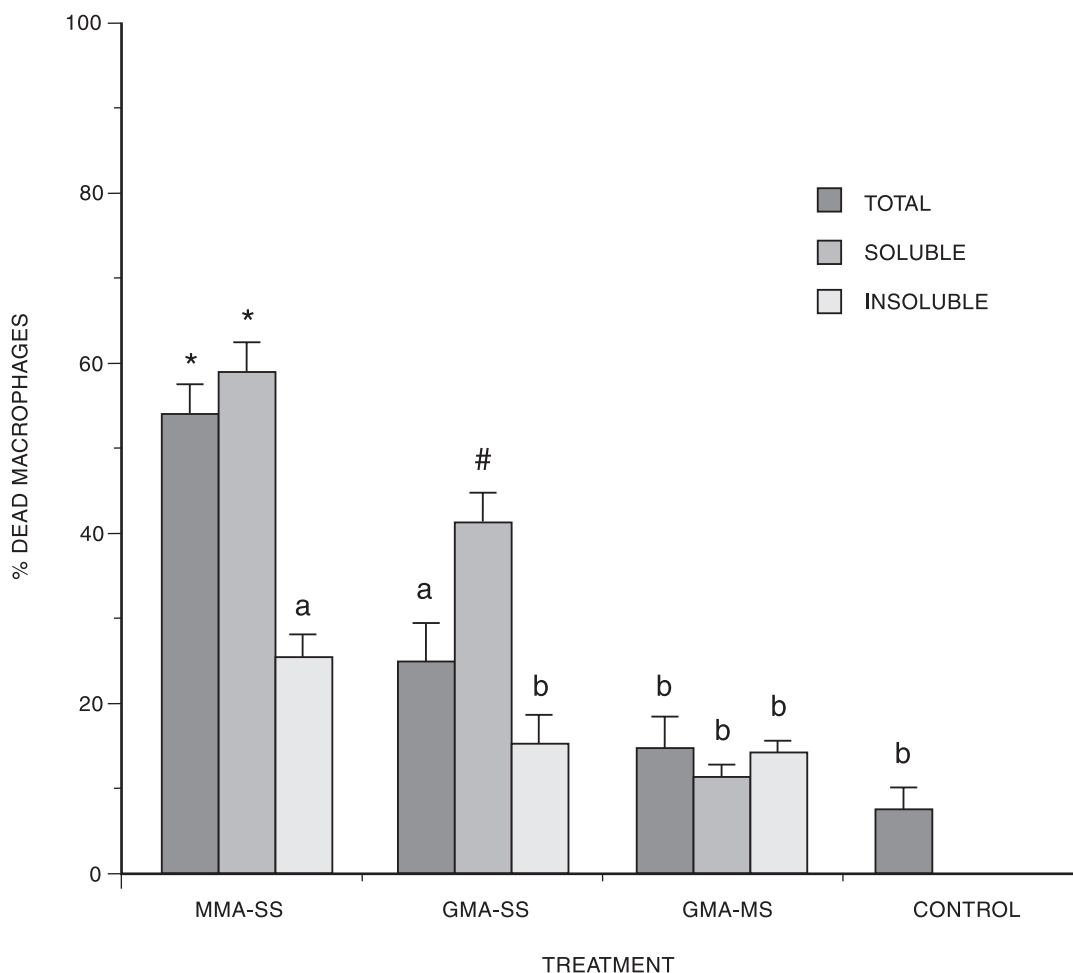
MMA-SS= SMAW of stainless steel
GMA-SS= GMAW of stainless steel
GMA-MS= GMAW of mild steel

