Effects of Welding on Health, XIV

American Welding Society®

Effects of Welding on Health, XIV

Prepared for the
AWS Safety and Health Committee

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Abstract

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

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Foreword

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 ongoing program sponsored by the committee. Previous work consists of the reports Effects of Welding on Health I through XIII each covering approximately 2 to 3 years. Conclusions based on this review and recommendations for further research are presented in the introductory portions of the report. The current report includes information published between January 2003 and December 2005. In addition, an appendix has been added with short summaries of articles on the effects of welding on human health published between 2006 and 2009.

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Glossary*

ACGIH	American Conference of Governmental Industrial Hygienists
BALF	Bronchoalveolar lavage fluid
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
Cr(III)	Trivalent chromium
Cr(VI)	Hexavalent chromium
CT	Computed tomography
ELF-EMF	Extremely low frequency electromagnetic field
Dyspnea	Difficulty breathing; shortness of breath
FCAW	Flux cored arc welding
GMAW	Gas metal arc welding
GTAW	Gas tungsten arc welding
Ig	Immunoglobulin
IL	Interleukin (a class of proteins or cytokines important in regulation of the immune system/lymphocyte function)
Leukocyte	White blood cell
MAC	Maximum Allowable Concentration
mRNA	Messenger ribonucleic acid (template for protein synthesis; mRNA transmits genetic information from DNA to the cytoplasm where proteins are synthesized)
n	Number
nm	Nanometer
NIOSH	National Institute for Occupational Safety and Health
OA	Occupational asthma
OR*	Odds ratio
OSHA	Occupational Safety and Health Administration
PAH	Polycyclic aromatic hydrocarbons
PEL	Permissible Exposure Limit
PMN	Polymorphonuclear leukocyte
ROS	Reactive oxygen species
RR*	Relative risk
SMAW	Shielded metal arc welding
SMR*	Standardized mortality ratio
SOD	Superoxide dismutase
TLV	Threshold Limit Value
µm	Micrometer
µg	Microgram
UV	Ultraviolet

*Abbreviations for commonly used pulmonary function tests and for epidemiological terminology used in this document are found in Appendix 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.* Thirteen 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 2002. The current report includes information published between January 2003 and December 2005. In addition, an appendix has been added with short summaries of articles on the effects of welding on human health published between 2006 and 2009. This volume should be read in conjunction with 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 effects of welding on the respiratory tract continue to be examined and attention has been paid to the elevated incidence of pneumonia among active welders. Studies in animals suggest that SMAW of stainless steel may be responsible for this effect and that the soluble chromium component of SMAW fumes plays an important role in the suppression of the pulmonary defense responses against bacterial infection. The neurological effects of aluminum and manganese continue to receive attention. Much of the research has focused on whether exposure to manganese in welding fumes can cause Parkinson's disease or a Parkinson's disease-like syndrome (parkinsonism). Several large epidemiologic studies published during this report period addressed this question and most indicate that welders do not have an elevated risk for this condition.

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Executive Summary

Effects on the Respiratory Tract

Pulmonary Function. Decrements in pulmonary function that may be associated with inhalation of workplace pollutants can be evaluated using spirometric tests which measure the lung volume, the maximum amount of air that can be inhaled, and the flow rates that can be achieved after a maximal inhalation. Six studies examined the effects of welding exposures on pulmonary function (Ref. 34, 38, 77, 113, 147, 157). Significant decrements in pulmonary function among welders were observed in five of them. An increase in the respiratory symptoms cough, sputum production, wheezing, dyspnea (shortness of breath), and bronchitis was observed among welders in four of these studies (Ref. 34, 77, 147, 157), including the one in which no changes in pulmonary function were observed (Ref. 157).

In their study at four worksites in New Zealand, Fishwick et al. (Ref. 38) found that work-related respiratory symptoms reported by 27% of welders were significantly related to nickel exposures. Exposure to aluminum was significantly associated with a decline in FEV_1 of 5% or more after 15 minutes of work. Total fume exposure and cumulative welding experience of greater than 10 were non-significantly associated with the incidence of respiratory symptoms.

Occupational Asthma. Based on a review of published studies, the American Thoracic Society estimated that approximately 15% of asthma in the adult population is attributable to occupational exposures (Ref. 7). McDonald et al. (Ref. 106) analyzed all cases of work-related respiratory disease reported by thoracic and occupational health physicians to the National Heart and Lung Institute in London between 1992 and 2001. The study focused on diseases with a short latent period: occupational asthma (OA), allergic alveolitis, and illness caused by "inhalation accidents" (e.g., those resulting from inhalation of strong irritant gases). Occupational asthma accounted for 25% of these diseases. Reports from chest physicians identified welding as the causative agent for 3% of the cases of OA; other exposures to metals or metallic compounds accounted for an additional 4%.

It is compulsory for physicians in Finland to report all new cases of OA to the Finnish Register of Occupational Diseases. Piipari and Keskinen (Ref. 125) analyzed all of the cases of OA reported between 1988 and 1997 and found that 4% of them could be attributed to exposure to welding fumes.

In Norway, occupational diseases must be reported by physicians to the Labor Inspection Authority. Using the registry of these reports, Leira et al. (Ref. 89) investigated the incidence of OA during the period 1995–1999. Workers in the aluminum industry had the highest reported incidence of asthma. This was due, in part, to the recognition of OA as a disease among aluminum potroom workers in Norway and to the requirement for active screening of these workers, making it less likely that the disease would be underreported in this group than in the industrial population as a whole. Among the cases from outside the aluminum industry, male welders were the third most likely group to have been reported with OA. Since the majority of cases still had symptoms 2 to 6 years after their initial diagnosis, Leira et al. concluded that they were likely to have been reported at an advanced stage of the disease. They recommended that, since OA tends to become chronic and irreversible unless exposure is reduced when symptoms first develop, it is advisable to transfer workers with OA to an exposure-free workplace at an early stage of the disease.

El-Zein et al. (Ref. 30, 31) performed a prospective study of 286 apprentice welders in whom changes in pulmonary function and signs of asthma were followed during the course of their 15 months in welding school. Data concerning respiratory symptoms suggestive of asthma (e.g., cough, wheezing, and tightness in the chest) experienced by the apprentices were collected at the beginning and end of the study. Spirometric and methacholine provocation tests were completed with 194 of the apprentices before they commenced the apprenticeship and at the end of the 15-month study period. Significant changes were found in FEV_1 and FVC during that time. Persistent welding-related respiratory symptoms were found in 7.6% of the subjects. Based on symptoms and the response to methacholine provocation tests, six of these subjects were diagnosed with probable OA at the end of the study.

Hammond et al. (Ref. 59) compared rates of physician-diagnosed asthma among men who had worked in 1999 as car body welders, paint shop workers, or assembly workers in an automotive assembly plant. The welders were exposed to dusts, welding fumes, and pyrolysis products from coatings, fluxes, and oils while welding, brazing, and grinding of the car body in preparation for painting. The painters were exposed to vapors from solvents, primers, paints, reducers, and thinners, in addition to dust from sanding the various coats. The assembly workers had minimal exposure to vapors or metal fumes during their work installing engines, doors, tires, dashboards, seats, and other car parts. Physician-diagnosed asthma, chronic obstructive pulmonary disease (COPD), sinusitis, and allergy were more common among welders than among assembly workers, but this difference was significant only for diagnosis of COPD. The authors noted that 20% of the body welders and 16% of the painters reported symptoms of asthma. Health care providers had confirmed asthma in at least half of these cases. The expected incidence of asthma among these workers was only 3%.

Hannu et al. (Ref. 61) described the progression of OA in two men who had performed SMAW on different formulations of high chromium steel at a plant that manufactured machines for the pulp and paper industry. The first man had been welding for the same employer for over 20 years when he started welding SMO steel (19.5% Cr, 17.5% Ni, 6% Mo). He experienced dry cough, severe dyspnea, and wheezing on the evening following his first exposure and for the next 2 days as he continued welding this type of steel. He was hospitalized after the third day and was placed on sick leave for 2 weeks, during which time his symptoms subsided. Welding challenge tests with both mild steel and a common stainless steel produced negative results but when he welded the SMO steel, he experienced a delayed asthmatic reaction with a 37% drop in FEV_1. Six months later, after ceasing work with SMO steel, he continued to experience dyspnea after work. Pulmonary function tests administered at that time showed that his ratio of PEF/FEV_1 was suggestive of asthma.

The second case was 17 years old when he began working as a welder in 1984. He was examined in 2001 after he began to experience shortness of breath following welding of Duplex steel (21%–24% Cr, 3.5%–6% Ni, 0.1%–3% Mo). Welding challenge tests with mild and stainless steel produced negative results, but a similar challenge with Duplex steel resulted in a delayed reaction, with a 31% drop in FEV_1. Concentrations of metals measured in the inhalable dust during the challenge tests showed that nickel, chromium, and aluminum were considerably higher in the fumes from welding the SMO steel, but were only slightly higher in the Duplex steel fumes, compared with those of stainless steel. Nevertheless, the authors concluded that welding of the high-chromium special steels was the likely cause of these two cases of OA.

Pneumoconiosis. Siderosis (arc welder's lung) is a form of pneumoconiosis in which inhaled iron oxide particles accumulate in the lungs and cause tissue changes that are visible as radio-opacities in chest X-rays. Although siderosis has been considered to be a benign condition, more serious effects such as fibrosis or decreased pulmonary function have been reported in association with pneumoconiosis after long-term exposure to welding fumes. Studies in rats by Yu et al. (Ref. 170) have shown that repeated inhalation of fumes generated by SMAW of stainless steel can cause pulmonary fibrosis which is irreversible after prolonged exposure to high doses. Statistically significant dose-dependent decreases were seen in tidal volume (a lung function parameter) of exposed rats (Ref. 150). The tidal volume returned to normal after a 60-day recovery period following the last fume exposure in all rats except in those exposed to the dose that caused irreversible fibrosis.

Six welders with pulmonary siderofibrosis were described in case reports published by Buerke et al., Doherty et al., and Yokoyama et al. (Ref. 17, 27, 167). All of these cases had extensive histories of welding, some with exposure to high levels of welding fumes in poorly ventilated workplaces. Deficits in pulmonary function were observed in the five welders who were subjected to spirometric tests (Ref. 17, 27).

Six cases of systemic iron overload, as evidenced by elevated serum ferritin concentrations, were described in welders with siderosis (Ref. 27, 44, 75, 167). Chronically elevated iron levels can lead to serious conditions including liver cirrhosis, diabetes, cardiac arrhythmias, and heart failure. As with hemochromatosis, a hereditary disease in which excess iron is absorbed from food and accumulates in body tissues, the standard treatment for iron overload is phlebotomy, in which blood is periodically withdrawn by venipuncture to lower systemic iron levels. Concentrations of serum ferritin normally range from 30 ng/mL to 300 ng/mL. In most of the case reports of iron overload in welders with siderofibrosis, ferritin levels ranged from 1000 ng/mL to 2300 ng/mL. Serum ferritin levels of 6352 ng/mL were observed in a welder described as having progressive massive fibrosis (Ref. 167). Treatment by phlebotomy was successful in reducing blood iron levels in those cases where it was applied (Ref. 27, 44).

Cancer

Lung Cancer. Two studies (Ref. 129, 166) found a significantly elevated risk for lung cancer among welders. Richiardi et al. (Ref. 129) conducted a case-control study of lung cancer related to occupational exposures in northern Italy in which 1132 incident lung cancer cases were matched by sex and age with 1553 randomly-selected controls from the same geographic area. Significantly increased risks for lung cancer were found among welders and flame cutters. Yiin et al. (Ref. 166) analyzed the incidence of lung cancer and leukemia deaths among 13,468 civilians who had worked for at least one day at the Portsmouth Naval Shipyard in Kittery, Maine, between 1952 and 1992 and who had been monitored for radiation exposure. The primary emphasis of the study was to determine the effects of cumulative radiation dose on the risk of death from each of the two types of cancers. Asbestos and welding fume exposure were analyzed as covariates, along with demographics and solvent exposure. Of the employees surveyed, 3861 had died by the end of 1996, including 411 who died from lung cancer. Workers with any welding fume exposure had a significantly greater risk for lung cancer than did those with no welding fume exposure. The association between welding and lung cancer was somewhat dampened by the finding that the relative risk did not increase with increased exposure to welding fume.

Cancer of the Eye. Ocular melanoma, the most common malignancy of the eye in adults, is an uncommon disease with a poor prognosis. In a review of the literature on the association between ocular melanoma and welding, Dixon and Dixon (Ref. 26) noted that ocular melanoma is probably due to exposure to UV radiation. They stated that several studies have demonstrated an association between welding and the risk for developing this disease. Lutz et al. (Ref. 96) examined potential occupational risks for ocular melanoma in a population-based case-control study in which the 292 incident cases were recruited from the populations of nine European countries. A significant excess risk for ocular melanoma was found in welders and sheet metal workers. Shah et al. (Ref. 140) examined risk factors for ocular cancer in a meta-analysis of five studies with a total of 1137 cases. Ever having welded was found to be a significant risk factor for ocular melanoma.

Vajdic et al. (Ref. 158) conducted a population-based epidemiologic study in Australia of the risk of ocular melanoma associated with exposure to artificial sources of UV radiation. The study population comprised 290 cases diagnosed between 1996 and 1998. There was a weak non-significant relationship between risk for ocular melanoma and ever having welded. There were stronger, but still non-significant associations between ocular melanoma and having more than 22 years welding experience or having used both arc welding and oxy-acetylene welding techniques. The risk for melanoma increased with the duration of the welding experience, but the trend was not significant overall. The authors stated that the weak associations between welding and ocular melanoma found in their study may have been due to the more regular use of protective eyewear by welders in Australia than in other countries where related studies had been conducted. They concluded that, taken altogether, their results were supportive of the positive associations between welding and ocular melanoma observed by other investigators.

Cancer at Other Sites. Pan et al. (Ref. 122) performed a case-control study of malignant brain cancer in eight Canadian provinces. A total of 1009 incident cases and 5039 controls were included. No associations were observed between the risk for brain cancer and welding.

Two studies examined associations between occupational exposures and bladder cancer. Gaertner et al. (Ref. 45) investigated occupational risk factors for bladder cancer in seven Canadian provinces. The 887 incident cases of bladder cancer in adults age 20 to 74 were matched with 2487 randomly selected population controls. Welders were found to have a non-significantly elevated risk for bladder cancer. Gordon et al. (Ref. 51) performed a case-control study in southern Israel of 150 men with histologically confirmed cases of bladder cancer and 150 matched controls. Occupational exposures significantly associated with bladder cancer were organic solvents, aromatic amines and/or paints, and polycyclic aromatic hydrocarbons. Occupations significantly associated with bladder cancer were metal working and welding.

Zeegers et al. (Ref. 174) conducted a prospective study of prostate cancer among 58,279 men in the Netherlands. Men who had ever welded had a moderate, but non-significantly increased risk for developing prostate cancer.

A case-control study of endocrine gland tumors conducted by Hakansson et al. (Ref. 57) showed a significantly increased risk for all endocrine tumors among the population that had ever welded. There was an apparent exposure-response association between hours per week spent arc welding with all tumors combined and with parathyroid gland tumors. The authors stated that, while confounding from welding fume exposures could not be dismissed, the most likely factor in the association of welding with endocrine gland tumors was the extremely low frequency electromagnetic field generated during welding.

Inflammation and Oxidative Stress

Some conditions known or suspected to be associated with welding exposures, including metal fume fever, pulmonary fibrosis, bronchitis, and asthma, have been attributed to oxidative stress and/or inflammatory processes in the lung. Oxidative stress occurs when the generation of reactive oxygen species (ROS: superoxide, hydroxyl radicals, and hydrogen peroxide) and nitrogen species (nitric oxide and peroxynitrite) outbalance the quantity of antioxidants (e.g., superoxide dismutase, glutathione peroxidase, and reduced glutathione) available to inactivate them. The production of oxidizing species is a central part of the mechanism by which macrophages and polymorphonuclear leukocytes (PMNs) destroy pathogens; but the production of ROS by phagocytes when responding to the presence of non-pathogenic particles such as those in welding fume may also damage host tissues.

Inflammatory processes in the lungs are the first observable response to inhaled welding fumes. Proinflammatory cytokines such as interleukin-6 (IL-6) and IL-8, are released from lung cells and are measurable in bronchoalveolar lavage fluid (BALF). These cytokines are chemotactic for macrophages and neutrophils. Cytokines released from cells such as macrophages and neutrophils can further enhance the inflammatory process in the lungs potentially leading to fibrosis and other pulmonary conditions. They can also cause systemic effects, such as metal fume fever, as they are released from the lungs into the blood stream.

Five studies found significant differences in concentrations of biomarkers of oxidative stress or inflammation in blood from welders and controls (Ref. 34, 60, 84, 91, 175). Kim et al. (Ref. 84) found that, C-reactive protein, a marker of inflammation, was significantly increased in blood 16 hours after welding exposures. A significant increase in neutrophil count and a significant decrease in fibrinogen were seen in blood following welding fume exposure in non-smoking welders. Further work from this laboratory (Ref. 160) showed that the genes whose expression was altered following welding fume exposure were clustered in biologic processes related to the inflammatory response, oxidative stress, intracellular signal transduction, and cell cycle. The greatest variations in gene expression were seen in the non-smoking welders. The effects of welding fume exposure on gene expression were transient, and most of the observed effects diminished within 19 hours post exposure (Ref. 159).

Two studies (Ref. 34, 147) examined whether decrements in pulmonary function in welders were associated with biomarkers of oxidative stress. In the first, Fidan et al. (Ref. 34) found that the respiratory symptoms cough, sputum, and chronic bronchitis were significantly more prevalent among the welders than controls while the pulmonary function measures FEV_1/FVC, FEF_{25}, FEF_{75}, and $FEF_{25–75}$ were significantly lower in the welders than in the controls. Indicators of oxidative stress, plasma thiobarbituric acid reactive substances (TBARS: an indicator of lipid peroxidation) and protein carbonyl levels were elevated while total protein thiols (SH) and reduced glutathione levels in erythrocytes were significantly decreased in welders, revealing a reduction of available anti-oxidants. No significant correlations were found between serum oxidant/antioxidant levels and any of the pulmonary function test results, but TBARS levels were significantly elevated and SH and reduced glutathione levels were significantly reduced in welders with chronic bronchitis, suggesting a role of oxidative stress in the pathogenesis of that condition.

In the second study, Stepniewski et al. (Ref. 147) found that lung function, as measured by the spirometric tests FEV_1, %FEV, MEF_{50}, and $MEF_{25–75}$, was significantly reduced among welders compared with controls. Low, but significant, correlations were found between catalase concentrations in blood and FEV, and between total antioxidant status and FVC.

Infections

Analyses of occupational mortality data in Great Britain have shown that welders have a greater than normal risk of dying from infectious pneumonia (Ref. 20). The elevated mortality occurs only during the period of employment as a welder. Palmer et al. (Ref. 121) conducted a hospital-based case-control study to determine if the elevated risk is restricted to pneumonias caused by specific microorganisms, if it is related to exposure to specific metals, or if the elevated risk is for developing a pulmonary infection as well as for dying from it. The risk for pneumonia was found to be significantly associated with occupational exposure to metal fume during the year prior to the onset of illness but not with exposures to metal fume that had occurred more than a year prior to onset of illness. Fumes from iron and steel were associated with increased susceptibility to infectious pneumonia, but involvement of other metal fumes could not be ruled out. In cases associated with exposure to ferrous metal fumes, the risk was significantly elevated for lobar and segmental pneumonia, but not for bronchopneumonia, and the elevated risk was not limited to fatalities. The investiga-

tors postulated that the elevated risk for pneumonia could be related to oxidative damage to lymphocytes or macrophages or, alternatively, that inhaled iron particles could act as a nutrient source promoting the growth of certain microorganisms.

Antonini et al. (Ref. 5) investigated the effects of fumes from GMAW of mild and stainless steel (GMAW-MS and GMAW-SS, respectively) and SMAW of stainless steel (SMAW-SS) on pulmonary defense responses to bacterial infection in rats. The soluble and insoluble fractions of SMAW-SS fume were tested separately. Fume samples were introduced into rat lungs by intratracheal instillation on day 0 followed by the bacterium Listeria monocytogenes on day 3. Animals were sacrificed on days 6, 8, or 10 and the numbers of Listeria colony forming units were determined. Only the intact SMAW-SS fumes were found to alter lung infectivity. Clearance of Listeria from the lungs was markedly delayed in rats pretreated with SMAW-SS fumes compared with rats pretreated with the GMAW fumes or either the soluble or the insoluble fractions of the SMAW fume. By day 10, 30% of the rats treated with SMAW-SS had died whereas all of the rats in the other treatment groups were still alive. Histological examination of the lung tissue showed severe pneumonitis on day 10 in rats treated with SMAW-SS fumes but not in those treated with the other fume samples.

Several assays were performed to examine possible mechanisms by which SMAW-SS fumes may reduce lung defenses. Bronchoalveolar lavage fluid taken from rats that had been instilled with SMAW-SS fumes had elevated lactate dehydrogenase (an indicator of loss of membrane integrity in cells that are injured or dead) and albumin (an indicator of damage to the integrity of the alveolar-capillary barrier), and significant increases in numbers of macrophages, PMNs, eosinophils, and lymphocytes compared with BALF from rats instilled with saline alone. This suggested that immune and inflammatory responses were enhanced in rats treated with SMAW-SS fumes. It was also found that the proinflammatory cytokines TNF-α, IL-6, and IL-10 were elevated in BALF from rats treated with SMAW-SS fumes and Listeria. Reactive oxygen species and nitric oxide and its oxidation products (NOx: nitrate and nitrite) were markedly elevated in macrophages and BALF before and after infection in rats treated with SMAW-SS. Further tests showed that both the soluble and insoluble components of SMAW-SS fumes contribute to the inflammatory response elicited by the intact fume (Ref. 153) and that the soluble chromium component of SMAW fumes plays an important role in the suppression of the pulmonary defense responses against bacterial infection (Ref. 4).

Effects on the Nervous System

Aluminum. Giorgianni et al. (Ref. 48) administered neuropsychological tests to 50 aluminum welders. The welders scored significantly less well than controls on tests of memory and abstract reasoning and slightly less well on tests of attention. The investigators concluded that occupational exposure to aluminum welding fumes can affect cognitive function. In contrast to these findings, tests of a group of 98 aluminum welders by Buchta et al. (Ref. 16, 83) revealed no significant differences between welders and controls in motor-performance, short-term memory, or switching attention. Simple reaction time performance differed significantly between welders and controls. Since the differences between the two groups did not change during tests repeated three times over a 4-year period, the investigators concluded that the differences may have been due to random a priori differences between the groups and were most likely not associated with welding exposures.

Manganese: Subclinical Effects. Halatek et al. (Ref. 58) conducted a study of 59 welders from a Polish shipyard to assess whether neurophysiological tests could be used to detect early effects of exposure to low concentrations of manganese. Subjective neurological symptoms, including increased emotional irritability, headache, and sleepiness, were reported by half of the welders. Abnormalities found in electroencephalographs (EEG) of 32% of the welders and in visual evoked potentials (VEP) from 22% of the welders correlated both with current exposure to airborne manganese in excess of 0.3 mg/m^3 (the Polish TLV) and with a cumulative exposure index based on years of exposure and airborne manganese levels. The authors concluded that neurological tests, VEP, and EEG may be used to detect early effects of exposure to low levels of manganese.

He and Niu (Ref. 66, 118) assessed subclinical neurophysiological changes in 68 welders who worked in a factory in China and who had histories of chronic exposure to low levels of manganese. Mean exposures of 138.4 µg/m^3 manganese, 12.6 µg/m^3 cadmium, and 3.8 µg/m^3 nickel were measured in air samples collected at breathing height on the factory floor. Welders and controls were subjected to a battery of examinations and neurobehavioral tests. Changes were seen in EEGs and in brain electrical activity mapping of the welders. They also had lower test scores on more of the

neurobehavioral tests than did controls. Scores on the Profile of Mood States indicated a depressed emotional status in the welders. The investigators concluded that these changes were due to chronic exposures to low levels of manganese.

Bowler et al. compared neuropsychological function, emotional status, and visual function of 76 welders with that of 42 controls (Ref. 11). Welders had lower scores than controls in tests of motor function, verbal learning, working memory, cognitive flexibility, and visuomotor processing speed, while they scored as well as controls in tests of verbal skills, verbal retention, and auditory span. Tests of emotional status indicated that the welders had elevated levels of mood disturbance. The investigators noted that the welders worked in the chemical industry where they may have been exposed to solvents with neurotoxic effects which could have confounded the results of this study. Another confounding factor was that the welders selected for the study were involved with civil and workers' compensation litigation related to impairments incurred during their employment as welders. In their critique of this study, Lees-Haley et al. (Ref. 88) stated that this work was "fatally flawed by participant selection bias." Another difficulty pointed out by Lees-Haley et al. was that the welder population had a lower educational background than did controls which could have caused them to fare less well on some of the tests of cognitive skills.

Manganese: Clinical Effects. Chronic exposures to excessive levels of manganese can result in neurological damage, causing an array of symptoms (referred to as manganism or parkinsonism) that resemble those of idiopathic Parkinson's disease. Manganism and idiopathic Parkinson's disease are difficult to differentiate, especially in later stages. It has been reported that exposure to welding (Ref. 127) or to manganese in welding fumes can cause Parkinson's disease, but the evidence for this is limited and much research continues to be conducted towards resolving this issue.

Manganism and Parkinson's disease are both caused by degeneration of cells in the basal ganglia, a control center of the brain involved in the production of smooth, coordinated movements. Manganese accumulates selectively in the globus pallidus of the basal ganglia, where it can produce hyperintense signals in T1-weighted magnetic resonance images (MRI) of the brain. Manganese-related changes in MRI scans tend to disappear following withdrawal from the manganese source as manganese is cleared from the brain tissue, even though permanent neurological damage may have occurred.

Racette et al. (Ref. 128) compared the prevalence of parkinsonism in a large sample of welders from Alabama with that in a general population, age-adjusted sample of male residents from Copiah County, Mississippi. The welders from Alabama had been referred to the investigators for medical-legal evaluation for Parkinson disease. The prevalence of parkinsonism among residents of Copiah County had previously been determined in a study by Schoenberg et al. (Ref. 138). Racette et al. found that parkinsonism occurred more frequently among the Alabama welders than among the comparison population from Copiah County. Analysis of age of onset of parkinsonism supported Racette's earlier findings that Parkinson's disease occurred at an earlier age among welders than among controls (Ref. 127).

Reports that Parkinson's disease occurs at a younger age among welders or that welders have an increased incidence of parkinsonism have not been supported by recent epidemiologic studies (Ref. 40, 41, 50, 145). Using a population of 2072 patients being treated for Parkinson's disease or parkinsonism in movement disorder clinics located in New York, Atlanta, and San Jose, Goldman et al. (Ref. 50) investigated occupational associations with these conditions. The study focused on occupations (teaching, healthcare, farming, and welding) that had been associated with an increased risk of Parkinson's disease in previous studies. Three welders, all of whom had typical Parkinson's disease, were identified among the clinical patients. The frequency of Parkinson's disease or parkinsonism in welders was not significantly elevated compared with the control population. In addition, the mean age at which Parkinson's disease was first diagnosed in the welders did not differ significantly from that of the entire clinical population.

Stampfer (Ref. 145) examined mortality data in the U.S. National Center for Health Statistics (NCHS) National Cause of Death data base for evidence linking occupation as a welder with mortality from neurodegenerative diseases. The analysis included 4,252,490 men who died between 1985 and 1999. During the study period, Parkinson's disease accounted for 49,174 deaths and was listed as a contributing or underlying cause of death among 1.0% of the men with any welding-related exposure and 1.2% of the men in the reference population. Welders were slightly, but significantly less likely to have Parkinson's disease as the contributing or underlying cause of death. In addition, the risk of death from motor neuron disease, other diseases of the basal ganglia, and other extrapyramidal disorders did not differ significantly between welders and the reference population. Stampfer concluded that "the present study… suggests that employment as a welder is not associated with an increase in mortality from Parkinson's disease or other neurodegenerative conditions."

Fryzek et al. (Ref. 41) conducted a retrospective cohort study of the rates of hospitalization for Parkinson's disease and other neurodegenerative disorders among 27,839 Danish metal-manufacturing workers. This study included 9817 men

who were employed in departments engaged in mild or stainless steel welding, of whom 6163 were welders. The number of hospitalizations for Parkinson's disease among the welders or men working in welding departments did not differ from that expected for the entire cohort nor did the mean age of onset of Parkinson's disease differ between the welders and the other workers. The incidence of Parkinson's disease was not associated with the duration of the welding experience. The investigators concluded that the rates of Parkinson's disease and other neurological conditions among welders were consistent with those of the general population of Denmark.

Fored et al. (Ref. 40) examined the incidence of basal ganglia and movement disorders in Swedish welders and flame cutters by comparing the health and employment records of 49,488 male welders with those of 489,572 male workers who had no history of exposure to welding or flame cutting at work. Parkinson's disease and other neurological disorders occurred at a slightly lower rate among welders than in the comparison population. There was no difference in mean age of first occurrence of Parkinson's disease between the welders and flame cutters and the comparison cohort.

Marsh and Gula (Ref. 101) conducted a case-control study among the12,595 workers who had ever been employed between 1976 and 2004 at three Caterpillar heavy equipment plants in Illinois and were eligible to make medical insurance claims between 1998 and 2004. Cases of neurological disorders were identified from company medical claims and comprised the 70 persons who had filed claims for either idiopathic Parkinson's disease or secondary parkinsonism and the 153 persons who had filed claims for other progressive diseases of the basal ganglia and essential and other specific forms of tremor. Controls were drawn from members of the study population who were not identified as cases. No statistically significant associations between ever having welded in any Caterpillar plant and any of the neurological disorders studied were found.

Manganese: Bioavailability. In his analysis of the evidence for an association between manganese exposure in welding fumes and Parkinson's disease or parkinsonism, McMillan (Ref. 107) noted that the physicochemical properties of manganese emanating from different processes differ which could affect its bioavailability. Manganese in welding fumes is often present as complex oxides in ultrafine particles which are sometimes surrounded by a shell composed of silicon oxide. McMillan reasoned that manganese in that form may be less bioavailable than manganese in dusts or particles released from other processes such as mining. Particles in dusts released during mining are in much simpler forms and have been clearly related to manganism.

Yu et al. (Ref. 169) investigated the distribution of manganese in the rat brain following exposure by inhalation to fume generated by SMAW of stainless steel. The rats were exposed for 2 hours per day for up to 60 days to welding fume concentrations of 63.6 mg/m^3 or 107.1 mg/m^3 containing 1.6 mg/m^3 manganese and 3.5 mg/m^3 manganese, respectively. Groups of animals were sacrificed periodically and manganese concentrations were determined in samples of blood, brain, lung, and liver. Manganese concentrations in the lung and liver increased with the dose and with the duration of exposure. Statistically significant increases in manganese levels in the cerebellum were seen at all time points at both doses after 15 days of exposure but only slight increases were seen in the substantia nigra, basal ganglia (including the caudate, nucleus, putamen, and globus pallidus), temporal cortex, and frontal cortex after 60 days of exposure. Yu et al. compared their results with those obtained by St-Pierre et al. (Ref. 148) who exposed rats by inhalation to manganese dusts for 15 weeks. In that study, there was a high accumulation of manganese in the striatum and globus pallidus of the basal ganglia and a lower accumulation in the cerebellum. These findings suggest that the pharmacokinetics involved in absorption of manganese from welding fumes differ from those involved in absorption of manganese from neat manganese dusts.

Effects on Reproduction

Wong et al. (Ref. 162) examined the effects of lifestyle, occupation, and medical history on sperm count in a case-control study of 73 sub-fertile and 92 fertile Caucasian males. The sub-fertile males had significantly lower sperm counts and sperm motility and a significantly higher percent of abnormal spermatozoa than did the fertile males. Antibiotic use, a history of mumps, and occupational exposure to pesticides were significantly related to subnormal sperm counts. The risk for subnormal sperm counts was non-significantly elevated in men with occupational exposures to welding fumes.

Danadevi et al. (Ref. 24) compared the quality of semen collected from 57 welders who worked at a plant in South India and 57 controls. The percent of subjects with normal sperm morphology, normal sperm counts, and rapid linear sperm motility were significantly lower among the welders than among controls. Nickel and chromium concentrations in blood were positively correlated with the percentage of tail defects in semen from welders. Blood concentrations of chromium,

but not nickel, were significantly correlated with decrements in sperm count, sperm vitality, and rapid linear progressive motility. The investigators concluded that exposure to welding fumes containing nickel and chromium is associated with abnormal semen parameters.

Oxidative damage to DNA in sperm may be measured by the level of 7-hydro-8-oxo-2'-deoxyguanosine (8-oxodG) in sperm DNA. Working with 225 Danish couples who were planning to conceive their first child, Loft et al. (Ref. 92) investigated whether these DNA modifications affect sperm function. Semen samples were collected monthly for up to 6 months following the cessation of the use of contraception. There was a significant inverse relationship between the level of 8-oxodG in sperm DNA and the occurrence of pregnancy during this time. The level of 8-oxodG did not differ significantly in sperm from the 80 men who performed daily welding and the 145 men who did not.

Hjollund et al. (Ref. 67) investigated whether paternal stainless steel welding affects the incidence of spontaneous abortion among women who had become pregnant by in vitro fertilization. Rates of spontaneous abortion were compared among 319 couples in which the male partners were welders and 2925 couples in which the males had no known exposures to welding fumes. Spontaneous abortion of pregnancies before 28 weeks of gestation occurred in 18% of the couples with paternal exposure to stainless steel welding, in 25% of those with paternal exposure to mild steel welding, and in 28% of those with no paternal welding exposure. These differences were not statistically significant and it was concluded that welding does not affect the rate of spontaneous abortion in pregnancies that are initiated by in vitro fertilization.

Technical Summary

The Exposure

Fume Composition

Yoon et al. (Ref. 168) examined the effects of welding current on fume generation rates (FGR) and on the production of total chromium and hexavalent chromium [(Cr(VI)] during CO_2-shielded flux cored arc welding (FCAW) of stainless steel in a fume collection chamber. The FGR, total chromium, and Cr(VI) produced during FCAW increased with the welding current.

Sampling Strategies for Ultrafine Particles

Brouwer et al. (Ref. 15) compared three methods—a condensation particle counter, a scanning mobility particle sizer, and an electrical low pressure impactor—for measuring number concentrations and size distributions of ultrafine particles generated during welding. The investigators found that each of the measurement methods has its drawbacks, but that in combination they can be useful in providing insight into the characteristics of fine particles in the workplace.

Thoriated Electrodes

Gafvert et al. (Ref. 46) measured breathing zone concentrations outside the welder's helmet during full-time welding of steel and aluminum with thoriated electrodes in five workshops in Sweden. Welding with alternating current produced higher levels of thorium radioactivity in the breathing zone than did welding with direct current. Estimates of annual exposure to radioactivity from thorium calculated from the welding and grinding sampling data were well below the Nuclear Regulatory Commission exposure limits.

Saito et al. (Ref. 136) measured ^{232}Th exposure during welding and grinding with thoriated electrodes in a welding shop in Japan. Breathing zone samples were collected during gas tungsten arc welding (GTAW) of aluminum, GTAW of stainless steel, and during sharpening of the electrode tips on a grinding wheel. The estimated annual radiation dose derived from these data was well below the Japanese annual limit of 160 Bq.

Ultraviolet Light

Garcia-Guinea et al. (Ref. 47) examined the composition of 14 different consumable coated electrodes and found the coatings to consist of quartz, calcite, sodium and the potassium-rich feldspars, muscovite and rutile. Thermoluminescence measurements conducted on these materials showed that, with the exception of rutile, they all produced strong emission peaks in the UV-A range (320 nm–400 nm) and the UV-B range (280 nm–320 nm).

Incidental Exposures

Gjolstad et al. (Ref. 49) examined exposure of refrigerator repair workers to HF, HCl, phosgene, and volatile organic compounds during welding. HCl was detected during welding when difluorochloromethane was the refrigerant and HF

was detected during welding of refrigerant systems containing difluorochloromethane, tetrafluoroethane, or R404A (a mix of 1,1,1,2-tetrafluoroethane, pentafluoroethane, and 1,1,1-trifluoroethane).

Workplace Exposures

With the goal of characterizing the aerosol formed by natural mixing of welding fumes with the air in a typical industrial setting, Stephenson et al. (Ref. 146) sampled particle emissions during SMAW of carbon steel in a metal shed. In samples collected 3 m downwind of the welding, the number concentration of particles in the range of 0.05 μm to 0.5 μm increased by almost 100-fold, while the concentration of larger particles did not differ from background levels.

Matczak and Przybylska-Stanislawska (Ref. 104) measured concentrations of metals and fluorides in samples collected in the breathing zone of welders using ten types of welding wires during FCAW. Welding with certain types of flux cored wires resulted in breathing zone concentrations of total dust and manganese well in excess of regulatory limits.

Ventilation

Using a robotic welding apparatus, Iwasaki et al. (Ref. 76) tested the effectiveness of a push-pull ventilation system to control exposures to fumes produced by CO_2-shielded gas metal arc welding (GMAW). The investigators stated that the two important design criteria for a push-pull ventilation system—(1) the production of stable air velocity and direction in the vicinity of the weld, to prevent formation of blow holes and (2) the effective removal of welding fume from the occupied area—were both achieved when the ventilating air flow velocity was maintained between 0.3 m/s and 0.8 m/s.

Harris et al. (Ref. 63) evaluated the effectiveness of general dilution ventilation by means of exhaust fans in controlling a welder's exposure to manganese during SMAW in a confined space. With an exhaust rate of 2000 cubic feet per minute (CFM), manganese concentrations in breathing zone samples collected from the welder were less than the ACGIH TLV of 0.2 mg/m^3 for manganese. However, the TLV was exceeded in area sample locations that served as surrogates for welders' helpers, indicating that the exhaust flow rate of 2000 CFM recommended by OSHA for confined spaces may be insufficient to protect bystanders from excess manganese exposure.

Zaidi et al. (Ref. 173) examined the effectiveness of two local exhaust ventilation systems developed in rural India for use during welding. The systems were shown to reduce breathing zone concentrations of manganese from 22 μg/m^3 (portable unit) or 70 μg/m^3 (mobile unit) to 8 μg/m^3.

Accidents and Injuries

In a cross-sectional survey in Pakistan, Shaikh (Ref. 142) found that 61 of 208 welders sustained injuries during a period of 6 months. The most common types of injuries were burns on the limbs or trunk, and foreign bodies in the eye.

Effects of Welding on Human Health

Respiratory Tract

Pulmonary Function. Meo (Ref. 111, 113) administered pulmonary function tests to 50 male arc welders who worked in small shops with minimal ventilation in Pakistan. The welders had statistically significant reductions in maximal voluntary ventilation (MVV), forced expiratory volume (FEV_1), FEV_1/forced vital capacity (FVC), and peak expiratory flow. Fishwick et al. (Ref. 38) measured breathing zone exposures and pulmonary function in welders at four work sites in New Zealand. A significant positive correlation between respiratory symptoms and exposure to nickel was found. Pulmonary function tests showed a 5% decline in FEV_1 in 23% of the welders after the first 15 minutes of work which was significantly correlated with aluminum exposures, but not with total fume exposure. Jafari and Assari (Ref. 77) examined lung function and respiratory symptoms in a group of 63 welders from workshops in Hamadan, Iran. Significant decrements in vital capacity, FVC, FEV_1, and forced expiratory flow ($FEF_{25–75}$) were found when smoking welders were

compared with smoking controls and when non-smoking welders were compared with non-smoking controls. The incidence of chronic bronchitis was significantly higher among the welders than among controls. Tunc et al. (Ref. 157) found significantly higher incidences of cough, sputum, dyspnea, and bronchitis in welders than in controls but spirometric tests showed no differences in lung function between the two groups.

Fidan et al. (Ref. 34) found deficits in lung function and a significant increase in the prevalence of cough, sputum, and chronic bronchitis among welders in Afyon, Turkey. Chronic bronchitis was significantly correlated with a reduction in protein thiol and glutathione levels in erythrocytes and elevated thiobarbituric acid reactive substances in plasma. Stepniewski et al. (Ref. 147) examined pulmonary function and antioxidant enzymes in blood from 94 welders and 115 age-matched controls. Lung function was significantly reduced among the welders compared with the controls but the values for total antioxidant status, superoxide dismutase, and catalase activity measured in blood samples were not significantly different. Signs of chronic obstructive pulmonary disease (COPD) were more frequent in the welders than in the controls. In a case-control study designed to ascertain the risk of COPD associated with different occupations, Mastrangelo et al. (Ref. 102, 103) found that welders have a significantly greater risk for COPD which increases slightly, but significantly, with duration of exposure and age.

Occupational Asthma. McDonald et al. (Ref. 106) examined the incidence of asthma among cases of work-related respiratory disease reported by thoracic and occupational health physicians to the National Heart and Lung Institute in London between 1992 and 2001. Welding was identified as the causative agent for 3% of all cases of occupational asthma (OA). Piipari and Keskinen (Ref. 125) analyzed all cases of OA reported to the Finnish Register of Occupational Diseases during the period 1988–1997 and found that 4% of OA could be attributed to welding fumes. In Norway, occupational diseases must be reported by physicians to the Labor Inspection Authority. Using the registry of these reports, Leira et al. (Ref. 89) found that, among the cases of OA reported between 1995 and 1999 from outside the aluminum industry, male welders were the third most likely occupational group to have been reported with this condition.

El-Zein et al. (Ref. 32) examined data concerning respiratory symptoms associated with asthma and metal fume fever collected from 351 welders during a survey of industrial workers in Canada. The occurrence of two respiratory symptoms suggestive of OA was significantly related to the incidence of probable metal fume fever. El-Zein et al. (Ref. 30, 31) later performed a prospective study of apprentice welders in whom changes in pulmonary function, signs of asthma, and symptoms of metal fume fever were followed during the course of their 15 months of exposure in welding school. Significant changes were found in their performance on the lung function tests FEV_1 and FVC at the end of the 15-month study period and welding-related respiratory symptoms were found in 7.6% of the subjects; six of these subjects were diagnosed with probable OA at the end of the study.

Hammond et al. (Ref. 59) examined the incidence of respiratory symptoms among men who worked in an automotive assembly plant. Welders reported having been diagnosed with COPD significantly more frequently than did the other workers and about 10% of the welders had been diagnosed with asthma. Hoppin et al. (Ref. 71) examined the incidence of wheezing among 20,898 farmers in Iowa and North Carolina. They found that welding, which was engaged in by 57% of the farmers with reported wheeze, was associated with a significantly increased risk for wheezing.

Hannu et al. (Ref. 61) described the progression of OA in two men who had performed SMAW on different formulations of high chromium steel in the same workplace.

Pneumoconiosis. In 2002, Buerke et al. (Ref. 18) described 15 welders who had pneumoconiosis and clinical respiratory symptoms. Spirometric tests of three of the welders showed deficits in pulmonary function and examination of biopsied lung tissue revealed patchy interstitial fibrosis (Ref. 17). Particulate material with an elemental composition typical of welding fumes was found in activated alveolar macrophages and in lung tissue close to areas of fibrosis.

Doherty et al. (Ref. 27) described the cases of three welders who had both siderosis and elevated serum ferritin levels. Spirometric tests showed deficits in pulmonary function in these men, and examination of biopsied lung tissue revealed patchy interstitial fibrosis. Fukuda et al. (Ref. 44) described a case of pneumoconiosis and iron overload in a 26-year-old man who had worked as an arc welder without benefit of respiratory protection for 2 years. The numerous iron-laden alveolar and interstitial macrophages observed in lung biopsy specimens and his serum ferritin levels were markedly reduced following repeated treatments by phlebotomy. Other cases of welders with siderosis and iron overload were reported by Ishida et al. (Ref. 75) and by Yokoyama (Ref. 167).

Fireman et al. (Ref. 37) described the case of a 43-year-old welder who suffered from dyspnea. A high resolution computed tomography scan revealed small, well-defined micronodules throughout his lungs and multiple granulomas were

identified in a lung biopsy specimen. Scanning electron microscopy combined with energy dispersive X-ray spectroscopy revealed abundant particles of aluminum compounds in sputum and biopsy samples. The welder's condition was diagnosed as sarcoid-like granulomatous-induced aluminum disease. The case of a 23-year-old welder who was admitted with chest pain to a hospital in Turkey was described by Fidan et al. (Ref. 33). Chest X-rays revealed complete collapse of a lung which was caused by a large pneumothorax.

Respiratory Tract Infections. Exposure to ferrous welding fumes increases the susceptibility of welders to pneumonia. A case-control study conducted by Palmer et al. (Ref. 121) showed that the elevated risk is not restricted to pneumonias caused by specific microorganisms. They found that the risk for pneumonia is significantly associated with occupational exposure to metal fume during the year prior to the onset of illness and the risk is significantly elevated for lobar and segmental pneumonia, but not for bronchopneumonia.

Recent reports of pulmonary mycoplasma infections in welders have appeared in the Japanese literature. Matsushima described cases of pulmonary *Mycobacterium kansasii* infection in three welders who worked on the same line in a factory in Japan (Ref. 105). Fujita et al. described five cases of men with respiratory infection associated with siderosis (Ref. 42).

Cancer

Lung Cancer. In a case-control study of lung cancer related to occupational exposures in two areas of northern Italy, Richiardi et al. (Ref. 129) found significantly increased risks for lung cancer among workers identified by the International Standard Classification of Occupations codes as welders and flame cutters and as gas and electric welders. Finkelstein and Verma (Ref. 35) examined causes for mortality in a cohort of 25,285 members of a union of the plumbing and pipe fitting industry in Canada. Lung cancer mortality was significantly higher than expected among those employed for 20 or more years as plumbers, pipefitters, or sprinkler fitters. Yiin et al. (Ref. 166) analyzed the incidence of lung cancer and leukemia deaths among 13,468 civilians who had worked for at least one day between 1952 and 1992 at the Portsmouth Naval Shipyard in Kittery, Maine. Workers with any welding fume exposure had a significantly greater risk for lung cancer than did those with no exposure to welding fume. The relative risk did not increase with increased exposure to welding fume.

Mesothelioma. Nesti et al. (Ref. 117) analyzed data from the Italian National Mesothelioma Registry and found that welders were among those with the highest incidence of mesothelioma in the metallurgy and steel industries. Fujiwara et al. (Ref. 43) described the case of a welder who had been exposed throughout his 28-year career to asbestos dust generated when he sharpened slate pencils used to draw lines for arc cutting of steel plates. At the age of 53, he was diagnosed with pericardial mesothelioma, an extremely rare cancerous disease of the tissue layers surrounding the heart.

Cancer of the Eye. Lutz et al. (Ref. 96) examined occupational risks for ocular melanoma in a population-based case-control study. A significant excess risk for ocular melanoma was found in welders and sheet metal workers. In a meta-analysis of studies of risk factors for ocular cancer, Shah et al. (Ref. 140) found welding to be a significant risk factor for ocular melanoma. In a population-based epidemiologic study of the risk of ocular melanoma associated with exposure to artificial sources of UV radiation, Vajdic et al. (Ref. 158) found only non-significant relationships between risk for ocular melanoma and welding. They stated that the weak associations found in their study may have been due to the regular use of protective eyewear by welders in their study population and concluded that, taken altogether, their results were supportive of the positive associations between welding and ocular melanoma observed by other investigators.

Cancer at Other Sites. Gordon et al. (Ref. 51) performed a case-control study of 150 men with histologically-confirmed cases of bladder cancer and 150 matched controls in southern Israel. Occupations significantly associated with bladder cancer were metal working and welding. In a study of occupational risk factors for bladder cancer performed in seven Canadian provinces by Gaertner et al. (Ref. 45), welders did not have a significantly elevated risk for bladder cancer.

A case-control study of 140 cases of endocrine gland tumors by Hakansson et al. (Ref. 57) revealed a significantly increased risk for endocrine tumors among the population that had ever welded.

A prospective study of prostate cancer among 58,279 men in the Netherlands by Zeegers et al. (Ref. 174) showed that men who had ever welded did not have a significantly increased risk for developing prostate cancer. In a case-control study of malignant brain cancer in eight Canadian provinces, Pan et al. (Ref. 122) found no significant associations between brain cancer and welding.

Metal Fume Fever

Taniguchi et al. (Ref. 152) described the case of a 57-year-old welder who developed high fever and difficulty breathing after exposure to zinc oxide fumes while welding without a protective mask. He was diagnosed as having chemical pneumonia. Hassaballa et al. (Ref. 64, 65) described the case of a 25-year-old male welder who developed metal fume fever after working without wearing a respirator in a poorly ventilated area where galvanized steel was being cut. While on the job, he developed a cough and difficulty breathing. He later developed a rapid heart beat and abnormally rapid breathing; examination revealed pericarditis, pleuritis, and pneumonitis.

Effects on the Eye and Vision

Eye Injuries. Lombardi et al. (Ref. 93) used Workers' Compensation claims filed during the year 2000 with a U.S.-based insurance provider to examine the incidence of eye injury among welders. Eye injury accounted for 5% of the compensation claims made by all workers but represented 25% of the claims filed by welders. Foreign body injuries and UV-associated eye burns represented 71.7% and 19.7%, respectively, of the eye injuries sustained by the welders.

Cornea. Aziz and Rahman (Ref. 6) examined the incidence of corneal foreign bodies among people who sought medical attention at an emergency eye clinic in Bangladesh in 2002. Of the 200 persons for whom background data had been recorded, 20 corneal foreign bodies were sustained while welding and 31 occurred while grinding. Yen et al. (Ref. 165) assessed the causes of photokeratitis (arc eye) among the 106 patients who reported with this condition to the emergency room at a hospital in Taiwan over a period of 1 year. Only 4 of the 87 patients who had received their exposures from welding arcs were professional welders and none were wearing eye protection at the time of their accident.

Magovern et al. (Ref. 99) attributed spheroidal degeneration of the cornea in a 79-year-old man to his welding experience while serving in the Navy during World War II when he put in long days repairing PT boats and landing craft. At that time, he experienced photokeratitis 3 to 4 times a week. Magovern concluded that a degenerative effect was initiated during this relatively short period of intense UV exposure.

Doughty and Oblak (Ref. 28) examined 51 welders and 51 controls to determine whether high levels of UV radiation can damage the corneal epithelium. While the incidence of pingueculae in welders was twice that in controls, no evidence of an association between welding and damage to the corneal endothelium was found.

Retina. In a case control study conducted with workers from a large metal manufacturing facility in Austria, Maier et al. (Ref. 100) found no significant differences in function or morphology of the retina between welders and controls and no signs of phototoxic damage to the retina in welders.

Effects on the Ear

A case of a welder who had tympanic membrane injury was described by Simmons and Eibling (Ref. 143). A spark entered his ear while he was welding on an overhead gas line. He experienced a sharp, burning pain at the time of the incident and then developed intermittent episodes of purulent discharge from the injured external ear.

Effects on Connective Tissue—Scleroderma

Magnant et al. (Ref. 97) performed a prospective study of the association between occupational risk factors and severity markers of systemic sclerosis (SSc). Of the 39 SSc patients who had received occupational exposures to any of the materials under study, 20 were exposed to solvents, 3 were exposed to silica and welding fumes, 4 to a combination of solvents, silica, and welding fumes, and 7 to a combination of epoxy resins, solvents, silica, and welding fumes. These occupational exposures tended to be associated with diffuse SSc, the more severe form of the disorder. Magnant and Diot (Ref. 98) later concluded that while silica and solvents appear to play a causal role in the development of the disease, the available data did not justify conclusions about a role of epoxy resins or welding fumes in the development of SSc.

Effects on the Nervous System

Nervous System Diseases. Using death certificate data from 22 states, Park et al. (Ref. 123) conducted a case-control study of potential associations between mortality from neurodegenerative diseases and occupational exposures to solvents, pesticides, oxidative stressors, electromagnetic fields (EMF), and welding. Of the four diseases analyzed (Alzheimer's disease, Parkinson's disease, motor neuron disease, and pre-senile dementia), only Parkinson's disease was associated with welding, and this was true only for the 20 deaths from Parkinson's disease that occurred before the age of 65.

Hakansson et al. (Ref. 56) examined the association between occupational exposure to extremely low frequency electromagnetic fields (ELF-EMF) and mortality from amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Parkinson's disease, and multiple sclerosis. No significant associations were found between ELF-EMF exposure and the risk for Parkinson's disease or multiple sclerosis. The relative risks were significantly elevated for Alzheimer's disease and for ALS. It cannot be discerned from the data provided if ELF-EMF from welding contributed to the increased risk for either of these nervous system disorders.

Weisskopf et al. (Ref. 161) conducted a prospective study of the association between occupational exposures and ALS mortality among more than 1 million participants in the Cancer Prevention Study II of the American Cancer Society. Only two welders died from ALS and welding was not associated with the risk for this disease.

Effects of Aluminum. Giorgianni et al. (Ref. 48) administered neuropsychological tests to a group of 50 asymptomatic aluminum welders. The welders scored significantly less well than controls on tests of memory and abstract reasoning and slightly less well on tests of attention. In contrast to these findings, Buchta et al. (Ref. 16, 83) examined 98 aluminum welders who worked at a car manufacturing plant for neurotoxic effects that could be associated with exposure to aluminum fumes. No significant differences were found between welders and controls in tests of motor-performance, short-term memory, or switching attention. Simple reaction time performance differed significantly between the two groups, but since these differences did not change when the tests were performed three times over a 4-year period, the investigators concluded that the differences may have been due to random *a priori* differences between the groups and were most likely not associated with welding exposures.

Manganese: Subclinical Effects. Halatek et al. (Ref. 58) conducted a neurological study of 59 welders who were exposed to concentrations of manganese in air that ranged from 0.003 mg/m^3 to 3.37 mg/m^3 in a Polish shipyard. Subjective neurological symptoms, including increased emotional irritability, headache, and sleepiness, were reported by half of the welders. Abnormalities were found in electroencephalograms (EEG) of 32% of the welders and in visual evoked potentials from 22% of the welders. Abnormal results in these tests were strongly correlated with current exposure to airborne manganese in excess of 0.3 mg/m^3 and with a cumulative exposure index based on years of exposure and airborne manganese concentration.He and Niu (Ref. 66) assessed subclinical neurophysiologic changes in 68 welders who had histories of chronic exposure to low levels of manganese. Changes were seen in EEGs of the welders and in brain electricity activity mapping analyses. In other tests administered by Niu et al. (Ref. 118), welders had lower test scores on more of the neurobehavioral tests than did controls and the Profile of Mood States scores indicated a depressed emotional status.

Bowler et al. compared neuropsychological function of 76 welders with that of 42 controls (Ref. 11). Welders had lower scores than controls in tests of motor function, verbal learning, working memory, cognitive flexibility, and visuomotor processing speed while they scored as well as controls in tests of verbal skills, verbal retention, and auditory span. Tests of emotional status indicated that the welders had elevated levels of mood disturbance.

Manganese: Clinical Effects. Koller et al. (Ref. 87) conducted a double-blind study of the efficacy and safety of levodopa (L-dopa) treatment in 13 welders who had been diagnosed with manganese-induced parkinsonism. They found that L-dopa is not effective in welders with parkinsonism and concluded that L-dopa responsiveness may be useful for distinguishing between Parkinson's disease and manganese-induced parkinsonism.

Josephs et al. (Ref. 80) reviewed the medical records of eight welders who were referred to the Mayo Clinic with neurological problems and diagnosed with neurotoxicity associated with a history of welding. The characteristic manganese-associated increased T1 signal in the basal ganglia was seen in magnetic resonance images of the brains of all eight patients. Racette et al. (Ref. 128) examined the prevalence of parkinsonism in 1423 welders from Alabama who were referred to them by attorneys for medical-legal evaluation of Parkinson's disease. The investigators found that parkinsonism occurred more frequently and at an earlier age among the Alabama welders than among a comparison population of male residents from Copiah County, Mississippi.

Using a population of 2072 patients drawn from three movement disorder clinics, Goldman et al. (Ref. 50) investigated occupational associations with Parkinson's disease or parkinsonism. Three welders, all of whom had typical Parkinson's disease, were identified among the clinical patients. The frequency of Parkinson's disease or parkinsonism in welders was not significantly elevated compared with the control population. Fryzek et al. (Ref. 41) conducted a retrospective cohort study of the rates of hospitalization for Parkinson's disease and other neurodegenerative disorders among 27,839 male Danish metal-manufacturing workers. The rates of Parkinson's disease and other neurological conditions among welders were consistent with those of the general population of Denmark. No association was found between the incidence of Parkinson's disease with age or with the duration of the welding experience.

Using the U.S. National Center for Health Statistics (NCHS) National Cause of Death databases, Stampfer (Ref. 145) examined the relationship between occupation as a welder and mortality from neurodegenerative diseases. The study population included 4,252,490 men who died between 1985 and 1999; 107,773 had been welders. Welders were slightly, but significantly, less likely to have Parkinson's disease as the contributing or underlying cause of death. In addition, welders were not found to have increased odds of dying from Parkinson's disease at a younger age then men with other occupations.

Marsh and Gula (Ref. 101) conducted a case-control study among the12,595 workers who had ever been employed between 1976 and 2004 at any one of three Caterpillar heavy equipment plants in Illinois. Cases of neurological disorders were identified from company medical claims and comprised the 70 persons who had filed claims for either idiopathic Parkinson's disease or secondary parkinsonism and the 153 persons who had filed claims for other progressive diseases of the basal ganglia and essential and other specific forms of tremor. There were no significant associations between ever having welded in a Caterpillar plant and any of the neurological disorders studied.

In a study conducted in Sweden, Fored et al. (Ref. 40) examined the incidence of basal ganglia and movement disorders in welders and flame cutters. The health and employment records of 49,488 male welders were compared with those of 489,572 male workers who had no history of exposure to welding or flame cutting at work. Neurological disorders including Parkinson's disease occurred at a slightly lower rate among the welders than in the comparison population. There was no difference in mean age at first occurrence of Parkinson's disease between the welders and flame cutters and the comparison cohort.

Sadek et al. described the case of a 33-year-old man who developed signs of manganism after being employed as a welder for 3 years (Ref. 135). He had worked in the shipbuilding industry where he had welded a manganese steel alloy in confined spaces and had rarely used respiratory protection.

Manganese: Bioavailability. In his analysis of the evidence for an association between manganese exposure in welding fumes and Parkinson's disease or parkinsonism, McMillan (Ref. 107) noted that manganese emanating from different processes may differ in its physicochemical structure which could affect its bioavailability. McMillan (Ref. 107), Roth and Garrick (Ref. 134) and others have argued that, since iron and manganese compete for the same transfer systems across the blood-brain barrier, iron from welding fumes might actually reduce the passage of manganese into the brain.

Inflammation and Oxidative Stress

Kim et al. (Ref. 84) compared markers of inflammation, including C-reactive protein, fibrinogen, and numbers of neutrophils, in blood from 24 welders and 13 non-exposed controls. C-reactive protein levels were significantly increased 16 hours after welding exposures. A significant increase in neutrophil count and a significant decrease in fibrinogen were seen in blood following welding fume exposure in non-smoking welders. In further work from this laboratory, Wang et al. (Ref. 160) showed that the genes whose expression was altered following welding fume exposure were clustered in biologic processes related to the inflammatory response, oxidative stress, intracellular signal transduction, cell cycle, and programmed cell death. The greatest variations in gene expression were seen in the non-smoking welders. Wang et al. (Ref. 159) later showed that the effects of welding fume exposure on gene expression were transient, and most of the observed effects diminished within 19 hours post exposure.

Han et al. (Ref. 60) conducted a study to identify potential biomarkers of oxidative stress in the serum of 197 welders. Significant differences in total antioxidant status, total protein, aconitase, glutathione peroxidase, and isoprostane were found between welders and controls. Li et al. (Ref. 91) found that erythrocytic superoxide dismutase (SOD) activity and serum malondialdehyde levels were 24% lower and 78% higher, respectively, in welders than in controls, suggesting that

occupational exposure to welding aerosols induces oxidative stress. Zhu et al. (Ref. 175) found that average concentrations of SOD, catalase, glutathione peroxidase, and the antioxidants vitamins C and E in plasma were significantly decreased and concentrations of lipoperoxides in red blood cells were significantly increased in welders compared with controls.

Borska et al. (Ref. 8) compared humoral constituents of the immune system and indicators of inflammation in peripheral blood from 20 men who worked as welders and grinders of stainless steel with those of controls who lived in the same geographical area. The number of phagocytic cells was significantly greater in blood from welders and grinders than from controls. Concentrations of all but 5 of 17 proteins, many of which are associated with the immune system or inflammation, differed significantly in the blood from the exposed subjects and the controls.

Hoffer et al. (Ref. 69) examined whether the release of superoxide anions from stimulated polymorphonuclear leukocytes (PMNs) obtained from healthy donors was affected by pre-incubation with serum from welders or from unexposed individuals. No difference was seen when serum from all welders was compared with that from all controls or when serum from smoking welders was compared with smoking controls. However, significantly less superoxide was generated following treatment with serum from non-smoking welders under age 40 than with serum from non-smoking controls in the same age group.

Oxidative DNA Damage

Kim et al. (Ref. 85) monitored particulate exposures and 8-hydroxy-2'-deoxyguanosine (8-OHdG: an indicator of oxidative DNA damage and repair) concentrations in urine from boiler makers for 5 days during an overhaul of oil-fired boilers. The urinary concentration of 8-OHdG increased during the work shift and was significantly related to workplace concentrations of particles with aerodynamic diameters less than 2.5 μm and to the content of V, Mn, Ni, and Pb in fumes.

Effects on the Cardiovascular System

Gurevitz et al. (Ref. 54) developed a simple, low risk screening protocol to assess interactions between EMF produced by industrial equipment and the implantable cardioverter defibrillator (ICD) to determine whether it is safe for patients with ICDs to return to the workplace.

Effects on the Kidneys

Nogue et al. (Ref. 119) described a case of a welder with renal disease that was attributed to cadmium exposure. He was diagnosed with IgA mesangial glomerulonephritis, a condition in which circulating immunocomplexes containing the antibody IgA deposit in the glomerular mesangium of the kidney. Trevisan and Gardin (Ref. 156) described the case of a welder who was treated for a disorder in which proximal tubular function is impaired. He had been exposed to high levels of cadmium and his blood and urinary cadmium levels were greatly elevated. He developed kidney stones, which were attributed to chronic exposure to high concentrations of cadmium.

Effects on Reproduction

Wong et al. (Ref. 162) examined the effects of lifestyle, occupation, and medical history on sperm count in a case control study of 92 fertile and 73 sub-fertile men. The risk for oligozoospermia was non-significantly elevated in men with occupational exposures to welding. Danadevi et al. (Ref. 24) compared the quality of semen collected from 57 welders and 57 controls. The percent of subjects with normal sperm morphology, normal sperm counts, and rapid linear sperm motility was significantly lower among the welders than among controls. Nickel and chromium concentrations in blood were positively correlated with defects in semen.

Damage to DNA in sperm caused by oxidative stress may be measured by the level of 8-oxo-7,8-dihydro-2'deoxyguanosine (8-oxodG) in sperm DNA. A study by Loft et al. (Ref. 92) showed that oxidative damage to sperm DNA may adversely affect fertility but that the level of 8-oxodG does not differ significantly in sperm from men who performed

daily welding and those who did not. A study by Hjollund et al. (Ref. 67) showed that welding does not affect the rate of spontaneous abortion in pregnancies initiated by *in vitro* fertilization.

General Health

Rongo et al. (Ref. 133) surveyed 101 welders in Tanzania for information about occupational exposures and occupation-related health problems. Only 50 of the welders reported using face shields, and only ten used goggles or protective eyewear. The most common health complaints were skin burn, eye problems, headache, chest or throat pain, backache, hearing problems, and nasal and skin irritation.

Biological Monitoring

Chromium and Nickel. Stridsklev et al. (Ref. 149) examined the relationship between levels of chromium and nickel in air and in biological fluids from seven men engaged in FCAW of stainless steel. While the concentrations of nickel in air were not significantly associated with those in urine or blood, significant associations were found between the concentrations of Cr(VI) measured in air and those of total chromium in plasma and urine leading to the conclusion that post-shift urinary chromium concentrations may be useful for monitoring the uptake of chromium by welders.

Colli et al. (Ref. 21) evaluated the kinetics of urinary nickel excretion by three welders employed in SMAW of stainless steel. Mean urinary half-lives were calculated to be 59.5 hours during the work shift and 95.5 hours after the work shift and during the weekend, suggesting that nickel accumulates in two compartments in the body, with different elimination rates. The investigators concluded that measurement of nickel in a 24-hour urine sample collected throughout the entire work shift and during the 16 hours following exposure would yield the best information about exposures.

Polycyclic Aromatic Hydrocarbons. Mukherjee et al. (Ref. 115) measured concentrations of 1-hydroxypyrene (1-OHP: a biomarker for exposure to polycyclic aromatic hydrocarbons), Pb, V, Cr, Mn, Cu, and Ni in urine samples collected from boilermakers for five consecutive workdays. The concentration of 1-OHP was not significantly associated with the concentration of any of the metals at any time during the work week indicating that 1-OHP is not an appropriate surrogate marker for exposure to the metals studied.

Manganese. Wongwit et al. (Ref. 163) measured manganese concentrations in stool specimens and toenail clippings to determine if less invasive biological samples could be used in place of blood to monitor occupational exposures to manganese. The correlation of manganese concentrations among the three biological samples was found to be poor. It was concluded that blood remains the best medium for biomonitoring of manganese concentrations in occupationally-exposed individuals.

Lu et al. (Ref. 94) examined the relationship between exposure to manganese and serum concentrations of manganese in welders. Both iron and manganese tended to increase in serum with years of welding experience but the correlation was significant only for iron. The authors concluded that serum manganese may be useful as a biomarker for assessing recent, but not historic, exposures to airborne manganese. Based on arguments that manganese exposure modulates iron metabolism and the storage of iron in the body, Lu et al. investigated the relationship between serum concentrations of manganese, iron, and proteins involved in iron binding and transport. Levels of ferritin, but not of transferrin or transferrin receptor, increased significantly with years of welding experience. Serum concentrations of iron, ferritin and transferrin, but not transferrin receptor, were inversely associated with those of manganese.

Lead. Yang et al. (Ref. 164) described three welders found to have elevated blood lead levels (BLLs) during a survey taken in 1992 at a shipyard in Taiwan. When his BLL was found to be 54.1 µg/dL, the first welder was transferred to an office job. His BLL dropped to 31.6 µg/dL in 6 months and he returned to welding. Improvements in ventilation and regulations concerning use of personal protection devices were made at that time, and his BLL gradually decreased to 30 µg/dL by 2001. The other two welders, whose BLLs were about 50 µg/dL in 1992, were not removed from the job. They continued to weld in the same area and it took more than 4 years for their BLLs to decrease to less than 40 µg/dL after the ventilation was improved.

Genotoxicity

Danadevi et al. (Ref. 23) found that DNA damage, as measured by the comet assay in peripheral blood lymphocytes and by the frequency of micronuclei in buccal cavity epithelial cells, was significantly higher in welders than in controls.

Iarmarcovai et al. (Ref. 72) compared the levels of DNA damage in welders and controls using the comet and micronucleus assays in peripheral lymphocytes. The micronucleus assay showed a significant increase in the number of micronuclei in welders compared with controls indicating that welders had a higher frequency of chromosomal damage. The comet assay revealed significant differences between welders and controls at the end, but not at the beginning of the workweek, suggesting that DNA lesions induced by welding exposures are reversible.

Medeiros et al. (Ref. 110) compared the number of DNA-protein cross-links and the frequency of micronuclei in peripheral blood lymphocytes from tannery workers exposed to Cr(III), stainless steel welders exposed to both Cr(III) and Cr(VI), and non-exposed controls. The levels of DNA-protein cross-links were 2.5 times higher in welders than in tannery workers and were significantly higher in both exposed groups than in controls. The number of micronuclei was significantly elevated in lymphocytes from tannery workers, but not in welders.

Investigations in Animals and Cell Culture

Infectivity and Inflammation

Antonini et al. (Ref. 5) found that fumes from SMAW of stainless steel (SMAW-SS), but not from GMAW of mild steel (GMAW-MS) or stainless steel (GMAW-SS), enhanced infectivity by *Listeria monocytogenes* in rat lungs. Fume samples were introduced into rat lungs by intratracheal instillation followed, 3 days later, by instillation of *Listeria monocytogenes***.** Treatment with SMAW-SS fume reduced pulmonary clearance of the bacterium and reduced survival of the rats. Lactate dehydrogenase, albumin, and numbers of macrophages, PMNs, eosinophils, and lymphocytes were elevated in bronchoalveolar lavage fluid (BALF) after treatment with SMAW-SS fume.

Taylor et al. (Ref. 153) compared the inflammatory response in rats exposed by intratracheal instillation to fumes from GMAW-MS, GMAW-SS, and SMAW-SS, and to the water soluble and insoluble components of SMAW-SS fume. All of the samples caused pulmonary inflammation but this effect was greater and lasted longer with the SMAW-SS fume. Both the soluble and insoluble fractions contributed to the inflammatory response elicited by SMAW-SS fume. Subsequent studies from this laboratory (Ref. 4) showed that soluble chromium was the component of SMAW fume most likely to be responsible for suppression of the lung defenses against *Listeria* infection. These investigators (Ref. 2) also reported that the SMAW-SS fume caused DNA strand breaks when incubated with DNA and hydrogen peroxide in a cell-free assay.

McNeilly et al. (Ref. 108) examined the effects of three different stainless steel welding fumes and their soluble and insoluble fractions on the production of the pro-inflammatory cytokine IL-8, and on the activation of the nuclear translocation factors NF-kB and AP-1 by cultured human type II alveolar epithelial cells. IL-8 was significantly elevated following treatment with the soluble fraction of fumes produced with nickel-based and cobalt consumable electrode**s**. All fume samples and their soluble fractions depressed levels of the intracellular antioxidant glutathione within 2 hours after treatment. In a subsequent study, McNeilly et al. (Ref. 109) found that neutrophils were significantly elevated in BALF from rats treated with the whole fume or with the soluble fume fraction from the stainless steel welding electrodes; macrophages were significantly elevated in rats treated with the whole fume but not with the soluble fume fraction.

Pascal and Tessier (Ref. 124) treated cultured human lung epithelial cells with nickel, manganese, or potassium dichromate. At manganese or Cr(VI) concentrations between 0.2 μM to 200 μM, levels of IL-6 and IL-8 in the culture medium were up to 4.4 times greater than that found in controls. Levels of TNF-α were unchanged.

Fibrosis

Sung et al. (Ref. 150) measured pulmonary function and examined cells recovered in BALF from rats exposed by inhalation for up to 60 days to high and low doses of SMAW-SS fumes. The number of alveolar macrophages, PMNs, and

lymphocytes in BALF increased in a dose- and time-dependent fashion. After a 60-day recovery period, the number of all cell types remained significantly elevated in the high dose 60-day exposure group compared with controls but the cell numbers in BALF from the other exposure groups were declining. Statistically significant dose-dependent decreases were seen in the tidal volume which returned to normal after the 60-day recovery period in all rats except in those exposed to the high dose for 60 days. This correlated well with the investigators' earlier findings that the fibrotic changes seen in rats exposed to the high dose for 60 days were not fully reversible after a 90-day recovery period (Ref. 170).

In a subsequent study, these investigators examined inflammatory and genotoxic responses in the lungs of rats exposed by inhalation to SMAW-SS fumes for 30 days (Ref. 172). Lactate dehydrogenase and albumin increased significantly in BALF with duration of exposure. DNA damage resulted from 30 days of welding-fume exposure as measured by the comet assay and tests for 8-hydroxydeoxyguanine. These investigators (Ref. 131) later conducted a study of genes specifically expressed or down-regulated in rats exposed by inhalation to SMAW-SS fumes for 30 days. Gene expression profiles were analyzed in peripheral blood mononuclear cells. The expression of 261 genes was found to have been increased, while that of 772 genes was decreased among the 5200 genes analyzed.

Manganese Distribution in Rat Brains

Yu et al. (Ref. 169) investigated the distribution of manganese in the rat brain following inhalation exposure to fume generated by SMAW of stainless steel. Manganese concentrations in the lung and liver increased with the dose and with the duration of exposure and were significantly higher than in controls at all time points after initiation of exposure. Statistically significant increases in manganese levels in the cerebellum were seen at all time points after 15 days of exposure but only slight increases were seen in the substantia nigra, basal ganglia (including the caudate, nucleus, putamen, and globus pallidus), temporal cortex, and frontal cortex after 60 days of exposure.

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Effects of Welding on Health, XIV

Section One
The Exposure

1. Fume Composition

In metal arc welding, the rate of fume generation and the composition of the fume are influenced by many factors including arc voltage and welding current, the composition and flow rate of shielding gases in gas metal arc welding (GMAW), the composition of the flux in shielded metal arc welding (SMAW), the composition of alloying materials or slag formers in flux cored arc welding (FCAW), and the composition of the electrode or filler metal. Yoon et al. (Ref. 168) measured the effects of welding current on fume generation rates (FGR) and on airborne concentrations of total chromium and hexavalent chromium [Cr(VI)] during CO_2-shielded FCAW of stainless steel in a fume collection chamber. Six types of welding wire were tested at three welding currents: a low current of about 120 amperes (A), an optimum current of about 180 A, and a high current of about 230 A. The currents tested were consistent with those routinely used by welders to enhance productivity, and they tended to be higher than those suggested by manufacturers.

The Cr(VI) concentrations varied with the welding wire used and ranged from 0.15% to 1.08% of total fume. Most of the Cr(VI) was present in a soluble form. The FGR, total chromium, and Cr(VI) produced during FCAW all increased with the welding current. Each step up in welding current produced a doubling of the FGR for all types of welding wire. The percentage of total chromium in the fume increased two- to four-fold with increasing current, but changes in the percentage of Cr(VI) were far less dramatic, and the ratio of Cr(VI) to total chromium occasionally decreased as the current was increased above 120 A. Yoon et al. noted that the FGR and concentrations of total chromium were similar to those produced during SMAW, while the concentrations of Cr(VI) were similar to those produced during GMAW.