Macrophage viability was determined by trypan blue exclusion after a 24-hour incubation with total fume particulate and the soluble and insoluble fractions of the fume. Values are means ± SE. Groups with the same symbols are not statistically different ($p < 0.05$).
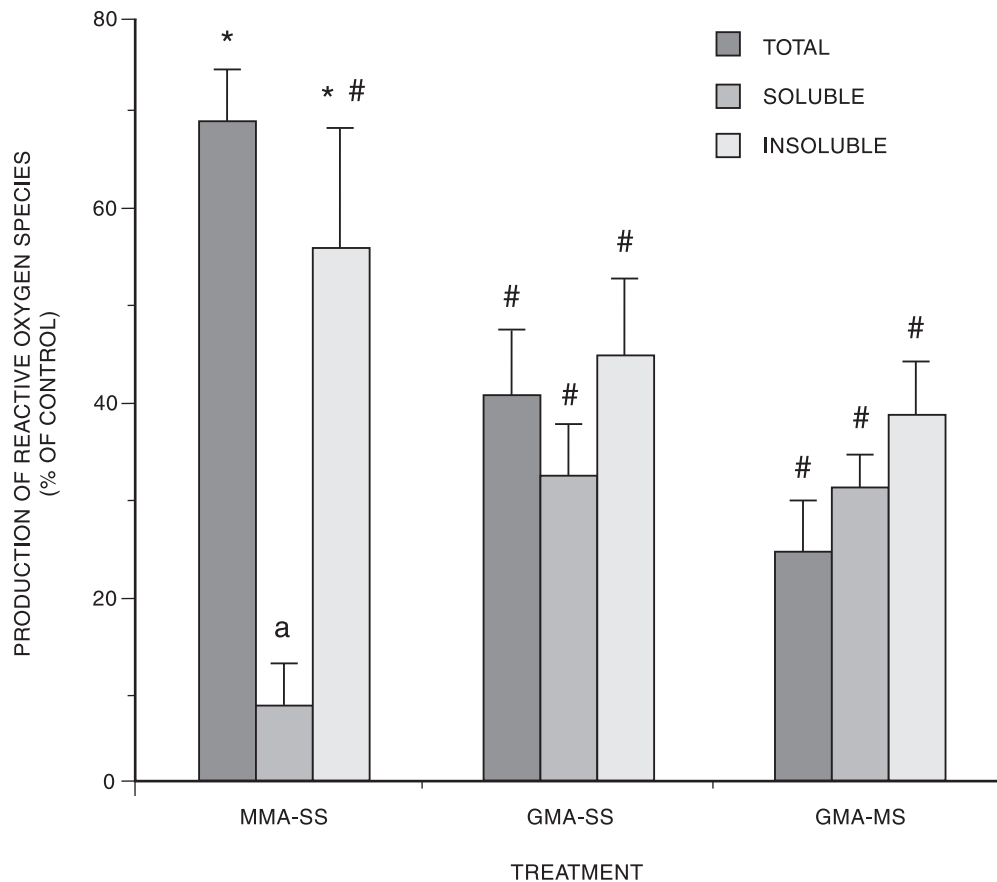
Data from Antonini et al., Ref. 11.

Figure 5—The Percentage of Dead Macrophages after Incubation with the Total Particulate, and Soluble and Insoluble Components of Fumes Generated by SMAW and GMAW of Stainless Steel, and GMAW of Mild Steel

ductively coupled argon plasma atomic emission spectrometry. The major metals present in stainless steel fumes were Fe, Mn, Cr and Ni, and those in mild steel fumes were Fe and Mn. Ninety-seven percent of the surface of particles generated by SMAW-MS consisted of complex fluoride ions, and 88% of the surface of GMAW-MS fume particles was Fe_2O_3. The surface of GMAW-SS fumes contained primarily Fe, Mn, Cr, and amorphous Si (Ref. 9). The main components (by weight percent) of the soluble fractions were Cr (87%) and Mn (11.7%) in SMAW-SS fumes; Mn (68.2 %), Ni (11.8%), Fe (9.26%), and Cu (4.5%) in GMAW-SS fumes; and Mn (93%) and Fe (4.6%) in GMAW-MS fumes. The inflammatory properties of SMAW-SS particles may be related to the high concentrations of fluoride compounds on their surface and to the their large component of soluble chromium.

MMA-SS = SMAW of stainless steel
GMA-SS = GMAW of stainless steel
GMA-MS = GMAW of mild steel

Values are means ± SE. Groups with the same symbols are not statistically different (p < 0.05).

Data from Antonini et al., Ref. 11.