2. Sampling Strategies for Ultrafine Particles

Brouwer et al. (Ref. 15) compared available methods for measuring ultrafine particles generated by welding. In a workplace study, measurements were made on three consecutive days during argon/CO_2-shielded GMAW with a copper-shielded stainless steel electrode. Local exhaust ventilation was not employed, but there were central air system blower inlets in the ceiling near the workstations. A laboratory study was also performed in a 7 m × 4 m × 2.5 m room; a mannequin was placed at a distance of 80 cm from the weld, and a mobile local exhaust ventilation unit was located opposite the mannequin. Argon/CO_2-shielded GMAW was performed on an iron pipe using an SG2 wire. Three types of instruments were used to measure particle emissions and particle size distributions: a condensation particle counter (CPC), a scanning mobility particle sizer (SMPS), and an electrical low pressure impactor (ELPI). In the workplace study, SMPS and CPC data showed the temporal variations in particle number concentrations at specific locations. The number concentration of fine particles was affected more by grinding, by diesel exhaust, and by re-suspension during fork-lift traffic than by welding. In the laboratory study, SMPS results showed that the percentage of ultrafine particles declined sharply at the commencement of welding and then increased back to the pre-welding value. In contrast, ELPI measurements showed an increase in the fraction of ultrafine particles during welding and a gradual decrease after welding ceased. Electron micrograph images showed that the welding aerosol was composed of agglomerates of very small particles. The diffuse shape of the welding particles causes the "mobility diameter" as measured by the SMPS to be greater than the aerodynamic diameter measured by the ELPI, leading to an overestimate of the number of particles by the latter instrument, consistent with the above findings. The authors concluded that each of the measurement methods has its drawbacks, but that in combination they can be provide useful insight into the characteristics of fine particles in the

workplace. They cautioned that the use of static samplers at fixed locations would hamper the attempt to characterize personal exposures of ambulatory workers.

3. Thoriated Electrodes

Thorium oxide is often incorporated into tungsten electrodes used in gas tungsten arc welding (GTAW) to provide arc stability and ease of starting, to improve the current-carrying capacity of the electrode, and, by preventing the electrode tip from melting, to decrease the rate of electrode degradation and weld contamination. Because all of its isotopes are radioactive, aerosols formed during welding with, or grinding of, thoriated electrodes may represent a potential health hazard to welders who use these techniques. Previous studies of workplace concentrations of ^{232}Th, the major isotope of thorium, have shown that, while there are occasional excursions of thorium activity greater than the maximum air concentration recommended by the U.S. Nuclear Regulatory Commission (NRC) of 1 picocurie per cubic meter (pCi/m^3) or 0.037 becquerel (Bq)/m^3, cumulative exposures do not often exceed the annual limit of 5 rem or, in international standard units, 50 millisievert (Ref. 22, 79, 95).

Gafvert et al. (Ref. 46) measured breathing zone concentrations outside the welder's helmet during full-time welding of steel (12 welders) and aluminum (8 welders) with thoriated electrodes in five workshops in Sweden. Separate breathing zone samples were collected during grinding. In general, welding with alternating current (AC) produced higher thorium activity in the breathing zone than did welding with direct current (DC). The highest breathing zone concentrations of radioactivity were found in samples collected from two welders who used an AC welding apparatus and were inexperienced in its use. Conservative and "realistic" estimates of annual thorium exposure for the welders were calculated from the welding and grinding sampling data. All estimates were well below the NRC limits and only in the cases of the two inexperienced AC welders did they exceed 0.010 Bq/m^3. Nevertheless, the authors recommended that substitutes such as lanthanum or cerium be made for thorium in the electrodes.

Saito et al. (Ref. 136) measured ^{232}Th exposure during welding and grinding with thoriated electrodes in a welding shop in Japan. A welder was outfitted with protective clothing and breathing zone samples were collected during GTAW of aluminum, GTAW of stainless steel, and during sharpening of the electrode tips on a grinding wheel. The annual intake of ^{232}Th was based on the breathing zone measurements and the estimated annual hours spent on each task. When it was assumed that respiratory protection was not used, the estimated annual dose of radiation ranged from 1.0 Bq to 33.2 Bq, well below the Japanese annual limit of 160 Bq. When the use of respiratory protection was assumed, the annual doses were no more than 2% of the annual limit. The authors recommended that workers be informed when radioactive electrodes are being used, and that they be provided with proper local ventilation and suitable facilities for cleaning dust from their persons.

4. Ultraviolet Light

Garcia-Guinea et al. (Ref. 47) discussed factors responsible for the production of ultraviolet (UV) radiation during SMAW. They explained that the UV radiation produced by SMAW is derived mainly from the mineral coatings on the electrodes and examined the UV produced by minerals used in the coats of electrodes produced by various manufacturers. Fourteen different common consumable coated electrodes were obtained from manufacturers in Europe and Argentina. The coatings were found by X-ray diffraction analysis to consist of quartz, calcite, sodium and potassium-rich feldspars, muscovite, and rutile. Thermoluminescence measurements were conducted on representative samples of the materials found in the electrode coatings (not on samples taken from the electrode coatings). All of the materials except rutile produced strong emission peaks in the UV-A range (320 nm–400 nm) and the UV-B range (280 nm–320 nm). The authors acknowledged that the alkali ions (Na^+, K^+, and Li^+) present in the coating materials associated with UV-A and UV-B emissions are necessary components of the electrode, facilitating re-ignition of the arc after interruptions of the welding current. They recommended that research into different alkali ions, minerals, and grain sizes should be conducted in an attempt to reduce UV emissions.

5. Incidental Exposures

Gjolstad et al. (Ref. 49) examined exposure of refrigerator repair workers to halogenated refrigerants. The study was performed in Norway where the refrigerants used were difluorochloromethane, tetrafluoroethane, or R 404A (a mix of 1,1,1,2-tetrafluoroethane, pentafluoroethane and 1,1,1-trifluoroethane). Welding represented only a small portion of the repair efforts and welding periods lasted for an average of 11.5 minutes. Exposure to the decomposition products hydrogen fluoride (HF), hydrogen chloride (HCl), phosgene, and volatile organic compounds were measured during welding. Phosgene was not detected in breathing zone samples when difluorochloromethane was the refrigerant but HCl (mean breathing zone concentration HCl: 5 mg/m^3) was detected during welding when difluorochloromethane was the refrigerant and HF was detected during welding of refrigerant systems with difluorochloromethane (mean concentration HF: 0.27 mg/m^3), tetrafluoroethane (mean concentration HF: 0.27 mg/m^3), or R 404A (mean concentration HF: 0.65 mg/m^3). The presence of HCL and HF indicated that thermal degradation of the refrigerants had occurred during welding.

6. Workplace Exposures

With the goal of characterizing the aerosol formed by natural mixing of welding fumes with the air in a typical industrial setting, Stephenson et al. (Ref. 146) sampled particle emissions during SMAW of carbon steel in a metal shed, 18 m wide, 52 m long, and 11 m high. Testing was conducted with building exhaust fans off, resulting in three to four air changes per hour. A fan placed behind the welder pulled fumes out of the breathing zone and provided mixing within the shed. Particle size and mass distributions were determined in samples collected in the welder's breathing zone and at stations located upwind and downwind from the welding operation. Time-weighted averages (TWAs), taken over 160 minutes, of total and respirable dusts collected in the welder's breathing zone were 3.14 mg/m^3 and 1.38 mg/m^3, respectively. The respective values at 8.5 m upwind were 1.74 mg/m^3 and 1.13 mg/m^3, and at 10 m downwind, they were 4.28 mg/m^3 and 1.55 mg/m^3. In samples collected 3 m downwind of the welding, the number concentration of particles in the range 0.05 μm to 0.5 μm increased by almost 100-fold, while the concentration of larger particles did not differ from background levels**.** Electron microscopy showed that the welding particles consisted of non-spherical clusters and aggregates of particles smaller than 0.1 μm in diameter. The authors considered the aerosol to be stable during its residence time in the building, and the particle size was slightly larger than is typically measured in laboratory fume-generation experiments due to the opportunity for particle growth as the fumes circulated in the building.

Matczak and Przybylska-Stanislawska (Ref. 104) measured concentrations of metals and fluorides in samples collected in the breathing zone of welders using ten types of welding electrodes during FCAW. The samples were collected in a power station and four shipyards and mechanical engineering plants. Welding with certain types of flux cored electrodes resulted in breathing zone concentrations of total dust (range: 0.2 mg/m^3–24.3 mg/m^3) and manganese (range: 0.01 mg/m^3–1.8 mg/m^3) well in excess of regulatory limits in some of the samples. Concentrations of calcium (range: 0.004 mg/m^3–2.5 mg/m^3) and iron (range: 0.2 mg/m^3–6.7 mg/m^3) also slightly exceeded Maximum Allowable Concentration (MAC) values in some of the breathing zone samples.

7. Ventilation

Local exhaust ventilation is used to reduce fume concentrations in the welder's breathing zone. In the case of GMAW, the effect of the ventilation on the shielding gas and, hence, on the quality of the weld must be considered in addition to the effectiveness of the ventilation. Iwasaki et al. (Ref. 76) tested the effectiveness of a push-pull ventilation system to control exposures to fumes produced by CO_2-shielded GMAW. With this type of ventilation, a stream of fresh air is blown in on one side of the welding operation and removed by an exhaust hood on the opposite side. Using a push-pull ventilation system with a robotic welding apparatus, these investigators measured the effects of ventilation air and shielding gas velocities on breathing zone fume concentrations and on the quality of the weld. All welding was done at a current of 300 A and at a constant welding speed while the CO_2 flow rate was set at 20, 30, or 40 liters per minute (L/min).

Welding fume concentrations in the breathing zone were below the Japanese Control Limit Value of 3 mg/m^3 when the ventilating air velocity was greater than 0.3 meters per second (m/s). With a shielding gas flow rate of 20 L/min, blow holes appeared in the work at air velocities greater than 0.8 m/s. At flow rates of 30 L/min and 40 L/min, blow holes were produced at air velocities greater than 1.2 m/s and 1.6 m/s, respectively. The authors stated that the two important

design criteria for a push-pull ventilation system—(1) the production of stable air velocity and direction in the vicinity of the weld to prevent formation of blow holes and (2) the effective removal of welding fume from the occupied area—were both achieved when the ventilating air flow velocity was maintained between 0.3 and 0.8 m/s.

Harris et al. (Ref. 63) evaluated the effectiveness of general dilution ventilation by means of exhaust fans in controlling a welder's exposure to manganese during SMAW in a confined space. Welding was conducted in an enclosed chamber with a volume of about 2200 ft^3. Air was drawn out of the chamber by two variable-speed exhaust fans on one side of the welding table, and make-up air entered through an open doorway on the opposite side. Three electrodes were tested: two had a manganese content typical of carbon steel electrodes and the third, the "Mangjet" which is used for cladding carbon steels, had a much higher concentration of manganese in the flux.

A welder fitted with personal air samplers welded for about 60 minutes with each of the two standard electrodes, and for about 30 minutes with the Mangjet electrode. Samples were collected for determination of total fume, total manganese, respirable manganese inside the helmet, and total fume outside the helmet. Air samples were also collected at a height of 54 inches in six locations at either side of the welder that served as surrogates for welders' helpers. Dilution ventilation was supplied at five different exhaust rates up to 2000 cubic feet per minute (CFM) across the work area. With an exhaust rate of 2000 CFM, manganese concentrations in breathing zone samples collected while the welder used standard electrodes were within 75% of the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 0.2 mg/m^3 for manganese. However, the TLV for manganese was exceeded at all flow rates in area sample locations that served as surrogates for welders' helpers, indicating that the exhaust flow rate of 2000 CFM prescribed by the Occupational Safety and Health Administration (OSHA) for confined spaces was insufficient to protect bystanders from excess manganese exposure. Manganese in breathing zone samples collected when the welder was using the Mangjet electrode exceeded the TLV of 0.2 mg/m^3 at all dilution rates. Finally**,** there was little difference between total fume concentrations inside and outside the helmet, or between total and respirable manganese concentrations, suggesting that the use of a cyclone sampler is not necessary when determining concentrations of respirable manganese. The authors concluded that it would be wise to use source capture ventilation or to provide personal respiratory protection during SMAW in confined spaces with the types of electrodes studied rather than to rely solely on dilution ventilation with exhaust fans, even when they are operated at the exhaust rate of 2000 CFM recommended by OSHA.

Zaidi et al. (Ref. 173) examined the effectiveness of two local exhaust ventilation systems developed in rural India for use during welding. One device, a mobile unit, was considerably heavier (150 kg) than the other, a portable unit (50 kg). Welding was conducted, using mild steel electrodes with flux containing less than 5% manganese by weight, in a high-ceilinged room without any forced ventilation other than that provided by the test units. Both units were shown to reduce the breathing zone concentrations of manganese. In separate experiments, the portable unit reduced the breathing zone concentration from 22 $\mu g/m^3$ to 8 $\mu g/m^3$ and the mobile unit reduced the manganese concentration from 70 $\mu g/m^3$ to 8 $\mu g/m^3$. The authors stated that the portable unit was more suitable for small shops and field locations. They concluded that these simple and affordable local exhaust ventilation units "might prove useful in developing … countries."

8. Accidents and Injuries

In 2001, Shaikh (Ref. 141) published the results of a cross-sectional survey which examined the prevalence of occupational injuries among 208 welders employed in the automobile industry in Rawalpindi and Islamabad, Pakistan. Data concerning accidents that occurred within the past 3 and 12 months were obtained by interviews. Thirty-nine (19%) of the welders reported having sustained an injury in the 3 months preceding the interview, while 63 (30%) of the welders reported being injured during the preceding year. Burns on the face, limbs, or trunk, and foreign bodies in the eye were the most common injuries. Similar data were obtained during two follow-up surveys performed at 3-month intervals after the initial study (Ref. 142). Sixty-one welders reported having 105 injuries and consequently losing 28 days from work during this 6-month follow-up period. None of the accidents resulted in permanent injuries. The pattern of the injuries was similar to that reported in the first study. The most common injuries sustained by the welders were foreign bodies in the eyes.

Section Two
Effects of Welding on Human Health

9. Respiratory Tract

9.1 Pulmonary Function. Decrements in lung function that may be associated with inhalation of workplace pollutants can be evaluated using spirometric tests which measure the lung volume, the maximum amount of air that can be inhaled, and the flow rates that can be achieved 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; forced expiratory volume (FEV_1), the volume that can be exhaled in one second; and FEV_1/FVC, the ratio of the previous two. FVC is reduced in restrictive lung disease (e.g., fibrosis and interstitial lung disease) and, to a lesser extent, in obstructive lung disease (e.g., bronchitis and asthma); FEV_1/FVC is reduced in obstructive but not in restrictive lung disease. Maximal voluntary ventilation (MVV) is the maximum volume of air that can be breathed into and out of the lungs in one minute; it is non-specific, reflecting the performance of the entire pulmonary apparatus. These and other pulmonary function measurements frequently used in epidemiological studies of workers are described in greater detail in Appendix A.

Meo (Ref. 111) examined the effects of exposure to welding fumes on MVV in 50 male arc welders and 50 male controls in Karachi, Pakistan. The welders were engaged in SMAW in small shops with minimal natural ventilation and no mechanical ventilation. They were individually matched by age, height, and weight with controls who were shopkeepers and salesmen in the same area of Karachi. All of the participants were non-smokers. There was a significant decrement in MVV among the welders compared with controls. When the data were analyzed by duration of employment, there was no significant difference between welders with less than 5 years experience and controls. Welders with 5 to 9 years experience had significantly greater decrements in MVV compared with controls. The dose-response relationship between years of welding experience and decreases in MMV was significant.

Additional spirometric tests performed with these subjects (Ref. 113) showed that welders had statistically significant reductions in lung function as measured by peak expiratory flow (PEF), FEV_1, and FEV_1/FVC (Table 1). Differences in FVC

Table 1
Percentage Changes in Lung Function of Welders Compared with Controls

Years Welding Experience:	<5[a] (n = 18)	5 to 8 (n = 12)	> 9 (n = 20)	All Welders (n = 50)
Lung Function Parameter				
FVC	–2.6 (NS)	–6 (NS)	–3.8 (NS)	–3.9 (NS)
FEV_1	–0.6 (NS)	–19.6 (P < 0.05)	–21.0 (P < 0.001)	–13.6 (P < 0.001)
FEV_1/FVC	+1.3 (NS)	–14.9 (NS)	–16.2 (p < 0.01)	–9.6 (p < 0.01)
PEF	+7.9 (NS)	–33.2 (NS)	–44.3 (p < 0.0005)	–24.6 (p < 0.005)
$FEF_{25–75}$	+6.5 (NS)	–21.8 (NS)	–9.1 (NS)	–6.2 (NS)

[a] Values shown represent mean percentage differences in lung function of welders compared with controls.

n = number of welders. NS = not statistically significant. Differences with p values less than 0.05 are statistically significant.

Data from Meo et al., Ref. 113.

and forced expiratory flow ($FEF_{25–75}$) were not significant. Among the 18 welders with less than 5 years of experience, there were no significant differences in the means of any of the lung function tests compared with matched controls. A significant reduction in FEV_1 was found in the 12 welders with 5 to 8 years of exposure, but there were no significant changes in any of the other lung function parameters for this group of welders. The 20 welders exposed for 9 or more years showed significant reductions in FEV_1, FEV_1/FVC, and PEF. Regression analysis showed statistically significant relationships between duration of exposure and reductions in FEV_1, FEV_1/FVC, and PEF. The authors concluded that their findings demonstrated obstructive lung impairment in non-smoking welders compared with matched controls, with a positive dose/response relationship between years of welding experience and decrements in lung function. Meo and Al-Khlaiwi (Ref. 112) recommended that workers susceptible to respiratory effects from welding fumes be identified and removed from the workplace.

Fishwick et al. (Ref. 38) revisited four of eight work sites in New Zealand where, 11 months earlier, they had documented excesses of respiratory symptoms, across-shift changes in FEV_1, and chronic bronchitis among welders but they had made no measurements of fume exposure (Ref. 14, 39). The original study included 137 welding-exposed workers, of whom 85 had worked at the four work sites where the follow-up investigation was conducted. Seventy-five of these workers, 49 of whom were welders, agreed to participate in the follow-up study. Breathing zone samples from 34 of the subjects were obtained using personal samplers and were analyzed for total fume and specific metals. Those subjects who did not participate in the air sampling were assigned exposure levels based on their location with respect to active welding.

Data concerning respiratory symptoms and pulmonary function from the previous study were used when available. Subjects who were new to the study completed the same questionnaire and were subjected to the same pulmonary function test regimen that had been applied to the returning subjects. Measurements were taken just before the shift started, 15 minutes after the start of a weld (or a corresponding time after start of work for those subjects not exposed to welding) and at 7 hours into the work shift. Sixteen of the 75 workers (26.5% of welders and 11.5% of non-welders) reported work-related respiratory symptoms. Multivariate regression analysis did not show any significant effects of smoking, age, or years of welding experience. But there was a significant positive correlation between symptoms and exposures to high levels of nickel. Pulmonary function tests were completed with 70 workers. A 5% fall in FEV_1 was observed in 16 workers after the first 15 minutes of work and was significantly correlated with exposure to high levels of aluminum, but not with smoking, age, or high levels of total fume exposure. The authors concluded that nickel exposure from welding is associated with work-related respiratory symptoms and that aluminum exposure from welding is associated with a fall in FEV_1 early in the work shift.

Jafari and Assari (Ref. 77) compared lung function and respiratory symptoms in a group of 63 welders from workshops in Hamadan, Iran, with those in a control group of 78 workers with similar demographics who had no current or previous welding exposure. Metal fume samples collected in the breathing zone of one worker showed an iron concentration of 31 mg/m^3 (TLV = 5 mg/m^3) and a manganese concentration of 0.36 mg/m^3 (TLV = 0.2 mg/m^3). Nickel, lead, and chromium levels were less than the TLV. Pulmonary function tests administered to both groups included vital capacity (VC), FVC, FEV_1, and $FEF_{25–75}$. Respiratory symptoms (nasal allergies, cough, phlegm, wheezing, and work-related shortness of breath) occurred significantly more frequently among the welders than among the controls. Chronic bronchitis, defined as regular phlegm production at any time of day for at least 2 years and at least 3 months of the year**,** was reported by 17. 5% of the welders and 3.8% of the non-welders; the difference was significant ($p < 0.001$). Asthma was reported more frequently by the welders than by the non-welders, but this difference was not significant. All of the pulmonary function tests administered showed significant decrements among smoking welders compared with smoking non-welders and among non-smoking welders compared with non-smoking non-welders. These results suggest that there may be a synergistic relationship between the effects of smoking and exposure to welding fumes. The authors recommended prevention programs, including local ventilation and use of respiratory protective devices.

Tunc et al. (Ref. 157) performed pulmonary function tests on 32 welders and 39 unexposed controls in a factory in Ankara, Turkey. Questionnaires concerning respiratory symptoms and exposure history were administered to all participants. The welders reported significantly higher incidences of coughing, excess sputum, and dyspnea (shortness of breath) than did controls. Chronic bronchitis was observed in 7 (22%) of the welders but in none of the controls. Pulmonary function tests revealed no significant differences between the two groups**.**

Exposure to oxidant gases, such as ozone and oxides of nitrogen, or to reactive metals released during welding may injure the respiratory tract and other organs by causing oxidative stress, a condition in which the quantity of oxidants in the body outweighs that of antioxidants available to inactivate them (see Section 16, Inflammation and Oxidative Stress).

Oxidative stress may play an important role in development of some welding-related disorders and the presence of this condition may be detectable by changes in patterns of blood constituents. Studies by Fidan et al. (Ref. 34) and Stepniewski et al. (Ref. 147) investigated the relationship between changes in ventilatory parameters, respiratory symptoms, and biomarkers of oxidative stress in welders.

Fidan et al. (Ref. 34) examined respiratory symptoms, lung function, and blood oxidant-antioxidant markers in 51 welders and 31 automotive electrical workers who served as controls. All participants were from Afyon, Turkey. There were no marked differences in demographics or smoking status between welders and controls. The respiratory symptoms cough, sputum, and chronic bronchitis were all significantly more prevalent among the welders than among controls. In the pulmonary function tests, FEV_1/FVC, FEF_{25}, FEF_{75}, and $FEF_{25–75}$ were significantly lower in the welders than in the controls. Blood samples were collected from 34 of the welders and 20 of the controls for analysis of indicators of oxidative stress. Plasma thiobarbituric acid reactive substances (TBARS: an indicator of lipid peroxidation) and protein carbonyl levels were significantly higher in welders than in controls. Total protein thiols (SH) and reduced glutathione levels in erythrocytes were significantly lower in welders than in controls, revealing a reduction of available anti-oxidants. No correlations were found between serum oxidant-antioxidant levels and any of the pulmonary function test results, but TBARS levels were significantly elevated and SH and glutathione levels were significantly reduced in welders with chronic bronchitis, suggesting a role of oxidative stress in the pathogenesis of that condition.

Stepniewski et al. (Ref. 147) examined pulmonary function and antioxidant enzymes in blood from 94 welders and 115 age-matched healthy workers who were unexposed to the welding environment. All of the subjects and controls were active smokers and worked in a steel mill in southern Poland. Ozone levels measured in the welding workshops varied between 0.1 and 0.4 ppm (the ACGIH TLV-TWA is 0.05 ppm for heavy work). Oxides of nitrogen in excess of the Polish occupational exposure limit (OEL) of 5 mg/m^3 were measured in some parts of the welding area. Blood samples were analyzed for total antioxidant status (TAS), alkaline phosphatase activity, catalase activity, superoxide dismutase (SOD), and for other enzymes. The participants completed questionnaires on respiratory and cardiac disease and were given physical examinations, electrocardiograms (EKG), chest x-rays, and spirometric tests. The values for TAS, SOD, and catalase did not differ significantly between welders and controls. Lung function measured by the spirometric tests FEV_1, %FEV, maximum expiratory flow (MEF_{50}), and $MEF_{25–75}$, was significantly reduced among the welders compared with the controls. Almost twice as many welders as controls were at risk for chronic obstructive pulmonary disease (COPD) as defined by normal spirometry with chronic cough and sputum production. Moderate symptoms of COPD, as defined by FEV_1 between 30% and 80% of normal and FEV_1/FVC less than 70% of normal, with or without chronic symptoms, were found in eight welders and in one control. Fully clinically developed COPD was found in none of the welders or controls. Low but significant correlations were found between catalase and FEV, and between TAS and FVC, but the authors concluded that the changes in the concentrations or activity of the blood constituents studied cannot be used as early markers of ventilatory dysfunction. Their major conclusions were that the antioxidant system was affected in welders exposed to ozone and oxides of nitrogen and that signs of COPD were more frequent in the welders than in the controls.

Chronic obstructive pulmonary disease includes two conditions: emphysema and chronic bronchitis. Shortness of breath is one of the most common symptoms of COPD. Mastrangelo et al. (Ref. 102, 103) conducted a case-referent study of 131 men with COPD who were discharged from a university hospital in Padua, Italy, between 1990 and 1997 and 298 randomly-selected male patients who were without respiratory disease. The diagnosis of COPD was based on a clinical history of shortness of breath and/or excess phlegm production in the winter for at least 2 years and an FEV_1 less than 80% of the predicted value that was only minimally reversible with bronchodilators, and did not improve during hospital observation periods. Data concerning demographic background, employment, and smoking histories were obtained from clinical records. Participants were placed into a job-exposure matrix with estimated exposures (none, low, or high) to biological dust, mineral dust, and fumes and gases in 16 job categories. Age, smoking, and duration of working career were strong risk factors for COPD. Welders were found to have a significantly greater risk for COPD than did office workers. The odds ratio[1] (OR) for COPD among welders increased slightly, but significantly, with duration of exposure (OR = 1.07, CI[2] = 1.01–1.13) and age (OR = 1.16, CI = 1.07–1.25). The risk for COPD was much greater in welders who smoked (current smoker: OR = 20.2, CI = 1.27–320; former smoker: OR = 25.6, CI = 1.54–426). The risk for COPD was

[1] See Appendix B for definitions of epidemiologic terms.
[2] CI = 95% confidence interval.

elevated in farmers, textile workers, and painters, as well as in welders, and the authors concluded that there is a causal relationship between COPD and working in those occupations.

9.2 Occupational Asthma. Occupational asthma (OA) is a reversible, generalized airway narrowing that results from exposure to airborne dusts, gases, vapors, or fumes in the work environment. Based on a review of published studies, the American Thoracic Society (Ref. 7) estimated that approximately 15% of asthma in the adult population is attributable to occupational exposure**.** Wheezing, the characteristic sign of asthma, can be traced to three types of workplace exposures**:** (1) strong irritants or corrosive substances such as chlorine may produce permanent lung damage and symptoms of asthma after one exposure, (2) allergic alveolitis, which is an Immunoglobulin G (IgG)-mediated response to biological materials, and (3) OA, which results from IgE-mediated sensitization to inhaled chemicals in the workplace. The onset of OA may occur as early as 2 weeks or as late as 6 months after the first workplace exposure. In the initial phase, episodes of respiratory distress are clearly associated with time spent at work. When the disease becomes chronic, the patient feels asthmatic most of the time, but still experiences improvement on weekends. Eventually, the only noticeable improvement occurs during extended periods of leave. Tests for confirmation of OA that are frequently used include: PEF measurements during periods at and away from work, bronchial challenge tests, demonstration of reversibility with the application of bronchodilators and steroids, and skin prick tests to detect sensitization to specific substances (Ref. 29, 126).

McDonald et al. (Ref. 106) analyzed the incidence of work-related respiratory disease reported by chest and occupational health physicians in the United Kingdom to the National Heart and Lung Institute in London between 1992 and 2001. This study used data collected by the Surveillance of Work-related and Occupational Respiratory Disease (SWORD) project, begun in London in 1988 and based on the voluntary reporting by chest specialists and occupational physicians of all newly-diagnosed cases of work-related respiratory disease (Ref. 114). The study excluded diseases with long latency that are rarely seen by occupational physicians and focused on diseases with a short latent period including occupational asthma, allergic alveolitis, and illness caused by "inhalation accidents" (e.g., those resulting from inhalation of strong irritant gases). Occupational asthma represented 25% of these diseases. The highest rate of OA was reported among workers in craft-related occupations. Reports from chest physicians identified welding as the causative agent for 3% of all cases of OA in the 10 years studied; other exposures to metals or metallic compounds accounted for 4%. Major causes were biological agents (35%), led by flour/grain and wood dusts, and irritant chemicals (32%), especially isocyanates. The reports by occupational physicians ranked irritant gases (42%), solvent vapors (18%), metallic fume (11%), and acid mists (9%) as the primary causes of OA among their cases. The authors explained that these physicians are associated with large manufacturing plants where biological agents are not prevalent. Welding fumes were included in the metallic fume category and were not independently evaluated.

It is compulsory for physicians in Finland to report all new cases of OA to the Finnish Register of Occupational Diseases (FROD). Piipari and Keskinen (Ref. 125) analyzed all cases of OA reported to the FROD during the period 1986 to 2002 and compiled them by year and attributed cause. Diagnoses were based on symptoms, exposure assessment, sensitization to the causative agent, and PEF measurements taken at and away from work. In all of the cases ascribed to non-biological exposures, the diagnoses were confirmed by specific respiratory challenge tests to the workplace agent. Most of the cases of OA were attributed to biological agents, mainly animal epithelia, flours, and molds. Non-biological chemicals accounted for about 25% of the OA cases. In a separate cumulative analysis of OA during the years 1988 to 1997, 4% of OA was attributed to welding fumes, the same percentage that was attributed to diisocyanates, the other leading non-biological cause.

In Norway, occupational diseases must be reported by physicians to the Labor Inspection Authority. Using the registry of these reports, Leira et al. (Ref. 89) investigated the incidence of OA in Norway between 1995 and 1999. Data concerning work situation, symptoms, the relationship of symptoms to work, and life style factors were obtained by questionnaires sent to the 1239 persons who had been diagnosed with OA during the study period and who could be located; 723 of the respondents met the criteria for OA used in the study. Workers in the aluminum industry had the highest reported incidence of asthma and accounted for 227 of the respondents with OA. This was due, in part, to the recognition in Norway of OA as a disease among aluminum potroom workers and to the requirement for active screening, making it less likely that the disease would be under-reported in this group than was the observed tendency in the industrial population as a whole. Among the male cases from outside the aluminum industry, welders were the third most likely group (after bakers/confectioners and car painters) to have been reported with OA, with an incidence of 1.34 cases per 1000 person years. Among females, welders were the second most affected group (0.80 cases per 1000 person years), but female car painters were assumed to be few in number and were not included in the analysis. Since the majority of cases still had

symptoms 2 to 6 years after they were first diagnosed, the authors concluded that they were likely to have been reported at an advanced stage of the disease. They recommended that, since OA tends to become chronic and irreversible unless exposure is reduced when symptoms first develop, it is advisable to transfer workers with OA to an exposure-free workplace at an early stage of the disease.

In an attempt to determine if there is a relationship between the prevalence of symptoms indicative of metal fume fever and those suggestive of OA, El-Zein et al. (Ref. 32) examined data collected from 351 welders during a telephone survey of industrial workers conducted in Montreal, Canada between 1977 and 1998. In the survey, data were collected concerning respiratory symptoms suggestive of OA (cough, wheezing, and chest tightness), systemic symptoms of metal fume fever (fever, feelings of flu, general malaise, chills, dry cough, metallic taste in the mouth, shortness of breath), and occupational history to quantify the number of years spent welding. Only metal fume fever symptoms that occurred at the beginning of the work week were considered because short-term tolerance can develop with repeated exposure**.** In this study, possible metal fume fever was defined as having at least two of the symptoms listed above, and probable metal fume fever was defined as having fever and two of the other symptoms. Among the welders in this survey, 26.6% reported at least one of the respiratory symptoms. Shortness of breath was reported by 44.4% of the respondents. The occurrence of two respiratory symptoms suggestive of OA was significantly related to both possible metal fume fever (OR = 3.97, CI = 2.06–7.63), and probable metal fume fever (OR = 4.15, CI = 1.98–8.71). The authors hypothesized that metal fume fever may be a predictor for development of respiratory symptoms related to OA.

This idea was further explored by El-Zein et al. (Ref. 30, 31) in a prospective study of apprentice welders in whom changes in pulmonary function, signs of asthma, and symptoms of metal fume fever were followed during the course of their 15 months of exposure in welding school. The study, which consisted of a baseline assessment at the beginning of the apprenticeship and follow-up examinations 8 and 15 months later, was conducted at four teaching institutions in or near Montreal, Canada. The 286 subjects, 41 of whom were women, were, on average, 25 years old. They practiced welding using SMAW, GMAW, FCAW, and GTAW on mild steel, stainless steel, and aluminum during their 15-month welding course. Respiratory protection was either not used or was improperly used by the apprentices during their welding practice. Data concerning respiratory symptoms suggestive of asthma (e.g., cough, wheezing, and tightness in the chest) experienced by the apprentices were collected at the beginning and end of the study, as were data concerned with symptoms of metal fume fever.

Spirometric and methacholine provocation tests were completed with 194 of the 286 students before they commenced the apprenticeship and at the end of the 15-month study period (Ref. 31). Significant changes were found in the lung function tests FEV_1 and FVC during that time. In particular, FEV_1 as a percent of the predicted value had declined by an average of 8.4%. At the end of the study, 7.6% of the subjects had persistent welding-related respiratory symptoms. Based on symptoms (a combination of cough, wheezing, and chest-tightness) and the response to the methacholine provocation test, six of the subjects (4 males, 2 females) were diagnosed with probable OA. From this work, the authors concluded that "exposure to welding fumes and gases is associated with pulmonary function changes and respiratory changes in welders … [and] it is relevant to examine whether these changes represent a predisposing factor to further … abnormalities."

Skin testing for IgE-mediated sensitization to eleven common allergens and to eight specific metals to which welders are exposed was performed with 203 of the students at the end of their 15**-**month apprenticeship (Ref. 30). These tests showed that 11.8% of the students had become sensitized to one or more of the metals. During the 15-month study, 39.2% of the apprentices had experienced at least one symptom of metal fume fever. After adjusting for age, atopy (positive response to skin tests with common environmental allergens), and smoking, there were significant relationships between having at least one symptom of metal fume fever and welding-related respiratory symptoms suggestive of occupational asthma. Bronchial responsiveness (as measured by methacholine challenge) was not significantly related to symptoms of metal fume fever. The authors presented two possible explanations for this finding: the respiratory symptoms were related to welding exposures but were not manifestations of welding-related asthma, or the symptoms represented mild, early signs of welding-related asthma, not yet detectable by bronchial reactivity tests. They concluded that having symptoms of "metal fume fever might be a predictor of welding related respiratory symptoms suggestive of welding-related asthma."

Hammond et al. (Ref. 59) compared rates of physician-diagnosed asthma among men who had worked in 1999 as car body welders, paint shop workers, or assembly workers in an automotive assembly plant**.** The welders were exposed to metal fume, dusts, welding gases, and pyrolysis products from coatings, fluxes, and oils while welding, brazing, and grinding of the car body in preparation for painting. The painters were exposed to vapors from solvents, primers, paints,

reducers, and thinners, plus dust from sanding the various coats. The assembly workers had minimal exposure to vapors or metal fumes during their work installing engines, doors, tires, dashboards, seats, and other parts.

Data concerning respiratory symptoms, exposure status based on work area and work activities, demographics, lifestyle, and general health were collected using questionnaires mailed to all present and former employees identified as having worked in one of the three job categories under study. Completed questionnaires were returned by 357 assembly workers, 234 welders, and 116 painters. Odds ratios were calculated for symptoms of allergy, asthma, and cough reported to have occurred in the previous 3 months. Industrial hygiene reports from the welding and painting areas between 1985 and 1999 were reviewed. No excursions over permissible limits were found in the welding area for zinc, tin, manganese, oil mist, and most of the heavy metals tested. One of 38 samples exceeded the OSHA Permissible Exposure Limit (PEL) for iron, 3 of 25 exceeded the PEL for lead, and 15 of 25 samples exceeded the PEL for copper fume. Exposures in the paint shop were well within the PELs for all of the solvents measured between 1985 and 1999 except in 1989, when solvents in 4 of 21 samples of paint spray mist exceeded the PEL.

All of the respiratory symptoms were reported significantly more frequently by the welders than by the painters or assembly workers. These differences were still apparent after the results were adjusted for age, weight, family history of a respiratory condition, race, smoking status, and gender. Physician-diagnosed asthma, COPD, sinusitis, and allergy were more common among welders than among assembly workers, but these differences were significant only for the diagnosis of COPD (OR = 2.88, CI = 1.08–7.69). The authors noted that 20% of the body welders and 16% of the painters reported asthma symptoms, and that health care providers had confirmed asthma in at least half of these cases, while the expected incidence of asthma among these workers was only 3%. In response to their recommendations, improvements were made in local exhaust ventilation in the body weld area before the study ended.

Hoppin et al. (Ref. 71) examined the incidence of wheezing among 20,898 farmers in Iowa and North Carolina. Data concerning history of wheezing and asthma were collected via questionnaires. Nineteen percent of the respondents reported at least one episode of wheezing or whistling in the chest in the past 12 months. Odds ratios, adjusted for age, smoking, asthma, and atopy, were calculated for activities reported by the farmers. Welding, which was engaged in by 57% of the farmers with reported wheeze, was associated with a significantly elevated odds ratio for wheezing (OR = 1.10, CI = 1.01–1.19). Other activities with significantly elevated odds ratios for wheezing were related to solvent exposure, maintenance, transportation, and planting, tilling, fertilizing, and picking of crops.

In their review of studies of the pulmonary effects of welding fumes in humans and animals, Antonini et al. (Ref. 3) concluded that there is incomplete information concerning causality and mechanisms relating welding fume inhalation and pulmonary disease, due in large part to the absence of animal model data. The association of welding with the development of asthma was noted to be uncertain. In a letter to the editor, Sjogren and Langard (Ref. 144) commented on the review by Antonini et al. They agreed with the conclusion that a definitive association between welding and OA has yet to be determined, but referred to some large studies (Ref. 81, 154) in which significant increases in asthma were observed in persons exposed to welding fumes.

9.3 Case Reports—Occupational Asthma. Hannu et al. (Ref. 61) described the progression of OA in two men who had performed SMAW on different formulations of high chromium steel in the same workplace. The first patient had been welding for one employer since 1972, and was examined in 1994 because of dyspnea; mild hyperresponsiveness to histamine was noted at that time. When he started welding SMO steel (19.5% Cr, 17.5% Ni, 6% Mo) in 1996, he experienced dry cough, severe dyspnea, and wheezing on the evening following his first exposure and during the next 2 days as he continued welding this type of steel. He was hospitalized after the third day and was placed on sick leave for 2 weeks, during which time his symptoms subsided. He was examined at the Finnish Institute of Occupational Health where results of spirometric tests were found to be normal and there was no hyperresponsiveness to histamine. Diurnal PEF/FEV_1 values were also normal. Challenge tests were performed in an 8.5 m^3 chamber; the patient welded for 30 minutes and was followed for the next 24 hours. Welding challenges with both mild steel and a common stainless steel produced negative results. In contrast to those findings, when the patient welded the SMO steel, he experienced a delayed asthmatic reaction with a 37% drop in FEV_1. Six months later, after ceasing work with SMO steel and using a bronchodilator, the patient continued to experience dyspnea after work. The values of his pulmonary function tests were normal, but the ratio of PEF/FEV_1 was suggestive of asthma, and an anti-inflammatory drug was prescribed.

The second case was 17 years old when he began working as a welder in 1984 for the same employer as the first case. He had a history of rhinitis associated with exposures to non-industrial allergens and was examined for dyspnea in 1994 and 1999. Results of spirometric tests were normal in both instances. He was examined again in 2001 after he began to expe-

rience shortness of breath following welding of Duplex steel (21%–24% Cr, 3.5%–6% Ni, 0.1%–3% Mo). His pulmonary function was found to be normal and there was no bronchial hyperresponsiveness to histamine. Skin prick tests with several common allergens were positive, but he showed no allergic response to metals. A diurnal decrease in PEF was present on work days. Welding challenge tests with mild and stainless steel produced negative results, but a similar challenge with Duplex steel resulted in a delayed reaction, with a 31% drop in FEV_1. Avoidance of Duplex steel welding was prescribed along with fluticasone/salmeterol, a long acting beta-adrenoceptor agonist therapy, but these measures were not effective in preventing his symptoms at the workplace. Concentrations of metals measured in the inhalable dust during the challenge tests showed that nickel, chromium, and aluminum were considerably higher in the fumes from welding the SMO steel, but were only slightly higher in the Duplex steel fumes, compared with those of stainless steel. Nevertheless, the authors concluded that welding of the high-chromium special steels was the likely cause of these two cases of OA.

9.4 Pneumoconiosis. Siderosis (arc welder's lung) is a common form of pneumoconiosis in welders in which inhaled ferric oxide particles accumulate in the lungs and cause tissue changes that are visible as radio-opacities in chest X-rays**.** Iron particle-laden macrophages are seen in biopsied tissues from affected areas of the lungs. Although siderosis has been considered to be a benign condition, more serious effects such as fibrosis or decrease in pulmonary function have been reported in association with pneumoconiosis after long-term exposure to welding fumes. Studies in rats (Ref. 170, 171) have shown that after multiple exposures to high doses, inhalation of fumes generated by SMAW of stainless steel can cause irreversible pulmonary fibrosis in the absence of other exposures (See Section 25, Fibrosis).

In 2002, Buerke et al. (Ref. 18) described 15 welders who had pneumoconiosis and clinical respiratory symptoms. All had extensive histories of exposures to high levels of welding fumes in poorly ventilated workplaces. Ten of the welders had signs of interstitial pulmonary fibrosis visualized by computed tomography (CT) and by scanning electron micrographs of biopsied lung tissue. Details concerning three of those patients with confirmed interstitial fibrosis were later provided by Buerke et al. (Ref. 17). Spirometric tests showed deficits in pulmonary function in these patients, and examination of biopsied lung tissue revealed patchy interstitial fibrosis. Particulate material with an elemental composition typical of welding fumes was found in activated macrophages and in lung tissue close to areas of fibrosis. Buerke et al. concluded that the evidence from their own studies of welders and from those of other investigators, combined with published results of animal studies, indicate a causal relationship between interstitial pulmonary siderofibrosis and long term exposure to high concentrations of welding fumes under poor working conditions.

Several cases of systemic iron overload, as evidenced by elevated serum ferritin concentrations,[3] were described in welders with siderosis (Ref. 27, 44, 75, 167). Chronically elevated iron levels can lead to serious conditions including liver cirrhosis, diabetes, cardiac arrhythmias, and heart failure. As with hemochromatosis, a hereditary disease in which excess iron is absorbed from food and accumulates in body tissues, the standard treatment for iron overload is phlebotomy, in which blood is periodically withdrawn by venipuncture to lower systemic iron levels.

Doherty et al. (Ref. 27) described the cases of three men who had both siderosis and elevated serum ferritin levels. The first two cases were 37 and 40 years of age and had been employed as welders for 20 years. They had chest X-ray patterns consistent with siderosis, and iron oxide-laden macrophages were observed in lung tissue specimens obtained by transbronchial biopsy. Both men had substantially elevated ferritin levels (1010 ng/mL and 2010 ng/mL for cases 1 and 2, respectively; normal range = 30 ng/mL–300 ng/mL); further examination and genetic testing indicated that neither was likely to be suffering from genetically acquired hemochromatosis. Blood was drawn biweekly from both men by venesection for about 1-1/2 years and then monthly for the next 18 months (case 1) or 2 years (case 2), which brought their serum ferritin levels into the normal range. Venesection therapy was re-initiated in case 2 because his ferritin levels rose to 1246 ng/mL after cessation of treatment. Case 3 was the 61-year-old brother of case 2. He had been employed as a welder throughout his adult life. Computed tomography scans and chest X-rays revealed mild pulmonary siderosis. While his serum ferritin was also high (1696 ng/mL), he chose not to undergo venesection therapy.

There was evidence of fibrosis in cases 1 and 2, and all three cases had symptoms of mild to moderate airflow obstruction. Case 1 developed obstructive lung function after his ferritin level returned to normal with an FEV_1 of 65% predicted and an FEV_1/FVC ratio of 61%. Case 2 had mild airflow obstruction, with an FEV_1/FVC ratio of 61%, and case 3 had mild airflow limitation with an FEV_1/FVC ratio of 66%. The authors concluded that the lung function abnormalities

[3] Ferritin is a protein which binds iron. Serum ferritin concentrations correlate with total iron stores in the body and can, thus, be used to estimate iron stores in the body.

and symptoms found in their patients were likely to have been due to "other constituents of welding fumes, rather than just the iron."

Fukuda et al. (Ref. 44) described a case of pneumoconiosis in a 26-year-old man who reported to the hospital with chest pains. He had worked as an arc welder without benefit of respiratory protection for 2 years. Diffuse ground glass opacities typical of siderosis were revealed in his lungs by chest CT, and numerous iron-laden alveolar and interstitial macrophages were observed in a lung biopsy specimen. To reduce the iron burden in his body, the welder was placed on a low iron diet and was subjected to biweekly phlebotomy during which 200 mL of blood was withdrawn until serum ferritin reached low normal levels. After that, he was maintained on the low iron diet alone. A lung biopsy specimen obtained 7 months later showed the number of iron-laden alveolar and interstitial macrophages to be markedly reduced.

Other cases of welders with siderosis and iron overload were reported by Ishida et al. (Ref. 75) and by Yokoyama (Ref. 167). Ishida et al. (Ref. 75) discussed the case of a 57-year-old man who had been employed as a welder for 40 years. Annual medical examinations conducted in the workplace revealed no signs of pneumoconiosis until he was assigned to a special project working in a tunnel for a period of one month. Chest X-rays taken on his next annual examination revealed reticular shadows and CT scans showed ground-glass opacities in his lungs. His serum ferritin was elevated (2309 ng/mL) and iron particles were detected in the alveoli of a transbronchial biopsy specimen and in sputum samples.

Yokoyama (Ref. 167) described the case of a 62-year-old welder whose chest CT scan revealed ground-glass opacities typical of siderosis and nodular shadows indicative of progressive massive fibrosis. Numerous iron particles were observed in the alveoli of a transbronchial lung biopsy specimen and in macrophages obtained by bronchoalveolar lavage. Ferritin was elevated in serum (6352 ng/mL) and bronchoalveolar lavage fluid (BALF). Considering both the clinical course and pathological findings, he was diagnosed with siderosis with progressive massive fibrosis.

Fireman et al. (Ref. 37) described the case of a 43-year-old man who suffered from dyspnea, without other symptoms such as cough, weight loss, or fatigue. He had spent 20 years as a welder and had worked with both stainless steel and nonferrous alloys. A high resolution CT scan (HRCT) revealed small, well-defined micronodules throughout the lungs. Multiple granulomas (collections of inflammatory cells) were identified in a lung biopsy. Pulmonary function tests revealed decrements in FVC, FEV_1, total lung capacity, and diffusing lung capacity for carbon monoxide. Scanning electron microscopy combined with energy dispersive X-ray spectroscopy revealed abundant particles of aluminum compounds in sputum and in transbronchial biopsy samples. Silica and iron-bearing particles were also seen. Sputum samples contained particle-laden macrophages and a high percent of T-lymphocytes. Sensitization to aluminum was demonstrated by blastic transformation of peripheral blood lymphocytes in the presence of soluble aluminum compounds. The welder's condition was diagnosed as sarcoid-like granulomatous-induced aluminum disease.

Fidan et al. (Ref. 33) described the case of a 23-year-old man who was admitted with chest pain to a hospital in Turkey. He had worked as a welder for 8 years, without respiratory protection in a non-ventilated space. Chest X-rays revealed complete collapse of a lung which was caused by a large pneumothorax, a condition in which a pocket of air forms between the outer lining of the lung and the chest wall. He was hospitalized and treated successfully by tube thoracostomy. High-resolution computed tomography revealed multiple nodules and ground-glass opacities. These observations, combined with findings of iron particle-laden macrophages in BALF and in biopsied lung tissue, as well as elevated ferritin levels in BALF and serum, led to a diagnosis of siderosis, complicated by pneumothorax.

9.5 Respiratory Tract Infections. Analyses of occupational mortality data in Great Britain have shown that welders have a greater than normal risk of dying from infectious pneumonia, principally from lobar pneumonia, but not from bronchopneumonia (Ref. 20). The elevated mortality occurs only during the period of employment as a welder; welders past the normal retirement age of 65 years show no excess mortality from pneumonia. Palmer et al. (Ref. 121) conducted a hospital-based case-control study to determine if the elevated risk is restricted to pneumonias caused by specific microorganisms, if it is related to exposure to specific metals, and if the elevated risk is for developing a pulmonary infection as well as for dying from it. The 525 cases were men, 20 to 64 years of age, who were admitted with community-acquired pneumonia to any of eleven hospitals in the West Midlands, England, during the years 1996 to 1999. The 1122 controls were admitted to the same hospitals, during the same period, with non-respiratory illnesses. Data concerning occupational history and exposure to metal fumes or other respiratory hazards were obtained by interview.

Altogether, 200 cases (38%) and 380 controls (34%) had experienced exposure to metal fume at some time during their career. The risk of pneumonia was significantly associated with occupational exposure to metal fume during the year

prior to the onset of illness (OR = 1.6, CI = 1.1–2.4). In agreement with earlier findings that the association between the disease and fume exposure was reversible following cessation of exposure, pneumonia was not associated with exposures to metal fume that had occurred more than a year prior to the onset of illness (OR = 1.1, CI = 0.8–1.4). Welders (n = 26)[4] and foundry molders, coremakers, or die casters (n = 14) were the most common occupations among the cases who were exposed to fumes within a year prior to onset of pneumonia. Fumes from iron and steel were found to be associated with increased susceptibility to infectious pneumonia, but involvement of other metal fumes could not be ascertained. In cases associated with exposure to ferrous metal fumes, the risk was significantly elevated for lobar (OR = 2.3, CI = 1.2–4.3) and segmental pneumonia (OR = 2.4, CI = 1.2–4.7), but not for bronchopneumonia (OR = 1.6, CI = 0.8–3.0). This study showed that the elevated risk is not limited to fatalities. While *pneumococcus* was the most prevalent infectious agent, other microorganisms such as *mycoplasma* also appeared to be associated with the elevated risk. The investigators postulated that the elevated risk of pneumonia could be related to oxidative damage to lymphocytes or macrophages or, alternatively, that inhaled iron particles could act as a nutrient source promoting the growth of certain microorganisms. They stressed the need for new research to focus on the mechanism by which pneumonia is promoted by metal fumes.

Recent reports of pulmonary *mycoplasma* infections in welders have appeared in the Japanese literature. Matsushima (Ref. 105) described cases of pulmonary *Mycobacterium kansasii* infection in three welders who worked on the same line in the same factory building in Okayama, Japan. The authors considered the possibility of human-to-human transmission of *M. kansasii*, in part because of this occupational cluster and another cluster of nine workers from an ironworks factory in the same city. Fujita et al. (Ref. 42) described eleven cases of men with respiratory infection associated with pneumoconiosis. The infective agent was the *Mycobacterium avium intracellulare*. Six of the patients had silicosis and five had siderosis. The five patients with siderosis had occupational histories of welding or exposures to metal fumes or dusts.

10. Cancer

10.1 Lung Cancer. In 1990, the International Agency for Research on Cancer (IARC) concluded that welding fumes are "possibly carcinogenic to humans." This conclusion was based on limited evidence in humans and inadequate evidence in animals (Ref. 74). Since that time, many studies have been conducted, some of them continuations of those reviewed by IARC, and several of them have found an excess of lung cancer among welders. Only a few of the findings of excess risk reached statistical significance and, in many of those cases, the results were confounded by smoking or exposure to asbestos. Although components of stainless steel, notably nickel and Cr(VI) have been identified as carcinogens, epidemiological studies have not consistently shown a greater risk of lung cancer among welders of stainless steel than among mild steel welders. Many studies that did find excess lung cancer among welders failed to establish a significant dose-response relationship between years of welding and development of lung cancer.

Richiardi et al. (Ref. 129) conducted a case-control study of lung cancer related to occupational exposures in two areas of northern Italy: the city of Turin and the eastern part of the Veneto region, each with about 900,000 residents. Cases were identified by weekly monitoring of all hospitals in the study areas over a 2-year period. The 1553 controls were randomly-selected from residents of the two geographic areas and were matched with the 1132 cases by sex and age. Occupational histories, smoking histories, and demographic data were compiled from questionnaires that were completed in face-to-face interviews. Job titles were coded according to the International Standard Classification of Occupations (ISCO); industries worked in were coded according to the International Standard Industrial Classification (ISIC). Using the ISCO-ISIC codes, the investigators placed each participant into one of three employment categories: those working in industries with known (List A) or suspected (List B) exposures to lung carcinogens, and those not employed in any of those industries. Odds ratios, adjusted for age, smoking, and number of jobs held, were calculated for the industries worked in and for job categories. In the List B industry of motor vehicle manufacturing and repair, welders and flame cutters had an increased risk for lung cancer, but this was not statistically significant (OR = 2.4, CI = 0.9–6.3). Welders in most industries were not included in either List A or List B. A separate analysis of males not included in either list showed significantly increased risks for lung cancer among workers identified by the ISCO codes as welders and flame cutters (17 cases, OR = 5.6, CI = 2.1–15) and those identified as gas and electric welders (13 cases, OR = 9.1,

[4] n = Number of subjects.

CI = 2.3–36). Among related workers, the risk for lung cancer was increased for plumbers and pipefitters (OR = 2.6, CI = 1.0–6.4).

Finkelstein and Verma (Ref. 35) examined causes for mortality in a cohort of 25,285 members of a union of the plumbing and pipe fitting industry in Canada, who had entered the trade after 1949. Standardized mortality ratios[5] (SMR) were calculated for deaths of pipefitters, refrigeration workers, plumbers, and sprinkler fitters, from all causes, from all cancers, and from specific types of cancer by years from start of membership in the union. Mortality from lung cancer was significantly greater than expected in the entire cohort (SMR = 1.26, CI = 1.14–1.38). Among those who had 30 or more years of union membership, pipefitters (SMR = 1.30) and plumbers (SMR = 1.19) had significantly increased rates of death from all cancers and pipefitters had a significantly increased mortality rate from lung cancer (SMR = 1.53). Lung cancer mortality was also significantly higher than expected among those employed for 20 or more years as pipefitters (SMR = 1.36, CI = 1.1–1.7) or sprinkler fitters (SMR = 1.43, CI = 1.2–1.8) and in the whole cohort (SMR = 1.27, CI = 1.13–1.42). Mortality was not significantly elevated for any cancers other than lung cancer in any of the trades or in the combined cohort. The seven deaths from pleural mesothelioma in the cohort were too few to permit the calculation of SMRs, but the presence of any deaths from this disease indicates that some members of the cohort were exposed to asbestos. The authors concluded that the mortality pattern among these workers was consistent with the effects of occupational exposure to asbestos, but that increased risk due to other suspected respiratory carcinogens, such as welding fumes, could not be excluded.

Yiin et al. (Ref. 166) analyzed the incidence of deaths from lung cancer and leukemia through 1996 among 13,468 civilians who had worked for at least one day between 1952 and 1992 at the Portsmouth Naval Shipyard in Kittery, Maine, and who had been monitored for radiation exposure. The primary emphasis of the study was to determine the effects of cumulative radiation exposure on the risk of death from each of the two types of cancer. Asbestos and welding fume exposure were analyzed as covariates, along with demographics, solvent exposure, and socioeconomic status (as a surrogate for smoking habits). Of the employees surveyed, 3861 had died by the end of 1996. Among the deceased, 411 (10.6%) died from lung cancer. The severity of exposures of decedents and surviving subjects to welding fume and asbestos was based on job histories. The relative risk (RR) for lung cancer was significantly greater among workers with any asbestos exposure than among those with no asbestos exposure (RR = 1.32, CI = 1.03–1.68). This relative risk was not related to the estimated severity of the asbestos exposure. Exposure to welding fume followed a similar pattern. Compared with workers with no exposure to welding fume, those with any welding fume exposure had a significantly greater risk for lung cancer (RR = 1.60, CI = 1.24–2.06). The relative risk did not increase with increased exposure to welding fume (RR = 1.65, CI = 1.26–2.15). Socioeconomic status was also significantly related to deaths from lung cancer. The authors concluded that exposure to welding fume or asbestos were significantly associated with lung cancer risk. In contrast to previous findings in this cohort, lung cancer was not found to be associated with radiation exposure once exposure to asbestos and welding fumes and socioeconomic status were included in the analysis. This finding was confirmed in later work by these investigators (Ref. 139).

10.2 Mesothelioma. Nesti et al. (Ref. 117) analyzed data from the Italian National Mesothelioma Registry which was established in 1991 to estimate the incidence of malignant mesothelioma in Italy, to assess the impact of the disease, and to identify underestimated sources of environmental asbestos contamination. Asbestos production in Italy peaked in 1970 and has been in sharp decline since then but, due to the 30- to 40-year lag time between first exposure to asbestos and diagnosis of mesothelioma, the authors predicted that mortality from malignant mesothelioma should continue to rise, peaking between 2010 and 2020. Of the 3446 cases of mesothelioma in the registry, the occupational exposures of 1440 were known. Among these cases, the industries with the greatest occupational exposures to asbestos were building and construction, metallurgy and steel, ship yards, and railway stock. Welders were among those with the highest incidence of mesothelioma in the metallurgy and steel industries.

Fujiwara et al. (Ref. 43) described the case of a welder who had been exposed throughout his 28-year career to asbestos dust generated when he sharpened slate pencils that were used to draw lines for arc cutting of steel plates. At the age of 53, he was admitted to the hospital with shortness of breath and edema where, on the basis of cytological tests and imaging data, he was diagnosed with pericardial mesothelioma, a rare cancerous disease of the tissue layers surrounding the heart (less than 5% of mesotheliomas originate in the pericardium). The patient was placed on palliative care and died four months later. Autopsy revealed a tumor located on the pericardium, but there were no tumors in the peritoneum or

[5] The standardized mortality ratio (SMR) is the ratio of the number of deaths from a disease divided by the expected number, adjusted for age and sex.

other parts of the body, suggesting that this was a case of primary pericardial mesothelioma associated with many years of occupational exposure to asbestos.

10.3 Cancer of the Eye. Ocular melanoma, the most common malignancy of the eye in adults, is an uncommon disease with a poor prognosis. Vajdic et al. (Ref. 158) conducted a population-based epidemiologic study of the risk of ocular melanoma associated with exposure to artificial sources of UV radiation. The study was conducted in Australia and the study population comprised 290 cases diagnosed between 1996 and 1998. Cases were identified by survey of ophthalmologists and through cancer registries. The 893 controls were randomly selected from electoral rolls and were matched to cases by age, sex, and area of residence. Information about solar and welding exposures and use of sunlamps or tanning booths was obtained by questionnaire and telephone interview. Ever having used sunlamps (10.6% of the cases) was weakly associated with ocular melanoma (OR = 1.9, CI = 1.0–2.8) but there was a significant relationship between increasing duration of the use of sunlamps and this disease. Ocular melanoma was not found to be associated with ever having welded (OR = 1.2, CI =0.8–1.7). There were stronger, but still non-significant, associations between ocular melanoma and with having more than 22 years welding experience (OR = 1.7, CI = 1.0–2.7) or with having used both arc welding and oxy-acetylene welding techniques (OR = 1.6, CI = 1.0–2.4). The risk for ocular melanoma increased with the duration of the welding experience, but the trend was not significant overall. Vajdic et al. noted that several epidemiologic studies of ocular melanoma conducted by other investigators had shown strong associations with welding exposures. They stated that the weaker associations found in their study may have been due to the more regular use of protective eyewear by welders in Australia than in other countries and concluded that, taken altogether, their results were supportive of the positive associations between welding and ocular melanoma observed by other investigators.

Lutz et al. (Ref. 96) examined potential occupational risks for ocular melanoma in a population-based case-control study conducted over a 2-year period in which the 292 incident cases were recruited from the populations of nine European countries. The 2062 population controls were matched to cases by age, sex, and region. Data concerning life style, medical history, and occupational history and exposures were obtained by interview. A significant excess risk for ocular melanoma was found in welders and sheet metal workers (n = 15; RR = 2.18, CI = 1.18–4.04).

In their review of the literature on the association between ocular melanoma and welding, Dixon and Dixon (Ref. 26) identified three studies that indicated that welders have a greater than average risk for developing this disease (Ref. 53, 70, 158). They noted that ocular melanoma is probably due to exposure to UV radiation and they stressed the need for advising welders to protect themselves from exposure to UV radiation.

Shah et al. (Ref. 140) conducted a meta-analysis of risk factors for ocular cancer. Chronic occupational exposure to sunlight was a borderline non-significant risk factor for ocular melanoma (4 studies, 572 cases; OR = 1.37, CI = 0.96–1.96). The available data were too limited to perform a meta-analysis on the association between incidents of photokeratitis and ocular melanoma. A meta-analysis of five studies with a total of 1137 cases, including those cited by Dixon and Dixon, showed ever having welded to be a significant risk factor (OR = 2.05, CI = 1.20–3.51) for ocular melanoma.

10.4 Brain Cancer. Pan et al. (Ref. 122) performed a case-control study of malignant brain cancer cases in eight Canadian provinces. A total of 1009 incident cases responded to a mailed questionnaire concerning demographics, education, diet, smoking, alcohol use, occupational history, and exposure to any one of 18 substances (including welding fumes) for more than one year at work. The 5039 controls responded to the same questionnaire and were matched with cases by age, sex, and province of residence. When the data were adjusted for age and province, exposure to asbestos, asphalt, mineral oil, benzene, isopropyl oil, welding, and wood dust were associated with an increased risk for brain cancer. When the potential confounders were accounted for, most of these associations, including that with welding, became non-significant (adjusted OR for welding = 1.26, CI = 0.98–1.45).

10.5 Bladder Cancer. Gaertner et al. (Ref. 45) investigated occupational risk factors for bladder cancer in seven Canadian provinces. Incident cases of histologically-confirmed bladder cancer in adults age 20 to 74 were identified using the provincial cancer registries. Cases were matched with randomly selected population controls. Using mailed questionnaires, data concerning occupational history, age, gender, and life style were collected from the 887 cases and 2487 controls. Among males, statistically significant increased risk**s** for bladder cancer were found for hairdressers (OR = 3.42, CI = 1.09–10.8), miners (OR = 1.94, CI = 1.18–3.17), primary metalworkers (OR = 2.40, CI = 1.29–4.50), mechanics (OR = 1.66, CI = 1.16–2.38), and auto mechanics (OR = 1.69, CI = 1.02–2.82). Among females, small significant excess risks for bladder cancer were found among nurses (OR = 1.54; CI = 1.03–2.31), general laborers (OR = 2.18, CI = 1.05–4.52), and clerks (OR = 1.48, CI = 1.01–2.17). Welders did not have a significantly elevated risk for bladder cancer (OR = 1.34, CI = 0.76–2.38).

Gordon et al. (Ref. 51) performed a case-control study in southern Israel of 150 men with histologically-confirmed cases of bladder cancer and 150 matched controls. Occupational exposures significantly associated with bladder cancer were organic solvents, aromatic amines and/or paints, and polycyclic aromatic hydrocarbons. Occupations significantly associated with bladder cancer were metal working and welding.

10.6 Prostate Cancer. Zeegers et al. (Ref. 174) conducted a prospective study of prostate cancer among 58,279 men in the Netherlands. In 1986, members of the cohort completed a self-administered questionnaire on potential cancer risk factors, including job history. The cancer incidence among the cohort was followed for the next 7 years by linkage with cancer registries and the Dutch national database of pathology reports. To minimize false positive results, confidence intervals of 99%, rather than the standard 95% were used to test for statistical significance. The only profession with a significant excess risk for prostate cancer was that of policeman. Men who had ever welded did not have a significantly increased risk for developing prostate cancer (age-adjusted RR = 1.41, 99% CI = 0.51–3.88).

10.7 Endocrine Gland Tumors. To analyze the risk of tumors of the endocrine glands in arc and resistance welders, Hakansson et al. (Ref. 57) performed a case-control study using a large cohort of Swedish welders that had previously been used in studies of the incidence of cancer (Ref. 55) and neurodegenerative diseases (Ref. 56) in resistance welders and other workers exposed to high levels of magnetic fields. Of the 174 incident cases of endocrine gland tumors identified in that cohort, sufficient data were available to include 140 cases in the study. The tumors were located in the adrenal gland (n = 29), parathyroid gland (n = 67), pituitary gland (n = 36), and in other glands (n = 8). Cases and controls were questioned concerning years of employment between 1985 and 1994 and exposure to welding, type of welding, and hours of exposure per week. They were similarly questioned about solvent exposure. Odds ratios for all tumors were calculated for all types of welding, resistance welding, and arc welding, using the fraction that never welded as the baseline.

There was a significantly increased risk for all endocrine tumors among the population that had ever welded (OR = 2.1, CI = 1.3–3.5) and those that had ever done arc welding (OR = 2.9, CI = 1.6–5.3). Resistance welding was not associated with an elevated risk for endocrine gland tumors. Ever having arc welded was associated with an elevated risk of tumors in two of the three glands studied: adrenal (OR = 3.4, CI = 1.0–12.2) and parathyroid (OR = 4.3, CI = 1.7–10.6). There was an apparent exposure-response effect of hours per week of arc welding with all tumors combined and with parathyroid gland tumors. A comparable exposure-response pattern was not observed for resistance welding. An association between solvent exposure and adrenal gland tumors was found (OR = 3.2, CI = 1.0–10.3), but there was no apparent interaction between welding exposure and exposure to solvents. The authors noted that, while confounding from welding fume exposures and ultraviolet radiation could not be dismissed, the most likely factor in the association of welding with endocrine gland tumors was the extremely low frequency electromagnetic field (ELF-EMF) generated during welding. Although the currents, and consequently the magnetic fields from resistance welding are generally much greater than those from arc welding, the authors stated that, because the arc welder often carries the cable over the shoulder, exposure to the head and neck area may actually be higher for arc welding than for resistance welding.

11. Metal Fume Fever

Metal fume fever, a common flu-like illness among welders, is caused by inhalation of metal oxide particles. Its symptoms, which include chills, fever, muscle or joint pain, difficulty breathing, headache, sore throat, and chest tightness, develop within several hours after exposure. Since a short-term tolerance can develop with repeated exposure to metal fumes, episodes of metal fume fever frequently occur on Mondays after a weekend break from exposure. Inhalation of zinc oxide fumes is among the most common cause of metal fume fever but it may also result from inhalation of other metal fumes, such as those of copper, magnesium, aluminum, antimony, iron, nickel, cadmium, and tin.

While the symptoms of metal fume fever usually resolve within 24 hours, occasional cases are reported in which the symptoms are more severe and persistent. Taniguchi et al. (Ref. 152) described the case of a 57-year-old welder who developed high fever and difficulty breathing after exposure to zinc oxide fumes while welding without a protective mask. He reported to the hospital where bilateral diffuse ground-glass opacities were seen by chest X-ray and CT, and diffuse alveolar damage was seen in specimens obtained by transbronchial lung biopsy. Arterial blood gas analysis showed that the partial pressure of oxygen (PaO_2) was below normal. He was diagnosed as having chemical pneumonia with diffuse alveolar damage resulting from inhalation of zinc oxide fumes. His symptoms improved following several days treatment with prednisolone.

Hassaballa et al. (Ref. 64, 65) described the case of a 25-year-old male welder who developed metal fume fever with unusual complications. His job involved demolition of a car manufacturing plant and he had been working without wearing a respirator in a poorly ventilated area where galvanized steel was being cut. One evening, he and some of his co-workers developed headaches and stiff necks which grew worse the next morning. He returned to work where he was cutting galvanized stainless steel conduit containing copper wire. While on the job, he developed a cough and difficulty breathing. He sought medical help and was treated unsuccessfully with intravenous antibiotics and corticosteroids for aseptic meningitis. He continued to have abnormally rapid breathing and developed a rapid heart beat; further examination revealed pericarditis, pleuritis, and pneumonitis. When details of his occupational exposure were obtained, treatment with antibiotics and steroids was stopped and was successfully replaced with oral indomethacin. The physicians concluded that he had suffered from metal fume fever with a severe systemic inflammatory response that caused inflammation of the tissues that line the lungs, heart, and other organs. They noted that this was an unusually severe response to fume inhalation and they stressed the importance of obtaining an occupational history.

12. Effects on the Eye and Vision

12.1. Eye Injuries. Lombardi et al. (Ref. 93) examined the incidence of eye injury among welders using the Workers' Compensation claims filed during the year 2000 with a U.S.-based insurance provider. Eye injury accounted for 5% of the compensation claims made by all workers but they represented 25% of the claims filed by welders. Of the 2175 workers who had submitted welding-related eye injury claims, 1353 (62%) were welders. The job titles of the 822 non-welders with welding-related eye injuries included mechanic, laborer, maintenance worker, assembler, pipefitter, boilermaker, ironworker, millwright, and rigger. Foreign body injuries and UV-associated eye burns represented 71.7% and 19.7%, respectively, of the eye injuries sustained by the welders. Injuries resulting from processes initiated by another worker (or co-worker) accounted for 4.7% of the injuries sustained by welders and 13.9% of those sustained by non-welders.

12.2 Cornea. Aziz and Rahman (Ref. 6) examined the cause of corneal foreign bodies among people who sought medical attention at an emergency eye clinic in Bangladesh in the year 2002. Of the 1655 persons who reported to the clinic during that time, 398 had corneal foreign bodies. Sufficient background data had been recorded to include 200 of these patients in the analysis; 84 of the injuries resulted from industrial accidents of which 20 occurred while welding and 31 occurred while grinding. The investigators noted that most of the patients had not used protective eye wear at the time of their injury**.**

Photokerattitis (also known as photokeratoconjunctivitis, arc eye, welders flash, or snow-blindness) is caused by exposure to UV radiation. This temporary condition affects the outer surface of the cornea. Symptoms include lachrymation, severe pain, redness, swollen eyelids, a gritty feeling in the eyes, seeing halos around lights, photophobia, and temporary loss of vision. These symptoms may not appear until 6 to 12 hours after UV exposure, and vision usually returns to normal within 24 to 48 hours following exposure. Photokeratitis can be caused by natural conditions, such as reflection of UV radiation at high altitudes from highly reflective snow fields, or by exposure to artificial sources of UV-B (wavelengths of 280 nm–315 nm) such as sun tanning beds, welding arcs, carbon arcs, photographic flood lamps, and electric sparks.

Yen et al. (Ref. 165) assessed the causes of photokeratitis among the 106 patients reporting with this condition to the emergency room at a hospital in Taiwan over the period of 1 year. The average age of these patients was 33.1 years, 102 (96.2%) were male, and 101 (95.2%) of the exposures occurred on the job. The four female cases received non-vocational exposures while looking at the welding arc during car or house repairs. Only 4 of the 87 patients who had received their exposures from welding arcs were professional welders. The remainder used welding equipment occasionally in their professions which included electricians (66 cases), signboard makers (9 cases), and mechanics (8 cases). The remaining 14 cases of photokeratitis were attributed to exposures from UV lamps, to sparks from short circuits, or to sparks generated from polishing. Only one of the cases had ever used protective eyewear, and he was not using such equipment at the time of his accident. The authors noted that many of these injuries could have been prevented by the use of protective gear. They stressed the importance of educating workers who are not professional welders about the hazards associated with welding equipment.

Spheroidal degeneration of the cornea is a relatively common condition in which round, drop-like protein deposits form at the corneal limbus (the border between the cornea and the sclera). The incidence and severity increase with age and

can lead to loss of visual acuity. Spheroidal degeneration of the cornea has been associated with exposure to UV radiation from either natural or artificial sources. Magovern et al. (Ref. 99) attributed this condition in a 79-year-old man to his welding experience while serving in the Navy at Guadalcanal during World War II when, as part of a team of welders, he put in very long days, 7 days a week, repairing PT boats and landing craft. While he had been issued UV protective eye shields, he frequently removed them due to the oppressive heat or to inspect his work. He experienced photokeratitis 3 to 4 times a week, necessitating 200 sick calls during his 11-month assignment on this job. Magovern concluded that a degenerative effect was initiated during this relatively short period of intense UV exposure, which eventually culminated in the spheroidal degeneration observed later in life. The condition was treated surgically in his left eye which led to an improvement in his visual acuity within 4 months.

The corneal endothelium, a monolayer of multisided cells that lines the innermost surface of the cornea, is essential for maintenance of its integrity. Corneal endothelial cells do not divide, so if some of these cells are damaged or destroyed, other corneal endothelial cells enlarge and change shape as they fill in the space once occupied by the damaged cells. Thus, damage to the corneal endothelium can be assessed by measuring the number and average volume of cells in a section of the endothelial cell layer. Based on findings that exposure to high levels of UV radiation damages the corneal epithelium in research animals, Oblak and Doughty performed studies in welders to determine whether humans are also at risk for this effect. In 2002, these investigators reported that the curvature and thickness of the cornea and the size and shape of the corneal endothelial cells did not differ substantially between 20 welders and 20 controls (Ref. 120). They later expanded this study to include a larger number of subjects (Ref. 28). Photomicrographs of the corneal endothelium were obtained from 51 welders and 51 controls. The welders had been employed for an average of 24 years in jobs that required routine welding. Controls were office workers who had had no known exposures to welding arcs and whose work experience had been entirely indoors. The average age of the welders and controls was 44 and 46.5 years, respectively. Most of the welders reported having experienced photokeratitis on multiple occasions, up to three times a year, indicating that they had received unprotected exposures to UV radiation from the welding arc. Ophthalmologic examination revealed no significant differences in the visual acuity between welders and controls. However, the incidence of pingueculae (small yellowish deposits on the conjunctiva near the cornea thought to be associated with UV exposure) in welders (n = 24) was twice that in controls (n = 12). Examination of the corneal endothelia revealed no differences in the average cell area or cell density between the welders and controls. Finally, among the welders, there was no relationship between the cell density and the reported number of incidents of photokeratitis. The investigators concluded that despite their multiple exposures to UV radiation, as evidenced by periodic episodes of photokeratitis, the UV exposures received by these welders were lower than those that would damage the corneal endothelium.