Figure 6—Production of Reactive Oxygen Species by Lung Macrophages after Incubation with the Total Particulate, and Soluble and Insoluble Components of Fumes Generated by SMAW and GMAW of Stainless Steel and GMAW of Mild Steel

In a final study, based on findings of other investigators that particles such as freshly fractured silica have greater concentrations of surface radicals and can cause more injury and inflammation in the lungs than aged particles (Ref. 198), Antonini et al. (Ref. 9) compared the lung inflammation and injury produced in rats by freshly-formed and by aged welding fume samples generated by GMAW of stainless steel. Fresh fume samples were administered to rats by intratracheal instillation within 30 minutes after they were collected. Aged samples were stored exposed to air for 1 and 7 days before being administered to rats. Animals were sacrificed and BALF was collected 24 hours after the fumes were in-

stilled. The numbers of neutrophils, and concentrations of albumin, lactate dehydrogenase (LDH), and (-NAG) in BALF were used as indicators of pulmonary injury and inflammation. Instillation of fresh and aged fume samples caused a marked increase in the number of cells in lavage fluid compared with saline controls, due largely to the infiltration of neutrophils. The total number of cells and the number of neutrophils were significantly greater in BALF from rats treated with fresh fumes than in that from rats treated with aged fumes. The concentration of -NAG, but not LDH, was significantly greater in BALF from rats treated with fresh fumes than in all other samples tested. No differences in

the inflammatory effects were seen between fumes aged for 1 and 7 days.

Tests with dichlorofluorescin indicated that more ROS were present on the surface of freshly formed fumes than on the surface of aged fumes. The ROS declined with aging and were substantially reduced in fumes aged for 30 days. Antonini et al. concluded that freshly formed fumes cause more lung inflammation than do aged fumes, which may well be due to the greater quantities of ROS on their surfaces.

21. Immunomodulation by Hexavalent Chromium

Aerosols containing soluble and insoluble Cr(VI) compounds and ozone are generated by some welding processes. Cohen et al. (Ref. 46) investigated whether co-exposure to ozone affects pulmonary retention and distribution of inhaled soluble or insoluble Cr(VI) compounds in the lungs of rats. Rats were exposed by inhalation for 5 hours/day, 5 days/week, for up to 4 weeks to 360 μg/m^3 potassium chromate [(soluble Cr(VI)] or barium chromate [(insoluble Cr(VI)], either alone or in combination with 0.3 ppm ozone. Rats were euthanized the day after the final exposure, and their lungs were removed and lavaged.

More cells were present in lavage fluid following exposure for 2 weeks to soluble Cr(VI) than to insoluble Cr(VI) compounds. Co-exposure to ozone and soluble chromate increased the total number of cells in BALF after a 2-week exposure. More chromium was retained in the lungs and was found engulfed by alveolar macrophages following exposure to insoluble Cr(VI) than soluble Cr(VI). Concomitant exposure to ozone increased the accumulation of chromium, especially insoluble chromate, in lung tissues.

The effects of the solubility of Cr(VI) and co-exposure to ozone on pulmonary macrophages was examined in cells recovered from the lavage fluid collected during the Cr(VI) deposition studies (Ref. 47). Macrophages were activated overnight with bacterial endotoxin and the concentrations of cytokines determined in the culture medium. Production of IL-1 and of ROS was inhibited by insoluble but not soluble Cr(VI). TNF production was inhibited by both soluble and insoluble chromate and IL-6 production was not altered by inhalation of either form of Cr(VI). Concomitant exposure to ozone did not alter the immunomodulatory effects caused by exposure to soluble or insoluble Cr(VI) compounds alone. The authors concluded that the retention and distribution of chromium in the lungs is dependent on its solubility and that the amount of chromium retained in the lungs may be altered by concomitant exposure to ozone. Solubility is also important in determining the immunomodulatory effects of inhaled Cr(VI) compounds upon pulmonary macrophages, but co-exposure to ozone does not modify these effects.

22. Dopamine Oxidation

Based on the premise that welding fume components, in particular manganese and iron, contribute to the development of neurologic disorders by promoting oxidation of dopamine to melanin, or by causing peroxidation of lipids in the brain, Hudson et al. (Ref. 88, 89) tested the ability of welding fume components to oxidize dopamine or lipids in cell-free extracts of brain tissue. Fumes were produced by GMAW of mild steel plates using solid or flux-cored electrodes, with argon (95% Ar + 5% CO_2) or carbon dioxide (98% CO_2 + 2% O_2) as the shielding gas. Water-soluble components of fume samples were incubated in tissue culture medium with dopamine or homogenates of mouse brain tissue for 10 minutes. Dopamine oxidation and lipid peroxidation were measured spectrophotometrically.