12.3 Retina. Welding-related lesions of the retina are less common than lesions of the outer surface of the eye but short exposures to intense blue visible light or infrared radiation from the welding arc can injure the retina. Since this condition affects the macula (a small oval area on the inner surface of the retina near the optic nerve), it is often referred to as welding arc maculopathy. The macula may appear normal immediately after exposure, but a well-defined lesion develops over the next few weeks. Visual acuity is usually reduced within a few days after exposure. It frequently returns to normal within a year, although a lesion may remain on the macula. In some cases, however, the quality of vision is permanently affected by a blind spot or distortions.

Maier et al. (Ref. 100) conducted a case control study with workers from a large metal manufacturing facility in Austria to assess whether welding arc maculopathy should be considered to be an occupational disease and whether current safety regulations are sufficient to prevent this disorder. The study included 89 men who had worked as welders for at least 5 years and had a mean duration of welding work of 21.9 years. The 81 age-matched controls had never been exposed to arc welding radiation. The mean age of welders and controls was 40.7 and 39.4 years, respectively. Cases and controls were subjected to clinical examinations, interviews to gain information about medical histories and occupational exposures, tests of visual acuity, and a complete ophthalmologic examination including examination of the retina by multifocal electroretinography.

While, on average, the visual acuity of the welders appeared to be better than that of the controls (90% of the controls and 60% of the welders wore spectacles), no significant differences were found in function or morphology of the retina between the two groups and no signs of phototoxic damage to the retina were identified. The investigators concluded that the protective eyewear routinely used by the welders who participated in this study was sufficient to prevent phototoxic damage to the retina and that arc welding maculopathy should be considered a “working accident and not an occupational disease.”

13. Effects on the Ear

Burns of the outer ear and ear canal and perforation of the tympanic membrane (eardrum) are among the most frequently encountered ear injuries in welders. A case of a welder with tympanic membrane injury with long-lasting effects was described by Simmons and Eibling (Ref. 143). The patient had worked as a welder for 45 years. At the age of 46, a spark entered his ear while he was welding on an overhead gas line. He experienced a sharp, burning pain at the time of the incident and then developed intermittent episodes of purulent discharge from the injured external ear. Medical examination 30 years later revealed two pieces of retained metal slag in the injured ear and a perforation of the tympanic membrane. The authors noted that the welder had been wearing a helmet with flaps that covered his ears at the time of the accident. They stressed that such protection is insufficient to prevent sparks from contacting the ears from behind the flaps when welding is performed on overhead objects**.** They recommended that welders who may be required to work in positions where sparks could enter behind the ears should use ear plugs in addition to ear flaps.

14. Effects on Connective Tissue—Scleroderma

Systemic sclerosis (SSc or scleroderma) is a disorder in which fibrous connective tissue is deposited in the skin, lungs, other internal organs, and small arteries. The condition is more common in women than in men. Its etiology is not understood, but exposures to silica, to certain organic solvents, and to equipment that causes hand-arm vibrations are suspected risk factors. In 1988, LeRoy et al. (Ref. 90) classified SSc as limited or diffuse to distinguish between localized and generalized disease, respectively. The prognosis is better in the more prevalent form, in which cutaneous deposits of fibrous tissue are limited to certain areas of the body. In the more rapidly advancing diffuse SSc, skin involvement is more extensive and will eventually encompass large areas of the body, and there may be abnormalities in cardiac, pulmonary, gastrointestinal, or renal function. Other distinguishing features are the presence of antibodies to topoisomerase I in 30% of patients with diffuse SSc and of anticentromere antibodies in 70%–80% of patients with the limited form.

In 2002, Diot et al. (Ref. 25) published the results of a case-control study which showed that the risk for SSc was increased among persons with exposures to crystalline silica, various solvents, epoxy resins, or combined exposures to silica and welding fumes. That study included 80 patients (69 women, 11 men) admitted from 1998–2000 to the University Hospital of Tours, France. This investigation was later expanded into a prospective study (Ref. 97) of the association between occupational risk factors and the severity markers of SSc described by LeRoy et al. All SSc patients (88 women and 17 men) admitted from 1998 to 2002 to the University Hospital of Tours were included in the study. Only 39 of the patients had received occupational exposures to any of the agents (silica dust, welding fumes, solvents, and epoxy resins) under study**.** Cases of SSc were considered to be limited when there was no pulmonary involvement, when the dermal involvement was limited, and when patients were positive for anticentromere antibody. Cases with widespread skin involvement, pulmonary involvement, or antibodies against topoisomerase were considered to be diffuse.

Of the 39 patients (24 women and 15 men) who had received occupational exposures to any of the materials under study, 20 were exposed to solvents, 3 were exposed to both silica and welding fumes, 4 to a combination of solvents, silica, and welding fumes, and 7 to a combination of epoxy resins, solvents, silica, and welding fumes. These occupational exposures tended to be associated with diffuse SSc, the more severe form of the disorder. The strongest associations were between epoxy resins ($p = 0.06$), white spirit ($p = 0.07$), aromatic solvents ($p = 0.07$), and silica coupled to welding fumes ($p = 0.10$). The investigators concluded that occupational exposures to toxic agents influence the severity of SSc. Magnant and Diot later concluded that while silica and solvents appear to play a causal role in the development of the disease, the available data do not justify conclusions about the role of epoxy resins or welding fumes in SSc (Ref. 98).

15. Effects on the Nervous System

15.1 Nervous System Diseases. Park et al. (Ref. 123) conducted a case-control study of potential associations between mortality from neurodegenerative diseases and occupational exposures to solvents, pesticides, oxidative stressors, electromagnetic fields (EMF), and welding. Alzheimer's disease, Parkinson's disease, motor neuron disease, and pre-senile dementia were investigated. Data concerning occupation, industry worked in, and primary and contributing causes of death were obtained from death certificates in 22 states using the NIOSH database National Occupational Mortality Surveillance System. Controls were decedents taken from the same data base who had no record of diseases of the nervous

system. Decedents who had used arc welding equipment included welders and cutters, boilermakers, structural metal workers, millwrights, plumbers, pipefitters, and steamfitters.

Of the more than 2 million deaths in the data base that occurred between 1992 and 1998, 112,805 (4.3%) were associated with neurodegenerative diseases. Of these, 47,783 (1.8%) were associated with Alzheimer's and 33,678 (1.3%) were associated with Parkinson's disease. Mortality odds ratios (MOR)[6] were calculated to relate deaths from specific diseases to various occupations and occupational groups. Occupations with exposures to 60 Hz magnetic fields were significantly associated with deaths that occurred under the age of 65 from Parkinson's disease (MOR = 1.87, CI = 1.14–2.98) or from motor neuron disease (MOR = 1.63, CI = 1.10–2.39). A small but significant association was also seen between exposure to EMF and deaths at any age from Alzheimer's disease (MOR = 1.12, CI = 1.05–1.2). Of the four diseases analyzed, only Parkinson's disease was associated with welding, and this was only true for the 20 deaths from Parkinson's disease that occurred before the age of 65 (MOR = 1.77; CI = 1.08–2.75). The investigators concluded that this observation supports the association between manganese exposures from welding and a Parkinson's disease-like syndrome that had been reported by other investigators.

Hakansson et al. (Ref. 56) examined the association between occupational exposure to ELF-EMF and mortality from amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Parkinson's disease, and multiple sclerosis. The study population was a cohort of Swedish engineering industry workers matched against census records and the Causes of Death Registry. This cohort was previously used by these investigators in a study of the cancer risk associated with exposure to ELF-EMF (Ref. 55). The study population of 484,643 men and 162,051 women was divided into four groups according to their estimated exposures (low, medium, high, and very high) to ELF-EMF. Occupational data were obtained from the Swedish censuses of 1980, 1985, and 1990 and from work descriptions provided in income tax returns. The severity of exposures was estimated from a job exposure matrix developed earlier by these investigators**.** Seventy percent of the subjects in the very high exposure group (>0.530 μT per day) were resistance welders.

The relative risks (RR) of the nervous system diseases investigated were determined from the causes of death or contributing causes of death among the 16,661 men and 2,948 women who died between 1985 and 1996. No significant associations were found between ELF-EMF exposure and the risk for Parkinson's disease or multiple sclerosis. The relative risks were significantly elevated for Alzheimer's disease (n = 8; RR = 4.0, CI = 1.4–11.7) and for ALS (n = 13; RR = 2.16, CI = 1.01–4.66). Only one of the cases with Alzheimer's disease and none of the cases with ALS were female. The number of welders with Alzheimer's disease or ALS was not given and, hence, it cannot be discerned from the data provided if ELF-EMF from welding contributed to the increased risk for either of these nervous system disorders.

Weisskopf et al. (Ref. 161) conducted a prospective study of the association between occupational exposures and ALS. The study population consisted of 415,418 men and 573,499 women from the Cancer Prevention Study cohort of the American Cancer Society. The median age at entry into the cohort in 1982 was 57 years for men and 56 years for women; participants provided data concerning their occupational history at that time. Members of the cohort who were alive in 1989 were included in the study. During the period of the study (1989 to 2002), there were 507 documented deaths from ALS among men and 430 among women. Rate ratios (RaR)[7], adjusted for smoking, age, and alcohol consumption, were significantly elevated for male laboratory technicians (n = 10; RaR = 1.96, CI = 1.04–3.66) and male programmers (n = 3; RaR = 4.55, CI = 1.46–14.2). Only two welders died from ALS and welding was not associated with the risk for ALS (RaR = 0.75; CI = 0.19–3.01). Machine assembler was the only occupation among women with significantly elevated mortality from ALS (RaR = 2.81; CI = 1.05–7.53). The investigators noted that, since the number of deaths from ALS was small, the results should be interpreted with caution.

15.2 Effects of Aluminum. Giorgianni et al. (Ref. 48) examined cognitive function in a group of 50 aluminum welders who had worked near a shipyard in Messina, Italy, for an average of 15 years (range: 1 to 26 years). The average age of the welders was 38 years and they were all asymptomatic. The age-matched controls had not been exposed to aluminum fumes. The Wechsler Memory Scale, the Stroop Color-Word Test (a test of directed attention), and Raven Progressives Matrices (a test of abstract reasoning) were administered to all participants. The welders scored significantly less well on tests of memory and abstract reasoning and slightly less well on tests of attention than did controls. The investigators concluded that occupational exposure to aluminum welding fumes can affect cognitive function.

[6] Mortality odds ratio: the fraction of the occupational group that died from a particular disease divided by the fraction of the general population that died from that disease**.**

[7] The rate ratio is calculated to compare the ratio of events occurring at any given point in time. Rate Ratio = Incidence Rate exposed population/Incidence Rate controls.

In contrast to these findings, no effects on attention or memory were observed in a longitudinal study of aluminum welders conducted by Buchta et al. (Ref. 16). This work compared motor performance, logical thinking, perceptual speed, and short-term and working memory in 98 aluminum welders (mean age 37 years) and 50 unexposed controls (mean age 36 years). All of the subjects worked at the same car body manufacturing plant. The welders had a median of 6 years exposure to aluminum welding fumes at the start of the study. Neurotoxicity tests and determination of aluminum concentrations in blood and urine were performed in 1999 and repeated in 2001. Median concentrations of aluminum in urine from welders were 57.6 μg/g creatinine in 1999 and 52.4 μg/g creatinine in 2001. No significant differences were found between welders and controls in tests of motor-performance, short-term memory, or switching attention. Simple reaction time performance differed significantly between welders and controls but since these differences between the two groups did not change across the 2-year testing period, the investigators concluded that the differences may have been due to random *a priori* differences between the groups and were most likely not associated with welding exposures. This conclusion was supported by a follow-up study performed by Kiesswetter et al. in 2003 in which the same participants were subjected to the same battery of neurobehavioral tests (Ref. 83). No differences in the performance on neurobehavioral tests were seen between welders and controls over the 4-year period. The investigators concluded that the "repeated measurement models of both studies showed no adverse neurobehavioral effects of Al welding."

15.3 Manganese: Subclinical Effects. Subclinical neurophysiological effects are not accompanied by clinical manifestations and are either based on self-reporting by the affected individual or are detected by neuropsychological testing. They may be reversible in the earlier stages.

Halatek et al. (Ref. 58) conducted a study of welders to assess whether neurophysiological tests could be used to detect early effects of exposure to low concentrations of manganese and, if so, whether such effects were related to manganese concentrations in air or to cumulative manganese exposures. The study included 59 welders from a Polish shipyard who were matched by age and smoking habits with 23 mechanics and electricians who were not exposed to welding fumes. Manganese concentrations in blood, urine, and breathing zone air samples were measured for welders and controls. All participants were subjected to the pulmonary function test vital capacity (VC). Subjective neurological symptoms, visual evoked potentials (VEP), and electroencephalographs (EEG) were examined in welders and were correlated with cumulative exposure indices (the product of the concentration of manganese determined in breathing zone samples and the exposure duration in years). Neurological tests were not administered to controls.

Breathing zone concentrations of manganese ranged from 0.003 mg/m^3 to 3.37 mg/m^3 among the welders and from 0.001 mg/m^3 to 0.17 mg/m^3 among controls. As expected, urinary manganese concentrations did not differ between the two groups (manganese is excreted mainly in the feces) but manganese levels in blood were higher among the welders (11.42 μg/L in welders vs. 6.07 μg/L in controls), although the difference was not statistically significant. Subjective neurological symptoms were reported by 29 of the 59 welders. The subjective complaints most frequently reported by the welders were increased emotional irritability (49.3%), headache (29.3%), and sleepiness (14.7%). Abnormalities were found in EEGs of 31.5% of the welders and in VEPs from 22% of the welders. Fifteen of the welders had normal results in all of the tests.

Multi-regression analysis showed that abnormal results in the neurophysiological tests VEP and EEG were strongly correlated with both current exposure to airborne manganese in excess of 0.3 mg/m^3 (the Polish TLV) and a cumulative exposure index based on years of exposure and airborne manganese concentration. A consistent decrease in the lung function parameter VC among welders compared with controls was statistically significant among the welders who had subjective neurological symptoms or both subjective neurological symptoms and EEG abnormalities. The change observed in pulmonary function was attributed by the authors to components of the welding fume other than manganese. They concluded that abnormal results in the tests of VEP and EEG may be used to detect early effects of exposure to low levels of manganese.

He and Niu (Ref. 66) assessed subclinical neurophysiological changes in 68 welders who had histories of chronic exposure to low levels of manganese; 42 controls participated in the study. The welders had worked for an average of 16 years in a factory in China that built machinery. Air samples collected at breathing height on the factory floor showed mean exposures of 138 μg/m^3 manganese, 12.6 μg/m^3 cadmium, 581 μg/m^3 iron, and 3.8 μg/m^3 nickel. Participants were subjected to a battery of tests including EEG, brain electric activity mapping (BEAM), and tests of the autonomic nervous system in which heart rate was tested following various maneuvers. Heart rates following activities such as deep breathing and standing up quickly from a relaxed prone position were significantly lower in welders than in controls, an effect attributed by the authors to altered autonomic nervous system activity and altered cardiovascular regulation in the welders. Changes were also seen in EEGs of the welders and in the BEAM analyses, which the investigators attributed to

effects of manganese on the central nervous system. In further studies, a battery of neurobehavioral tests was administered to 56 of the welders in this factory (Ref. 118). The welders had lower test scores on more of the neurobehavioral tests than did controls. Scores on the Profile of Mood States indicated a depressed emotional status. The investigators concluded that these changes were due to chronic exposures to low levels of manganese.

Bowler et al. compared neuropsychological function, emotional status, and visual function of 76 welders with that of 42 controls (Ref. 11). The welders had been involved primarily in steel welding for an average of 25 years. They had often worked in poorly ventilated environments and fewer than 30% had access to respirators on their last job. Controls were from the same geographical area in Texas as the welders and had no occupational welding exposures. Welders had lower scores than controls in tests of motor function (motor speed, hand grip strength, and tactile manipulative ability), verbal learning, working memory, cognitive flexibility, and visuomotor processing speed while they scored as well as controls in tests of verbal skills, verbal retention, and auditory span. Tests of emotional status indicated that the welders had elevated levels of mood disturbance. Welders also had reduced color vision compared with controls. The investigators noted that the welders worked in the chemical industry and may have been exposed to organic solvents with neurotoxic effects which could have confounded the results of this study.

Another confounding factor was that the welders selected for the study were involved in litigation and/or workers' compensation claims related to impairments incurred during their employment as welders. In their critique of this study, Lees-Haley et al. (Ref. 88) stated that, among the problems in its design, this work was "fatally flawed by participant selection bias." Another problem pointed out by Lees-Haley et al. was that the welder population had a lower educational background than did controls which could have caused them to fare less well on some of the tests of cognitive skills.

A later study by Bowler et al. (Ref. 12) included 47 welders who had been employed for up to 2 years in the construction of piers for a new span of the San Francisco Bay Bridge. Much of the welders' work was done in confined spaces with poor ventilation and inadequate personal protective equipment which led to high fume exposures. Manganese levels were often above the TLV of 0.2 mg/m^3. The investigators administered a series of neuropsychological and neurological tests to the study participants. Data obtained earlier from 46 controls who had participated in a previous study by these investigators (Ref. 13) were used for comparison. The welders performed poorly on tests that measured verbal and visuomotor speed of information processing, concentration, and motor skills compared with controls. The investigators concluded that the neurological health of the welders had been highly impacted by exposure to manganese.

This study was confounded by several factors. The subjects, who were all complainants in a law suit, sought out Bowler et al. for help with their cases and the funding for the study was provided by the welders' attorneys. Also, there was a significant difference ($p < 0.01$) in the number of years of education of the welders (11.3 years) and that of the controls (13.1 years). Santamaria et al. (Ref. 137) noted that the results of the examinations of the welders were compared with the results from 46 controls from a previous study (Ref. 13) who had been chosen at random from a telephone directory "in one of the Southern states where many of the welders resided." Santamaria et al. stated that "comparing the results of the welders to data collected on control subjects that were not matched to the welders (e.g., by age or socioeconomic status) from a different study conducted several years earlier is highly problematic and can introduce a significant source of bias into the results." Rohling and Demakis (Ref. 132) performed a meta-analysis to compare the results of the two studies by Bowler and colleagues described above (Ref. 11, 12). They concluded that "Taken together, these [two] articles do not support the claim that chronic manganese exposure in welders results in a specific and identified pattern of neuropsychological impairment."

15.4 Manganese: Clinical Effects. Chronic exposures to excessive levels of manganese can result in neurological damage, causing an array of symptoms, referred to as manganism or parkinsonism, that resemble those of idiopathic Parkinson's disease. Manganism and idiopathic Parkinson's disease are difficult to differentiate, especially in the later stages. 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. The face may become expressionless or "masked" due to loss of control of the facial muscles.

Manganism and Parkinson's disease are both caused by degeneration of cells in the basal ganglia, a control center of the brain involved in the production of smooth, coordinated movements. Manganese accumulates selectively in the globus pallidus of the basal ganglia, where it can produce hyperintense signals in T1-weighted magnetic resonance images (MRI) of the brain. These changes in MRI scans tend to disappear following withdrawal from exposure to the manganese source as manganese is cleared from the tissue, even though permanent neurological damage may have occurred.

Because these MRI patterns are present before the toxic effects of manganese become manifest, and because manganese exposure is not amenable to biological monitoring in the blood or urine, Kim (Ref. 86) suggested that the MRI could be used as a biomarker for manganese exposure.

While levodopa (L-dopa) is effective in treatment of certain stages of Parkinson's disease, it has been less successful in treating parkinsonism. Response to treatment with L-dopa is, therefore, sometimes held to be a distinction between the two neurological disorders. To explore this issue, Koller et al. (Ref. 87) conducted a double-blind study of the efficacy and safety of L-dopa treatment for manganese-induced parkinsonism in welders. The 13 subjects were men, average age 61.5 years, who had been diagnosed with manganese-induced parkinsonism. The diagnosis was based on signs of parkinsonism in the patients and their long-term exposure to manganese from welding, but idiopathic Parkinson's disease could not be definitively ruled out. The subjects had experienced symptoms of parkinsonism for a mean of 7.9 years prior to the study and had an average of 25.2 years welding experience. Many of them said they had worked in confined spaces with inadequate ventilation.

The subjects were treated with either L-dopa or a placebo for a period of 4 weeks, followed by a drug-free period of 2 weeks. They were then re-randomized into new treatment and placebo groups, and the drug treatment was repeated for 4 weeks. At the beginning and end of each treatment period, patients were assessed using a modified Unified Parkinson's Disease Rating Scale for postural and kinetic tremors, a timed walking test, and finger tapping test. A subjective impression of the effectiveness of the drug treatment (no change, improvement, or worsening of symptoms) was obtained from each patient. There were no significant differences in any of these measures between patients treated with L-dopa and those treated with a placebo. While recognizing that the number of participants in the study was small, the investigators concluded that L-dopa is not effective in welders with parkinsonism and that L-dopa responsiveness may be useful for distinguishing between Parkinson's disease and manganese-induced parkinsonism.

In their critiques of this study, Chu (Ref. 19) and Jankovic (Ref. 78) questioned how Koller et al. distinguished parkinsonism from idiopathic Parkinson's disease in these patients. Chu noted that the diagnosis of manganese-induced parkinsonism was based solely on the presence of signs of parkinsonism (which can be difficult to differentiate from Parkinson's disease) and a history of long-term exposure to manganese in welding rods. Chu and Jankovic both found that the evidence that the subjects in this study did not have idiopathic Parkinson's disease was not convincing.

Josephs et al. (Ref. 80) reviewed the medical records of eight patients who were referred to the Mayo Clinic with neurological problems and were diagnosed with neurotoxicity associated with a history of welding. All men had had intense, chronic exposure to welding fumes, and had often welded without the benefit of adequate ventilation or proper personal respiratory protection. They had welded from 1 to 25 years before experiencing their first neurological symptoms. The characteristic manganese-associated increased T1 signal in the basal ganglia was seen in MRIs of the brains of all eight patients. Three of the patients were diagnosed with parkinsonism which was differentiated from idiopathic Parkinson's disease by the presence of headaches, head tremor, cognitive impairment, and the relatively early age of onset (32 to 46 years) of symptoms. Treatment with L-dopa produced slight improvement in one of these three patients. Although moderate improvement in hand tremor was seen in the other two after L-dopa treatment, they still had substantial signs of parkinsonism. Two other patients suffered from multifocal myoclonus (spontaneous muscle jerking), headache, and cognitive impairment. Two patients had a mixed syndrome with vestibular-auditory dysfunction, hearing loss, and lightheadedness, and the eighth patient had minor subjective cognitive impairment, anxiety, and sleep apnea. Serum manganese was mildly elevated in seven patients and was at the upper end of normal in one patient. That their neurological condition was caused by manganese was suggested by the hyperintensity in the basal ganglia on T1 weighted MRI scans. The investigators concluded that symptoms of parkinsonism, multifocal myoclonus, mild cognitive impairment, and vestibular-auditory dysfunction were associated with welding without proper protection. In his review of the association between welding and manganism or Parkinson's disease, McMillan (Ref. 107) noted that since some of the patients had been engaged in cutting steel hardened with manganese, it may have been more prudent for Josephs et al. to conclude that the observed symptoms were associated with "employment as a welder rather than specifically to welding."

Racette et al. (Ref. 128) compared the prevalence of parkinsonism in a large sample of welders from Alabama with that in a general population, age-adjusted sample of male residents from Copiah County, Mississippi. The prevalence of parkinsonism among residents of Copiah County had previously been determined in a study by Schoenberg et al. (Ref. 138). The 1423 welders from Alabama who were screened for Racette's study were referred to the investigators by attorneys for medical-legal evaluation of Parkinson's disease. Data concerning exposure to welding fumes and job titles were provided by the patients. All patients with tremors and an additional randomly selected 112 patients were subjected to rigidity screens and were assessed using the Unified Parkinson's Disease Rating Scale motor subsection 3. Based on these

tests, patients were categorized as having either definite Parkinson's disease, probable Parkinson's disease, or were unclassified. Liberal and conservative diagnoses were assigned based on the criteria used for the diagnosis of Parkinson's disease. Then, assuming that the welders rated as having Parkinson's disease were representative of all of the welders with this disorder in Alabama, the prevalence of Parkinson's disease among welders in Alabama was calculated. The investigators then compared this value with the prevalence of Parkinson's disease among the general population in Copiah County, Mississippi, and found that parkinsonism occurred more frequently among the Alabama welders than among the comparison population. With the liberal method for diagnosis, the prevalence ratio was 10.19 (CI = 4.43–23.43); with the conservative method, it was 7.60 (CI = 3.27–17.65). In addition, an analysis of age of onset of Parkinson's disease supported their earlier findings (Ref. 127) that Parkinson's disease occurred at a younger age among welders than among controls.

Sadek et al. described the case of a 33-year-old man with rigidity, tremors, slowing of movements, and gait instability (Ref. 135). The patient also suffered from cognitive slowing, inattention, forgetfulness, and difficulty performing complex activities of daily living. He had been employed as a welder for 3 years and had begun to develop symptoms within months after starting to weld. He was able to work until 1 month prior to his medical evaluation by the authors. Two months prior to this evaluation, he had been examined by another physician and placed on L-dopa which brought about no improvement in his condition. In addition, while many of his symptoms were similar to idiopathic Parkinson's disease, he was unusually young, inattention and forgetfulness occurred early in the course of the disorder, and he had a "cock-walk" gait that is atypical of Parkinson's disease. Increased signal intensities in the basal ganglia seen on T1-weighted brain MRI suggested to the authors that he may have been suffering from manganism. His serum manganese was mildly higher than that normally seen in the general population, which prompted the physicians to inquire about his occupational history. They learned that he had worked as a welder in the shipbuilding industry where he had welded a manganese steel alloy in confined spaces and had rarely used respiratory protection. The authors explained that since manganese is cleared rapidly from the blood stream, and because there are normally delays between manganese exposure and neurological examinations, it is unusual for manganese levels in blood to be elevated at the time a patient first appears for neurological evaluation. Thus, an association between manganese overload and parkisonism is normally difficult to establish, except in the rare case where the disease develops so rapidly that manganese exposure continues almost until the time that the patient is examined, as happened in this case. In his review of the relationships between manganese exposure, welding, Parkinson's disease, and parkinsonism, Jankovic (Ref. 78) found the case report by Sadek et al. to be the only one published that suggested a possible link between welding, manganese, and parkinsonism.

Critical reviews of the evidence that exposure to manganese through welding is associated with Parkinson's disease or parkinsonism were published by Finley and Santamaria (Ref. 36), Kieburtz and Kurlan (Ref. 82), Lees-Haley (Ref. 88), McMillan (Ref. 107), and others. Finley and Santamaria evaluated studies which measured an increase in subclinical neurological effects [e.g., the study of Bowler et al. (Ref. 11] and concluded that they lacked convincing evidence for a causal relationship with manganese exposure due to deficiencies in study design or methodology. Finley concluded that the current weight of evidence does not support an association between welding and elevated risk of neurological effects, including Parkinson's disease. Lees-Haley et al., Jankovic, Finley and Santamaria, and McMillan stated that the use of patients involved in litigation, as in the studies of Racette (Ref. 127, 128) and Bowler (Ref. 11), introduces biases that detract from the credibility of the studies. In addition, noting the extensive litigation that has occurred in the United States, Kieburtz and Kurlan stated that "many experts researching and writing on this topic have been involved on one side or the other of this litigation, providing expert testimony, research data, or both. Hence, this is an area where the reader (and the writer) need to be careful about recognition and disclosure of potential conflicts of interest." In his review, Jankovic concluded that epidemiologic or experimental studies could provide no "convincing evidence that welding is a significant risk factor for Parkinson's disease or for parkinsonism." In general, these reviewers concluded that well-designed epidemiological studies with large populations and good exposure data are needed to provide answers to this important question. McMillan noted the need for a consensus among investigators on diagnostic criteria for subclinical and clinical manganism and premature idiopathic Parkinson's disease and stated that these criteria should be strictly adhered to. McMillan further stated that both "case-control and cohort studies including detailed exposure records should be conducted—the latter as a long-term measure to add to conclusions drawn from shorter cross-sectional case-control work, the urgency of the situation being too great to allow the luxury of awaiting the outcome of long-term follow up before taking any evidence-based action."

The results of several epidemiological studies designed to meet criteria such as these were published subsequent to most of these critiques. These studies examined large populations of welders for signs of neurological effects or parkinsonism and consistently found no association with occupation as a welder. In addition, reports that Parkinson's disease or par-

kinsonism occur at a younger age among welders (Ref. 127) have not been supported by recent epidemiologic studies (Ref. 40, 41, 50, 145).

Using a large patient population drawn from three movement disorder clinics, Goldman et al. (Ref. 50) investigated occupational associations with Parkinson's disease or parkinsonism. The study focused on occupations (teaching, healthcare, farming, and welding) that had been associated with an increased risk of Parkinson's disease in previous studies. The subjects were 2072 patients being treated for Parkinson's disease or parkinsonism in clinics located in New York, Atlanta, and San Jose. Parkinson's disease was diagnosed in 90.5% of the patients and the remaining patients were diagnosed with some other form of parkinsonism. The primary lifetime occupation for each of the patients was obtained from medical records at each clinic and compared with job frequencies for the general population in the geographic area of the clinic using Department of Labor regional statistics. The frequency of Parkinson's disease or parkinsonism was significantly elevated in physicians and dentists (combined), farmers, teachers, and administrators. The clinical patients included three welders, all of whom had typical Parkinson's disease. The frequency of Parkinson's disease or parkinsonism in welders was not significantly elevated compared with the control population. The mean age at which Parkinson's disease was first diagnosed was 62.5 for the entire clinical population and 54.7 for the welders; the reduced age of onset for the welders was not statistically significant ($p = 0.24$). The investigators concluded that their finding of elevated Parkinson's disease in persons whose occupations involved healthcare, teaching, and farming was consistent with previous studies. The incidence of parkinsonism in welders was not greater than that in the general population.

Stampfer (Ref. 145) examined mortality data in the U.S. National Center for Health Statistics (NCHS) National Cause of Death data base for evidence linking occupation as a welder and mortality from neurodegenerative diseases among men in the United States. The study was restricted to deaths that occurred in states where occupation was reported for at least 1 year. A total of 4,252,490 men who died between 1985 and 1999 were included in the analysis. Mortality data were examined for welders under two definitions: Group 1 ($n = 42,139$) consisted only of welders and cutters; Group 2 ($n = 107,773$) consisted of welders and cutters and other occupations with potential welding exposure including plumbers, pipefitters, steamfitters, boilermakers, structural metal-workers, and millwrights. Both groups were analyzed independently and the mortality odds ratios calculated by comparison with the remainder of the study population (the reference population).

During the study period, Parkinson's disease accounted for 49,174 deaths, and was listed as a contributing or underlying cause of death among 1.0% of the men with any welding-related exposure (group 2) and 1.2% of the men in the reference population. Age-adjusted mortality odds ratios associated with Parkinson's and other neurodegenerative diseases were calculated for welders in both groups compared with the reference population. Welders in both groups were slightly, but significantly, less likely to have Parkinson's disease as the contributing or underlying cause of death. The risk of Parkinson's disease was not increased in welders younger than 65 years of age and the risk may have been decreased in welders older than 65 years. In addition, the risk of death from motor neuron disease, other diseases of the basal ganglia, and other extrapyramidal disorders did not differ significantly between welders and the reference population. Stampfer noted that a key strength of this study was its size and that the inclusiveness of the NCHS data base made any selection bias implausible. He concluded that "[t]he present study … suggests that employment as a welder is not associated with an increase in mortality from Parkinson's disease or other neurodegenerative conditions."

Fryzek et al. (Ref. 41) conducted a retrospective cohort study of the rates of hospitalization for Parkinson's disease and other neurodegenerative disorders among 27,839 male metal-manufacturing workers from 79 iron and metal goods manufacturing companies in Denmark. The cohort had previously been established to study the incidence of cancer in metal workers, including welders and grinders (Ref. 62). This follow-up study of neurological diseases was conducted from 1977 to 2002 and included 9817 men who were employed in departments engaged in mild or stainless-steel welding, of whom 6163 were welders. Occupational history and life style data for 8190 of the 9817 men with potential exposures to welding fumes were obtained in 1986 by questionnaires or interviews. Data concerning hospital admissions for neurological diseases were obtained from the Danish National Register of Patients.

The standardized disease-specific hospitalization ratio (SHR) was defined as the number of first-time hospitalizations for a given disease among the subjects compared with that for the general population. Overall, there were 69 cases of Parkinson's disease in the entire study population, including 25 among all welding-exposed workers, and 11 among the welders. The number of hospitalizations for Parkinson's disease did not differ from that expected for the entire cohort (SHR = 0.9, CI = 0.7–1.2), for men working in welding departments (SHR = 1.0, CI = 0.7–1.5), or for welders (SHR = 0.9, CI = 0.4–1.5). Differences observed between the mean ages of onset of Parkinson's disease among the welders (67 years), the workers in welding departments (68 years), and among all the workers in the 79 companies (70 years) were

not statistically significant. The number of workers with other neurological conditions was small (among welders there was one case of parkinsonism, two cases of dystonia, and two cases classified as extrapyramidal and movement disorders) and was not significantly different from the number expected based on the incidence of these conditions among men of similar age in the general population of Denmark. Among welders, the incidence of Parkinson's disease was not associated with age or with the duration of the welding experience (Table 2). The investigators concluded that the rates of Parkinson's disease and other neurological conditions among welders were consistent with those of the general population of Denmark.

In a similar study conducted in Sweden, Fored et al. (Ref. 40) examined the incidence of basal ganglia and movement disorders in welders and flame cutters. The health and employment records of 49,488 male Swedish welders were compared with those of 489,572 male workers who had no history of exposure to welding or flame cutting at work and who were matched with the welders by area of residence and year of birth. Manganese exposure data were taken from a large Swedish study conducted in 1974 and 1975, in which breathing zone concentrations of air pollutants were measured at almost 500 welding stations from 70 industrial sites and 21 railway track welding sections. Geometric mean manganese exposure levels for welding of mild steel were 0.26 mg/m^3 for SMAW and 0.30 mg/m^3 for GMAW. For stainless steel GMAW welders, the mean manganese concentration was 0.14 mg/m^3.

Neurological disorders occurred at a slightly lower rate among the welders than in the comparison population. The incidence rate of basal ganglia and movement disorders was 28.1 per 100,000 person years among the welders and flame cutters, compared with 31.2 per 100,000 person years in the control cohort, yielding an adjusted incidence rate ratio (aRR) of 0.91 (CI = 0.81–1.01). Results for Parkinson's disease were similar (aRR = 0.89, CI = 0.79–0.99). Inclusion of mortality data did not change these results. There was no difference in mean age at first occurrence of Parkinson's disease between the welders and flame cutters (mean age 71.9 years) and the comparison cohort (mean age 72.0 years). A subcohort analysis of 4592 shipyard welders who may have had higher exposure to welding fumes because their work conditions may have involved welding within an enclosed environment revealed no increased rate of Parkinson's disease. Thus, this large, nationwide study, with up to 40 years of follow-up, revealed no statistically significant risks for Parkinson's disease or other basal ganglia and movement disorders in welders compared with a matched general population comparison cohort.

Table 2
Standardized Hospitalization Ratios (SHR) for Parkinson's Disease in Welders by Age and Duration of Welding Experience

	Person-years	Observed Cases of PD[b]	Expected Cases of PD	SHR	95% CI[c]
Calendar Time					
1977–1992	89,022	4	5.01	0.80	0.21–2.04
1993–2002	53,443	7	7.91	0.88	0.35–1.82
Attained Age					
Less than 65 years old	129,838	5	4.43	1.13	0.36–2.63
65 years or older	12,626	6	8.50	0.71	0.26–1.54
Duration of time spent welding[a]					
Less than 10 years	67,268	4	4.48	0.89	0.24–2.28
10 to 20 years	41,912	3	2.73	1.10	0.22–3.21
More than 20 years	31,781	4	5.16	0.77	0.21–1.98

[a] Information for duration of welding was missing for 110 people.
[b] PD = Parkinson's disease.
[c] CI = Confidence Interval.

Source: Data from Fryzek et al., Ref. 41.

Marsh and Gula (Ref. 101) conducted a case-control study among the 12,595 workers who had ever been employed between 1976 and 2004 at any one of three Caterpillar heavy equipment plants in Illinois and were eligible to make a medical insurance claim between July, 1998 and July, 2004. While exposure levels were not available, the three plants were chosen for the study because a higher proportion of the workers were welders than at other Caterpillar plants. Cases of neurological disorders were identified from company medical claims and comprised the 70 persons who had filed claims for either idiopathic Parkinson's disease or secondary parkinsonism and the 153 persons who had filed claims for other progressive diseases of the basal ganglia and essential and other specific forms of tremor. Controls were drawn from members of the study population who were not identified as cases and were matched to cases by birth year, race, and sex.

There were no statistically significant associations between ever having welded in a Caterpillar plant and any of the neurological disorders studied. Further analyses showed that there were also no statistically significant associations between neurological disorders and the plant at which the welders worked. This study supports the conclusion that employment as a welder is not associated with Parkinson's disease, parkinsonism, or related neurological disorders.

15.5 Manganese: Bioavailability. In his analysis of the evidence for an association between manganese exposure in welding fumes and Parkinson's disease or parkinsonism, McMillan (Ref. 107) noted that manganese emanating from different processes may differ in its physicochemical structure which could affect its bioavailability. Manganese in welding fumes is often present as complex oxides in ultrafine particles which are sometimes surrounded by a shell composed of silicon oxide. McMillan reasoned that manganese in that form may be less bioavailable than manganese in dusts or particles released from other processes such as mining. Particles in dusts released during mining are in much simpler forms and have been clearly related to manganism. He stated that studies of welders should not include related occupations such as flame cutting or hardfacing because the composition of particles and the proportion of manganese in fumes released by those processes may differ markedly from that released by welding, potentially altering the risk of adverse health effects. If operators of such processes are included, this should be documented and considered in the study results.

McMillan (Ref. 107), Roth and Garrick (Ref. 134), and others have argued that, since iron and manganese compete for the same transfer systems across the blood-brain barrier, iron from welding fumes might actually reduce the passage of manganese into the brain. Transport of divalent metals across cell membranes and the blood brain barrier is mediated by divalent metal transporter 1 (DMT1). Both manganese and iron uptake and transport in the body involve transport by transferrin, transferrin receptors, and DMT1. Roth and Garrick noted that the dispositions of manganese and iron are interdependent and are influenced by iron stores within the body since the two metals bind to and compete for transferrin and DMT1. Iron deficiency will lead to increased manganese levels in the body and conversely iron overload decreases manganese uptake. As stated by Roth and Garrick, this "raises the very important question as to whether iron status influences the susceptibility to develop manganism."

16. Inflammation and Oxidative Stress

Some conditions known or suspected to be associated with welding exposures, including metal fume fever, pulmonary fibrosis, bronchitis, and asthma, have been attributed to oxidative stress and/or inflammatory processes in the lung. Oxidative stress occurs when the generation of reactive oxygen species (ROS: superoxide, hydroxyl radicals, hydrogen peroxide) and nitrogen species (nitric oxide, peroxynitrite) outbalances the quantity of antioxidants (e.g., SOD, glutathione peroxidase, and reduced glutathione) that are available to inactivate them. The production of oxidizing species is a central part of the mechanism by which macrophages and polymorphonuclear leukocytes (PMNs) destroy pathogens; but the production of ROS by phagocytes when responding to the presence of non-pathogenic particles such as those in welding fume may also damage host tissues. Reactive oxygen species can interact with DNA, proteins, and lipids to cause mutations or membrane instability, thereby affecting normal cell function.

Inflammatory processes in the lungs are the first observable response to inhaled welding fumes. Proinflammatory cytokines (proteins involved in the amplification of inflammatory reactions), such as interleukin-6 (IL-6) and IL-8, are released from lung cells and are measurable in BALF. These cytokines are chemotactic for macrophages and neutrophils. Cytokines released from activated macrophages and neutrophils can further enhance inflammatory processes in the lungs that may eventually lead to fibrosis and other pulmonary conditions. Cytokines released in the lungs can also cause systemic effects, such as metal fume fever, as they are transported from the lungs into the blood stream.

Kim et al. (Ref. 84) measured markers of inflammation, including C-reactive protein, fibrinogen, and numbers of neutrophils, in blood from 24 welders (42% smokers) and 13 non-exposed controls (23% smokers). The subjects were monitored at a welding school in Quincy, Massachusetts. The welders were exposed to fumes from SMAW, GTAW, plasma arc cutting, and grinding, primarily of carbon steel. The controls were office workers at the school. The mean age of the welders was 35 years and that of the controls was 41.5 years. Air sampling showed that welders were exposed to significantly higher concentrations of particles in the $PM_{2.5}$ range[8] than were controls.

Blood samples were collected at the start and end of the work day from all of the subjects and at the start of the succeeding work day from 13 of the welders. C-reactive protein levels were significantly increased 16 hours after welding exposures, but no changes in fibrinogen levels, total white blood cells, or numbers of neutrophils were observed. However, when non-smoking subjects were evaluated independently, a significant increase in neutrophil count and a significant decrease in fibrinogen were seen in blood following welding fume exposure. The investigators concluded that exposure to high levels of welding fume induces acute systemic inflammation and "that smoking may modify the effect of welding fume exposure on specific inflammatory markers."

Further work from this laboratory tested whether the expression of genes responsible for systemic inflammation is altered by exposure to welding fumes. Using cDNA microarray techniques, Wang et al. (Ref. 160) analyzed whole-blood RNA to compare gene expression in boilermakers before and after exposure to welding fumes. The subjects were recruited from the welding school in Quincy. Blood was collected from 15 boilermakers before and after they had welded for about 6 hours in the workshop and from 7 controls who worked in the classroom or office at the school. The investigators found that the genes whose expression was altered following exposure to welding fumes were clustered in biologic processes related to the inflammatory response, oxidative stress, intracellular signal transduction, cell cycle, and apoptosis (programmed cell death). Recent studies by Wang et al. showed that the effects of welding fume exposure on gene expression are transient, and most of the observed effects diminished within 19 hours post exposure (Ref. 159). In agreement with their earlier results (Ref. 84, 160), the greatest variations in gene expression were seen in the non-smoking welders.

Li et al. (Ref. 91) examined the effects of welding on erythrocyte levels of SOD (a cytoplasmic enzyme that catalyzes the conversion of superoxide free radicals to oxygen and hydrogen peroxide) and serum levels of malondialdehyde (an indicator of lipid peroxidation)**.** The 37 welders in the study worked for a vehicle manufacturer in Beijing, China, and the 50 controls worked at a nearby food factory. Concentrations of manganese and iron in serum and lead in blood were significantly higher in the welders than in the controls. Erythrocytic SOD activity and serum malondialdehyde levels were found to be 24% lower and 78% higher, respectively, in welders than in controls, supporting the observations of other investigators that occupational exposure to welding aerosols induces oxidative stress.

Han et al. (Ref. 60) conducted a study to identify potential biomarkers of oxidative stress in the serum of welders. Blood samples were collected from 197 asymptomatic shipyard welders in South Korea and 150 non-exposed male controls. Welders were divided into three groups according to their years of experience: 1 to 10 years (n = 142), 11 to 20 years (n = 27), and 21 or more years (n = 28) work experience. The welders used GMAW with a carbon dioxide shielding gas. Mean fume exposures determined with personal samplers were 13.2 mg/m^3, more than twice the OSHA PEL of 5 mg/m^3. Serum levels of manganese and lead were comparable to those of reference populations. Serum concentrations of albumin, manganese SOD, heat shock protein 70, and the potential to generate reactive oxygen species (as determined by monitoring luminol-mediated chemiluminescence) did not differ between welders and controls. However, there were significant differences in total protein, total antioxidant status, and concentrations of aconitase, glutathione peroxidase, and isoprostane. The greatest increases were seen for isoprostane (a common by-product of lipid peroxidation) and aconitase (a mitochondrial enzyme involved in the citric acid cycle) which increased 2.4- and 1.7-fold, respectively, in serum from welders. These differences between welders and controls were not affected by adjustments for age or smoking. The investigators concluded that exposure to welding fumes can evoke changes in serum biomarkers of oxidative stress and suggested that such changes may be useful in clinical monitoring of disease development and in assessing whether reduction of worker exposures is needed.

Zhu et al. (Ref. 175) examined the effect of welding exposures on levels of SOD, catalase, glutathione peroxidase, and lipoperoxides in erythrocytes and vitamins C and E in plasma from electric arc welders. Concentrations of these biomolecules in blood samples from 70 arc welders (43 males and 27 females) at two worksites in China were compared with

[8] $PM_{2.5}$: Particulate matter with an aerodynamic mass median diameter equal to or less than 2.5 μm.

those from 70 healthy volunteers (45 males and 25 females) of the same age range who had no exposures to welding or toxic materials in the workplace. Ozone measurements in the welding areas ranged from 0.159 to 0.371 mg/m^3. Average concentrations of the antioxidants SOD, catalase, and glutathione peroxidase, and of vitamins C and E were significantly decreased and concentrations of lipoperoxides in red blood cells were significantly increased in welders compared with controls. The investigators concluded that long-term exposure to welding aerosols can induce oxidative stress in welders.

Borska et al. (Ref. 8, 9) compared humoral constituents of the immune system and indicators of inflammation in peripheral blood from men who worked as welders (n = 11) and grinders (n = 9) of stainless steel for an average duration of 8 years in a plant in the Czech Republic with those of a group of healthy men who lived in the same geographical area and had no exposures to environmental pollutants. The average age of the exposed subjects was 31 years and that of the controls was 38 years. About half of the members of both populations were smokers. Welding was done with GTAW. Airborne chromium concentrations ranged from 0.56 to 16.34 mg/m^3 and exceeded the maximum permitted concentration of 0.1 mg/m^3 in all air samples collected during welding and grinding. Nickel concentrations ranged from 0.34 to 10.13 mg/m^3 and exceeded the permitted concentration of 1.0 mg/m^3 in some of the air samples. Manganese concentrations were within permitted values. Significantly more phagocytic cells were found in blood from welders and grinders than from controls. Concentrations of 17 proteins, many of which are associated with the immune system or with inflammation, were compared in blood from the exposed subjects and the controls. Concentrations of all but five of these proteins differed significantly between the two groups (Table 3).

As part of their antibacterial function, PMNs release the highly reactive superoxide anion. In 2001, Aloufy et al. (Ref. 1) reported that, when they are stimulated *in vitro*, PMNs extracted from the blood of welders release less superoxide than do those collected from non-welders. Based on the hypothesis that this difference is due to soluble mediators of the immune response that are released into the blood stream under conditions of oxidative stress, these investigators later examined the effect of serum from welders on the function of PMNs extracted from the blood of healthy, unexposed donors (Ref. 69). The 44 welders who participated in the study were 20 to 60 years of age and were engaged in a variety of welding processes. They were matched by age to 44 non-exposed controls who were school teachers.

Table 3
Concentrations of Components of the Humoral Immune System in a Group of Welders and Grinders Compared with Unexposed Controls

Parameter	Mean ± SD (Welders)	Number Welders	Mean ± SD (Controls)	Number Controls	p Value
IgG (g/L)	9.46 ± 1.01	20	13. 39 ± 3.06	100	< 0.001
IgA (g/L)	2.08 ± 0.67	20	2. 75 ± 0.77	100	< 0.001
IgM (g/L)	1.10 ± 0.33	20	1.70 ± 0.72	100	< 0.001
C3 complement (g/L)	1.05 ± 0.19	20	0.71 ± 0.19	100	< 0.001
C4 complement (g/L)	0.29 ± 0.07	20	0.30 ± 0.09	100	0.4
IgE total (lU/ml)	269.55 ± 405.81	20	129.30 ± 207.49	100	0.458
Beta-2-microglobulin (mg/L)	1.44 ± 0.16	20	0.92 ± 0.38	48	< 0.001
Neopterin (nmol/L)	11. 86 ± 2.08	20	8.35 ± 2.62	48	< 0.001
IL-l beta (pg/mL)	3.35 ± 1.34	20	2.59 ± 1.45	35	0.062
Transferrin (g/L)	2.52 ± 0.32	20	3.00 ± 0.45	50	< 0.001
Alpha-1-antitrypsin (g/L)	1.45 ± 0.23	20	3.15 ± 0.68	50	< 0.001
Alpha-2-macroglobulin (g/L)	1.54 ± 0.28	20	2.05 ± 0.52	50	< 0.001
Haptoglobin (g/L)	1.25 ± 0.53	20	1.62 ± 0.31	50	< 0.001
Orosomucoid (g/L)	0.89 ± 0.18	20	0.75 ± 0.18	50	0.004
Prealbumin (g/L)	0.31 ± 0.03	20	0.32 ± 0.05	50	0.943
Ceruloplasmin (g/L)	0.37 ± 0.05	20	0.42 ± 0.08	50	0.018
CRP (g/L)	2.93 ± 6.27	20	2.50 ± 1.25	50	0.642

Mean = arithmetic mean; SD = standard deviation; n = number of persons; CRP = C-reactive protein.

Source: Data from Borska et al, Ref. 8.

Polymorphonuclear leukocytes obtained from healthy unexposed donors were incubated *in vitro* with serum from welders or controls and the release of the superoxide radical was determined following the addition of the stimulant phorbol myristate acetate. No difference in the production of superoxide was seen when serum from all welders was compared with that from all controls or when serum from smoking welders was compared with that from smoking controls. However, significantly less superoxide was generated following treatment with serum from non-smoking welders under age 40 than with serum from non-smoking controls in the same age class. The serum concentrations of the cytokines TNF-α, IL-2, and IL-6 did not differ between these two groups indicating that they are not responsible for the suppression of ROS production by PMNs. From these findings, the investigators concluded that PMN function is affected by factors in serum related to age, smoking, and exposure to welding fumes.

16.1 Oxidative DNA Damage. Kim et al. (Ref. 85) measured particulate exposures and monitored 8-hydroxy-2'-deoxyguanosine (8-OHdG) concentrations in urine from 20 boiler makers for 5 days during an overhaul of oil-fired boilers where they were exposed to metal-laden fine particulates from residual oil fly ash and from welding, burning, and grinding. The 8-hour time-weighted average fume concentration was 0.44 mg/m^3. The urinary concentration of 8-OHdG, which is an indicator of oxidative DNA damage and repair, increased during the work shift and was significantly related to workplace concentrations of particles with aerodynamic diameters less than 2.5 μm. There were also positive relationships between urinary 8-OHdG concentrations and the content of vanadium, manganese, nickel, and lead in the fumes. The authors concluded that healthy young boilermakers exposed to high levels of metal-containing particulate matter may be at risk of oxidative DNA injury.

17. Effects on the Cardiovascular System

An implantable cardioverter defibrillator (ICD) is a medical device that uses electrical impulses to treat life-threatening rapid heart rhythms and to prevent sudden death due to arrhythmia. A frequent concern raised about ICDs and pacemakers is whether, after having one implanted, it is safe to return to an industrial job where strong EMFs could potentially cause such devices to malfunction (Ref. 151). Gurevitz et al. (Ref. 54) used a simple, low risk screening protocol to assess interactions between EMFs produced by industrial equipment and the ICD to determine whether it is safe for patients with ICDs to return to the workplace. Eighteen patients, including two welders, with ICDs that were implanted due to ventricular arrhythmias were the subjects of the study. The patients had ICDs which could be adjusted to beep during each QRS (the QRS complex represents the electric current flowing through the heart during activation of the ventricles) or to produce a different tone if electromagnetic interference was sensed. During the screening, the patients walked through their respective workplaces and operated each piece of equipment that they would normally use when at work. ICD outputs were monitored during contact with 114 types of equipment, including 31 arc welding machines. Interference with the ICD was detected only once, and that was while a patient was within 6 feet of a large electromagnet being attached to a crane. He was advised not to return to his job. The remaining patients all returned to their previous jobs. Seventeen patients were available for follow-up 4 years later. Of these, three patients had changed to non-industrial jobs within two years after the study, and seven were still working at the jobs held at the time of the testing. None of the 17 had experienced loss of consciousness or ICD discharges while on the job. Only one participant reported having felt an ICD discharge during work, but no shock episodes had been recorded by his ICD. Gurevitz et al. concluded that proper testing can determine the long-term safety of returning to industrial jobs for ICD patients. They cautioned that wear and tear or replacement of machines could alter the electromagnetic field encountered in the workplace, necessitating re-testing of the ICD. They stated that, should a patient experience light-headedness or a shock, he must be removed from the workplace immediately and receive medical evaluation.

18. Effects on the Kidney

Inhaled cadmium accumulates in the kidney and liver, and is excreted through the kidneys. Cadmium excretion is very slow with a half life of 20 to 40 years. The kidney is one of the main organs affected by chronic cadmium exposure. Two cases of renal disease that were attributed to cadmium exposure in welders were published between 2002 and 2005. The first, by Nogue et al. (Ref. 119), involved a 39-year-old welder who had worked for 12 years in a company that produced alloys for cutting marble and granite. Autogenous welding was performed using electrodes that contained 39% silver, 25% cadmium, 22% copper, and 14% zinc. No provisions were in place for fume extraction or respiratory protection. The welder was referred to Nogue et al. for evaluation of glomerular nephropathy. At that time, he was in relatively good

health, with no respiratory symptoms, but he had proteinuria and hematuria (protein and blood in the urine) and his serum and urinary cadmium levels were elevated. Following a renal biopsy, he was diagnosed with IgA mesangial glomerulonephritis, a condition in which circulating immunocomplexes containing the antibody IgA deposit in the glomerular mesangium of the kidney resulting in the characteristic symptom of blood in the urine. The authors suggested the possibility of a causal association between this kidney condition and their patient's cadmium exposure.

In the second case report, Trevisan and Gardin (Ref. 156) described the follow-up of a patient they had treated in 1982 for a Fanconi-like Syndrome, a disorder in which proximal tubular function is impaired. At the time of his first treatment, the patient was 42 years old and had worked as a welder for 20 years (Ref. 155). Personal sampling had shown that he had been exposed to cadmium concentrations of 0.22 mg/m^3 with, and 1.2 mg/m^3 without aspiration devices. His blood and urinary cadmium levels were greatly elevated. He was treated for this condition and removed from cadmium exposure at that time. While lower than in 1982, his cadmium levels were still substantially elevated in blood and urine when he returned for treatment 10 years later. At this time, he had developed nephrolithiasis (calcium phosphate kidney stones). He was treated by lithotripsy but continued to have several incidents of kidney stones per year after that. His blood and urinary cadmium levels were still substantially higher than reference values 20 years after cessation of exposure. The authors concluded that chronic exposure to high concentrations of cadmium were responsible for the nephrolithiasis observed in this patient and that lesions of the tubular cells may lead to development of kidney stones in susceptible persons.

19. Effects on Reproduction

Wong et al. (Ref. 162) examined the effects of lifestyle, occupation**,** and medical history on sperm count in a case-control study of 73 sub-fertile and 92 fertile Caucasian males. The cases were identified through records at a fertility clinic and hospital in Nijmegan, the Netherlands. Sub-fertile males with below normal sperm counts (oligozoospermia) were recruited from couples who had not conceived during 1 year of regular unprotected sexual intercourse. Controls were recruited from midwifery practices in the Nijmegan area and were men with normal sperm counts (20 million sperm/mL or greater) whose wives had conceived during a 1-year period of unprotected sex. The average age of controls and cases was 34 years. Data concerning lifestyle, medical history, and occupational exposures to pesticides, paints, welding, and disinfectants were obtained by questionnaire. The sub-fertile males had significantly lower sperm counts and sperm motility and a significantly higher percent of abnormal spermatozoa than did the fertile males. Antibiotic use (OR = 15.4; CI = 1.4–163), a history of mumps (OR = 2.9; CI = 1.3–6.7), and occupational exposure to pesticides (OR = 8.4; CI = 1.3–52.1) were significantly related to subnormal sperm counts. The risk for oligozoospermia was non-significantly elevated in men with occupational exposures to welding (OR = 2.8; CI = 0.9–8.7).

Danadevi et al. (Ref. 24) compared the quality of semen collected from 57 welders who worked at a welding plant in South India and 57 controls matched for age, lifestyle, and economic status. The mean age of the subjects was 32 years. The welders had been exposed for a mean of 11 years (range: 2–21 years) to chromium- and nickel-containing welding fume; the controls had no known exposures to hazardous chemicals. Concentrations of nickel and chromium were measured in blood taken from 28 exposed workers and 27 controls. There were significant positive correlations ($p < 0.01$) between blood levels of both of these elements and years of exposure to welding fumes.

The percent of subjects with normal sperm morphology, normal sperm counts, and rapid linear sperm motility was significantly lower among the welders than among the controls (Table 4). Nickel and chromium concentrations in blood were positively correlated with the percentage of tail defects in semen from welders. Blood concentrations of chromium, but not nickel, were significantly correlated with decrements in sperm count, sperm vitality, and rapid linear progressive motility. The investigators concluded that exposure to welding fumes containing nickel and chromium is associated with abnormal semen parameters. They noted that the effects of these exposures on male fertility were not addressed in the study and could not be evaluated from their data.

Damage to DNA in sperm caused by oxidative stress can be measured by the level of 7-hydro-8-oxo-2'-deoxyguanosine (8-oxodG) in sperm DNA. Working with a population of 225 Danish couples who were planning to conceive their first child, Loft et al. (Ref. 92) investigated whether such DNA modifications affect sperm function. The participants were members of trade unions for metalworkers, office workers, nurses, or daycare workers. Semen samples were collected monthly for up to 6 months following the cessation of the use of contraception. There was a significant inverse relation-

Table 4
Semen Characteristics of Controls and Welders (mean ± SD)

Semen parameter	Controls (n = 57)	Welders (n = 57)
Ejaculate volume (mL)	2.5 ± 0.5	2.4 ± 0.5
Sperm count ($\times 10^6$/mL)	62.8 ± 43.7	14.5 ± 24.0[a]
Sperm motility		
Rapid linear progressive motility (%)	63.5 ± 5.3	32.2 ± 15.3[a]
Slow linear progressive motility (%)	12.5 ± 1.9	21.7 ± 11.5[a]
Nonprogressive motility (%)	11.6 ± 2.7	15.1 ± 8.9[a]
Immotile (%)	12.4 ± 7.0	31.0 ± 16.6[a]
Normal morphology (%)	69.0 ± 8.0	37.0 ± 14.3[a]
Head defects (%)	16.4 ± 5.6	38.3 ± 9.7[a]
Mid-piece defects (%)	9.8 ± 3.8	19.5 ± 9.2[a]
Tail defects (%)	4.8 ± 0.8	5.2 ± 4.9
Sperm vitality (%)	80.4 ± 6.8	67.6 ± 22.8[a]
Nonspecific aggregation (%)	14.0 ± 12.0	49.0 ± 22.0[a]

[a] $P < 0.001$, Mann Whitney U-test.

Source: Danadevi et al., Ref. 24.

ship between the level of 8-oxodG in sperm DNA and the occurrence of pregnancy during the 6-month follow-up period. While oxidative damage to sperm DNA appeared to adversely affect fertility, the level of 8-oxodG was not significantly associated with smoking, consumption of alcohol or caffeine, or any of the occupational factors examined. The level of 8-oxodG did not differ significantly in sperm from the 80 men who performed daily welding and the 145 men who did not.

Hjollund et al. (Ref. 67) investigated whether paternal stainless steel welding affects the incidence of spontaneous abortion among women who had become pregnant by *in vitro* fertilization. Potential participants were identified through the Danish *In Vitro* Fertilization Registry and selection for participation in the study was based on responses to mailed questionnaires. Rates of spontaneous abortion were compared between 319 couples in which the male partners were welders and 2925 couples in which the males had no known exposures to welding fumes. Spontaneous abortion of pregnancies before 28 weeks of gestation occurred in 18% of the couples with paternal exposure to stainless steel welding, in 25% of those with paternal exposure to mild steel welding, and in 28% of those with no paternal welding exposure. These differences were not statistically significant and it was concluded that welding does not affect the rate of spontaneous abortion in pregnancies that are initiated by *in vitro* fertilization. The authors noted that these results were not in agreement with an earlier study they had conducted (Ref. 68) in which paternal stainless steel welding was associated with a significantly increased risk of spontaneous abortion in natural pregnancies. They suggested that differences in the mechanisms of natural fertilization and *in vitro* fertilization may have accounted for the differences in the results obtained in the two studies.

20. General Health

Rongo et al. (Ref. 133) surveyed workers in small-scale industries in Dar es Salaam, Tanzania for information about occupational exposures and occupation-related health problems. The sample of 310 workers comprised 101 welders, 86 painters, 62 woodworkers, and 61 metalworkers engaged mainly in soldering. The workplaces consisted of garages or temporary shelters. Data on exposure to fumes and dust, excessive noise, and heat or direct sunlight were obtained by interview and by observation in the workplace. Additional information obtained from the workers included the use of protective equipment and health complaints. Only 50 of the welders reported using face shields, and only ten used goggles or protective eyewear. Roughly half of the welders were exposed to fumes for more than 2 hours per day and to excessive noise (defined as noise that makes it difficult to communicate without shouting). All of the welders were exposed to direct sunlight or heat throughout the work week. The most common health complaint among welders was

skin burn (86.1%), followed by eye problems (81.2%), headache (76.2%), chest or throat pain (71.3%), backache (60.4%), nasal irritation (52.5%), skin irritation (29.7%), and hearing problems (9.9%). None of the other groups of workers experienced the degree of skin burn reported by the welders. Backache, skin irritation, eye problems, and hearing problems were common among the metal workers. Headache and chest or throat pains were reported by more than 50% of the painters, and hearing problems were reported by a majority of the woodworkers. In discussion groups, the workers in this study recognized the health hazards of their workplaces and expressed the need for health information concerning their workplace exposures and for the availability of protective devices. They placed a higher priority, however, on making their workplaces permanent than upon occupational health and safety concerns. The authors noted that the temporary nature of these workplaces did not encourage investment in occupational health and safety procedures. The findings of this study illustrate the nature and extent of some of the health problems associated with welding when little or no precautions are taken for the health and safety of the welders.

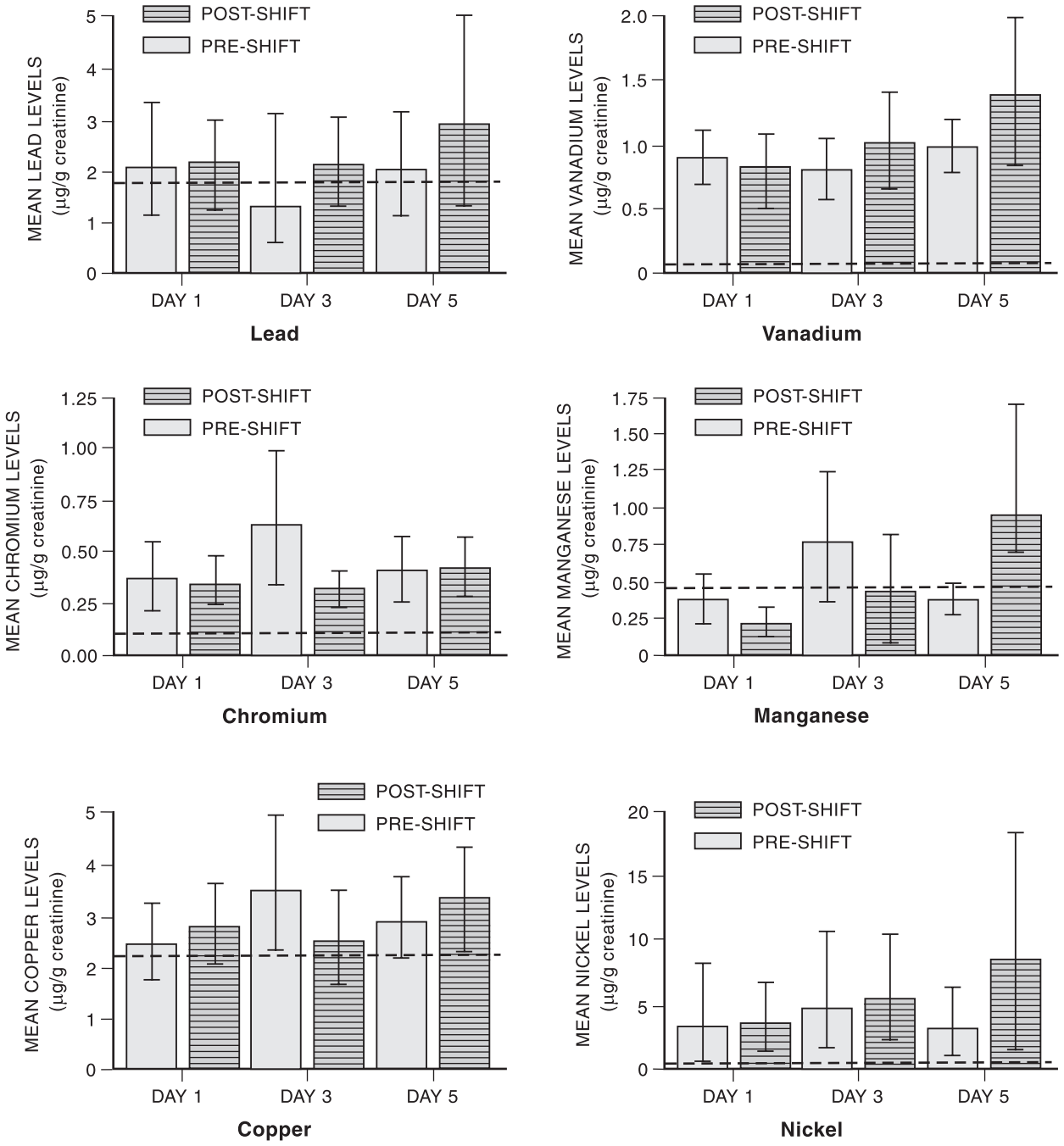
21. Biological Monitoring

21.1 Chromium and Nickel. Stridsklev et al. (Ref. 149) examined the relationship between levels of chromium and nickel in air and those in blood and urine from seven men engaged in FCAW of stainless steel. Four of the men wore respiratory protection while welding. One of the welders worked inside a stainless steel tank; the others worked in the same area as men using GMAW or SMAW. Referents were white collar workers from the same company as the welders; none of them had ever welded or grinded stainless steel. Breathing zone and area air samples were collected for five of the welders. Urine samples were collected upon arising in the morning, and at the start and end of the work shift for five consecutive work days. Blood was collected before and after work on Monday, Wednesday, and Friday.

The mean air concentrations were 200 μg/m^3 for total chromium, 11.3 μg/m^3 for Cr(VI), and 50.4 μg/m^3 for nickel. The levels of chromium and nickel in biological fluids varied among workplaces and were higher in welders than in referents. Nickel concentrations were below the detection limit in many of the whole blood and plasma samples. The mean concentration of nickel in whole blood samples taken at the end of the workday increased slightly during the work week, but the concentrations of nickel in air were not significantly associated with those in urine or blood. However, significant associations were seen between the concentrations of Cr(VI) measured in air and those of total chromium in plasma and urine. The concentrations of chromium in blood samples were significantly associated with those in urine. The authors concluded that post-shift urinary chromium concentrations may be useful for monitoring the uptake of Cr(VI) by welders.

Colli et al. (Ref. 21) evaluated the kinetics of urinary nickel excretion by three welders engaged in SMAW of stainless steel containing 18% chromium and 10% nickel. Urine samples were collected during the work shift, during the 16 post-exposure hours after the work shift, and on weekends for two consecutive weeks. Nickel was monitored in personal air samples throughout the work shifts. Mean urinary half-lives were calculated to be 59.5 hours during the work shift and 95.5 hours after the work shift and on the weekend. These results suggested that nickel accumulates in two compartments in the body, with different elimination rates. The investigators concluded that, for purposes of biological monitoring, measurement of nickel in a 24-hour urine sample collected throughout the entire work shift and during the 16 hours following exposure would yield the best information about the actual exposure. Since the half-life did not vary with the day of the week, samples could be collected on any work day.

21.2 Polycyclic Aromatic Hydrocarbons. Mukherjee et al. (Ref. 115) investigated whether urinary excretion of 1-hydroxypyrene (1-OHP) could be used as a surrogate to monitor the quantities of metals absorbed by boilermakers from welding and cutting fumes. This work was based on an earlier study (Ref. 116) which showed that urinary excretion of 1-OHP, a metabolite of pyrene, may be useful as a biomarker for polycyclic aromatic hydrocarbon (PAH) exposure in fly ash-exposed boilermakers, particularly in non-smokers. To determine if the urinary concentration of 1-OHP also reflects the concentration of metals absorbed from fumes, urine was collected from 20 boilermakers who were exposed to PAH in fly ash as well as to metals in fumes generated by welding and cutting. Concentrations of 1-OHP, lead, vanadium, chromium, manganese, copper, and nickel were measured in spot urine samples collected at the start and end of the work shift for five consecutive workdays. The urinary concentrations of the metals were greater than general reference population values; these differences were significant for vanadium, chromium, and nickel. While there was marked variability in the concentrations of metals before and after individual work shifts, all post shift values on day 5 were higher than pre-shift values on day 1 of the workweek (Figure 1), which was consistent with the supposition that the boilermakers



Data from days 2 and 4 are not shown.
The dotted line shows general population reference values.

Source: Mukherjee et al., Ref. 115.

Figure 1—Geometric Mean Levels and 95% Confidence Intervals (CI) of Urinary Metals from Boilermakers by Workday

had absorbed the metals being studied. The concentration of 1-OHP was not significantly associated with the concentration of any of the metals at any time during the work week indicating that 1-OHP is not an appropriate surrogate marker for exposure to the metals measured in this study.

21.3 Manganese. Wongwit et al. (Ref. 163) examined manganese levels in stool samples and toenail clippings to determine if less invasive biological samples could be used in place of blood to monitor occupational exposures to manganese. Blood samples, stool specimens, and toenail clippings were collected from 135 welders who worked at the Electricity Generating Authority of Thailand. Manganese concentrations in all samples were determined by atomic absorption spectroscopy. The correlation of manganese concentrations among the three biological samples was found to be poor. The investigators concluded that blood remains the best medium for biomonitoring of manganese concentrations in occupationally-exposed subjects.

Lu et al. (Ref. 94) examined the relationship between concentrations of manganese measured in the breathing zone and serum of Chinese career welders. The subjects worked in a vehicle manufacturing plant in Beijing where SMAW was used daily. The subjects included 97 welders (24 of whom were female) and 91 office workers from the same factory who were not exposed to welding fumes. Breathing zone manganese levels were highest inside the vehicle (mean = 1.5 mg/m^3), and ranged from 0.5 to 0.9 mg/m^3 during welding on the outside of the vehicle. All of these levels were higher than the Chinese MAC of 0.2 mg/m^3. Concentrations of manganese and iron in serum from welders were about 3-fold ($p < 0.001$) and 1.2-fold ($p < 0.001$) higher, respectively, than in serum from controls. Both iron and manganese tended to increase in serum with years of welding experience but the correlation was significant only for iron. The authors concluded that serum manganese may be useful as a biomarker for assessing recent, but not historical, exposures to airborne manganese.

In further work with these subjects, Lu et al. examined the relationship between serum concentrations of manganese, iron, and proteins involved in iron binding and transport (ferritin, transferrin, and transferrin receptor). Levels of ferritin, but not of transferrin and transferrin receptor, increased significantly ($p = 0.044$) with years of welding experience. Levels of serum transferrin and ferritin were increased by 15% to 20% and that of transferrin receptor were decreased by 16% compared with controls. Serum concentrations of iron, ferritin, and transferrin, but not transferrin receptor, were inversely associated with serum concentrations of manganese ($p < 0.05$). The authors concluded that these findings reflect the effects of manganese on iron metabolism and regulation. They stated that their findings suggest that exposure to welding fume "disturbs serum homeostasis of manganese, iron, and the proteins associated with iron metabolism."

21.4 Lead. In the U.S.A., OSHA requires that workers with blood lead levels equal to or greater than 50 µg/dL be temporarily removed from the job until blood lead levels are no greater than 40 µg/dL in two consecutive monthly tests. In Taiwan, similar restrictions are recommended but, according to Yang et al. (Ref. 164), they are difficult to implement. Yang et al. described the cases of three welders found to have elevated blood lead levels (BLLs) during a survey taken in 1992 at the shipyard in Taiwan where they worked. The first case was 44 years old with 13 years of welding experience when his BLL was found to be 54.1 µg/dL. His work had entailed repair of ship bodies and his exposure was thought to be related to welding surfaces coated with lead-based paints. He was transferred to an office job and was monitored monthly for the next year. His BLL dropped to 31.6 µg/dL in 6 months and he returned to welding. Improvements in ventilation and regulations concerning use of personal protection devices were made at that time and annual blood tests showed that his BLL gradually decreased to 30 µg/dL by 2001. Two of his co-workers, whose BLLs were close to or above 50 µg/dL in 1992, were not removed from the job. They continued to weld in the same area and their BLLs decreased gradually after the ventilation was improved. In contrast to the progress of the first welder, it took 3-1/2 years before their BLLs dropped below 40 µg/dL. The authors concluded that removal from the worksite is an effective way to avoid chronic lead poisoning. They noted, however, that the BLLs of none of the cases fell to general population values. This, they assumed, was due in part to their continued exposure to low levels of lead and also to the constant release of lead from bone tissue where it is stored in the body.