All the fume extracts inhibited lipid peroxidation and enhanced dopamine oxidation. Rates of dopamine oxidation were higher with extracts of fumes generated with flux-cored electrodes compared with solid electrodes and with fumes generated using the carbon dioxide shielding gas compared with the argon shielding gas. The dopamine oxidation potential of the fume extracts also varied with the welding current and voltage. It decreased as the current across the arc increased for both the flux-cored and solid electrodes. Analysis of metals in the welding fumes showed that soluble compounds of iron and manganese caused higher dopamine oxidation rates than did soluble compounds of chromium and nickel. In general, the rates of dopamine oxidation or lipid peroxidation increased as the ratio of iron to manganese increased, but the rates were highest when some manganese was present, suggesting a synergism between the two metals or a role for manganese in this process. Because lipid peroxidation was inhibited by the soluble fraction of welding fumes, the investigators concluded that lipid peroxidation is not involved in the mechanism of neurotoxicity associated with chronic exposure to welding fumes containing iron and manganese. They stated, however, that the ability of welding fume solutes to oxidize dopamine to melanin is consistent with neurotoxic activity.

23. Distribution of Inhaled Iron

Noda et al. (Ref. 141) exposed male rats to freshly-formed welding fumes by inhalation and examined

various organs for histopathological changes and iron deposits. Rats were exposed to welding fumes for 3 hours a day, 3 days a week for 8 weeks. The rats were sacrificed, two at a time, over a period of 1 year following the start of exposures. At the end of the year, macrophages with engulfed iron particles were seen in the lungs and iron deposits were found in the broncho-pulmonary lymph nodes. Sixteen weeks after the start of exposures, regenerative changes, accompanied by iron deposits, were seen in some cells in the kidneys. Iron deposits were observed in the renal tubular cells 1 year after treatment. Iron deposits were observed in the liver and spleen of both control and treated animals, indicating that they were not related to the exposures. Iron deposits were not observed in the other organs examined (pancreas, bladder, and testes).

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Nonmandatory Annexes

Annex A

Common Measurements of Pulmonary Function

Test	Abbreviation	Notes
Forced Vital Capacity	FVC	Maximum volume of air that can be exhaled after a maximum inhalation. FVC is reduced in restrictive lung disease* and to a lesser extent in obstructive disease**
Residual Volume	RV	Air remaining in lung after maximum exhalation.
Total Lung Capacity	TLC	Sum of FVC and RV.
Forced Expiratory Volume	FEV_1	Volume that can be exhaled in one second with maximum exertion. FEV_1 is reduced in restrictive lung disease and in obstructive lung disease.
FEV_1 as a Fraction of FVC	FEV_1/FVC	Reduced in obstructive lung disease, normal or slightly increased in restrictive lung disease. FEV_1 is normally about 80% of FVC.
Volume of Trapped Gas	VTG	Increase in VTG is a sensitive indicator of asthma.
Diffusing Lung Capacity for Carbon Monoxide	DLCO	A decrease in the pulmonary diffusing capacity, as measured by DLCO, may be seen in patients with diffuse interstitial disease who have normal spirometric tests.
Airway Responsivenessto Methacholine	PD_{20}	The provocative cumulative dose of methacholine causing a 20% decrease in FEV_1. Positive responses at relatively low doses of methacholine are indicative of asthma.

Forced Expiratory Flow
  Mid range (25-75%)
  Terminal flow (75-85%).
	FEF
	FEF_{25-75}
	FEF_{75-85}
		Flow rate measured during forced exhalation.Reductions in mid range and terminal flow indicate impairment in small airways (alveolar region of the lung).

Maximum Expiratory Flow	MEF_{25} MEF_{50} MEF_{75}	Measured at 25% of FVC. Measured at 50% of FVC, also known as maximum mid expiratory flow (MMEF). Measured at 75% of FVC.
Peak Expiratory Flow Rate	PEFR	Peak momentary expiratory flow rate during maximum exhalation. Subnormal or declining values in PEFR are indicative of asthma.