22. Genotoxicity

Some chromium and nickel compounds are genotoxic and can cause alterations or mutations in the genetic material (DNA). Tests for DNA damage or chromosome aberrations are useful for assessing whether workers have been exposed

to mutagenic chemicals. Several techniques are available for measurement of genotoxic effects in cells collected from exposed workers. The micronucleus assay is used to detect breaks in chromosomes or loss of whole chromosomes. If a chromosome break or loss occurs, a micronucleus may form which is visible in the cytoplasm by light microscopy. The comet assay, a technique that quantifies single strand breaks in DNA from isolated cells, is used to evaluate DNA damage and repair. These two assays were used in genotoxicity studies of welders in India (Ref. 23) and in France (Ref. 72).

Danadevi et al. (Ref. 23) coupled the comet assay with the micronucleus assay to quantify DNA damage in cells collected from 102 welders who worked in plants in Hyderabad, India. The welders all used SMAW with consumable stainless steel electrodes containing approximately 20% chromium and 10% nickel. None of the welders used respiratory protection. An equal number of men with no known exposures to welding fumes or to chemical agents in the workplace served as controls. Chromium and nickel were measured in blood taken from 51 of the welders and 49 of the controls. Metal concentrations were significantly higher in blood from welders (Cr: 151.7 μg/L; Ni: 132.4 μg/L) than in that from controls (Cr: 17.9 μg/L; Ni: 16.9 μg/L). The frequency of micronuclei, measured in buccal cavity (inside of the cheek) epithelial cells taken from 58 welders and 53 controls, was significantly higher in welders than in controls ($p < 0.001$). The frequency of micronuclei increased significantly with age, with duration of welding exposure, and with concentrations of chromium, but not nickel, in blood. DNA damage, as measured by the comet assay of peripheral blood lymphocytes collected from all of the subjects, was significantly higher in welders than in controls ($p < 0.001$) and increased significantly with the duration of the welding experience ($p < 0.05$) and with the concentrations of nickel and chromium in blood. The investigators concluded that chronic occupational exposure to chromium and nickel during welding could lead to increased levels of DNA damage and that education of welders about the hazards associated with exposure to heavy metals and the need for respiratory protection is essential.

In the study conducted in France, Iarmarcovai et al. (Ref. 72) compared the levels of DNA damage in welders and controls using the comet and cytokinesis-blocked micronucleus assays in peripheral lymphocytes. The study included 60 welders and 30 controls who were office workers and had no exposure to welding fumes or other chemical or physical agents in the workplace. Concentrations of eight metals (aluminum, cadmium, chromium, cobalt, lead, manganese, nickel, and zinc) were measured in blood and urine by inductively coupled plasma mass spectrometry. Blood and spot urine samples were collected before the work shift at the beginning of the week and at the end of the work shift at the end of the week. Concentrations of chromium, nickel, and lead were higher in blood and urine from welders than from controls. None of the metals increased in concentration in blood between the beginning and end of the week, but urinary concentrations of manganese increased in all welders and urinary chromium increased in group 2 welders during that time.

The micronucleus assay, performed with cells isolated from blood collected from the Group 1 welders and controls at the beginning of the week, showed a significant increase in the number of micronuclei in welders compared with controls indicating that welders had a higher frequency of chromosomal damage.

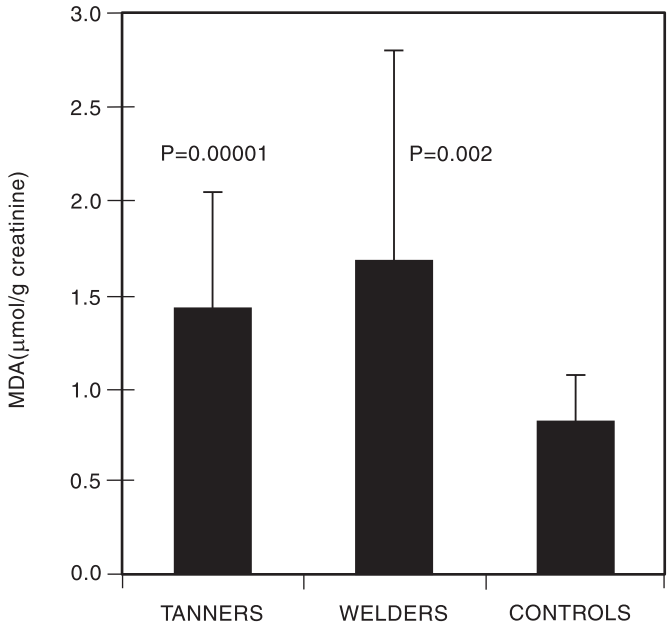
The comet assay was performed with lymphocytes taken from 30 welders at the beginning and end of the work week and from 22 controls. There were no significant differences between welders and controls at the beginning of the work week, but a significant increase in DNA strand breaks was observed in 20 of the 30 welders tested at the end of the work week. These data suggest that the lesions induced by welding exposures are reversible. Analysis of metals in bodily fluids from the welders showed positive correlations between the extent of DNA damage and the concentrations of aluminum, cobalt, nickel, and lead in blood (Ref. 10).There was also a positive correlation between DNA damage and concentrations of manganese in urine. In more recent analyses, Iarmarcovai et al. (Ref. 73) combined genetic analyses with the micronucleus assay and showed that the increased micronucleus frequency that they observed in welders is related to both aneugenic (loss or gain of whole chromosomes) and clastogenic (breaks in chromosomes) effects.

Hexavalent chromium has been classified by IARC as a known human carcinogen (Ref. 74). The carcinogenicity of Cr(VI) is thought to be related to its potential to damage DNA. While Cr(VI) may not react directly with DNA, it can pass through cell membranes where it can be reduced to other chromium species that readily interact with the genetic material. Trivalent chromium [Cr(III)] is considerably less toxic than Cr(VI), apparently due to its poor membrane permeability. Based on studies that showed that Cr(III) can interact with DNA *in vitro* producing DNA-protein cross links and disturbing the fidelity of DNA replication, Medeiros et al. (Ref. 110) investigated whether DNA-protein cross links could be useful as a biomarker of exposure to Cr(III). DNA-protein cross-links were measured in peripheral blood lym-

phocytes collected from 33 tannery workers exposed to Cr(III), 5 shielded metal arc stainless steel welders exposed to both Cr(III) and Cr(VI), and 30 non-exposed controls. The frequency of DNA-protein cross-links was compared with that of micronuclei in peripheral lymphocytes collected from all subjects.

Concentrations of chromium were determined in plasma and urine collected from all subjects at the end of the workweek. Chromium was highest in fluids collected from tannery workers and was significantly higher in tannery workers and welders than in controls. The number of micronuclei was significantly elevated in tannery workers, but not in welders. The levels of DNA-protein cross-links were 2.5 times higher in welders than in tannery workers and were significantly higher in both exposed groups than in controls. Medeiros et al. concluded that "chronic occupational exposure to trivalent chromium can lead to a detectable increase in lymphocyte DNA damage which correlates with a significant exposure of the cells to the metal."

In a related study, Goulart et al. (Ref. 52) compared concentrations of lipoperoxidation products as markers of oxidative stress in urine from 33 tannery workers, 16 stainless steel welders, and 30 non-exposed controls. Urinary concentrations of malondialdehyde, a stable lipoperoxidation product, were significantly higher in welders and tannery workers than in controls (Figure 2), indicating that oxidative damage of membrane lipids had occurred. In addition, there was a positive correlation between urinary malondialdehyde and total chromium in plasma from welders but not from tanners, reflecting the stronger oxidative properties of Cr(VI) compared with Cr(III). Concentrations of glutathione were significantly depressed in lymphocytes from welders but not from tanners, again reflecting the stronger oxidative properties of Cr(VI) and the differences in the transport of Cr(VI) and Cr(III) across the cell membrane.



Note: Values are presented as mean ± S.D. P values refer to Student's t-test between exposed and control groups.
Source: Goulart et al., Ref. 52.

Figure 2—Concentration of Malondialdehyde in Urine from Tanners, Welders, and Controls

Section Three
Investigations in Animals and Cell Culture

23. Infectivity and Inflammation

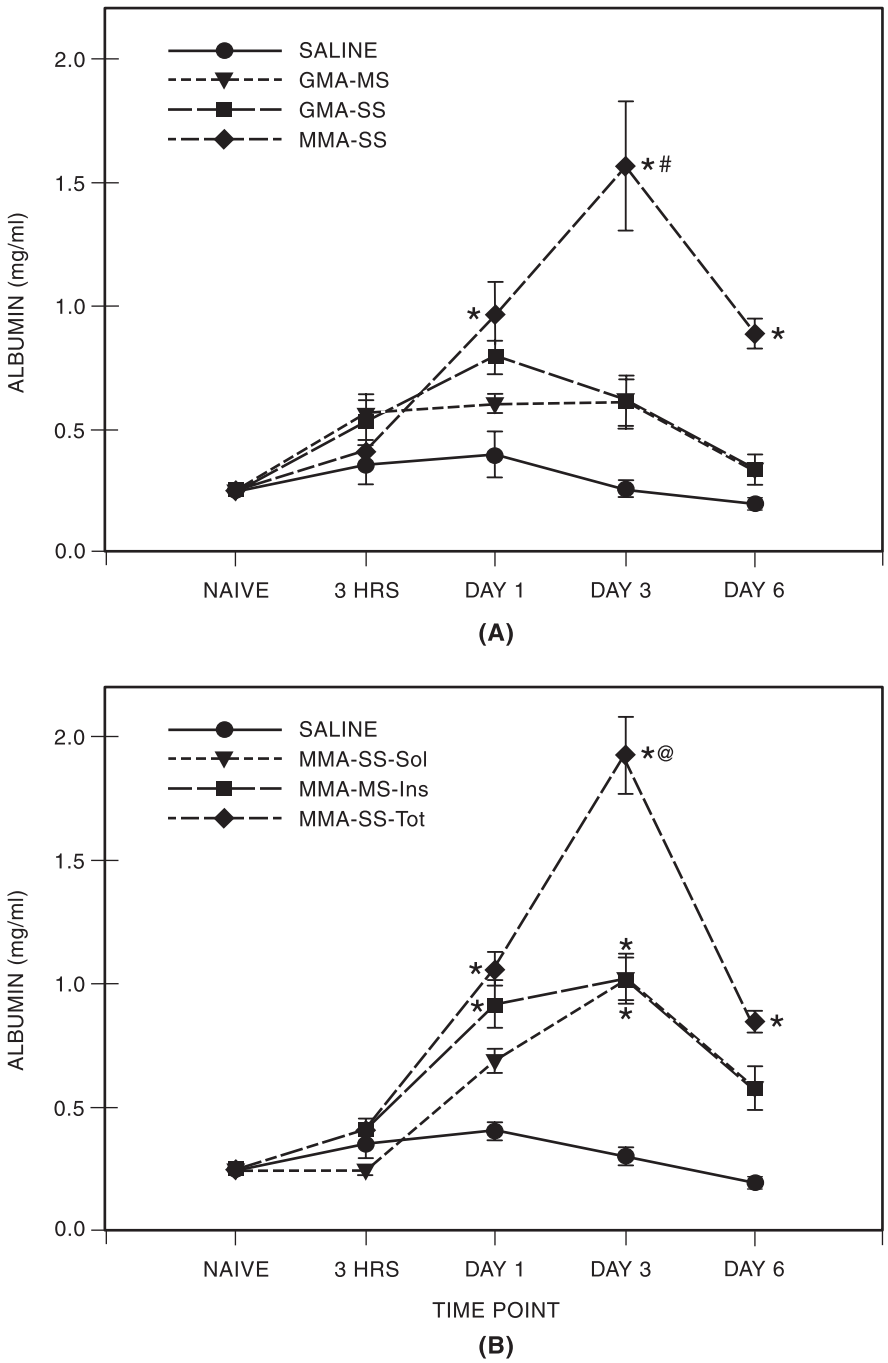
Welders have an increased risk of contracting pneumonia, but little is known about the mechanism of this phenomenon or the welding procedures responsible for it. Antonini et al. (Ref. 5) investigated the effects of fumes from GMAW of mild and stainless steel (GMAW-MS and GMAW-SS, respectively) and SMAW of stainless steel (SMAW-SS) on lung defense responses to bacterial infection in rats. The SMAW-SS fume was divided into its soluble and insoluble components which were tested separately in rats. The soluble fraction contained 87% chromium and 11% manganese and the major metallic constituents of the intact SMAW fume were iron, manganese, chromium, and nickel. The GMAW fumes were relatively insoluble and, hence, only the intact GMAW fume samples were tested. Fume samples were introduced into rat lungs by intratracheal instillation on day 0 followed by instillation of the bacterium *Listeria monocytogenes* on day 3. Animals were sacrificed on days 6, 8, or 10 and the numbers of *Listeria* colony forming units were determined to assess the clearance of bacteria from the lungs.

Only the intact SMAW-SS fume was found to increase lung infection by *Listeria*. Clearance of the bacteria from the lungs was markedly delayed and the rats lost more body weight when pretreated with the intact SMAW-SS fume than when pretreated with the other fume samples. Treatment with SMAW-SS reduced survival following exposure to *Listeria* and**,** by day 10, 30% of the rats in that treatment group had died whereas all of the rats in the other groups were still alive. Histological examination of the lung tissue showed severe pneumonitis on day 10 in rats treated with SMAW-SS fume but not in those treated with the other fume samples. Neither the soluble nor the insoluble fraction of SMAW-SS fumes produced these effects.

Several assays were performed to examine mechanisms by which SMAW-SS fumes may reduce lung defenses. Bronchoalveolar lavage fluid taken from rats that had been instilled with SMAW-SS fume had elevated lactate dehydrogenase (LDH: an indicator of loss of membrane integrity in cells that are injured or dead) and albumin (an indicator of damage to the integrity of the alveolar-capillary barrier) both before and after exposure to *Listeria*, compared with BALF from rats instilled with saline. Significant increases in numbers of macrophages, PMNs, eosinophils, and lymphocytes were seen in BALF after treatment with SMAW-SS which suggested enhanced immune and inflammatory responses. It was also found that reactive oxygen species (ROS) and nitric oxide and its oxidation products (NOx: nitrate and nitrite) were markedly elevated in macrophages and BALF before and after infection in rats treated with SMAW-SS; NOx was not elevated in rats treated with *Listeria* alone. The proinflammatory cytokines tumor necrosis factor-α (TNF-α), IL-6, and IL-10 were elevated in BALF from rats treated with SMAW-SS fumes and *Listeria*. Interleukin-2, which is involved with T-cell proliferation, was significantly decreased by SMAW-SS. The authors suggested that "alterations in defense against infection could be attributed to the effect of SMAW-SS exposure on immune cell signaling in lungs" and that reactive oxygen and nitrogen species could have contributed to the lung injury observed after treatment with SMAW-SS fumes.

Further studies from this laboratory showed that both the soluble and insoluble fractions contribute to the inflammatory response elicited by intact SMAW-SS fumes (Ref. 153). Rats were treated with GMAW-SS, GMAW-MS, or SMAW-SS fume samples by intratracheal instillation and were sacrificed at 3 hours, and at 1, 3, and 6 days after treatment. All treatments caused an increase in the numbers of macrophages and neutrophils recovered in BALF and an increase in lung weights; these levels reached a maximum on day 3 in rats treated with the GMAW fumes but continued to increase until day 6 in animals that had been treated with the SMAW-SS fume.

Other parameters measured in BALF were albumin, LDH, and the pro-inflammatory cytokines TNF-α, IL-1β, IL-6, and IL-10. Malondialdehyde and 4-hydroxyalkenals (4-HNE), which are markers of lipid peroxidation, were measured in lung tissue. Albumin levels peaked 1 day after instillation of GMAW fumes but were never significantly greater than those elicited by saline**.** In contrast, albumin levels peaked 3 days after instillation of intact SMAW-SS fumes and were significantly greater on days 1, 3, and 6 than those elicited by saline (Figure 3a). Albumin levels were significantly elevated on days 1 and 3 after treatment with the soluble and insoluble fractions of SMAW-SS fume and their effects appeared to be additive (Figure 3b). Lactate dehydrogenase in BALF and malondialdehyde and 4-HNE in lung tissue were all elevated on the third day after instillation of fume samples. The response was substantially higher with the SMAW fume than with the GMAW fumes, and both the soluble and insoluble fractions of the SMAW fume appeared to



Rats were treated by intratracheal instillation with (A) GMAW-MS (GMA-MS), GMAW-SS (GMA-SS), SMAW-SS (MMA-SS), or the saline vehicle, or with (B) intact SMAW-SS fumes (MMA-SS-Tot), the soluble fraction (MMA-SS-Sol), the insoluble fraction (MMA-MS-Ins), or saline. Albumin was measured in BALF 3 hours, or 1, 3, or 6 days following treatment. Values are means ± SE.

* Significantly different from saline.
# Significantly different from GMAW-MS.
@ Significantly different from SMAW-SS-Insol.

Source: Taylor et al., Ref. 153.

Figure 3—Effect of Welding Fume Treatment on Albumin in Bronchoalveolar Lavage Fluid (BALF)

contribute to it. TNF-α was significantly elevated on the first day after treatment with both stainless steel fume samples and with the soluble fraction of the SMAW-SS fume sample. IL-6 was significantly elevated on day 1 after treatment with the SMAW-SS fume only. Levels of IL-1β and IL-10 did not change significantly in response to treatment with any fume sample.

These studies showed that both the water soluble and insoluble fractions contribute to the inflammatory response elicited by SMAW-SS fumes. The insoluble fraction caused an increase in neutrophils, the soluble fraction caused an increase in eosinophils, and both fractions caused an increase in macrophages in BALF. Both fractions contributed to the increase in albumin and LDH in BALF and to lipoperoxidation, although the insoluble fraction contributed more to the oxidation of lipids than did the soluble fraction.

To examine which metal components in the SMAW-SS fume contribute to the alterations in lung defenses against *Listeria*, Antonini et al. (Ref. 4) treated rats by intratracheal instillation with SMAW-SS fume or with ferric oxide (Fe_2O_3), nickel oxide (NiO), or sodium dichromate ($Na_2Cr_2O_7$) alone or in combination, at concentrations equal to that found in the total fume. *Listeria* was introduced into the lungs on day 3, and colony forming units in the lungs were measured on days 6, 8, and 10. The bacterial count in the lungs and lung tissue damage significantly increased in rats treated with the intact fume, the soluble chromium salt, or the mixture of the three metals. When instilled alone, the iron and nickel salts had no effect. The numbers of macrophages and PMNs and the concentrations of LDH, albumin, IL-6, and IL-12 were elevated in BALF following treatment with sodium dichromate. No changes were seen in TNF-α or IL-10. These findings suggested that soluble chromium is the component of the SMAW-SS fume most likely to be responsible for suppression of the lung defenses against *Listeria* infection. These investigators (Ref. 2) also reported that the SMAW-SS fume caused DNA strand breaks when incubated with DNA and hydrogen peroxide in a cell-free assay. This was attributed to the formation of the biologically reactive hydroxyl radical resulting from the reduction of Cr(VI) to Cr(V) via a Fenton reaction.

McNeilly et al. (Ref. 108) exposed cultured human type II alveolar epithelial cells to welding fumes or their soluble and insoluble fractions and determined the effects upon the production of the pro-inflammatory cytokine IL-8, and the activation of the nuclear translocation factors NF-κB and AP-1. The fumes tested were produced by welding with a cobalt-based stainless steel consumable electrode (COBSTEL6) and with nickel-based (NIMROD 182 and NIMROD c276) consumable electrodes. Chromium represented more than 80% of the metal in the soluble fractions from all fumes; manganese, nickel, and iron comprised most of the remaining metal in the soluble fractions with the exception of the soluble fraction of the COBSTEL6 fume which contained substantial amounts of cobalt.

Cells were treated for 6 or 24 hours with concentrations of welding fumes or their fractions ranging from 2 μg/mL to 63 μg/mL and IL-8 was measured in the culture medium. IL-8 was significantly elevated at the two highest doses of NIMROD c276 and COBSTEL6 fumes or their soluble fractions at both time points. The particulate fume fraction had no effect. Treatment of the soluble fume fractions with a transition metal chelator[9] before addition to the cell culture obliterated this effect, demonstrating that soluble metals in the fumes were responsible for stimulating the release of IL-8.

Levels of IL-8 mRNA were increased at 6 hours, but not at 24 hours following treatment of cells with NIMROD c276 or COBSTEL6 fumes or with their soluble fractions, which showed that the inflammogenic response to the fumes occurs within 6 hours of exposure. All fume samples and their soluble fractions caused a depletion in levels of the intracellular antioxidant glutathione within 2 hours after treatment. Levels of glutathione rebounded by 6 hours and were higher than normal at 24 hours. Intracellular ROS levels were elevated following treatment with fumes from the nickel-based welding rods, but not the cobalt rod. The investigators concluded that "the soluble fractions of welding fumes play a fundamental role in mediating pro-inflammatory responses in alveolar epithelial cells as shown by increased expression of IL-8" and that the soluble metal component is responsible for this effect. Their data "support the hypothesis that an enhanced inflammatory response, mediated by transition metals and oxidative stress in the lungs following inhalation of welding fume particles, is a potential mechanism for metal fume fever and potentially other adverse heath effects of welding fume exposure."

In a subsequent study, McNeilly et al. (Ref. 109) examined whether soluble transition metals in welding fume also drive the inflammatory response *in vivo*. Rats were treated with NIMROD c276 fume samples by intratracheal instillation and the cell population in BALF was examined 24 hours later. Macrophages were significantly elevated in rats treated with

[9] The soluble fume fraction was treated with chelex-100 beads. Cations present in solution are chelated onto the surface of the beads and removed from the supernatant by centrifugation.

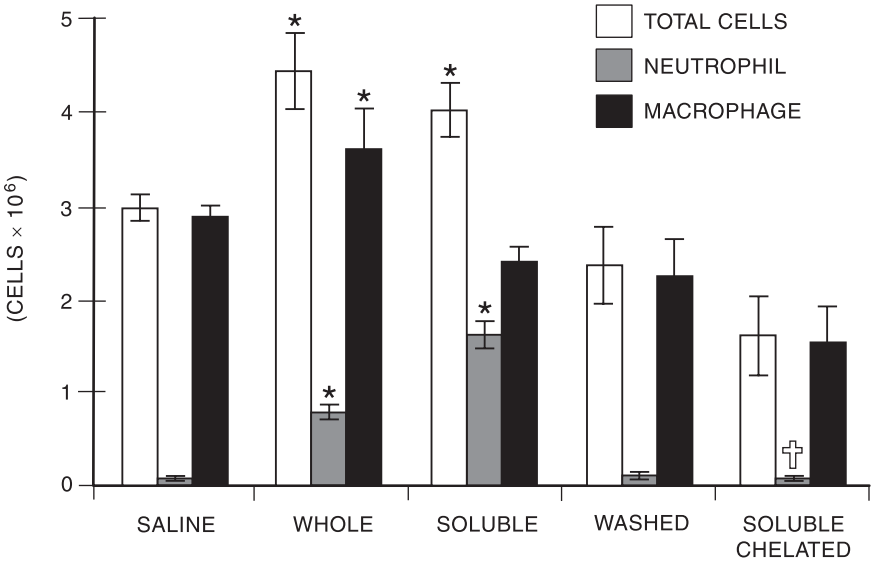
the whole fume sample and total cells and neutrophils were significantly elevated in rats treated with either the whole fume or the soluble fume fraction (Figure 4). The cell population in BALF from rats treated with particulate alone or with the chelated soluble fraction did not differ significantly from that of saline-treated controls. Similarly, macrophage-inflammatory protein-2 (MIP-2)[10] in BALF, and AP-1 and NF-kB binding to DNA were significantly elevated following treatment with whole fumes or the soluble fume fraction but not with washed particulate or the chelated soluble fraction. The investigators concluded that "soluble transition metals present in welding fumes cause inflammation via activation of the redox-sensitive transcription factors NF-κB and AP-1."

That soluble metals present in welding fumes can induce the release of cytokines from cells was also demonstrated in an *in vitro* study by Pascal and Tessier (Ref. 124). These investigators treated cultured human lung epithelial cells with nickel, manganese, or potassium dichromate, a soluble Cr(VI) salt. Manganese and Cr(VI), but not nickel, were cytotoxic at concentrations of 0.2 μM to 200 μM. At these concentrations, levels of IL-6 and IL-8 in the culture medium were up to 4.4 times greater than those found in controls. Levels of TNF-α were unchanged. The investigators concluded that "the observed effects of chromium(VI) and manganese in lung epithelial cells demonstrate a mechanism through which the toxicity of these metals to epithelial cells can result in recruitment of cells of the immune system."

24. Fibrosis

In earlier work, Yu et al. conducted a series of inhalation studies in rats which examined particle deposition and fibrogenic characteristics of fumes generated by SMAW-SS. In one of these studies (Ref. 171), groups of rats were exposed for 2 hours per day for 1, 15, 30, 60, or 90 days to fume concentrations of 63.6 mg/m^3 (low dose) and 107.1 mg/m^3 (high

[10] Macrophage-inflammatory protein-2 is a chemokine involved in the migration of neutrophils to sites of inflammation.



Columns represent the mean of four animals per treatment and the bars represent ± S.E.M.

* Denotes significantly ($P < 0.05$) greater than saline value for that index.
+ Denotes significantly ($P < 0.05$) less than soluble.

Source: McNeilly et al., Ref. 109.

Figure 4—Total Number of Cells in BALF 24 hours after Intratracheal Instillation of Welding Fumes

dose). The animals in each group were sacrificed after their final exposure. Examination of respiratory tract tissues revealed little evidence of fibrosis in the low-dose rats. In the high-dose rats, there were particle-laden macrophages in alveolar spaces and signs of early fibrosis after 15 days of exposure. By 60 days, granulomatous regions, distinct fibrosis in perivascular and peribronchiolar areas, and some interstitial fibrosis were evident. In a later study**,** rats were exposed under the same conditions but were allowed a 90-day recovery period following the last exposure before they were sacrificed (Ref. 170). In high-dose rats, the fibrotic regions seen following 15- to 30-day exposures had completely resolved and were no longer evident after the recovery period. However, the fibrotic changes seen at 60 and 90 days of exposure were not fully reversible after the 90-day recovery period.

In a continuation of this research, these investigators (Ref. 150) measured pulmonary function in exposed rats and examined the cell population of BALF. Groups of rats were exposed for 2 hours per day for 1, 15, 30, or 60 days to SMAW-SS fume concentrations similar to those used in earlier studies: 65 mg/m^3 (low dose) and 108 mg/m^3 (high dose). Some of the rats in the 30- and 60-day exposure groups were allowed a 60-day recovery period following the last exposure before sacrifice.

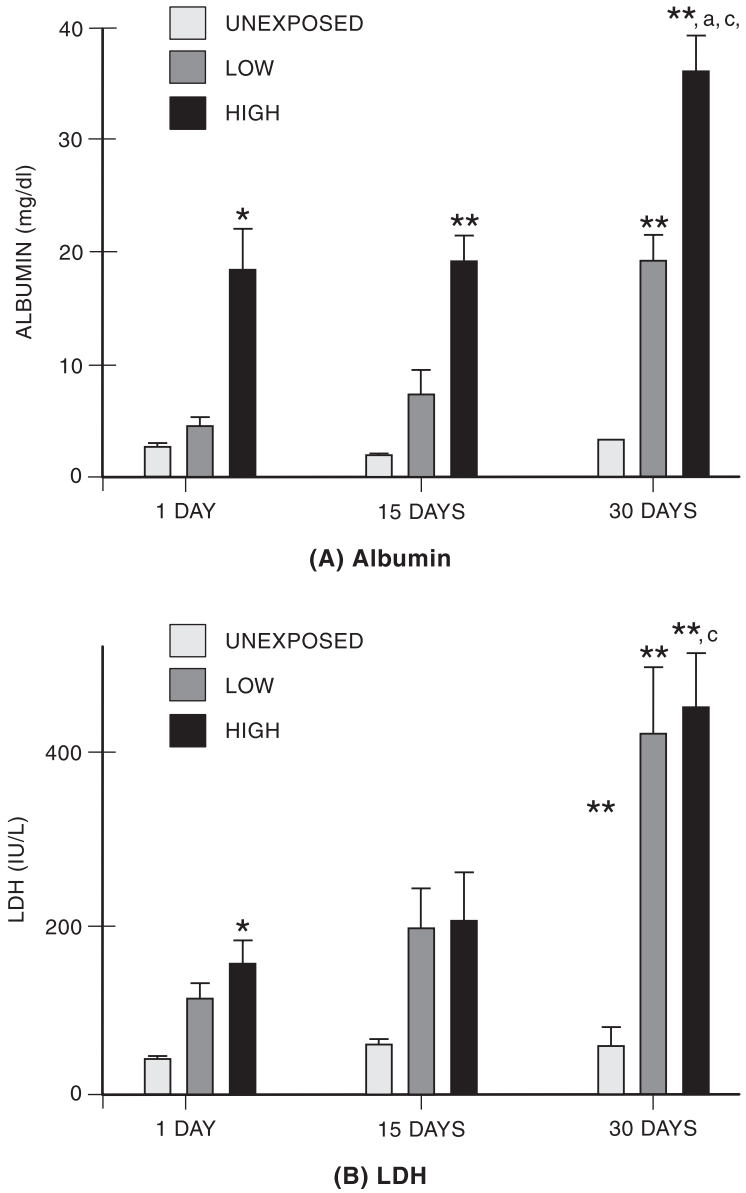
The number of cells recovered in BALF increased in a dose- and time-dependent fashion in all exposure groups. Alveolar macrophages accounted for most of the cells in the BALF cell population but the numbers of PMNs and lymphocytes were also significantly increased at most time points compared with the controls. After the 60-day recovery period, the number of all cell types remained significantly elevated in the high dose 60-day exposure group compared with controls but the number of cells in BALF from the other exposure groups was returning towards normal**.**

Pulmonary function tests, including tidal volume, minute volume, breathing frequency, inspiratory time, expiratory time, peak inspiratory flow, and PEF, were conducted once weekly**.** Statistically significant dose-dependent decreases were seen in the tidal volume but none of the other pulmonary function measures differed from those of controls. The tidal volume returned to normal after the 60-day recovery period in all rats except those exposed to the high dose for 60 days. The investigators noted that these observations concurred with their earlier findings that the fibrotic changes seen in rats exposed to the high dose for 60 days were not fully reversible after a 90-day recovery period. They concluded that their results "suggest that a decrease in the tidal volume could be used as an early indicator of pulmonary fibrosis induced by welding-fume exposure in Sprague Dawley rats, and fibrosis would seem to be preventable if the exposure is short-term and moderate."

A subsequent study by Yu et al. (Ref. 172) examined inflammatory and genotoxic responses in the lungs of rats exposed to SMAW-SS fume concentrations of 66 mg/m^3 (low dose) and 117 mg/m^3 (high dose) for 2 hours per day for 1, 15, and 30 days. Indicators of inflammation and lung damage assessed in BALF at all time points included albumin to detect changes in permeability of the bronchoalveolar capillary wall, LDH to detect general cytotoxicity, and N-acetyl-β-D-glucosaminidase (a lysosomal enzyme secreted by alveolar macrophages) to detect phagocytic activity. Concentrations of albumin and LDH increased significantly in BALF with duration of exposure (Figure 5). Concentrations of N-acetyl-β-D-glucosaminidase and of the cytokines TNF-α, and IL-1β in BALF did not differ significantly from controls during the 30-day exposure period.

Using immunochemical methods for detecting 8-OHdG, evidence of oxidative DNA damage was found in lung tissue from rats exposed for 30 days. DNA damage was further assessed in lungs from exposed animals using the comet assay. The tail moment, a measure of single strand breaks and DNA cross links, was significantly higher in lungs from exposed animals than from controls (Figure 6).

These investigators then examined the genes that are specifically expressed or down-regulated in rats with early stage fibrosis associated with welding fume exposure (Ref. 131). Rats were exposed by inhalation to 108 mg/m^3 SMAW-SS fumes for 2 hours per day for 30 days. Then RNA was extracted from peripheral blood mononuclear cells and, using suppression subtractive hybridization and cDNA microarray, gene expression profiles were analyzed. The expression of 261 genes was found to have increased, while that of 772 genes was decreased among the 5200 genes analyzed. The expression of five of these genes was increased by 90% or more, and that of 36 genes was decreased by more than 59%. The investigators concluded that prolonged welding-fume exposure substantially down-regulated many genes. The development of c-DNA microarray methods potentially useful for monitoring welders for early detection of pneumoconiosis is the subject of more recent work by these investigators (Ref. 130).

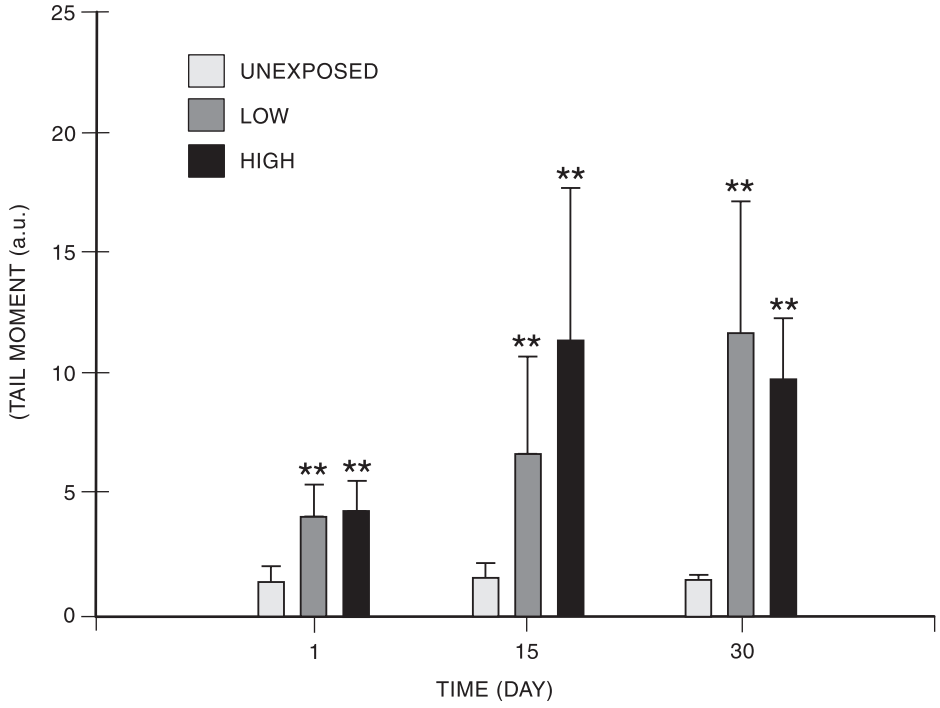


The error bars indicate standard error:

* $P < 0.05$ (low and high dose group vs. unexposed).
** $P < 0.01$ (low and high dose group vs. unexposed).
(a) $P < 0.01$ (low dose vs. high dose).
(c) $P < 0.01$ (30 days vs. 15 days).

Source: Yu et al., Ref. 172.

Figure 5—Changes in the Inflammatory Parameters Albumin and LDH during 30 days of Welding Fume Exposure



The tail moment = tail length × %DNA in tail.
The error bars indicate the standard error (**$P < 0.01$).
Source: Yu et al., Ref. 172.

Figure 6—Detection of DNA Strand Breaks in Individual Lung Cells using the Comet Assay

25. Manganese Distribution in Rat Brains

Yu et al. (Ref. 169) investigated the distribution of manganese in the rat brain following exposure by inhalation to fume generated by SMAW of stainless steel. The rats were exposed for 2 hours per day for 1, 15, 30, or 60 days to welding fume concentrations of 63.6 mg/m^3 (low dose) or 107.1 mg/m^3 (high dose) containing 1.6 mg/m^3 manganese and 3.5 mg/m^3 manganese, respectively. Groups of animals were sacrificed after 2 hours, 15, 30, and 60 days of exposure and manganese concentrations were determined in samples of blood, brain, lung, and liver. Manganese concentrations in the lung and liver increased with the dose and with the duration of exposure and were significantly higher than in controls at all time points after initiation of exposure. Changes in concentrations of manganese in blood were slight and were only significantly different from controls after 60 days of exposure. Statistically significant increases in manganese levels in the cerebellum were seen at all time points at both doses after 15 or more days of exposure but only slight increases were seen in the substantia nigra, basal ganglia (including the caudate, nucleus, putamen, and globus pallidus), temporal cortex, and frontal cortex after 60 days of exposure. Yu et al. compared their results with those obtained in a study by St-Pierre et al. (Ref. 148) who exposed rats by inhalation to manganese dusts for 15 weeks. In that study, there was a high accumulation of manganese in the striatum and globus pallidus of the basal ganglia and a lower accumulation in the cerebellum. These findings suggest that pharmacokinetics involved in absorption of manganese from welding fumes differ from those involved in absorption of manganese from pure manganese dusts. It would be of interest to see a rat inhalation study conducted in which the tissue distribution of manganese from manganese dust and from welding fumes were performed side-by-side, under identical conditions, in the same laboratory. Such a study would more definitively examine important questions concerning the potential effects of the physicochemical structure of manganese in welding fumes on its bioavailability and tissue distribution.