 *Obstructive lung disease affects airflow through the airways and includes pathological conditions such as bronchial asthma, chronic bronchitis and emphysema.

**Restrictive lung disease affects diffusion of gases through the lung parenchymal tissue and includes conditions such as interstitial lung disease and diffuse pulmonary fibrosis.

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Annex B

Occupational Epidemiology

Epidemiology is the study of the comparative frequency of a disease or disorder in different populations. **Endpoints** in the studies may be **incidence** of the disease under study or **mortality** from it.

Occupational epidemiology is the study of the occupational environment as a risk factor for disease in groups of workers. Compared with population studies, workplace studies have the **advantage** of the availability of documentation of exposure from individual work records, and often groups of control subjects can be chosen from within the same plant. The major **disadvantage** is that working populations are usually healthier than the general population. Thus, except for diseases that are rare in the general population, a large excess incidence of a disease must occur in the occupational group under study before causation can be established. This phenomenon is referred to as **the healthy worker effect. Selective migration**, movement of persons adversely affected by an industrial environment to a less hazardous one, may combine with the **healthy worker effect** to bias the results of occupational epidemiology studies.

A **cohort study** is a **longitudinal** study of the occurrence of a disease over time. It may be **retrospective**, in which case the exposure and incidence data are **historical**. A major disadvantage of a **retrospective** study is that exposure data are usually incomplete. A **prospective** study is undertaken in real time and has the advantages of better control of the experimental variables and the ability to measure exposure. It has the disadvantages of high cost and time delay. Both types of **cohort** studies require large **populations** of workers (thousands of person-years of exposure) in order to have a reasonable chance of detection of an excess incidence of a disease in the occupational group under study. This is particularly true for diseases such as lung cancer that are not rare in the general population.

Risk ratios are the means of reporting the outcomes of cohort studies. **Relative risk (RR)** is the ratio of the incidence rate of disease in the population studied (for example, welders of stainless steel) and that of another population not exposed in the same way (for example, welders of mild steel, or non-welders in the same factory). Dividing the number of cases in the study population by the expected number, based on incidence statistics for the general population, yields the **standardized incidence ratio (SIR)**. The **standardized mortality ratio (SMR)** is calculated from mortality data in the same manner. Both of these ratios are usually represented as percents [(number of cases observed/number of cases expected) × 100%].

In **case-control studies** (also known as **case-referent studies)** of a particular disease, a population with the disease (**cases**) is matched with a population without the disease (**controls** or **referents**). The **odds ratio** (**OR)** for the disease in an occupational group (e.g., welders) is the fraction of cases who are members of the occupational group divided by the fraction of controls who are in the same occupational group. For example: OR for lung cancer in welders = (**percent** of cases who are welders)/(percent of controls who are welders). **Case-control studies** cannot provide an estimate of the true frequency of a disease in the population studied, because the control groups are small in size relative to the numbers in population studies and often are not chosen to represent the population at large. They have the advantages of small sample size, and relatively low expenditure of money and time. A major disadvantage is the difficulty of obtaining equally reliable information from cases and controls.

Confounding is distortion due to mixing of the exposure being studied with extraneous risk factors. **Confounders**, or **confounding factors**, are both **independent** and **correlated** with the occupational factors being studied. **Controlling** for **confounders** may be accomplished by **restricting** the population under study (for example, excluding smokers or workers who have been exposed to asbestos from lung cancer studies) or, especially in **case-control** studies, by **matching** the frequency of the

confounders in the **controls** with that in the occupational group being studied. **Risk ratios** may also be adjusted for known effects of **confounders** when exposures to them are not consistent across groups.

Statistical analyses are applied to all of the **risk ratio** calculations to develop a 95% **confidence interval (CI).**

When the upper and lower boundaries of the **CI** are both greater than one, there is a **statistically significant** finding of a greater risk for the disease among the group under study than among the **controls**. Conversely, when the upper and lower boundaries of the **CI** are both less than one, the decreased incidence of the disease in the study group is also **statistically significant**.

From Shy (Ref. 164)