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Figure 1. From Mukherjee et al., Urinary metal and polycyclic aromatic hydrocarbon biomarkers in boilermakers exposed to metal fume and residual oil fly ash. *Am. J. Ind. Med.* 47(6): 484–493, 2005.

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Figure 4. Reprinted from McNeilly et al., Soluble transition metals in welding fumes cause inflammation via activation of NF-kappaB and AP-1. *Toxicol. Lett.* **158**(2)**:** 152–157, 2005, with permission from Elsevier.

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Table 2. From Fryzek et al., A cohort study of Parkinson's disease and other neurodegenerative disorders in Danish welders. *J. Occup. Environ. Med.* **47**(5)**:** 466–472, 2005, with permission from Wolters Kluwer Health.

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Appendix 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[a] and to a lesser extent in obstructive disease.[b]
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. FEV1 is normally about 80% of FVC.
Maximal Voluntary Ventilation	MVV	The maximum volume of air that can be breathed into and out of the lung in one minute. MMV is a non-specific measure of the performance of the entire pulmonary apparatus.
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 Responsiveness to Methacholine	PD_{20}	The provocative cumulative dose of methacholine causing a 20% decrease in FEV1. Positive responses at relatively low doses of methacholine are indicative of asthma.
Forced Expiratory Flow	FEF	Flow rate measured during forced exhalation.
Mid range (25%–75%)	$FEF_{25–75}$	Reductions in mid range and terminal flow indicate impairment in small airways (alveolar region of the lung).
Terminal flow (75%–85%)	$FEF_{75–85}$	
Maximum Expiratory Flow	MEF_{25}	Measured at 25% of FVC.
	MEF_{50}	Measured at 50% of FVC, also known as maximum mid expiratory flow (MMEF).
	MEF_{75}	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.

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

[b] 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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Appendix 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) $\times$ 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**). **Incident cases** refer to all new cases of the condition or disease under study that are identified within a specific population during a specified time period. 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**.

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Appendix C

Summaries of Studies on the Effects of Welding on Human Health Published Between 2006 and 2009[11]

Respiratory Tract

Pulmonary Function. Seven studies examined the effects of welding exposures on pulmonary function (Ref. 11, 18, 33, 40, 46, 47, 56). Deficits in air flow were found in all but two of them. An increase in respiratory symptoms was found among welders in three of the four studies that examined these effects (Ref. 40, 46, 47, 56).

Loukzadeh et al. (Ref. 46) conducted a cross-sectional study of lung function and respiratory symptoms among 137 spot welders and 129 office staff who worked in an automobile assembly plant in Iran. Welding fume concentrations were below the ACGIH TLV. The average values for forced expiratory volume/forced vital capacity (FEV_1/(FVC), forced expiratory flow ($FEF_{25–75}$), and FEV_1were significantly lower and the prevalence of respiratory symptoms (sputum production and shortness of breath) was significantly higher in spot welders than in controls.

Luo et al. (Ref. 47) compared lung function values and respiratory symptoms in 41 spot welders, 76 arc welders, and 130 controls who worked in automobile manufacturing plants in Taiwan. Concentrations of zinc, copper, and nickel in post-shift urine samples were used as the measure of exposure levels. Among the spot welders, there was a significant dose-response relationship between exposure and declines in FVC and peak expiratory flow rate (PEFR). A significant decline in PEFR was seen in arc welders in the high exposure group. The incidence of respiratory symptoms (cough, phlegm, chronic bronchitis) was significantly related to exposure levels in both arc and spot welders.

Ould-Kadi et al. (Ref. 56) compared pulmonary function in 114 welders and 123 non-exposed controls. The welders worked in two manufacturing plants in Algeria where SMAW of steel was the main welding process used. It was found that FVC and FEV_1 were slightly, but significantly, lower in the welders than in the controls. No differences were seen in the prevalence of respiratory symptoms such as chronic cough, sputum production, shortness of breath during low to moderate physical activity, or in symptoms of asthma or allergy.

Bowler et al. (Ref. 11) measured pulmonary function in 43 welders who had been involved with construction of the new span of the San Francisco Bay Bridge for a mean of 16.5 months where they had worked in confined spaces with little personal protection. A decrease in FEV1/FVC was found in 33% of the subjects.

Pulmonary function was assessed in welders by Gube et al. (Ref. 33) using spirometry combined with the newer techniques Impulse Oscillometry (IOS) and Capnovolumetry (CV). Pulmonary function measurements taken at the start of the work shift did not differ between welders and controls. Declines in pulmonary function were demonstrated by IOS and CV during the work shift and with years of welding experience.

Jayawardana and Abeysena (Ref. 40) compared the results of spirometric tests and the prevalence of respiratory symptoms among 41 welders and 41 non-exposed office workers in Sri Lanka. The values for FVC, FEV_1, $FEF_{25–75}$, and PEFR did not differ significantly between the welders and controls. The incidence of chronic bronchitis, however, was significantly higher among the welders.

Christensen et al. (Ref. 18) investigated whether long-term exposure to welding fumes accelerates the decline in lung function that normally occurs with aging. Forced expiratory volume (FEV_1) was measured by spirometry in 68 steel welders and 32 non-welding production workers who had been tested 18 years earlier as part of another study (Ref. 8).

[11] Short summaries of some documents published during this period appear in the main text instead of this appendix, as appropriate.

The rate of decline did not differ significantly between welders and controls and was not related to cumulative exposures to welding fumes estimated for the 18-year follow-up period.

Occupational Asthma. Bakerly et al. (Ref. 5) examined trends in occupational asthma (OA) in the West Midlands, England. Occupational and chest physicians were requested to submit details about OA cases that were diagnosed over a 15-year period. A total of 1461 cases were reported of whom 68% were male. Welders (9%) and workers in health care-related professions (9%) were the most frequently reported occupations to have OA.

Lillienberg et al. (Ref. 45) examined the incidence of asthma and chronic bronchitis in 316 men whose welding activities at work varied from less than 1 hour to more than 4 hours per day. Symptoms of chronic bronchitis were significantly associated with frequent welding of galvanized iron or steel and with shielded metal arc welding of stainless steel in this study population. Welding of painted metals was associated with wheezing.

Hannu et al. (Ref. 35) discussed the cases of 34 male stainless steel welders who were diagnosed with OA at the Finnish Institute of Occupational Health between 1994 and 2003. The patients had a mean age of 44 years and had worked as welders for a mean of 22.4 years. Respiratory symptoms first appeared after they had worked as welders for an average of 18 years. Patient history, lung function tests, and welding challenge tests formed the basis of their diagnoses. The most frequently reported work-related respiratory symptom was dyspnea. It was determined that, because of the severity of their asthma, 21 of the patients should not continue working as welders.

Hannu et al. (Ref. 36) described the progression of OA in a machinist who worked near an area where stellite (a metal alloy whose primary components are cobalt and chromium) was welded. Measurements of peak expiratory flow in the workplace were suggestive of OA. Mild bronchial hyperresponsiveness was revealed by histamine challenge. Challenge tests in a welding exposure chamber where mild steel was welded with a stellite electrode induced an immediate asthmatic reaction.

Munoz et al. (Ref. 53) described three welders, mean age 42 years, diagnosed with OA by welding challenge tests. Increases in neutrophils and concentrations of interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), and TNF-β were present in their sputum after the challenge.

Wittczak et al. (Ref. 83) described the case of a 42-year-old welder with work-related shortness of breath. The proportion of eosinophils and basophils was increased in his sputum at 4 and at 24 hours after an inhalation challenge with a solution of 0.1% manganese chloride. Shortness of breath and a significant decrease in FEV_1 were observed during the challenge. The authors stated that "To our knowledge, this is the first well-documented case of manganese-induced occupational asthma."

Pneumoconiosis. Qiu et al. (Ref. 62) investigated the incidence of pneumoconiosis in 813 welders from Guangdong province in China. Chest X-rays revealed pneumoconiosis in 19 of the welders. The average age of the welders with pneumoconiosis was 33.5 years and the average duration of their welding experience was 8 years.

Di Lorenzo et al. (Ref. 22) described the case of a welder with pneumoconiosis that was confirmed by histological, immunohistochemical, and mineralogical examination of biopsied lung tissue. Patel et al. (Ref. 61) described two welders who had siderosis evident in lung biopsies along with systemic iron overload. Modrykamien et al. (Ref. 51) described the case of a 38-year-old man with 15 years welding experience who developed chest pain and shortness of breath. Evidence of siderosis was seen in a high-resolution computed tomography (CT) scan of the chest. His serum ferritin level was 1634 ng/mL (normal range: 30 ng/mL to 300 ng/mL). Deficits in the pulmonary function measures FEV_1, FEV_1/FVC, and FVC were revealed by spirometric tests.

McCormick (Ref. 49) described the case of a 66 year-old-man who had pulmonary fibrosis in conjunction with siderosis as revealed by chest radiography and CT scan. He had suffered from shortness of breath upon exertion for about 2 years. He had performed a substantial amount of welding during his 20-year job as an engineer but had always worn a face shield. Spirometric tests revealed a significant reduction in lung function. Balkissoon (Ref. 6) described a 26-year-old aluminum welder with severe chronic obstructive pulmonary disease. He had suffered from shortness of breath for about 1 year prior to examination. Evidence of pulmonary inflammation consistent with aluminum pneumoconiosis was found by analysis of biopsied lung tissue.

Laryngitis. A 50-year-old man who experienced symptoms of laryngitis while welding stainless steel was described by Hannu et al. (Ref. 34). A stainless steel welding inhalation challenge test caused erythema, edema, and hoarseness of his voice within 30 minutes. These effects were not seen following a challenge test with welding of mild steel.

Hypersensitivity Pneumonitis. Miyazaki et al. (Ref. 50) described the case of a 55-year-old man who developed fever, cough, and dyspnea after welding galvanized steel. The number of lymphocytes in bronchoalveolar lavage fluid was elevated and lymphocytic alveolitis was observed in lung biopsy specimens. He reacted positively to zinc in skin patch tests and was diagnosed as having hypersensitivity pneumonitis caused by exposure to zinc fumes.

Respiratory Tract Infections. Avashia et al. (Ref. 4) described the cases of two metal workers who died from pneumonia associated with *Bacillus cereus* infection. The first case was a 39-year-old welder with 19 years experience and the second case was a 58-year-old man who performed molding and grinding operations in a foundry. They had lived and worked in different parts of Texas. While *B. cereus* does not usually cause serious illness in non-immunocompromised hosts, analysis by polymerase chain reaction of the organisms isolated from both cases showed that they contained anthrax toxin genes that may have been responsible for their virulence (37). A similar organism had been isolated from a welder who died from pneumonia in Louisiana in 1994 (Ref. 38).

Cancer

Lung Cancer. In 1997, Moulin et al. (Ref. 52) conducted a meta-analysis which combined the data from 36 studies of lung cancer in welders published between 1954 and 1994. They concluded that welders have a 30% to 40% increased relative risk for lung cancer. No difference in the incidence of lung cancer was found between mild steel and stainless steel welders. These investigators later updated this analysis to include 60 studies published between 1954 and 2004 (Ref. 2). The update showed a 26% excess of lung cancer among welders and, again, no difference was seen in the incidence of lung cancer between mild steel and stainless steel welders.

The risk of lung cancer among mild steel and stainless steel welders was examined by Sorensen et al. (Ref. 73) in a cohort of male metal workers who had been employed for at least 1 year in the Danish steel industry between 1964 and 1984. The 4539 welders in the cohort were followed from 1968 to 2003 during which time 75 cases of primary lung cancer were identified through the Danish Cancer Registry. The risk for lung cancer was significantly increased among the welders. A positive exposure-response relationship was found among the stainless steel welders, but not among the mild steel welders.

Two studies examined the possible association between welding and particular histological types of lung tumors. Paris et al. (Ref. 58) conducted a case-case study of the relationship between lung adenocarcinoma and occupational risk factors. Lung cancer cases diagnosed in two hospitals in France between 1997 and 2006 were examined. The study included 1493 lung cancer cases, of which 489 were adenocarcinomas. Exposure to welding fumes was found to be significantly associated with lung adenocarcinoma (OR 1.62, C = 1.14–2.31). The correlation was higher for lung adenocarcinoma than for other histological tumor types.

Using data from the Finnish Cancer Registry and from the Finnish census records, Siew et al. (Ref. 71) examined potential associations between occupational exposure to iron and welding fumes and the lung cancer incidence among Finnish men. The study population included 1.2 million men from the Finnish workforce who participated in the 1970 population census. Based on exposure estimates, the highest excess risk among welders was found for squamous cell carcinoma. A less consistent pattern was found for adenocarcinoma and no excess risk was found for small cell carcinoma.

Cancer in Other Organs. D'errico et al. (Ref. 21) conducted a case-control study of occupational risk factors for sinonasal cancer. The 113 incident cases included in the study were reported between 1996 and 2000 to the regional Sino-nasal Cancer Registry by hospitals in the Piedmont region of Italy. Exposure to welding fumes was found to be significantly associated with squamous cell carcinoma (OR = 4.1; CI = 1.66–10.13) and the incidence was positively associated with the duration of exposure.

Dixon (Ref. 23) described the case of a 71-year-old woman with numerous squamous cell carcinomas on her hands, two on her face, and one basal cell carcinoma on her neck. She also had ultraviolet (UV) skin damage on her hands, face, and neck. While she had never welded, she had assisted her son with his welding business by holding together metal pieces to be welded. She had worn no personal protective equipment while assisting with this work.

Walschaerts et al. (Ref. 79) conducted a hospital-based case-control study of testicular cancer in which 229 cases and 800 controls were compared. Occupation as a welder was found to be associated with an elevated risk for this cancer (OR = 2.84, CI = 1.51–5.35).

Effects on the Eye

Woo and Sundar (Ref. 84) categorized the occupations of the 113 patients with eye injuries who reported to the Department of Ophthalmology in a hospital in Singapore during a 7-week period in 2005. They found that 56% of all the eye injuries were work-related and that 38% occurred while using high-powered tools in activities such as grinding, welding, and hammering. Most patients were not using personal protective equipment at the time of their injuries.

Noting that welders in Calabar, Nigeria, did not always wear protective goggles while welding, Davies et al. (Ref. 20) examined the eyes of 110 welders and compared them with 85 non-welding controls. The incidence of pingueculum, cataract, allergic conjunctivitis, corneal opacity, and keratoconjunctivitis (arc eye) was significantly higher in the welders than in the controls.

Sprince et al. (Ref. 74) analyzed activities associated with eye injury among 36 farmers in Iowa who sustained 40 eye injuries that necessitated medical advice or treatment. Welding accounted for three (7.5%) of the injuries.

Gerente et al. (Ref. 32) interviewed 123 patients with superficial corneal foreign body injuries who were seen at an emergency room in Sao Paulo, Brazil. Most of the injuries occurred at the workplace and resulted from construction-related activities (44.3%) or welding/soldering (11.3%).

Ultraviolet photokeratitis, also known as arc eye, is a condition in which there is inflammation of the cornea caused by exposure to UV light. Najjar et al. (Ref. 54) investigated whether there is detectable damage to the corneal endothelium in patients with acute photokeratitis. The corneas of 20 consecutive patients who visited their clinic with photokeratitis and of 20 age-matched healthy controls were examined by non-contact specular microscopy. No statistically significant differences were seen in the mean size or the mean density of corneal endothelial cells between these two groups. The investigators concluded that exposure to UV light does not have a direct immediate effect on the corneal endothelium in persons with photokeratitis.

Chen et al. (Ref. 16) interviewed 283 patients at seven medical centers in Taiwan with work-related eye injuries. Photokeratitis caused by welding was experienced by 30% of the patients and was the most common type of eye injury.

An 18-year-old man who developed a severe infection in both eyes following a 3 hour welding exposure without proper eye protection was described by Yilmaz (Ref. 85). His eyes became red and painful immediately following exposure and worsened, with some loss of vision, over the next week. He was diagnosed with a corneal infection caused by *pseudomonas aeruginosa* which was successfully treated with antibiotics.

A 21-year-old man with phototoxic maculopathy was described by Vukicevic and Herio (Ref. 78). He had been welding without using the tinted visor on his welding mask. He saw an ophthalmologist 3 days later but the injury resulted in sustained loss of vision. Vedantham (Ref. 77) described a case of chronic welder's maculopathy observed in a 23-year-old man who, for 6 months, had occasional exposure to radiation from GMAW without using eye protection. He had endured no ocular pain but had suffered some loss of visual acuity.

Kim et al. (Ref. 43) described the case of a 39-year-old welder with more than 20 years welding experience who was diagnosed with macular edema after experiencing acute intense pain in his left eye with continuous lacrimation while welding. Because of his young age and history of an acute painful eye injury, he was diagnosed with maculopathy caused by exposure to the welding arc rather than with age-related macular degeneration.Choi et al. (Ref. 17) described the case of a 37-year-old man who developed photic retinal injury while performing plasma arc welding. His visual acuity was reduced one day after the exposure but showed improvement when examined one month later.

Effects on the Ear

Eleftheriadou (Ref. 24) described the case of a man who suffered an ear burn while welding. He was welding overhead when a drop of molten metal fell into his ear. He suffered some hearing loss and 6 months later a foreign body, 2.2 mm in diameter, was detected in his middle ear by a CT scan, and was surgically removed.

Effects on the Skin

Richtig et al. (Ref. 65) described a 55-year-old man with persistent brown to bluish gray macules[12] on the front of his lower legs. He had been a welder until he was 45 years old. His lesions were attributed to spatters that had penetrated his skin while welding without using proper skin protection. Examination of biopsied lesions by scanning electron microscopy and energy-dispersive x-ray spectrometry revealed multiple particles, 0.1 μm to 1 μm in size, composed of metals including aluminum, silicon, molybdenum, vanadium, chromium, and iron.

Effects on the Nervous System

Aluminum. Kiesswetter et al. (Ref. 42) performed a longitudinal study in which a full complement of neurobehavioral tests was administered to aluminum welders three times over a 4-year period. Aluminum concentrations were determined in breathing zone air and in blood and urine concomitantly with the neurobehavioral tests. The twenty subjects were aluminum welders, 41 to 45 years of age, who worked in the train and truck construction industry. Tests of verbal intelligence, logical thinking, psychomotor behavior, memory, and attention span were administered to welders and controls. There was no correlation between aluminum concentrations in biological fluids and performance on the neurobehavioral tests nor were there significant differences between the welders and controls in the performance on the neurobehavioral tests. The levels of nervous system symptoms reported by the welders also did not differ significantly from those reported by the controls.

Manganese Subclinical Effects. Chang et al. (Ref. 14) subjected 43 welders and 29 controls to a range of tests for subclinical neurological effects. Blood manganese and the pallidal index (PI: an estimate of the amount of manganese accumulated in the globus pallidus as determined by brain MRI) were determined for each subject. Tests of simple reaction time, postural sway, smell, and the Profile of Mood States revealed no differences between welders and controls. However, welders performed less well on complex figure and grooved pegboard tests and the results were significantly associated with blood manganese concentrations. Results of the digit symbol, digit span backward, grooved pegboard, Stroop word, and Stroop error index tests were significantly associated with the PI. The investigators concluded that "PI is a better predictor of neurobehavioral performance than blood manganese levels in asymptomatic welders."

Ellingsen et al. (Ref. 27) compared neurobehavioral function in 96 welders and 96 controls. Air sampling conducted at the time of the study showed that the welders were exposed to a mean manganese concentration of 0.12 mg/m^3. Mean blood manganese concentrations were 8.6 μg/L for the welders and 6.9 μg/L for the controls. Scores on the finger tapping test were significantly associated with mean manganese exposures of 0.42 mg/m^3 (range 0.204 mg/m^3–2.32 mg/m^3). Performance on the digit symbol test was significantly associated with the highest blood manganese concentrations (mean concentration: 12.6 μg/L). The investigators also subjected a separate group of 27 welders who had been diagnosed with and compensated for manganism related to their welding exposures (average duration of work as welders was 23.1 years) to the same neurobehavioral test battery. Finger tapping speed and grooved pegboard performance were their most impaired neurobehavioral functions on these tests.

Yuan et al. (Ref. 86) subjected welders with 16 years experience to the Neurobehavioral Core Test Battery (NCTB) recommended by the World Health Organization. The average concentration of manganese in the welders' workplace was 0.14 mg/m^3. Welders performed faster than controls on tests of visual simple reaction time and fast simple reaction time but less well on tests of digital span. Confusion, depression, fatigue, and anxiety were more common among welders than among controls. Urinary concentrations of 5-hydroxyindoleacetic acid, a break-down product of the neurotransmitter serotonin, were depressed in welders compared with controls.

In a study designed to explore the effects of metals on the nervous system, Wang et al. (Ref. 82) administered the NCTB to 82 welders and 51 controls. Concentrations of lead, manganese, and cadmium were determined in blood samples taken from each subject. Concentrations of lead and cadmium, but not manganese, were significantly higher in blood from welders than from controls. The prevalence of nervous system symptoms, determined by questionnaire, was significantly greater among welders than controls. Welders scored significantly less well on the Profile of Mood States than did controls. The controls fared better than the welders in the NCTB, especially in the areas of emotional irritation, fatigue, response velocity, quick memory, manual dexterity, and hand-eye coordination. Welders with the highest blood

[12] A macule is a small, flat, colored area of the skin that does not include a change in skin texture.

lead levels (≥ 120 μg/L) scored lower than other welders or controls in tests of fatigue, inertia, confusion, manual dexterity, and other neurobehavioral parameters. Poor scores on the digit span tests correlated with exposure to manganese. None of the nervous system impairments in welders were related to exposure to cadmium. The investigators concluded that the prevalence of neurological signs and symptoms observed in welders could be attributable to concomitant exposures to lead and manganese.

Bowler et al. (Ref. 10) performed neurological tests and measured blood manganese levels in 43 welders who had been employed on the San Francisco Bay Bridge project. They had welded in confined spaces with poor ventilation for a mean of 16.5 months. Exposure data for manganese were available for much of this time. More than half of the measured manganese exposures exceeded 0.2 mg/m^3. Significant dose-related changes were seen for several neurological effects (IQ, executive function, sustaining concentration, sequencing, verbal learning, and working and immediate memory) and self-reported symptoms (sexual function, fatigue, depression, and headache). The University of Pennsylvania Smell Identification Test showed impairment of olfactory function in 88% of the welders. There was no relationship between scores on the smell identification test and blood manganese levels (Ref. 3). These investigators later conducted a risk assessment for manganese exposure based on performance of welders in ten neuropsychological performance tests (Ref. 60). The subjects included 44 of the welders who had participated in previous studies (Ref. 10, 11). Using the benchmark dose method for determining risk, the investigators calculated that "more than one-third of workers would be impaired after working 2 years at 0.2 mg/m^3 manganese."

Konstantinova et al. (Ref. 44) described two welders with apparent manganese intoxication. Both men had characteristic neurological symptoms and had had lengthy exposures to manganese in excess of the Maximum Allowable Concentration.

Parkinson's Disease and Parkinsonism. To evaluate the role of occupational exposures in the etiology of Parkinson's disease, Park et al. (Ref. 59) conducted a retrospective cohort study among male workers who had been employed for at least 1 year between 1970 and 2002 in a shipyard in South Korea. New cases of Parkinson's disease diagnosed among the cohort between 1998 and 2003 were identified through the records of the National Health Insurance Corporation. The study cohort included 24,963 blue collar and 13,507 white collar workers. The blue-collar workers were placed into one of three groups**:** (1) welding, (2) fitting, grinding, finishing, and cutting, and (3) other. Mean manganese exposures measured in personal air samples were 0.88 mg/m^3 for workers in group 1 and 0.1 mg/m^3 for workers in group 2. Manganese exposures were very low among workers in Group 3. Neither the age of onset of Parkinson's disease nor the risk for Parkinson's disease differed significantly between welders and the other workers or controls. The investigators concluded that this "longitudinal study of shipbuilding workers supports our previous case-control studies suggesting that exposure to manganese does not increase the risk of Parkinson's disease."

Tanner et al. (Ref. 76) conducted a multi-center case-control study with 519 cases and 511 controls to examine the risk of parkinsonism among workers in agriculture, education, health care, welding, and mining and among those exposed to solvents and pesticides. Patients diagnosed with parkinsonism were recruited from eight movement disorders centers in North America. Neither the risk of parkinsonism nor its age of onset were found to be associated with welding.

Fang et al. (Ref. 28) examined the records of the Vanderbilt Movement Disorders Clinic in Tennessee and found that, of the 1126 medical charts reviewed over a 3-year period, eleven patients had been welders. The clinical presentation of the movement disorder in the welders was compared with that of 41 patients at the clinic who had no history of welding. Three of the 11 welders and 5 of the 41 non-welders had been diagnosed with parkinsonism. All of the parkinsonism patients responded to dopaminomimetic therapy. While, the age of onset of the movement disorder was younger in the welders, the investigators concluded that the prevalence rates for parkinsonism and dystonia were similar among the welders and non-welders.

Transcranial sonography (TCS) is a method that allows visualization of the brain through the intact skull. Using this technique, Berg (Ref. 7) found increased echogenicity in the substantia nigra (SN) in about 90% of Parkinson's disease patients. Increased SN echogenicity is rare in patients with parkinsonian syndromes, providing a method for differential diagnosis of the two disorders. Walter et al. (Ref. 80) compared TCS findings in two patients with parkinsonism and 3 age-matched patients with Parkinson's disease. The two patients with parkinsonism had worked as welders for many years in confined spaces with inadequate ventilation. Both of these men exhibited normal echogenicity of the substantia nigra when examined by TCS whereas the three patients with Parkinson's disease exhibited marked echogenicity in the substantia nigra.

Racette et al. (64) described a screening method using videotapes to perform rapid assessment of parkinsonism in large groups of subjects. Using this method, they found that parkinsonism was common among a group of 2081 welders referred to them for medical-legal screening.

Bowler et al. (Ref. 9) described the case of a 33-year-old welder who sought medical assistance for cognitive and motor difficulties. He suffered from tremor, bradykinesia, gait disturbance, and cogwheel rigidity, all of which are symptomatic of Parkinson's disease, but his neuropsychological signs, young age, and cock-walk gait were suggestive of manganism. Concentrations of manganese in serum and urine samples were elevated, and increased T1-weighted signal intensities in the basal ganglia was seen in brain MRIs. Results of neuropsychological tests performed 2 years later supported a diagnosis of early onset parkinsonism which the authors attributed to welding.

A 32-year-old welder who developed parkinsonism with severe postural instability and dystonia was described by Kenangil et al. (Ref. 41). He had welded for 10 years when he was first seen and his condition worsened markedly during the next 3 years. He did not benefit from treatment with any dopaminergic agents. Evidence of manganese exposure was found by MRI of the brain.

Da Silva et al. (Ref. 19) described a 41-year-old man who sought medical help because of memory deficits experienced in the last 3 years. He had not used respiratory protection during his 20 year career as a welder. Neuropsychological tests indicated deficits in attention and short- and long-term memory. He also had symptoms of parkinsonism including bradykinesia, cogwheel rigidity in his upper limbs, and a slight postural and resting tremor in one limb. Signs of manganese accumulation were seen in an MRI scan of the brain.

Effects on the Cardiovascular System

Scharrer et al. (Ref. 69) examined the effects of short-term exposure to welding fumes on heart rate variability (HRV) and on the number of inflammatory cells, concentrations of inflammatory mediators (e.g., IL-6, IL-8, C-reactive protein, TNF), and concentrations of hemostatic proteins (e.g., fibrinogen, endothelin-1, antithrombin III, factor VIII). Twenty individuals were exposed for 1 hour to welding fumes on two separate days. Five hours after the second exposure, HRV was measured and blood samples were collected. No changes in pulmonary function or HRV were detected. With the exception of endothelin-1 (a protein that constricts blood vessels and raises blood pressure) which fell significantly after exposure, no changes were seen in the concentrations of the other mediators or cell types examined. The investigators concluded that their "data did not indicate effects of clinical significance of a short-term high-level exposure to welding fumes on HRV or a set of blood hemostatic and acute inflammatory parameters in healthy subjects" and that "welding fumes are not likely to exert acute cardiovascular effects in healthy individuals."

Changes in HRV were found to be associated with exposure to welding fume in a series of studies performed at the Harvard School of Public Health. In one of the these studies, Chen et al. (Ref. 15) examined average heart rate (HR) and HRV in ten boilermakers who were classified according to their coronary risk profiles. Personal $PM_{2.5}$ particulate exposures were monitored during welding. Heart rate was found to increase and HRV to decrease with increases in $PM_{2.5}$ measured over the preceding 4 hours. These responses were greater in high-risk subjects than in low-risk subjects.

Later, HRV was measured by ambulatory ECG during the evening after welding in 26 boiler makers and the association with the metal content of $PM_{2.5}$ examined (Ref. 13). The decline in nighttime HRV following welding exposure was greater than the daytime decline and there was a positive association between the decline in HRV and the content of manganese in the particles. However, the metal content of the particulate fraction was insufficient to account for the reduction of HRV, suggesting that non-metallic components of the particulate fraction may also be responsible.

To assess the role of vascular function, the augmentation index (a measure of arterial stiffness associated with cardiovascular risk) was measured in 26 welders over 24 hour periods during which they either had or had not performed welding (Ref. 30). Pre- and post-shift augmentation indices were determined; personal $PM_{2.5}$ exposures were measured for 6 hours on welding and non-welding days. The association between augmentation index and $PM_{2.5}$ exposures was positive in post-shift measurements and negative in pre-shift measurements suggesting that "exposure to the $PM_{2.5}$ component of welding fume elicits acute adverse vascular responses." Subsequent studies by Fang et al. (Ref. 29) showed that systemic inflammation, as measured by levels of C-reactive protein, and reduced vascular function, as measured by the augmentation index, appear to enhance declines in heart rate variability among workers exposed to welding fumes.

Effects on Reproduction

Using the data base compiled by the Finnish Prenatal Environment and Health Study, Quansah and Jaakkola (Ref. 63) assessed whether exposure to welding fumes or metal dusts during pregnancy affects the risk of pre-term delivery, or the birth weight or size of the newborn. The study population of 1,670 women who worked during pregnancy included 68 who were exposed to welding fumes and/or metal dust. The risk for low birth weight was significantly increased in women exposed to welding fumes during pregnancy but, as noted by the authors, the number of women exposed to welding fumes was small and the study lacked data for exposure concentrations.

Effects on the Endocrine System

Ellingsen et al. (Ref. 25) compared concentrations of the hormones inhibin B and prolactin in serum from 96 current welders, 96 controls, and 23 former welders who were patients diagnosed with welding-related manganism. Both hormones are involved in reproductive function. Serum inhibin B levels, which correlate with testicular volume and sperm counts, are depressed in infertile men. Elevated serum prolactin levels are associated with impotence and loss of libido. In this study, the current welders were exposed to manganese concentrations of 0.12 mg/m^3 in workplace air. Concentrations of prolactin and inhibin B were higher in serum from welders than from controls. Serum prolactin in the former welders did not differ from that of the controls, but their mean inhibin B concentration was significantly lower. The investigators stated that the return of prolactin to control levels in the former welders suggests that the effect of welding on the pituitary, where prolactin is synthesized, is reversible.

Inflammation and Oxidative Stress

Imamoglu et al. (Ref. 39) compared concentrations of markers of oxidative stress in red blood cells from 35 welders who performed SMAW of stainless steel and 30 controls. Concentrations of malondialdehyde were similar in welders and controls but the activities of catalase and SOD were significantly higher in the welders and correlated with the duration of the exposure to welding fumes. Sharifian et al. (70. Sharifian) measured levels of antioxidants in blood from 46 spot welders exposed to ELF-EMF (magnetic field strength = 8.8–84 microTesla). Superoxide dismutase and glutathione peroxidase activities were significantly lower in red blood cells from the welders than from unexposed controls.

Luo et al. (Ref. 48) examined the relationships between concentrations of zinc, copper, and nickel in urine and concentrations of white blood cells, glutathione, and IL-6 in blood from welders who worked at an automobile plant. The concentrations of the metals in urine were significantly associated with hours spent welding. The number of white blood cells and concentrations of IL-6 and glutathione were significantly associated with urinary zinc levels. Glutathione levels were positively associated with concentrations of copper but were inversely associated with urinary concentrations of nickel.

Nakata et al. (Ref. 55) compared the concentrations of components of the cellular and humoral immune system in the blood from 21 welders and 21 controls and related the results to blood manganese levels. They found that levels of T lymphocytes, especially CD8+ and CD4+CD45RA+ T lymphocytes, as well as CD19+ B lymphocytes are inversely correlated with the concentration of manganese in blood. A similar study by Yuan et al. (Ref. 86) did not corroborate the findings of Nakata et al. These investigators determined concentrations of a similar array of B and T lymphocytes in blood from welders with an average of 17 years experience. No significant differences were found between welders and controls.

Palmer et al. (Ref. 57) compared markers of the inflammatory response in induced sputum from 27 ferrous metal welders and 31 controls. No differences were found in the numbers of inflammatory cells, or levels of IL-8, TNF-α, myeloperoxidase, matrix metalloproteinase-9, immunoglobulin-A, or alpha-2-macroglobulin in induced sputum obtained from welders and controls.

Biological Monitoring

Schaller et al. (Ref. 68) examined the kinetics of aluminum, nickel, and chromium in blood and urine following accidental exposure of a welder performing thermal spraying. The welder had been working in a confined space with a metal containing high concentrations of nickel and aluminum. The exhaust ventilation was apparently defective and he became very ill after work. He was diagnosed with chemical pneumonia and was hospitalized for the next 3 months. Metal concentrations were measured in blood and urine samples collected five times during the year following his exposure. The half-lives for aluminum were 140 days in urine and 160 days in plasma. Biphasic elimination patterns were observed for chromium and nickel.

Hexavalent Chromium. Based on earlier work that showed that *in vitro* exposure of human fibroblasts to hexavalent chromium [Cr(VI)] resulted in up-regulation of the glycoprotein Apolipoprotein J/Clusterin (ApoJ/CLU), Alexopoulos et al. (Ref. 1) investigated whether serum levels of ApoJ/CLU could be used to monitor the exposure of shipyard welders to Cr(VI). They found that reduction of chromium levels at the worksite was associated with a decrease in levels of ApoJ/CLU in serum.

To examine the contribution of grinding to the levels of chromium and nickel in biological fluids from welders of stainless steel, Stridsklev et al. (Ref. 75) compared the levels of these metals in the breathing zone and in blood and urine from nine grinders who were not performing welding with those of stainless steel welders. Concentrations of nickel in the urine from grinders were comparable to those of welders, but concentrations of chromium in biological fluids collected from the grinders were low even though high levels of total chromium were measured in air samples. The authors attributed this to their finding that most of the chromium released into the air by grinding is in the metallic or trivalent form and that Cr(VI) was undetectable in most air samples collected during grinding.

Manganese. Ellingsen et al. (Ref. 26) compared concentrations of manganese in blood and urine from 96 current welders, 96 controls, and 27 former welders who had been diagnosed with manganism and had ceased welding about 6 years prior to the study. The concentration of manganese in blood was about 25% higher in both groups of welders than in controls, but urinary manganese concentrations did not differ significantly from controls. Smith et al. (Ref. 72) found that levels of manganese in whole blood, but not in plasma or urine, were significantly associated with the cumulative respiratory exposure index of the San Francisco Bay Bridge welders.

Wang et al. (Ref. 81) investigated whether manganese concentrations in saliva could be used as a non-invasive biomarker of manganese exposure among welders. They found that manganese and copper concentrations were significantly higher in saliva from welders than in saliva from controls and that concentrations of manganese and copper in saliva were significantly associated with those in serum. Manganese concentrations in saliva increased with years of welding experience.

Aluminum. Riihimaki et al. (Ref. 66) assessed the utility of measuring aluminum in urine and serum for use in biomonitoring. Concentrations of aluminum in air and biological samples were determined with 12 aluminum welders. It was found that aluminum in biological fluids is not suitable for biological monitoring because a large fraction of the inhaled aluminum is retained in the body and is excreted slowly over time.

Similar results were obtained by Rossbach et al. (Ref. 67) during a 5-year annual survey of air, blood, and urine samples collected from 62 aluminum welders. In this work, aluminum was determined in pre- and post-shift urine and plasma samples and total dust was determined in personal air samples. No substantial differences were found between aluminum concentrations in biological fluids collected before and after the work shift nor were there any relationships between personal dust exposures and aluminum in urine or plasma. The investigators suggested that this "might be caused by the slow elimination kinetics and low systemic bioavailability of Al."

Monitoring Saliva and Exhaled Air. Boyce et al. (Ref. 12) determined the pH of exhaled breath condensate (EBC) in 14 workers exposed to welding fumes and 8 non-exposed controls. The median pH of EBC samples collected at the start and end of the work shift were 7.21 and 7.49, respectively, for the welders and 7.39 and 7.42, respectively, for the controls. The authors concluded that exposure to metal fumes "may be associated with an acute increase in EBC pH values."

Fireman et al. (Ref. 31) determined pH values in EBC from 30 welders exposed to aluminum and iron and 16 exposed to cadmium, chromium, iron, lead, and nickel. The pH was significantly lower in EBC from the latter group of welders than from controls. The concentration of hydrogen peroxide was higher in EBC from all welders than from controls.

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